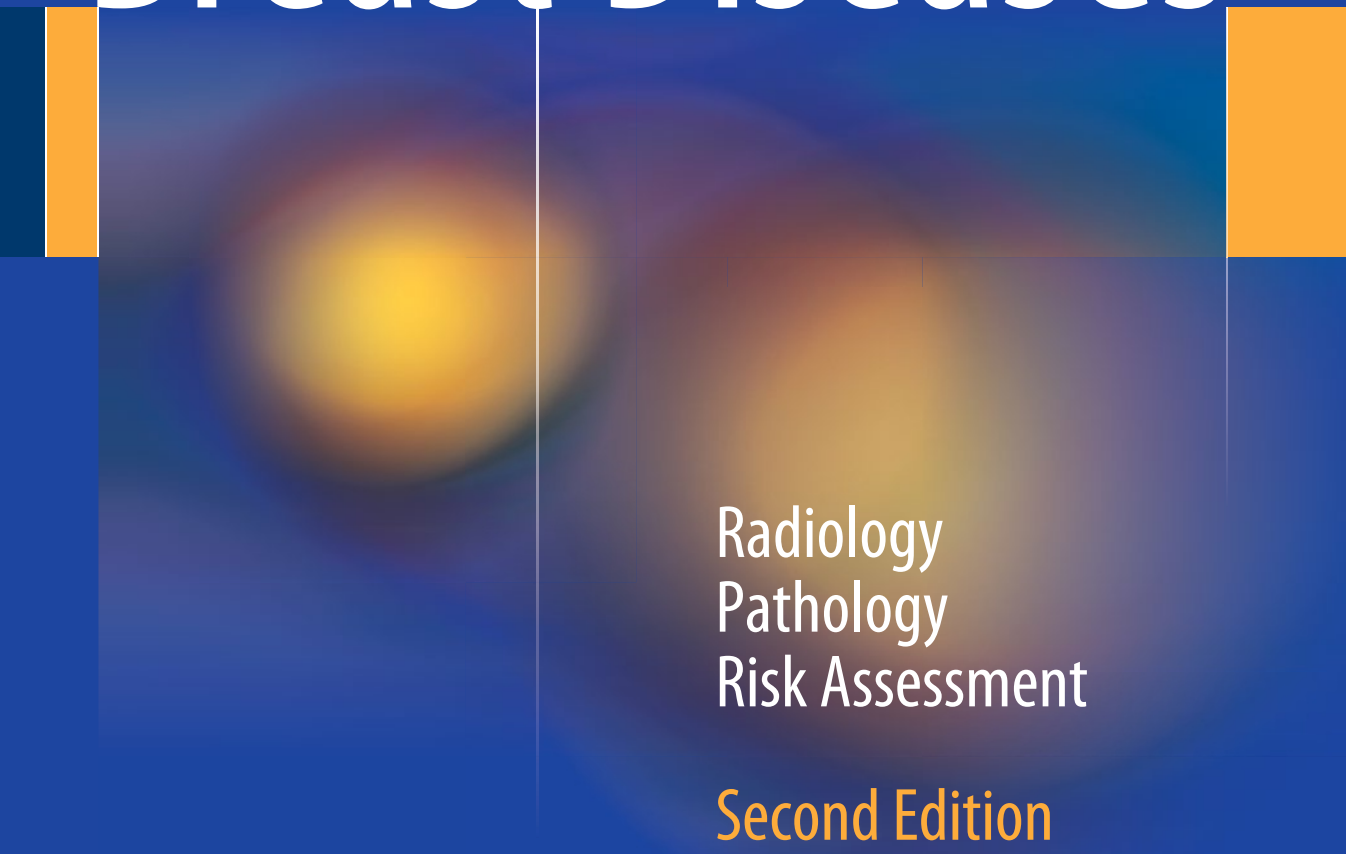
Catherine N. Chinyama

Benign Breast Diseases



Radiology
Pathology
Risk Assessment

Second Edition

Springer

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ISBN 978-3-642-41064-2 ISBN 978-3-642-41065-9 (eBook)
DOI 10.1007/978-3-642-41065-9
Springer Heidelberg New York Dordrecht London

Library of Congress Control Number: 2013957064

Printed on acid-free paper

Springer is part of Springer Science+Business Media (www.springer.com)

In memory of my parents
Nora and James Chinyama

Preface I

The majority of textbooks on breast disease understandably concentrate on cancer and related prognostic factors, with minimal space devoted to benign conditions. With widespread use of screening mammography and improvements in imaging equipment, smaller and smaller cancers are being detected. This has also resulted in detection of indeterminate micro-calcification and soft tissue densities, which invariably leads to diagnostic fine needle aspiration cytology or needle core biopsy. Although most of the mammographically indeterminate lesions are benign, biopsies also detect potentially malignant lesions, which include atypical hyperplasias, lesions of undetermined malignant potential such as columnar cell change and other epithelial proliferations. These lesions require proper radiological and pathological assessment at multidisciplinary meetings for appropriate patient management.

The objective of this book is to provide an overview of radiological and pathological features of benign lesions with an emphasis on screen-detected lesions, with illustrated examples. Although the radiological and pathological correlations concentrate on the screen-detected benign lesions, it was not possible to limit the discussion of the radiology and pathology to just screen-detected lesions. This is because mammographic screening became routine in developed countries only in the past few decades, and there are insufficient follow-up data in the literature on patients with screen-detected benign disease. Secondly, although breast disease is arbitrarily classified into symptomatic and screen-detected, all women who attend specialised breast units invariably undergo some form of imaging, mostly mammography or ultrasound. Emphasis on screen-detected lesions also highlights the heterogeneous array of benign diseases in this age group, which in the future may create significant breast disease workloads as longevity becomes the norm in the developed world.

The pathological discussions will also include possible aetiological factors and the pathogenesis of the disease processes. Most importantly, where applicable, the associated risk factors of individual conditions will be discussed based on previously published data. The assessment of the potential risk of progression to malignancy is increasingly playing an important part in the management of patients with benign breast disease. However, the discussion of risk factors related to benign lesions is not intended to alarm the reader, because the risk of progression to malignancy in most benign lesions is very small. In addition, due to the complicated nature of the studies required to determine the risk of subsequent malignancy, the majority of the risk

assessment is relative rather than absolute. As illustrated in the different chapters, with the exception of lesions such as atypical ductal hyperplasia, there is no consensus among investigators as to the level of risk associated with most benign lesions. The author therefore gathered both the supporting and the contradicting evidence on risk factors on individual benign lesions to give readers the opportunity to make up their own minds when making a clinical decision. The clinician should not apply these risk factors to patients without taking into account other parameters such as family history, previous history of cancer, menopausal status or use of hormonal therapy.

The radiological features of benign diseases using different modalities such as mammography, ultrasonography and magnetic resonance will also be discussed. Detailed radiological techniques and routine interpretation of mammograms are extensively covered in appropriate textbooks, some of which have been included in the references in the appropriate chapters. Likewise, detailed histological techniques are not part of this book. The book should be useful to breast radiologists, surgeons, pathologists and other health workers who look after women with breast disease in their practices. Post-graduate students should find this a quick reference book.

Guernsey, UK
August 2003

Catherine N. Chinyama

Preface II

Since the publication of the first edition of this book in 2004, there have been a lot of advances in radiology, pathology and molecular pathology of both benign and malignant breast diseases. There are very few books on benign breast disease, which is a gap that needs to be filled, because understanding of the biological behaviour of benign breast lesions will assist the clinician and the patient to assess the risk of malignancy and formulate a follow-up strategy or take appropriate preventative measures. This book has therefore attempted to evaluate the radiological and pathological features of common benign lesions and the associated risk of subsequent breast cancer and, where possible, included the management of these lesions. Since the first edition, there has been improved understanding of the pathology of columnar cell lesions and mucocoele-like lesions, and these chapters are much longer than in the first edition. To aid better understanding of benign breast lesions, a chapter on normal breast has been included. Other new chapters include: an overview of benign breast lesions (Chap. 2), inflammatory lesions (Chap. 6) and male breast lesions (Chap. 15). Phyllodes tumour has been included in the chapter on fibroepithelial lesions (Chap. 10) as the lesion shares clinical, radiological, pathological and genetic features with the fibroadenoma. The statistics involved in risk assessment are complex, but statistics are also becoming routine in patient management. To this end, the author has expanded the chapter on risk assessment to include some definitions. This chapter also includes the different models used in risk assessment of breast cancer which will no doubt become routine as part of patients' personalised medicine. The second edition also includes more radiological and pathological illustrations to reflect the heterogeneous nature of the benign lesions. Genetic assessment is becoming part of patient management for both malignant and benign lesions. Where applicable, genetic assessment is included as part of risk assessment with regards to whether a lesion is clonal and, therefore neoplastic, or polyclonal and hyperplastic. The previous edition concentrated mostly on screen-detected benign lesions, and this has been rectified by discussing common symptomatic breast lesions, some of which have no associated risk to breast cancer. As multidisciplinary team management of patients is now the norm rather than the exception, this book will be valuable to doctors, nurses and other allied health professionals who look after patients with breast diseases in a multi-professional environment.

St. Martin's Guernsey, UK — Catherine N. Chinyama

Disclaimer

Although this book attempted to provide information on risk factors in benign diseases available at the time of going to press, rapid advances in fields of medicine such as radiology and molecular biology may negate or contradict the information published herein. In addition, most of the risk assessments documented in this book are based on studies in symptomatic patients, which may or may not be applicable to screen-detected lesions. It is therefore the responsibility of the treating physician to assess the patient's risk on an individual basis. Neither the author nor publisher assumes any responsibility for any damages arising from the use of information published in this book.

Acknowledgements

It is always harder to update or rewrite a book than write one as a fresh project. There was a lot of information to be added, deleted, cut and pasted in updating a book. For this, I am indebted to my private secretary Michelle Oland who tirelessly updated the book and filled in a lot of gaps my fountain pen had missed. I am grateful to Jodie Knight and Anne Marie Nolan at the Princess Elizabeth Hospital library for their help in obtaining reference articles for me. Finally, I wish to say thanks to my biology teacher Miss Thomas ('Auntie' Mary) for her support throughout my career in medicine.

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Abbreviations

AA	Apocrine adenosis
ACR	American College of Radiology
ADH	Atypical ductal hyperplasia
ALH	Atypical lobular hyperplasia
AMGA	Atypical microglandular adenosis
ANDI	Aberrations of normal development and involution
AP	Antero-posterior
ASBS	American Society of Breast Surgeons
BASO	British Association of Surgical Oncology
BCPT	Breast Cancer Prevention Trial
BMI	Body mass index
BI-RADS	Breast Imaging Reporting and Data System
CCC	Columnar cell change
CCL	Columnar cell lesion
CEA	Carcino-embryonic antigen
CGH	Comparative genomic hybridisation
CI	Confidence interval
CIS	Carcinoma in situ
DCIS	Ductal carcinoma in situ
DCISM	DCIS with microinvasion
DHEA	Dihydroepiandrosterone
DIN	Ductal intra-epithelial neoplasia
EGFR	Epidermal growth factor
EMA	Epithelial membrane antigen
ER	Oestrogen receptor
ERα	Oestrogen receptor α
ERβ	Oestrogen receptor β
EUSOMA	European Society of Mastology
FEA	Flat epithelial atypia
FNAC	Fine needle aspiration cytology
FSH	Follicle stimulating hormone
GCDFP	Gross cystic disease fluid protein
H&E	Haematoxylin and eosin
HPF	High power field
HRT	Hormone replacement therapy
HUT	Hyperplasia of usual type
IDC	Invasive ductal carcinoma

IDP	Intraductal papilloma
IGM	Idiopathic granulomatous mastitis
ILC	Invasive lobular carcinoma
LC-BBD	Lower category benign breast disease
LCIS	Lobular carcinoma in situ
LH	Luteinising hormone
LN	Lobular neoplasia
LOH	Loss of heterozygosity
MGA	Microglandular adenosis
MLL	Mucocoele-like lesion
MR	Magnetic resonance
MRI	Magnetic resonance imaging
NHS	National Health Service
NHSBSP	NHS Breast Screening Programme
NICE	National Institute for Health and Care Excellence
NSABP	National Surgical Adjuvant Breast and Bowel Project
NST	No special type
PASH	Pseudoangiomatous stromal hyperplasia
PCR	Polymerase chain reaction
PDWA	Proliferative disease without atypia
PR	Progesterone receptor
RR	Relative risk
RS	Radial scar
SA	Sclerosing adenosis
SD	Standard deviation
SEB	Surgical excision biopsy
SEER	Surveillance Epidemiology and End Results
SERM	Selective oestrogen-receptor modulator
SHBG	Steroid hormone binding globulin
SMA	Smooth muscle actin
TDLU	Terminal duct lobular unit
TNFa	Tumour necrosis factor alpha
UDH	Usual ductal hyperplasia
WHO	World Health Organisation

Contents

The Normal Female Breast

1

Learning Points

- The breast tissue develops from the milk line.
- At birth there is no difference between male and female breasts.
- Pubertal growth is due to glandular and fibrofatty proliferation.
- The amount of fibroglandular tissue decreases with age.
- Benign breast disease and cancer arise in the terminal duct–lobular unit.
- Multiple hormonal stimulation significantly increases the volume of the breast tissue during pregnancy.

1.1 Embryology of the Breast

The breast tissue develops from the milk line from approximately 7 weeks gestation. The ducts arise from the ectodermal mammary ridge which develops into a budding stage by the 12th week. The milk line extends from the axilla to the groin and is responsible for vestigial accessory nipples. However the axilla to groin concept of the nipple line in humans has been challenged as accessory nipples are only found in the axillo-pectoral region (Mansel et al. 2009). The most common embryological vestige is accessory breast in the axilla (Fig. 1.1).

Whist developing in utero, the breast epithelium and stroma are under the influence of growth factors and placental hormones, which include prolactin, oestrogen and progesterone (Forsyth 1991). Falling of maternal oestrogens in the neonatal period stimulates the production of prolactin which induces secretory changes in the breast. This results in unilateral or bilateral enlargement of the breasts which may be associated with secretion of 'witches milk'. At birth there is no difference between the male and female breast tissue, but the presence of testosterone leads to the involution of the male breast.

1.2 Pubertal Changes

Thelarche, which commences between 10 and 12 years, heralds the rapid growth of the breast at the onset of puberty. The pituitary hormones follicle-stimulating hormone (FSH) and luteinising hormone (LH) stimulate the production of oestrogen and progesterone, resulting in the enlargement of the areola and the nipple, development of the lobules and associated acini and increase in intralobular stroma and fat. Abnormal secretion of the hormones can result in premature thelarche which is characterised by unilateral or bilateral development of breast tissue before puberty. Erroneous interpretation of breast enlargement in premature thelarche as pathological can lead to surgical excision rendering the child amastic. The breast tissue in premature thelarche regresses with time.

C.N. Chinyama, *Benign Breast Diseases*,
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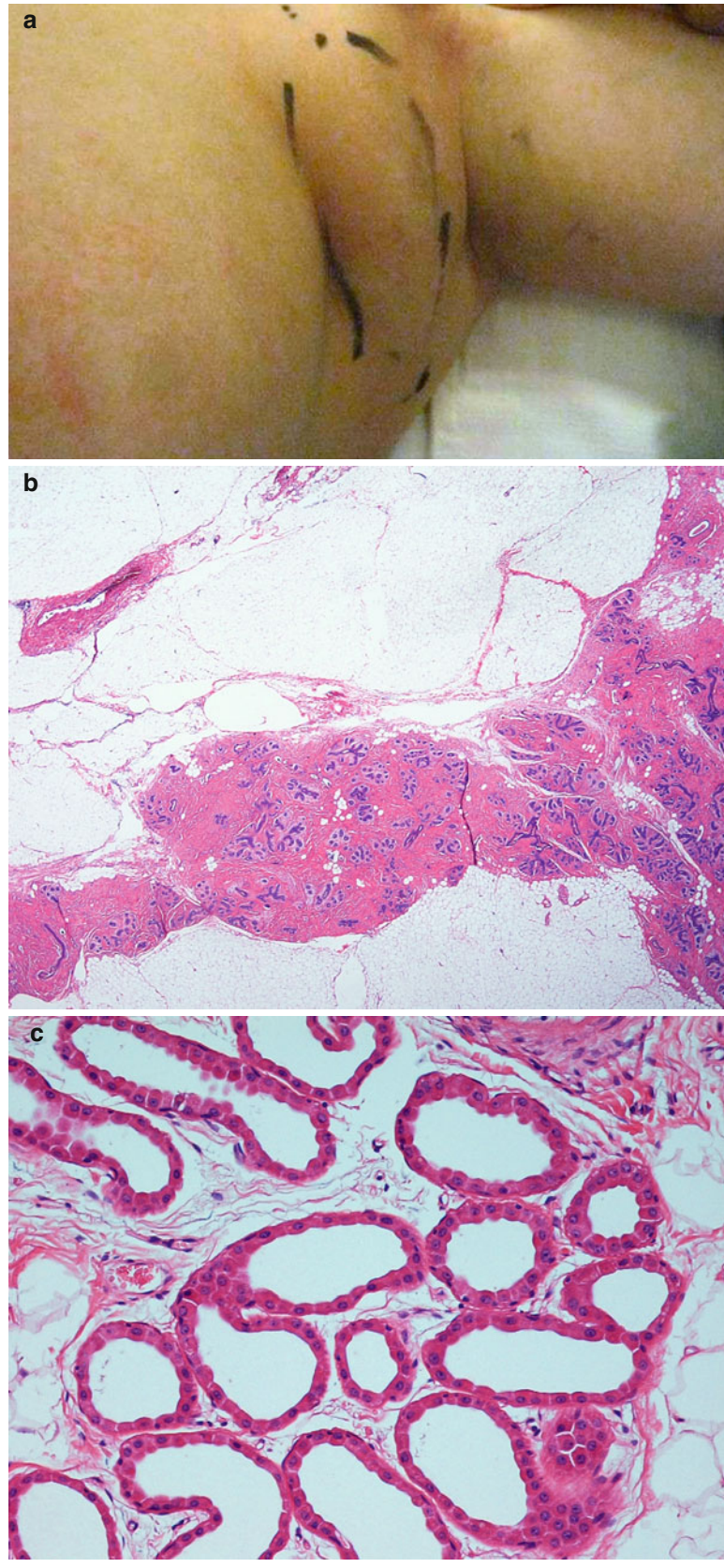

Fig. 1.1 (**a**) Accessory breast tissue which presented as an axillary mass. (**b**) The histology shows normal breast lobular units. (**c**) The presence of apocrine sweat glands in the surrounding tissue confirmed axillary origin of the breast tissue

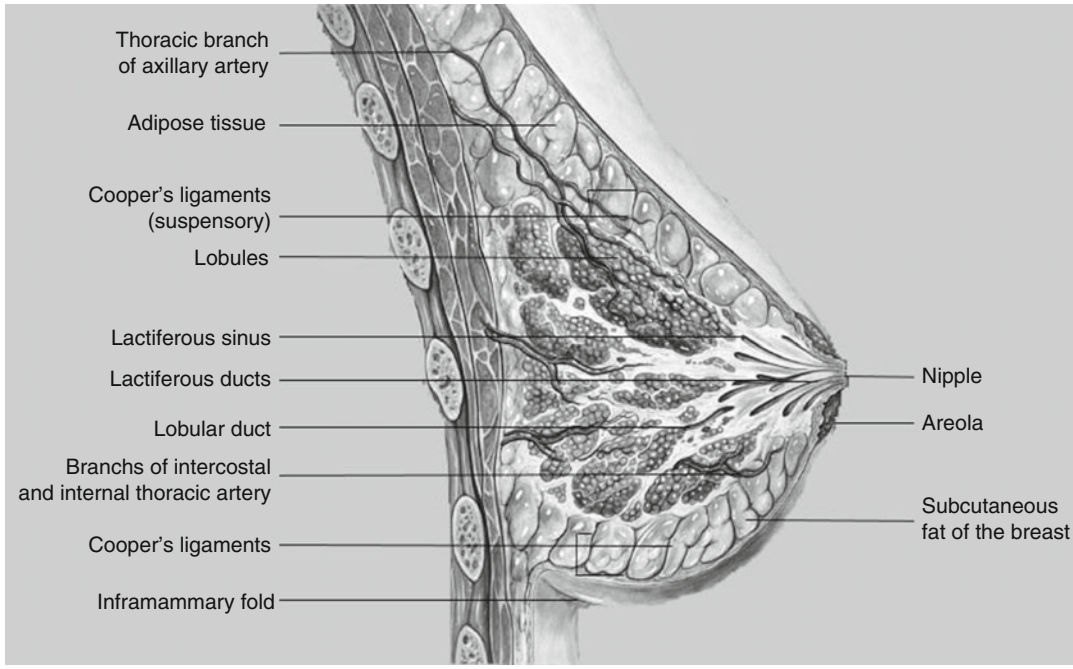

Fig. 1.2 This is a pictorial presentation of the normal breast (Reproduced and modified with permission from Patrick J. Lynch, Senior Digital Officer Office of Public Affairs & Communications Yale University)

1.3 Gross Anatomy of the Adult Female Breast

Adequate understanding of the anatomy of the breast is important for surgery of both cancer or benign disease. The female breast overlies the pectoralis muscle and extends from the second or third rib to the sixth or seventh rib on the anterior chest wall. The large volume of the breast is due to adipose tissue. The nipple–areola complex is pigmented. Studded circumferentially around the nipple are Montgomery tubercles which represent modified sebaceous glands. The breast tissue is located between fascia over the chest wall. Fibrous septa extend from the dermis into the breast parenchyma to create the suspensory ligaments of Cooper. Loss of tension in the suspensory ligaments of Cooper leads to pendulous breast usually seen in older women or nulliparous women. Figure 1.2 illustrates the normal anatomy of the adult breast.

The mammographic density of the breast depends on the amount of fibrofatty stroma and the epithelial elements. Increased mammographic density of the breast is more apparent in young women when compared to postmenopausal women whose breasts tend to be fatty following loss of hormonal stimulation. The mammographs in Fig. 1.3 compare a dense breast in a 34-year-old woman with a fatty postmenopausal breast in a 73-year-old woman. Magnetic resonance imaging (MRI) is a preferred modality of investigating dense breasts than mammography as cancers can be masked by dense tissue and missed on mammography. Dense breasts in younger women are one of the arguments for not screening women before the age of 50.

1.4 Microscopic Anatomy of the Adult Female Breast

The adult female breast consists of 15–25 functional lobes which are distributed in the stroma in multiple lobules (Fig. 1.4). The lobes drain into multiple ducts which coalesce and subsequently drain into lactiferous ducts which terminate at the nipple. The ducts and lobular units are supported by fibrofatty stroma which is a major component of the breast tissue. The breast lobule consists of 20–40 acini or alveoli which are the basic secretory unit of the breast. The acini consist of two layers of epithelium, the inner secretory layer which rests on a myoepithelial layer bound by a

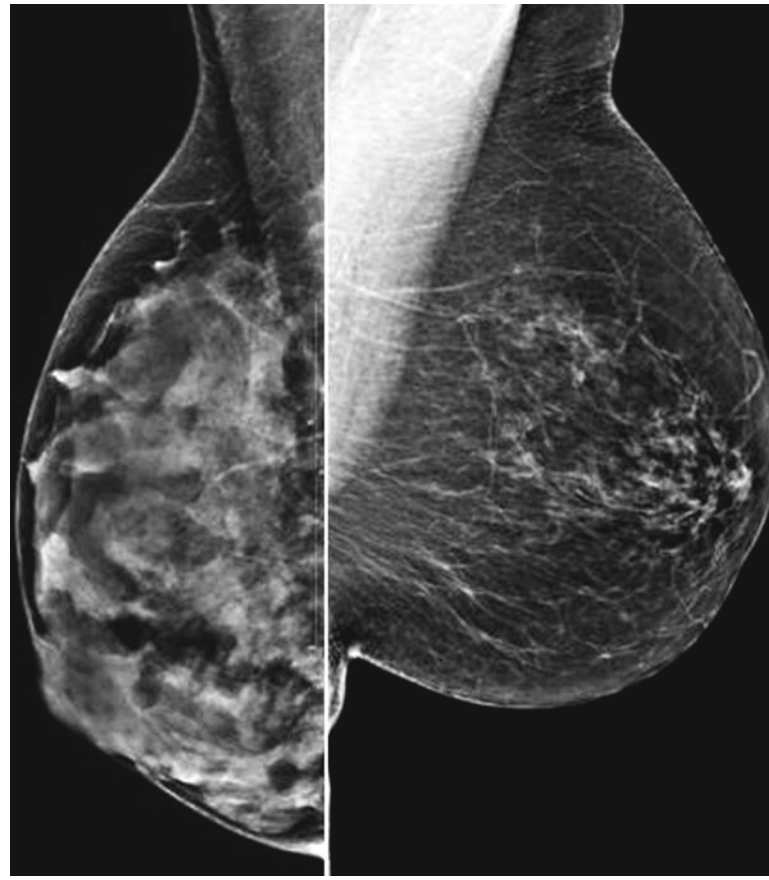

Fig. 1.3 Comparison of mammographic appearance of dense breast tissue in a 34-year-old woman and fatty breast tissue in a 73-year-old woman

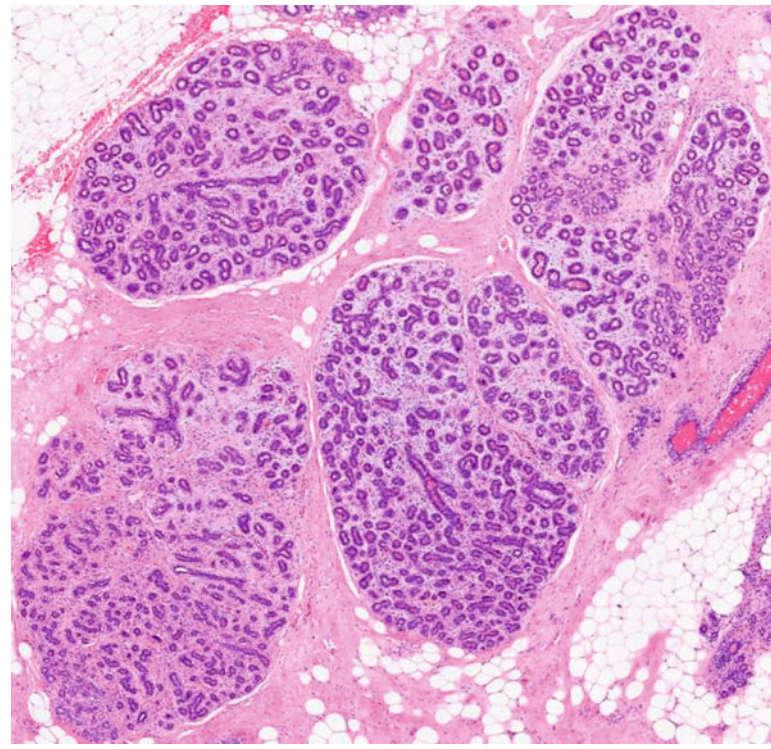

Fig. 1.4 Normal breast lobules separated by fibrous stroma

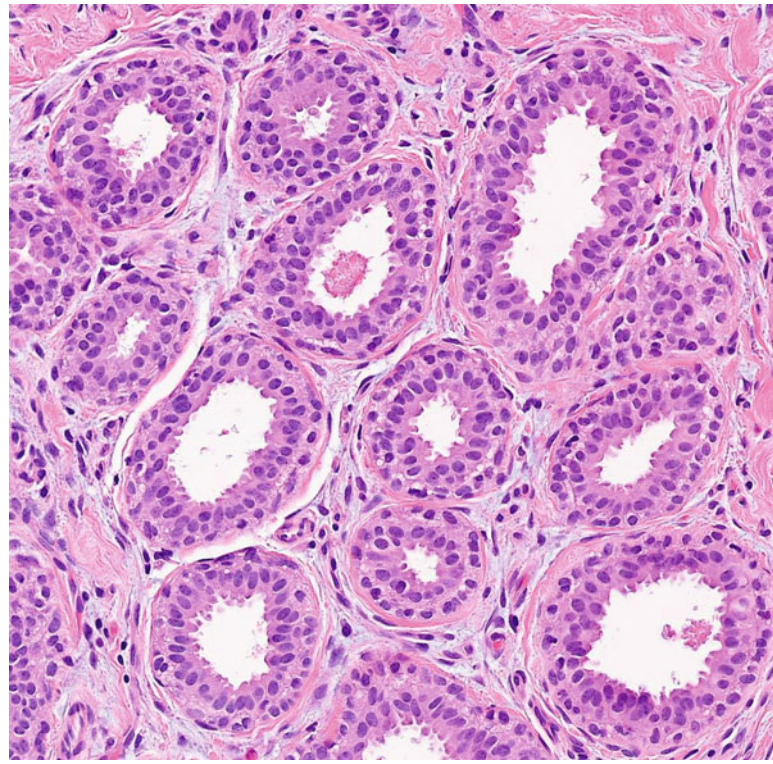

Fig. 1.5 The lobules consist of acini or glands lined by an outer myoepithelial cells and an inner secretory cells, also known as luminal cells

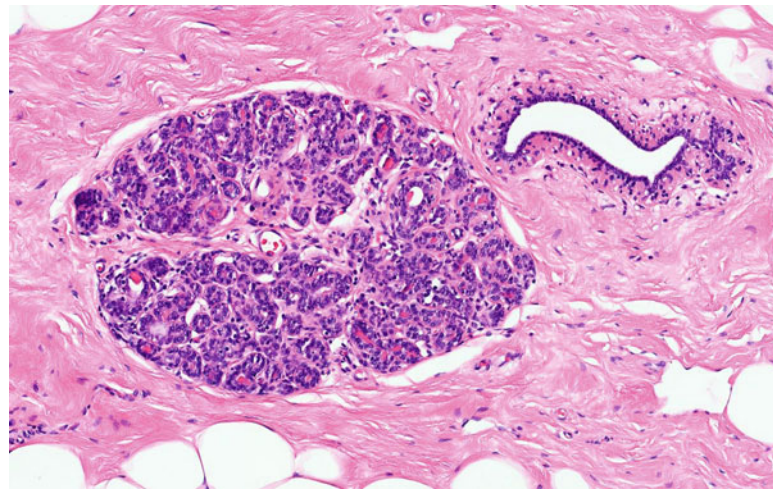

Fig. 1.6 The terminal duct–lobular unit (TDLU) consists of a duct leading into a lobule in a woman under the age of 50. Note the surrounding dense stroma and luminal secretions

basement membrane (Fig. 1.5). The myoepithelial cells have a contractile function to empty the milk into the ducts. The lobule and the first or terminal duct arising from it constitute the terminal duct–lobular unit (TDLU) (Fig. 1.6). The TDLUs are important sites for the development of cancer and benign proliferations of the breast. Both cells are under the influence of hormones. In the postmenopausal woman, the acini become atrophic and the two cell layers are barely discernible.

1.5 The Breast During the Menstrual Cycle

The breasts respond to the cyclical variation of the ovarian hormones during the menstrual cycle, punctuated by variation in the size and texture of the breast tissue (White et al. 1998). The breast is less nodular at mid-cycle and the end of the follicular phase. Mammograms performed during

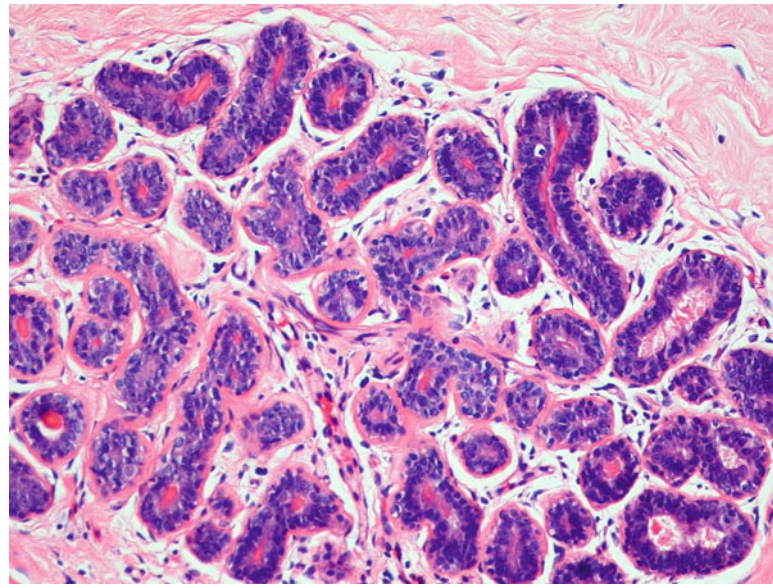

Fig. 1.7 Eosinophilic (*pink*) luminal contents in a secretory lobule in the second half of the menstrual cycle

the follicular phase tend to be less dense than those taken in the second half of the menstrual cycle. As part of clinical assessment, it is important therefore to record the woman's date of last menstrual period if malignancy is suspected to assess the breast clinically and mammographically around the mid-cycle. MRI enhancement during the second half of the menstrual phase can give a false positive for malignancy in a premenopausal woman (Muller-Schimpfle et al. 1997; Cameron et al. 1990). Histologically the lobules show increased mitotic activity in the follicular phase of the menstrual cycle and luminal secretion in the luteal phase (Fig. 1.7).

1.6 Pregnancy and Lactation

During pregnancy the breast is subjected to multiple hormonal stimulation which includes placental lactogen, oestrogen, progesterone, cortisol, growth hormone and prolactin. In response, the areola increases in pigmentation and the breasts increase in size. The increase in size is due to proliferation of the terminal duct and lobular units with associated oedema and increased vascularity. If malignancy is suspected during pregnancy, ultrasonography is the preferred method of assessment. Mammography poses radiation risk to the developing foetus but can be performed if necessary with appropriate precautions. MRI assessment is inappropriate due to increased physiological enhancement.

Increase in the glandular tissue during pregnancy is associated with a corresponding decline in the fatty composition in the breast. By the second trimester, the epithelial cells become vacuolated, and milk starts accumulating in the glandular lumina in response to prolactin stimulation. After lactation, the breast lobules involute following the withdrawal of prolactin stimulation.

1.7 The Postmenopausal Breast

The postmenopausal woman's breast is characterised by glandular atrophy in response to withdrawal of ovarian oestrogen and progesterone. Mammographically the breasts appear fatty and easy to assess (Fig. 1.2). Histologically in the breasts, there is increase in interlobular fibrosis which tends to separate the lobules (Fig. 1.8). Cysts may be present due to incomplete postlactational involution.

Hormone replacement therapy in postmenopausal women has the tendency to increase the parenchymal density on mammography and may be associated with breast tenderness (McNichols et al. 1994).

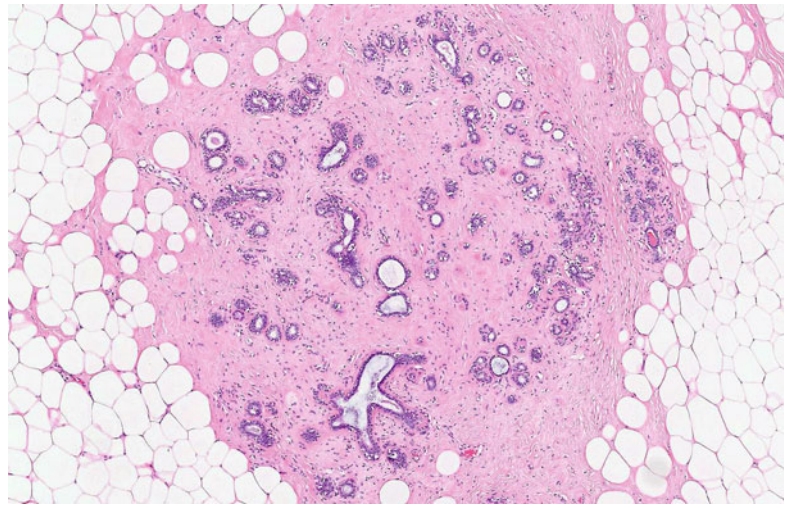

Fig. 1.8 Atrophic post-menopausal lobule surrounded by adipose tissue. The acini are irregular and separated by fibrous stroma. Incomplete post-lactational involution causes irregular glands

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Overview of Benign Breast Lesions

2

Learning Points

- Benign breast lesions are more prevalent than breast cancer.
- Benign breast lesions are a heterogeneous group of conditions.
- Most benign breast lesions are incidental findings in specimens resected for breast cancer that are detected mammographically.
- Benign breast lesions require triple assessment.
- Accurate classification of benign breast lesions is important as to aid risk assessment for breast cancer.

2.1 Background

Most women who present at the breast clinics have benign breast conditions which range from non-specific breast pain to discrete lumps such as fibroadenomas. Benign breast lesions consist of heterogenous conditions which in the majority of women go undetected and are identified incidentally during screening mammography or in the surgical specimens for cancer. Although most women present with benign breast conditions than with cancer, there is more written about breast cancer than benign lesions because this is the most common malignant tumour in women. Nomenclature of benign breast lesions was confusing in the past with the use of terms such as aberrations of normal development and involution (ANDI), which is supposed to encompass both the pathogenesis and the degree of abnormality (Hughes et al. 1987). The terminology used in this book for benign breast disease is based on the classification by the College of American Pathologists (Hutter 1986; Fitzgibbons et al. 1998) which is used by the UK NHS Breast Screening Programme (2005).

2.2 Clinical Presentation of Benign Breast Lesions

The incidence of benign breast disease begins to rise during the second decade of life and peaks in the fourth and fifth decades, which is in contrast to cancer whose incidence increases after menopause (Guray and Sahin 2006). The clinical presentation of benign breast conditions includes pain, lumps and nipple discharge (Santen 2010). Cyclic breast pain occurs during the late luteal phase of the menstrual cycle in association with the premenstrual syndrome or independently and resolves after onset of menses (Santen 2010). A study of 1,171 healthy American women reported that 11 % experienced moderate to severe cyclic breast pain and 58 % mild discomfort (Ader and Shriver 1997). Breast pain interfered with sexual activity in 48 %, with physical (37 %), social (12 %) and school (8 %) activity.

The proliferation of the duct–lobular units manifests as a breast lump which is detected by

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DOI 10.1007/978-3-642-41065-9_2, © Springer-Verlag Berlin Heidelberg 2014

the patient or their clinician. Ninety percent of these nodules or lumps in premenopausal women are benign, usually fibroadenomas (Goehring and Morabia 1997). Other lesions which present as lumps include cysts, sclerosing adenosis and multiple intraductal papillomas.

Nipple discharge is a common presenting symptom, and this represents 6.8 % of referrals to the Breast Clinic, and only 5 % of the patients are found to have serious pathology (Santen 2010). Careful history and examination is important to determine the underlying cause of the discharge. It is important to determine whether the discharge is spontaneous or expressive and whether the discharge is from a single duct or multiple ducts (Santen 2010). Nipple discharge can be physiological or pathological. Physiological discharge is usually non-spontaneous (expressible), from multiple ducts, bilateral and non-bloody. In contrast, pathological discharge is typically spontaneous, serous or bloody, unilateral and from a single duct (Santen 2010). Pathological nipple discharge can be caused by duct ectasia, papilloma or cancer. Patients who present with galactorrhoea require assessment of prolactin.

With the widespread use of screening mammography, most benign lesions are detected mammographically which will represent the majority of the lesions discussed in this book. Screening mammography has led to the detection of hitherto previously unknown lesions such as mucocoele-like lesions and columnar cell lesions.

2.3 Investigation of Benign Breast Lesions

As with breast cancer, women who present with clinically benign breast disease require triple assessment, i.e. clinical examination, radiological assessment and pathological evaluation of the lesion by either fine needle aspiration cytology or needle core biopsy. The patient should be managed with multidisciplinary team which includes the breast surgeon, the radiologist, the pathologist and the clinical nurse specialist in breast care.

The type of imaging depends on the symptomatology and age of the patient. Mansel et al. (2009) provide an algorithm for management of these patients: thus, for a milky nipple discharge in a woman under the age of 40 with no lump, exclude mechanical stimulation, drugs and hormones and reassure; women with watery, serosanguineous and bloody discharges will require radiological investigations and, if symptoms persist, may require subareolar resections. In most hospitals in the UK, the patients have cytological evaluation of the nipple discharge. The presence of cells on the smear is classified as C3, i.e. atypical cells probably benign (NHS BSP Publication No. 58 (2005)). If inflammatory cells and macrophages are present in the smears of non-bloody nipple discharge, usually bilateral with a normal imaging, the cytology will be in keeping with duct ectasia.

A bloody nipple discharge is not always due to underlying breast lesion e.g., a patient on warfarin for atrial fibrillation presented with unilateral nipple discharge. The radiological investigations were normal. On cytology, the nipple discharge was heavily blood stained and contained haemosiderin-laden macrophages. There were no epithelial cells. As a papillary lesion could not be excluded, the patient underwent subareolar resection. The surgical specimen contained duct ectasia with associated haemorrhage but no papillary lesion (Fig. 2.1).

In the presence of discrete lumps, ultrasonography is the preferred method of assessment in women below the age of 35 because of its ability to penetrate through dense breast tissue commonly found in younger women (Santen 2010). If there is a cyst, this can be aspirated, and if bloodstained, the fluid is submitted for cytological evaluation. Non-bloodstained fluid is discarded to reduce the risk of atypical C3 reports from degenerate cells which will prompt further examination and cause unnecessary patient anxiety. Patients with recurrent multiple cysts are managed by radiologists with aspiration as required (Fig. 2.2). Complex, multiloculated cysts may require biopsy of the wall under ultrasound guidance to exclude a high-grade lesion. Solid palpable lumps require both

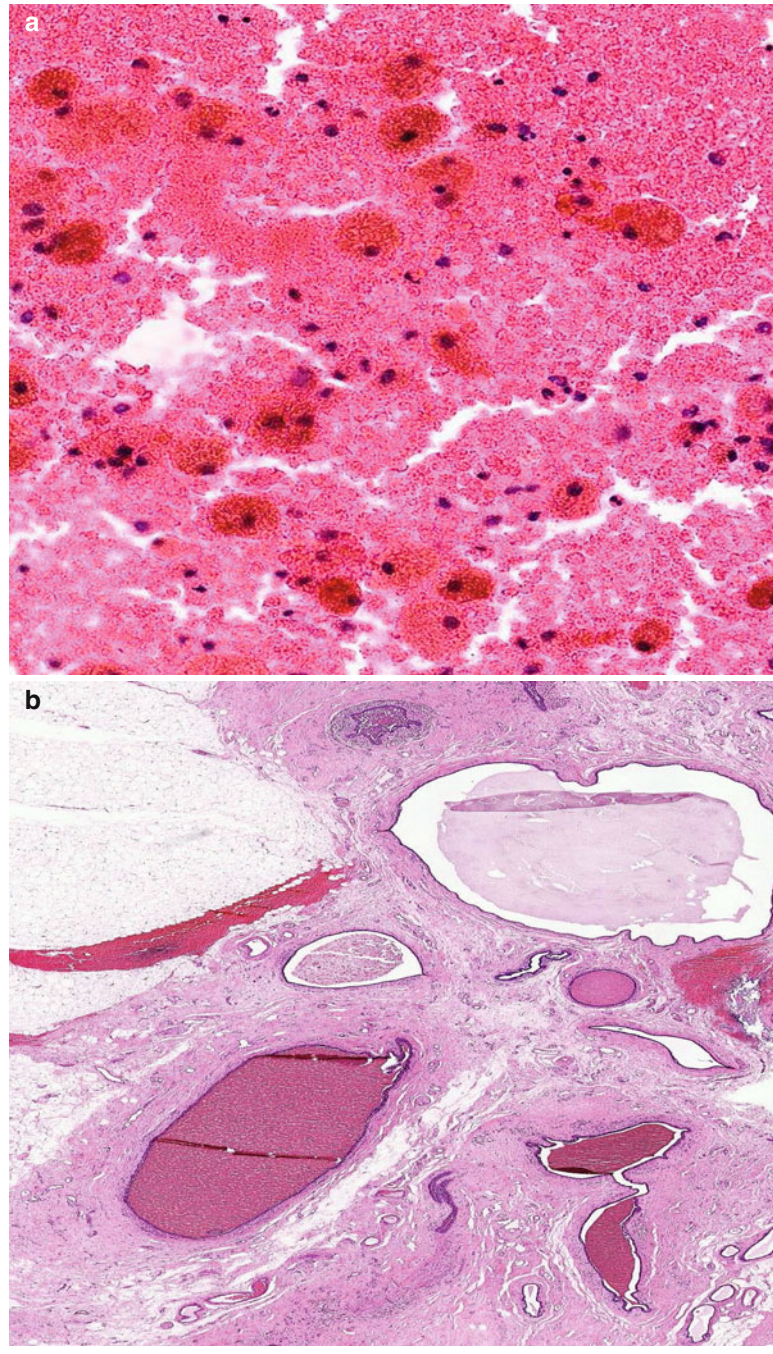


Fig. 2.1 (**a**) The cytology of a bloody nipple discharge from a patient on warfarin showed blood and haemosiderin-laden macrophages (H&E-stained slide). (**b**) The subareolar resection showed haemorrhage in the duct ectasia and no papillary lesion

mammographic and ultrasound assessment, especially in women with dense breasts where the lump can be mammographically occult (Shetty et al. 2003).

Mammographically detected abnormalities such as soft tissue architectural distortion, masses and calcification are usually biopsied under stereotactic guidance and may also require ultrasound evaluation. Biopsy of a microcalcification is usually under stereotactic guidance. Most the lesions to be illustrated in the next chapters will have mammographic images.

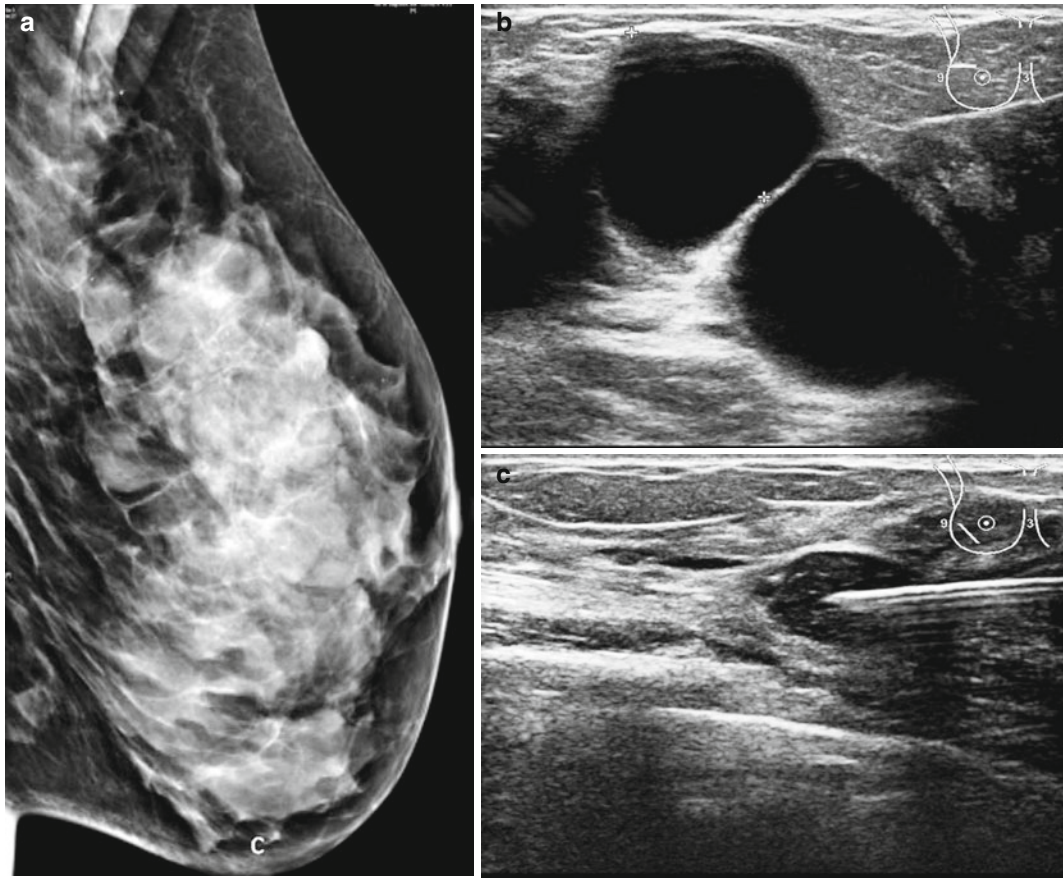


Fig. 2.2 (**a**) The mammogram of a patient with dense breasts which obscure multiple cysts. (**b**) The multiple cysts are readily visible in ultrasound images. (**c**) The cysts disappeared on aspiration

Magnetic resonance imaging (MRI) is not routinely used to assess benign breast disease. However, as the image in Fig. 2.3 illustrates, benign breast disease can enhance sufficiently to raise the suspicion of malignancy. The patient had had biopsy-proven lobular carcinoma of the left breast, and she had MRI to assess the extent of the cancer and exclude bilateral disease. Because of the mammographic abnormality in the other breast, she opted for bilateral mastectomy. The histology illustrates the heterogeneity of benign breast disease. The right breast contained a mixture of benign proliferations consisting of fibrocystic change with apocrine metaplasia, duct ectasia with periductal mastitis, intraductal papillomas, florid usual ductal hyperplasia (UDH) without atypia and benign calcification, columnar cell change and fibroadenomatoid change.

2.4 Significance of Benign Breast Lesions

The main reason for assessing benign breast disease is to exclude malignancy and to determine the risk of progression to malignancy. Several studies have reported an increase of risk of malignancy following the diagnosis of different benign disease (Duport and Page 1985; Carter et al. 1988; Duport et al. 1993; Hartman et al. 2005). The more complex the benign disease, the higher the risk of progressing to breast cancer.

In assessing the individual woman's risk of progressing to malignancy, the pathology of the benign proliferation is assessed in conjunction with other factors such as family history of breast cancer, hormone replacement therapy and body

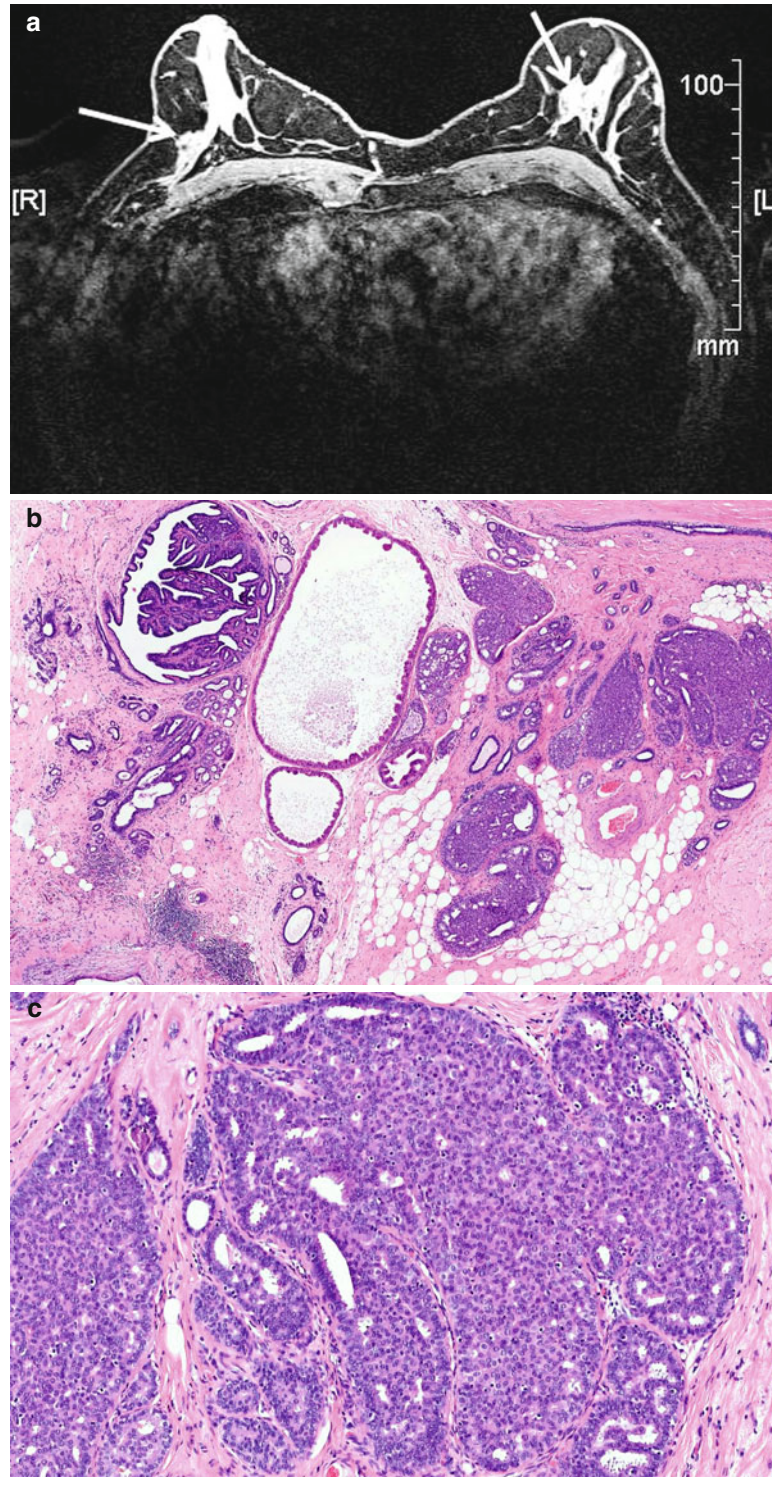


Fig. 2.3 (**a**) MRI of enhancing invasive lobular carcinoma in the left breast and enhancing mixed benign breast disease on the right side. (**b**) The histology showed multiple benign lesions, consisting of (**c**) usual ductal hyperplasia without atypia, (**d**) intraductal papilloma, (**e**) duct ectasia, (**f**) cysts with apocrine metaplasia and (**g**) calcification in benign lobules

Fig. 2.3 (continued)

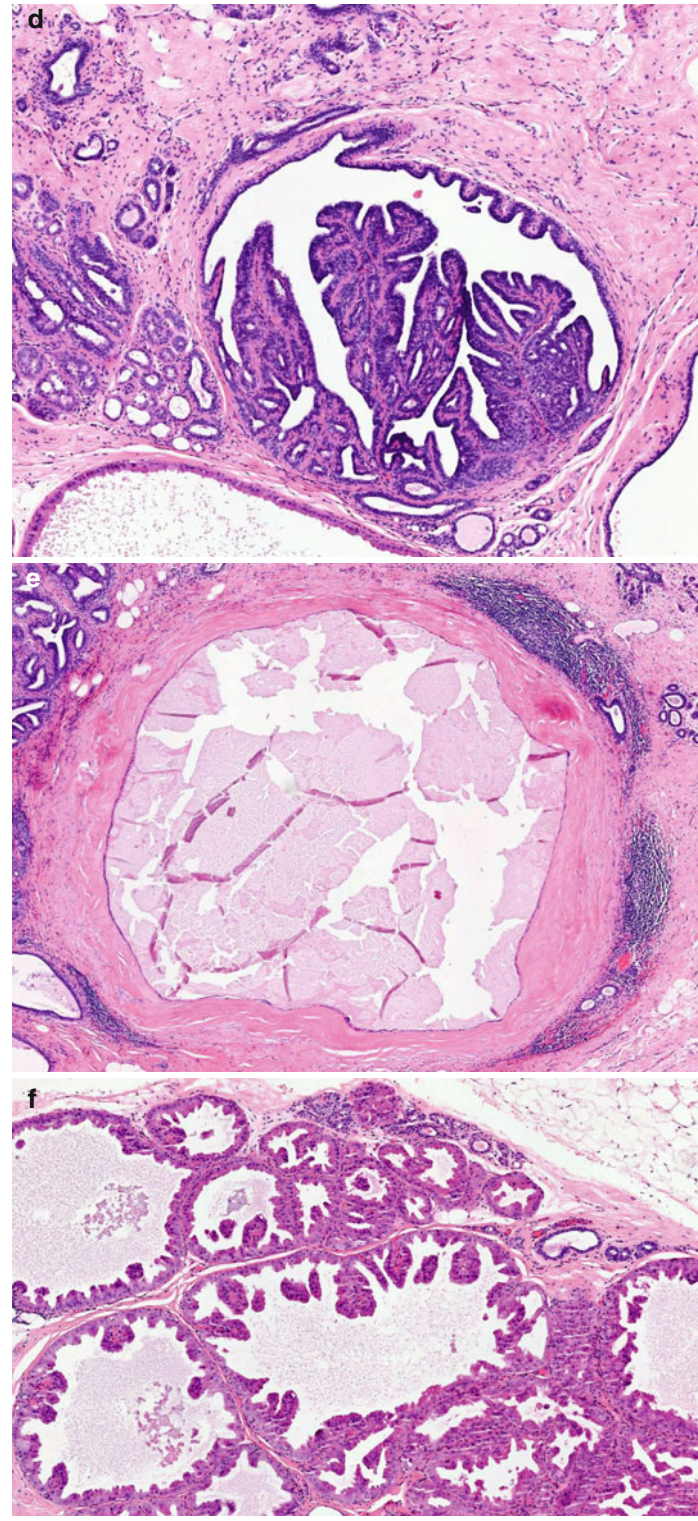
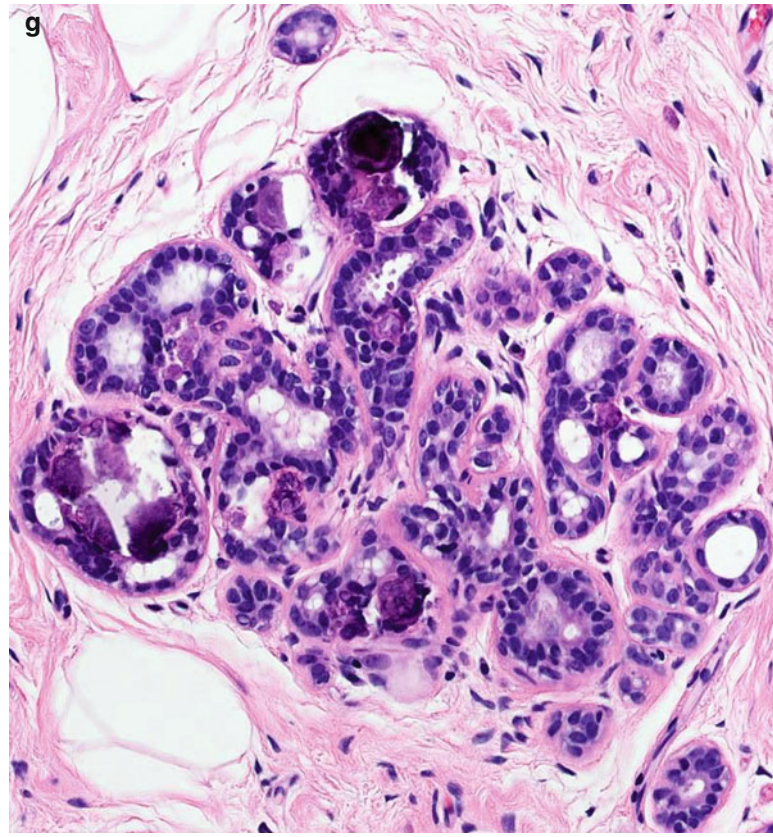


Fig. 2.3 (continued)



mass index (Huang et al. 1997). The risk attributed to different benign proliferations will be assessed for each condition in the different chapters. Three different models are currently in use to assess the risk of cancer in individual women, namely: the Gail model (1989), Claus model (1994) and Tyrer–Cuzick model (2004). These risk assessment models and others are evaluated in detail in Chap. 16.

By the use of molecular pathology, interest is now focussed in identifying genetic markers which can predict the increased risk of developing breast cancer in benign breast disease. The presence of aberrant p53, p21, interleukin 16 and TNF-α in benign breast disease has been associated with increased relative risk of breast cancer (Garcia-Tunon et al. 2006). Her2 amplification and proliferative disease are associated with increased risk of progression to invasive cancer (Stark et al. 2000; Chlebowski et al. 1999).

Benign breast disease is getting more attention now than the condition did before. This is because if a risk factor for cancer can be identified, there is a potential for prevention of cancer by giving the woman the option of chemoprevention (Gail et al. 1999; Chlebowski et al. 1999).

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Radiology of Benign Breast Lesions

3

Learning Points

- A few benign lesions such as oil cysts, calcified fibroadenomas and vascular calcification have diagnostic mammographic features.
- Most mammographic calcification in benign lesions is indeterminate.
- Ultrasound is the best investigation to differentiate cysts from solid lesions.
- MRI is better for assessing lesions in dense breasts than other methods.
- Directional vacuum-assisted core biopsies can remove small benign calcified lesions.

3.1 Background to Benign Breast Lesions

Screening mammography has been successful in detecting small and early cancers, resulting in favourable prognoses. At the same time, this has also resulted in detection of previously occult benign breast disease. The distinction between benign and malignant lesions is not always simple. Although some mammographically detected lesions such as calcifying fibroadenomas, oil cysts, intramammary lymph nodes, vascular calcification and lipomas have pathognomonic features, a relatively large group of soft tissue lesions or calcifications are mammographically indeterminate. In these cases, the diagnosis can be confirmed only by needle core biopsy or surgical excision.

Most publications on benign breast disease are based on symptomatic lesions, and the true incidence in the screening age group is unknown. However, the prevalence of benign disease ranges from 6 % to 27 % in the screening age group (Burnett et al. 1995; White et al. 2001). Because of the increase in longevity, most screening programmes now invite women in the 50–70 age group for mammographic screening. Some institutes screen women up to the age of 75 (Chinyama et al. 2003; Ernst et al. 2002; Jonsson et al. 2003). UK NHS screening programme extended the screening age group to 70 in 2006. Screening older women invariably increases the number of mammographically indeterminate lesions. If a conclusive diagnosis cannot be attained by non-operative techniques such as fine needle aspiration cytology (FNAC) or needle core biopsy, this will prompt an excisional biopsy. Screening older women will have an impact on the workloads in breast disease units.

Detection of breast disease by imaging techniques depends on soft tissue abnormalities and calcification, which can occur in isolation or in combination. Architectural abnormalities exhibit different shapes and sizes, which also result in

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C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_3, © Springer-Verlag Berlin Heidelberg 2014

variable imaging density. Benign breast lesions produce a heterogeneous array of soft tissue densities caused predominantly by an increase in fibrosis or a mixture of fibrosis, elastosis and epithelial proliferations. Soft tissue mammographic abnormalities include coarse fibrosis, ill-defined fibrosis, single or multiple nodular densities, generalised increase in density or stellate structures such as radial scars.

Several studies have reported an increased risk of breast cancer in women with increased soft tissue density on mammography (see Chap. 16). However, assessment of mammographic density is associated with inter- and intraobserver variation. Jackson and co-workers (1991) studied the radiographic densities in 91 biopsy-proven (51 benign, 40 malignant), nonfatty, non-calcified breast masses. The kappa statistics interobserver agreement was low (0.22–0.49), with an overall sensitivity of 48 %, specificity of 80 % and both negative and positive predictive values of 66 %. The authors concluded that in isolation, mammographic density was of limited value in predicting the nature of non-calcified benign or malignant lesions. Although it is accepted that mammographic density is high in young women, assessment of breast tissue in postmenopausal women taking hormone replacement therapy can also be difficult because of an increase in density or water retention.

Calcification occurs both in benign and malignant lesions. Mammographic calcification plays an important part in detecting early in situ cancer. The microcalcification noted mammographically is usually much larger than that identified microscopically. For this reason small microcalcifications are often detected in lobules in histological sections in the absence of mammographic calcification. Calcification related to individual lesions is described in detail in the specific chapters.

3.2 Mammography

Mammography is the main radiological modality used in breast screening and applies similar principles to ordinary X-ray. However, to obtain meaningful results, adequate breast compression should be performed. Although for patient management purposes, breast disease is classified into symptomatic and screen-detected, in most breast units, symptomatic patients are also assessed mammographically or by ultrasound to increase diagnostic accuracy. The main mammographic features of benign breast disease are parenchymal abnormalities caused by increase in soft tissue density or calcification, which can occur independently or in combination. Mammography is more sensitive and specific in assessing fatty breasts than dense breasts. Dense breast tissue is particularly difficult to assess in young women (see above). A definite benign diagnosis is possible mammographically with lesions such as oil cysts, calcified fibroadenomas, lipomas, intramammary lymph nodes and possibly hamartomas. Mammography is also used in assisting needle core biopsies and for localisation of impalpable lesions.

The American College of Radiology (1998) devised a reporting system, the BI-RADS lexicon (Breast Imaging Reporting and Data System), which is intended to produce uniformity in mammographic reports. The lexicon is reproduced with permission of the American College of Radiology (ACR).

3.2.1 BI-RADS Assessment Categories

3.2.1.1 Assessment Is Incomplete

Category 0
Need Additional Imaging Evaluation: Finding for which additional imaging evaluation is needed. This is almost always used in a screening situation and should rarely be used after a full imaging workup. A recommendation for additional imaging evaluation includes the use of spot compression, magnification, special mammographic views and ultrasound. The radiologist should use judgement in how vigorously to pursue previous studies.

3.2.1.2 Assessment Is Complete: Final Categories

Category 1
Negative: There is nothing to comment on. The breasts are symmetrical, and no masses, architectural disturbances or suspicious calcifications are present.

Category 2
Benign Finding: This is also a negative mammogram, but the interpreter may wish to describe a finding. Involuting, calcified fibroadenomas, multiple secretory calcifications and fat-containing lesions such as oil cysts, lipomas, galactocoeles, and mixed density hamartomas all have characteristic appearances and may be labelled with confidence. The interpreter might wish to describe intramammary lymph nodes, implants, etc. while still concluding that there is no mammographic evidence of malignancy.

Category 3
Probably Benign Finding–Short-Interval Follow-Up Suggested: A finding placed in this category should have a very high probability of being benign. It is not expected to change over the follow-up interval, but the radiologist would prefer to establish its stability. Data are becoming available that shed light on the efficacy of short-interval follow-up. At the present time, most approaches are intuitive. These will likely undergo future modification as more data accrue as to the validity of an approach, the interval required and the type of findings that should be followed.

Category 4
Suspicious Abnormality–Biopsy Should Be Considered: These are lesions that do not have the characteristic morphologies of breast cancer but have a definite probability of being malignant. The radiologist has sufficient concern to urge a biopsy. If possible, the relevant probabilities should be cited so that the patient and her physician can make the decision on the ultimate course of action.

Category 5
Highly Suggestive of Malignancy–Appropriate Action Should Be Taken: These lesions have a high probability of being cancer.

3.2.2 Advantages of Category Reporting

The advantage of the lexicon is that there are precise definitions of lesions that are probably benign and this allows the woman with a category 3 lesion to choose either surveillance mammography or biopsy. Caplan et al. (1999) analysed the data from the National Breast and Cervical Cancer Early Detection Program and found that 7.7 % of the 372,760 mammograms were classified in the BI-RADS category 3. This category was more likely to be reported in young women who were symptomatic and had abnormal clinical examination. Reporting of category 3 also varied among radiologists from different regions or states and ranged from 1.4 % to 14 %. In a separate study, Lacquement et al. (1999) reported a high percentage of women with category 3 mammographic reports who were referred for image-guided biopsies. The authors reviewed 688 image-guided biopsies: category 3 lesions represented 46.8 % of the biopsies, followed by category 4 with 34 % of the biopsies and category 5 with 15.4 %. The authors concluded that the BI-RADS did not improve the quality of the risk assessment information by making the positive predictive value more specific to a patient's mammogram. The findings were in contrast to those previously reported by Liberman and colleagues (1998). Of the 492 mammographically

detected, impalpable lesions that were referred for surgical excision, only 8 (2 %) were reported as category 3, 355 (72 %) as category 4 and 129 (26 %) as category 5.

Since the publication of the first edition, the BI-RADS system has further been developed. Repeat mammography should be complete within 6 months as there is a 2 % risk of breast cancer in this category (ACR 2003). The classification also includes category 6 which are lesions identified on imaging with cancer proven on biopsy and the patient is awaiting definitive treatment (Eberl et al. 2006). The BI-RADS system is also applicable to ultrasound and MRI (ACR website).

The UK National Health Service Breast Screening Programme (NHSBSP) applies a similar reporting system, which was adopted by the European Society of Mastology with the following reporting categories: R denotes radiology (Perry 2001).

R1 = Normal/benign breast tissue
R2 = A lesion with benign characteristics
R3 = An abnormality with indeterminate significance
R4 = Features suspicious of malignancy
R5 = Malignant features

According to the NHSBSP, women with R1 and R2 mammographic reports require routine follow-up according to local screening guidelines (every 2–3 years). Women with R3 mammographic reports require biopsy, and the decision for short-term follow-up should be considered at a multidisciplinary meeting and agreed with the woman. The NHSBSP standard requires that fewer than 1 % of screened women should be placed on short-term recall. Short-term recall should not be used as an alternative for proper assessment, which could be viewed as failure in decision-making (NHSBSP 2001). Needle core biopsy is mandatory for R4 and R5 lesions.

Sickles (1995) recommends that the BI-RADS category 3, probably benign, should be restricted to impalpable lesions and interpretation should be performed in conjunction with previous mammograms to exclude a progressive lesion. In a separate study, Brenner and Sickles (1997) compared the cost of surveillance mammography and stereotactic core biopsies of probably benign lesions. They compared 3,184 women who underwent surveillance mammography with 161 patients who underwent needle core biopsies. The cost of managing probably benign breast lesions with surveillance mammography was US$ 3,307,575 less than if all the lesions had been managed by needle core biopsies. The cost ratio of needle core biopsies to surveillance mammography was 8:1. The authors concluded that, with similar false-negative rates, needle core biopsies were more costly than surveillance and this has a negative effect on the management of probably benign breast lesions, unless the lesion had altered during surveillance, which should prompt a diagnostic biopsy.

3.3 Ultrasonography

The technique of ultrasound depends on the fact that different tissue textures produce sound at different frequencies, detected by a transducer; this is converted into an image, which is interpreted as a specific disease process. The use of ultrasound transducers with a frequency range of 5–7.5 MHz is usually adequate. However, improved ultrasound transducer technology has allowed the use of much higher frequencies for visualisation of breast lesions, including microcalcifications. Transducer frequencies of 12–15 MHz are now frequently employed in screening clinics as an adjunct to mammography. Lesions less than 5 mm can be detected by this method in otherwise fatty breast tissue. Ultrasound assesses the shape of the lesion by the state of its border, which can be smooth or irregular, or its contour. The latter represents the demarcation of the lesion from the surrounding tissue and can be well circumscribed or ill defined. Shadowing is caused by refraction of the sound waves, which become stronger and sharper the more vertical the lateral borders of the lesion are (Zonderland 2002). Ultrasound images can be anechoic, isoechoic, hypoechoic or hyperechoic in relation to the surrounding breast tissue. The breast adipose tissue is hypoechoic, whereas the associated fibroglandular tissue is hyperechoic. Echogenicity can be homogeneous or heterogeneous. Complex lesions tend to be heterogeneous, with anechoic foci.

Although ultrasonography is increasingly becoming an indispensable adjunct to mammography, its role as a screening tool has yet to be established. This is due to the variable echogenicity of breast cancers. Benign breast disease may produce hypoechoic foci in areas of localised fibrosis or adenosis, and acoustic shadowing can be associated with hypoechoic foci in lesions such as sclerosing adenosis or radial scars. These changes can also occur in breast cancer. Ultrasonography is useful in differentiating cysts from solid lesions, assessing ectatic ducts, delineating masses difficult to assess on mammography and assessing palpable masses obscured by dense tissue on mammography, especially in young women. Non-palpable lesions visible at mammography, palpable lesions not visible at mammography and benign conditions such as mastitis and abscesses can also be assessed more effectively by use of ultrasonography (Heywang-Köbrunner et al. 2001; Zonderland 2002). The most important role of ultrasound in breast imaging is the differentiation of solid from cystic lesions. The diagnostic accuracy of ultrasound in simple cysts approaches 100 % (Bassett and Kimme-Smith 1991). Solid palpable lumps require both mammographic and ultrasound assessment (Fig. 3.1) especially in women with dense breasts where the lump can be mammographically occult (Shetty et al. 2003).

The European Society of Mastology (ESOMA) recommends that the same criteria used in reporting mammography are also applied to ultrasound imaging, i.e. U1, U2, U3, U4 and U5, where U denotes ultrasound (Perry 2001). Percutaneous fine needle aspiration and core biopsies can also be performed under ultrasound guidance.

3.4 Magnetic Resonance Imaging

Magnetic resonance (MR) is an imaging technique, which examines the breast and other organs in the body in sections without use of radiation. The MR images are generated by use of radio waves, which excite protons in the water and fat of the magnetic field. The excitation energy is emitted as radio waves and registers as an image. The intensity of the signal depends on the pulse sequences that excite the protons and the properties of the tissue under examination. Despite the different signal intensities produced by tissues (due to the presence of fat, water, increased cellularity or fibrosis), unenhanced or native MR mammography is not accurate in differentiating benign from malignant breast disease (Heywang-Köbrunner and Boetes 2002). For better images, administration of gadolinium–DTPA contrast media is now routinely used to enhance the images (enhanced MR mammography).

Even with the use of contrast medium, MR imaging (MRI) is not used routinely in breast screening. As with ultrasound, MRI is used to assess difficult mammographically detected lesions. Benign breast disease gives low signal intensity when compared to fatty tissue on MRI. Contrast enhancement occurs in only 25–30 % of benign breast disorders, and the remaining disorders give little or no signal enhancement. Enhancement usually occurs in lesions with significant epithelial hyperplasia or inflammatory lesions such as mastitis, whereas most of the breast disorders that give little or no enhancement consist of fibrous breast tissue (Heywang-Köbrunner et al. 2001). Contrast enhancement of benign breast disease is also affected by the menstrual cycle or other hormonal stimulation such as hormone replacement therapy (Müller-Schimpfle et al. 1997). These authors noted that MR enhancement was significantly lower in days 7–20 of the menstrual cycle than in days 21–26; they recommended breast assessment in the first half of the menstrual cycle. Irregular focal enhancement can occur in foci of malignancy, fibrocystic change, fibroadenomas, papillomas and foci of necrosis (Heywang-Köbrunner and Boetes 2002). A biopsy is advisable in these circumstances to exclude malignancy. In older women in whom fibroadenomas and papillomas are fibrotic, MR images may not enhance.

MRI is highly sensitive in detecting invasive carcinoma, and the lack of enhancement in approximately 70 % of benign disease is fairly reliable in excluding cancer. Another advantage of MRI is that small foci of cancer can be detected in dense non-enhancing benign breast disease. This is important in young patients with a family history of cancer in whom

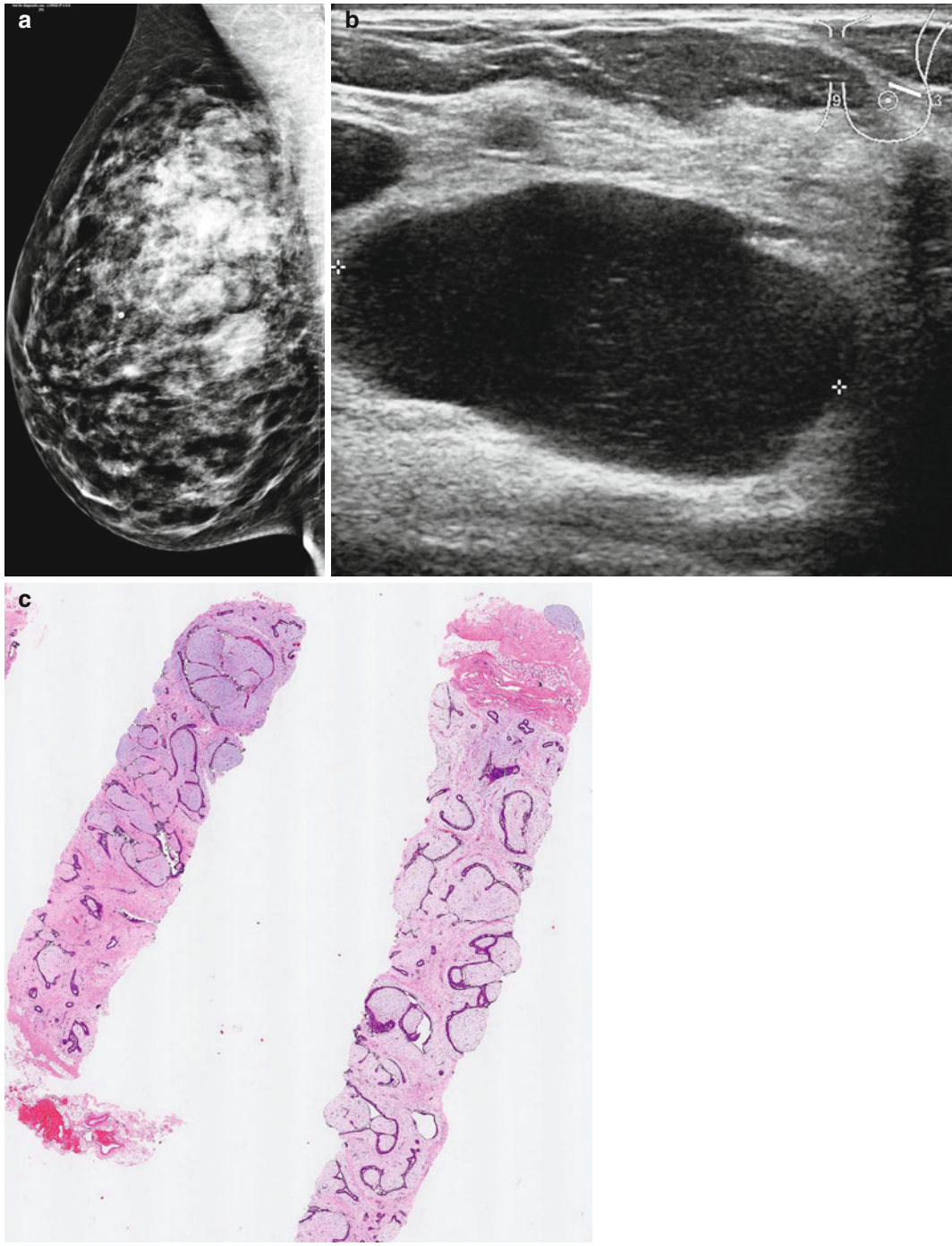


Fig. 3.1 (**a**) Palpable lumps in left breast present as ill-defined lesions in the mammogram (R2). (**b**) The ultrasound highlights two well-circumscribed lesions. (**c**) The biopsy showed a fibroadenoma (B2)

mammographic interpretation is usually difficult. However,generalised diffuse enhancement or localised enhancement in benign disease restricts the capability of MRI to exclude malignancy. In postsurgical follow-up, MRI is valuable in assessing scar tissue, as it does not enhance after complete fibrosis. Ruptured silicone implants are also better assessed with MR mammography.

MRI is not suitable for differentiating benign from malignant calcification. To confirm this, Westerhof et al. (1998) assessed mammographically detected suspicious microcalcification in 63 patients in an attempt to differentiate benign from malignant disease by using dynamic magnetic resonance. Surgical biopsies were assessed histologically, and they reported five stage 1 invasive carcinomas, 33 ductal carcinomas in situ (DCIS), 13 cases of proliferative fibrocystic disease, eight non-proliferative fibrocystic disease and four sclerosing adenosis. MRI had a sensitivity of 45 %, specificity of 72 % and overall accuracy of 56 % in differentiating benign from malignant calcification. Although MRI confirmed all invasive tumours, surgical management was not altered in view of the MRI findings.

3.5 Image-Guided Diagnostic Procedures

Radiologists utilise both ultrasound and mammography to assist in FNAC, needle core biopsies for both symptomatic and screen-detected lesions and preoperative needle localisation for impalpable lesions. The most commonly applied mammographic technique is stereotactic-guided sampling, which utilises two views in the same plane to allow the accurate localisation of a lesion within the breast tissue. The technique is ideal for lesions that are neither palpable nor visible on ultrasound, such as altered density, some parenchymal deformities and microcalcification. Accurate needle placement requires time and meticulous patient positioning, minimum patient movement and correct selection of the area to be sampled. Careful explanation to the patient is essential to obtain her cooperation during the procedure. Stereotactic biopsies can be performed with the patient upright or in the prone position. Digital mammography allows image acquisition for stereotactic biopsy. This provides instant images, thereby reducing the time required for the biopsy and improving accuracy. Occasionally MR is used for percutaneous tissue sampling. Percutaneous biopsies or FNAC allows the radiologist, pathologist and surgeon to obtain a tentative or definitive diagnosis and discuss appropriate management of the patient at multidisciplinary team meetings. This reduces patient morbidity and avoids unnecessary surgical procedures for benign lesions. In patients with cancer, preoperative cutaneous sampling reduces the re-excision rates when compared with patients who undergo primary excision biopsy of a mammographically detected lesion (White et al. 2001).

Ultrasound-guided FNAC or core biopsies are preferable to stereotactic techniques in sampling impalpable lesions. Ultrasound-guided techniques are fast and simple. The operator has real-time control of the position of the needle within the lesion. The procedures can be performed in different positions and can be applied to mammographically ill-defined lesions (Dronkers 2002).

3.5.1 Fine Needle Aspiration Cytology

Fine needle aspiration cytology (FNAC) used to be the main preoperative diagnostic procedure for both symptomatic and screen-detected breast disease, but this has been largely superseded by wide-bore needle core biopsies. FNAC is a relatively non-invasive, rapid method of sampling tissue for diagnosis and can be performed free hand for palpable lesions or under ultrasound or stereotactic guidance for non-palpable lesions. The sensitivity and specificity of FNAC depends on the experience of the aspirator and cytopathologist, but specificities of up to 86–95 % have been reported for detection of breast cancer (Helvie et al. 1990; Azavedo et al. 1989). FNAC is not suitable for diagnosis of ill-defined calcification to exclude malignancy. Fibrotic lesions, including lobular carcinomas, are also prone to false-negative results. Terminology applied in reporting cytology is detailed in Chap. 5. In the presence of malignancy, FNAC cannot exclude in situ from invasive carcinoma, and this leads to multiple surgical procedures. However, cystic and benign palpable breast lesions can easily be assessed with FNAC. In terms of discomfort, FNAC is more acceptable to the patient than wide-bore needle core biopsies. FNAC is performed with either 22 or 23 gauge needles.

3.5.2 Wide-Bore Needle Core Biopsies

Because needle core biopsies provide a more specific diagnosis than FNAC; most units utilise this method almost exclusively for symptomatic and impalpable screen-detected lesions. Needle core biopsies are almost standard method in working up patients with R3 or BI-RADS category 3 mammographic lesions. Core biopsies may be obtained using either spring-loaded devices or a spring-loaded gun into which different sizes of needles may be placed. The latter offers greater economy plus increased flexibility, as needles of both different length and gauge may be used in the same device. For maximum flexibility, the gun should also have the facility to vary the throw (distance travelled by the biopsy notch), to allow safe biopsy of very posterior lesions and also lesions in very small breasts. Needle gauges 16, 18 and 14 can be used for stereotactic- or ultrasound-guided biopsies. A malignant diagnosis on a needle core biopsy allows the multidisciplinary team to make a decision on therapeutic options such as chemotherapy or surgery with axillary dissection. Rarely would similar decisions be made on FNAC results. Most pathologists can report needle core biopsies, whereas FNAC requires specialist cytopathology training.

The larger the number of needle core biopsies, the higher the diagnostic yield. However, this also increases the rate of complications (see Table 3.1), but fewer samples are associated with inadequate diagnostic material. Most studies have shown that three to ten needle core biopsies are adequate for accurate diagnosis. Brenner and colleagues (1996) reported 97 % diagnostic accuracy with five samples. In our department, the radiologist samples six needle core biopsies, and we find this is less distressful to the patient. The needle core biopsies performed for calcified lesions are X-rayed using a Faxitron to confirm adequate sampling. The cores, which contain calcification, are placed in a separate container of formalin and, together with specimen X-ray, are transported to the pathologist for processing. The sequence of events in managing indeterminate calcification is illustrated in Fig. 3.2. The cores with calcification are processed separately, and if calcification is not identified in the initial serial sections of three levels, further levels can be examined from the paraffin-embedded tissue. Painting the needle core biopsies with calcification is also effective to avoid use of multiple cassettes. Liberman et al. (1994) reported that if calcification was present in a specimen X-ray in core biopsies, the calcification was noted on

Table 3.1 Comparison of image-guided techniques in diagnosis of screen-detected benign lesions

Criterion	FNAC	NCB	LEB
1. Patient discomfort	Minimal, local anaesthesia optional	Moderate, local anaesthesia essential	Significant, requires general anaesthesia
2. Speed of procedure	Outpatient, results can be available same day	Outpatient, results available in 24–48 h	Inpatient, results available in 48–96 h
3. Complications	Rare, haematoma, infection	Vaso-vagal attacks, haemorrhage, especially on anticoagulants, infection, penetration of chest wall, inadequate sampling	Anaesthetic complications, pneumothorax during wire localisation, haemorrhage, infection, wire dislocation
4. Pathology	Requires speciality reporting	Can be reported by general pathologists	Requires special processing with specimen X-rays
5. Diagnostic accuracy	Risk of false-negative report not suitable for scattered calcification	High degree of specificity (96–100 %)	Risk of overtreatment in the absence of preoperative diagnosis or repeat operations with malignant lesions
6. Cost	Quick procedure, cost-effective pathological processing simple	Quick procedure, cost-effective pathological processing, multiple levels may delay reporting	Requires inpatient bed occupancy, pathological processing complicated, which may require specimen X-ray

FNAC fine needle aspiration cytology, *NCB* needle core biopsy, *LEB* localisation excision biopsy

histological examination in 78 % of the cases. Histology detected 13 % of cases with calcification not present in the specimen X-ray. Reporting of needle core biopsies is detailed in Chap. 5.

Needle core biopsies have been reported to achieve sensitivities and specificities of 98 and 100 %, respectively (Parker et al. 1994). White and colleagues (2001) evaluated 939 patients with 1,042 mammographically detected lesions who had undergone stereotactic or ultrasound needle core biopsies. Of these patients, 77 % had benign biopsies and 23 % had malignant diagnoses. There were 17 false-negative core biopsy results, 15 of which were correctly diagnosed in the excision specimens within 4 months of the biopsy. For malignant lesions, the sensitivity and specificity of the needle core biopsy for detection of invasion were 89 % and 96 %, respectively. A separate study reviewed stereotactic biopsies from 1,026 patients over a 6-year period (Tate et al. 2001). The most common benign diagnosis was fibrocystic change (72 %), followed by fibroadenoma (19 %), lymph node (2 %) and papilloma (2 %). Invasive carcinoma was present in 40 % of the cases, DCIS in 32 % and mixed invasive and DCIS in 19 %. BI-RADS category 3 was associated with 2 % detection of malignancy. Atypical ductal hyperplasia on stereotactic biopsy

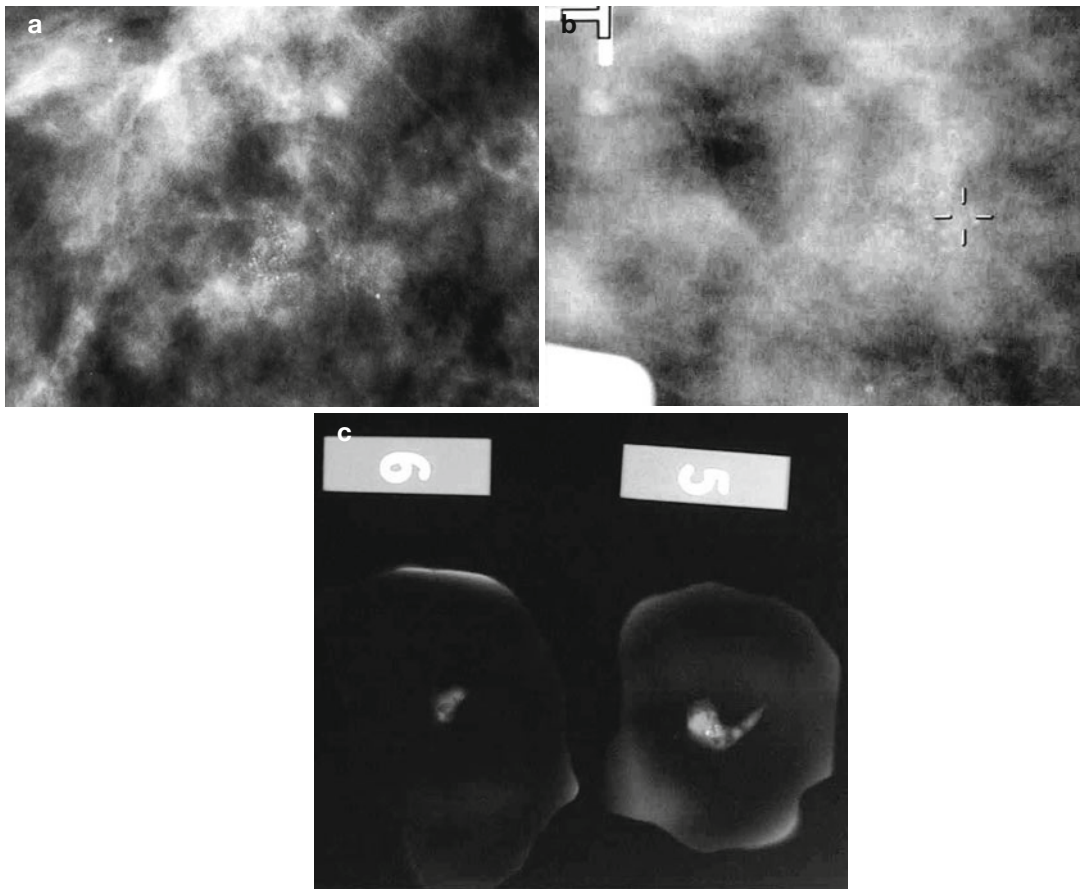
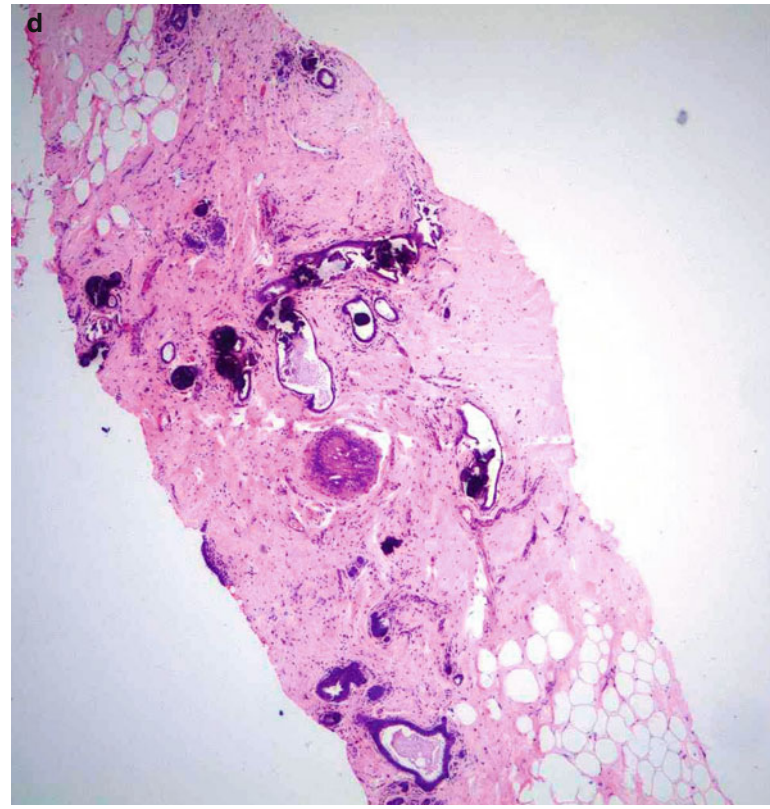
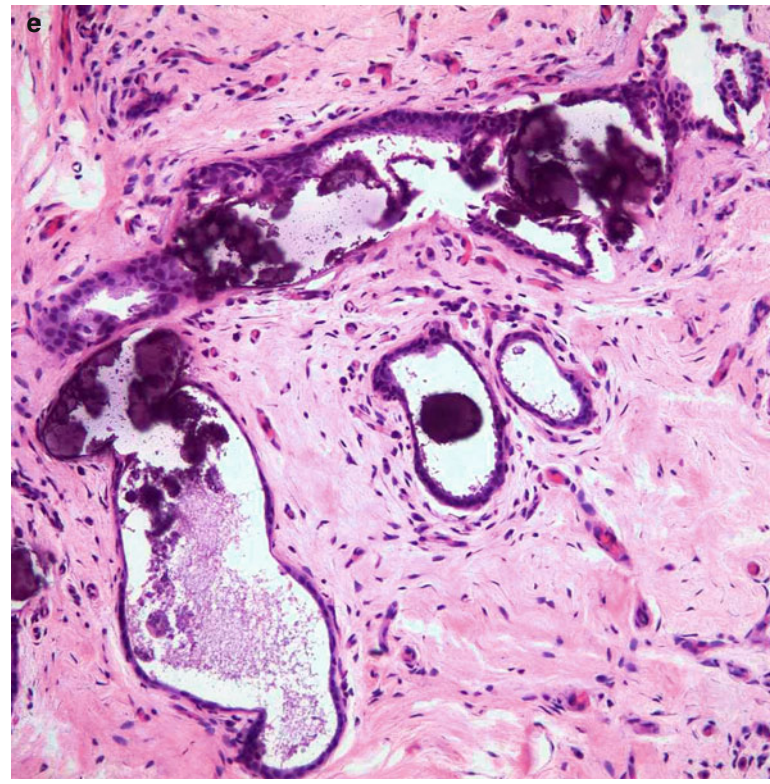


Fig. 3.2 (**a**) A focus of magnified ill-defined cluster of mammographically detected intermediate microcalcification in a 61-year-old woman graded as R3. (**b**) Stereotactic localisation of the calcification. (**c**) Specimen X-ray of the needle core biopsies shows microcalcification in core 5 but not in 6. Two other biopsies not shown in this field had microcalcification. The biopsies with calcification are placed in a separate pot and processed separately. (**d**) The biopsies show amorphous microcalcification in benign duct–lobular units. This pattern of microcalcification is usually seen in high-grade DCIS. (**e**) At higher power the duct–lobular units are dilated. The associated epithelium is attenuated. There is no atypia. The woman was returned to biannual screening

Fig. 3.2 (continued)





was upgraded to malignant diagnosis in 19 % of the cases. The false-negative rate was 0.4 % (sensitivity 99 %). False-negative core biopsy results tended to occur if the pathologist reported normal breast tissue in the presence of a mammographic abnormality without adequate pathological radiological correlations. Table 3.1 highlights the differences between the diagnostic modalities used in sampling screen-detected lesions.

3.5.3 Directional Vacuum-Assisted Core Biopsy

Directional vacuum-assisted needle core biopsies utilise large needles (gauges 11 or 14) and the principle of negative pressure. The needle is placed within the lesion, and the tissue is cut off in a rotating manner by the use of a vacuum mechanism. The tissue is then transported through the needle to the end of the probe for removal (Heywang-Köbrunner et al. 2001). The advantages of vacuum-assisted biopsies over automated biopsies are the following: (a) more contiguous tissue can be sampled; (b) tissue can be sampled further from the probe, not just from the line fire; and (c) multiple specimens are obtained from a single probe insertion. Because of the large amount of tissue volume sampled, the risk of sampling errors is minimised, especially with scattered microcalcification. Smaller lesions can also be removed in their entirety (Philpotts et al. 1999; Sniege et al. 2003), reducing the need for excision biopsy. However, this method is not ideal for malignant lesions, which require surgical excision for assessment of margins.

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Surgery of Benign Breast Lesions

4

Learning Points

- Fine needle aspiration cytology and needle core biopsies are more cost-effective methods of diagnosing benign breast disease than open surgical biopsy.
- Pathologically indeterminate lesions of B3 category require surgical excision.
- The B3 category lesions include ADH, lobular neoplasia, radial scar, columnar cell lesions, mucocoele-like lesions, microglandular adenosis, papillary and fibroepithelial lesions.
- Radiologically B3 lesions are excised to exclude high-risk lesions such as DCIS and invasive cancer.
- Excision of a B3 lesion also assists in evaluating the overall risk of malignancy.
- At least 30 % of B3 lesions contain a high-risk lesion in the excision biopsy.

4.1 Why Excise Benign Breast Lesions?

When faced with an indeterminate radiological and pathological result, the questions the multidisciplinary team looking after women with this abnormality have to consider are as follows:

(i) Do they follow up the patient clinically and radiologically and re-biopsy if there is a change in the lesion?
(ii) Do they repeat the biopsy immediately?
(iii) Will the repeat biopsy give the answer they want?
(iv) What if they miss the lesion on repeat biopsy and distress the patient?
(v) Do they excise the lesion?

Each patient should be managed on an individual basis because there are no correct answers to these questions.

4.2 The Advantages of Nonsurgical Diagnostic Procedures

As part of the triple assessment, nonsurgical procedures such as fine needle aspiration cytology (FNAC) and needle core biopsies are cost-effective when compared with surgical excision biopsy in the management of symptomatic or mammographically detected lesions. Although most savings are apparent with FNAC, studies in the USA revealed that core biopsies produce cost savings of up to 300 % when compared with surgical excision biopsies. Burkhardt and Sunshine (1999) estimated the input resource cost of a needle core biopsy to be US$ 243, compared with US$ 698 for an excisional biopsy. The actual billed costs for the procedures were $ 3,764 and $ 1,496 for excisional and core biopsies, respectively. The costs of surgical biopsies were on average 2.5–3 times those of needle core biopsies ($P<0.001$). In a separate study, Liberman et al. (1998) reported that although needle core biopsy

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_4, © Springer-Verlag Berlin Heidelberg 2014

was more cost-effective than excisional biopsy, ultrasound-guided biopsies had better cost savings than stereotactic-guided biopsies. In addition to cost savings, nonsurgical diagnostic procedures offer better patient comfort and appropriate planned management. These costs have obviously increased with time.

4.3 Quality Assurance in Surgery of Benign Breast Lesions

The aim of nonsurgical diagnostic procedures is to minimise unnecessary operations for benign lesions. The UK quality assurance guidelines for surgeons in breast cancer screening (NHSBSP 2009) recommend minimising unnecessary open biopsy surgical procedures where there is a definite histological diagnosis of benignity to fewer than 15 per 10,000 women screened in the prevalent round and fewer than 10 per 10,000 women screened in the incident round. Similarly, the European Society of Mastology (EUSOMA) recommends the limitation of the number of unnecessary surgical excisional biopsies and the benign:malignant ratio should not exceed 0.5:1. Excisions due to patients' requests should be excluded if the benign diagnosis has been confirmed by other tests. For acceptable cosmesis, 90 % of diagnostic biopsies for impalpable lesions that turn out to be benign should weigh less than 30 g (Perry et al. 2001). Besides complications associated with surgery, another reason cited for avoiding surgery for benign disease is tissue scarring, which would make interpretation of subsequent mammograms difficult. However, in a retrospective study comparing women who had undergone surgery for benign disease with those who had not, Slanetz et al. (1998) reported that changes in patients' breasts due to previous surgery for benign disease rarely created diagnostic problems in interpretation of routine mammography.

4.4 Indications for Surgery in Benign Breast Lesions

The widespread use of nonoperative diagnostic procedures such as needle core biopsies, vacuum-assisted biopsies and fine needle aspiration biopsies can readily differentiate benign breast disease from cancer when the clinical and radiological features concur with the pathological findings. However, with screen-detected abnormalities, pathologists may be unable to exclude malignancy confidently in a needle core biopsy, and this will prompt an excision biopsy. Indications for excision biopsies in lesions that turn out to be benign on histology include the following:

(i) Discordance between the radiological and histological features
(ii) Atypical calcification despite benign histological report
(iii) Calcifications in the posterior area of the breast, which are difficult to access by a needle core biopsy
(iv) Atypical lesions of unknown malignant potential on histology such as radial scars, papillomas, mucocoele-like lesions, columnar cell lesions, microglandular adenosis, atypical ductal hyperplasia and lobular neoplasia
(v) Fibroadenomas in patients over 35 years old in some institutions

Open excision biopsies of these atypical lesions are in line with European guidelines for quality assurance in breast cancer screening and diagnosis (Perry et al. 2006). The lesions which prompt an open diagnostic biopsy are considered to be at risk of developing cancer (Shaaban et al. 2002; Schnitt 2003; Hartmann et al. 2005). Manfrin et al. (2009) reviewed 510 open biopsies performed on screen-detected lesions which they classified according to risk of developing cancer as follows:

(i) Histology 1 (Histo 1) referred to normal breast histology with no lesion detected at biopsy.
(ii) Histology 2 (Histo 2) category was 'pure' benign lesions with no risk of developing cancer, and these lesions included adenosis, ductal micropapillomatosis, fibroadenoma, lipoma, lymphadenitis, mastitis, fibrocystic disease and pseudo-angiomatous stromal hyperplasia.
(iii) Histology 3 (Histo 3) referred to benign proliferative epithelial lesions with a 'low risk' of developing cancer such as mucocoele-like

lesions, multiple papillomatosis, papilloma, cellular fibroepithelial lesions and radial scars.

(iv) Histology 4 (Histo 4) referred to benign proliferative epithelial lesions with a 'high risk' of developing cancer: thus, ADH, ALH and atypical columnar cell hyperplasia.

This classification is in variance with that of the UK NHS Breast Screening Programme guidelines for pathology reporting. Although Histo 1 and Histo 2 lesions correspond to B1 and B2 lesions according to the UK NHS Breast Screening Programme guidelines for pathology reporting, Histo 3 and Histo 4 lesions would be collectively classified as B3 lesions, i.e. atypical lesions of uncertain malignant potential. Based on this classification, Manfrin and colleagues reported cancer in 83.7 % (427) of the 510 open biopsies and benign lesions in 16.3 % (83) of the biopsies with a malignant:benign ratio of 5:1. On further analysis of the benign lesions, 4.8 % (4/83) were classified as normal breast histology (Histo 1), 37.4 % (31/83) as pure benign lesions (Histo 2), 31.3 % (26/83) as benign proliferative lesions with low risk of developing cancer (Histo 3), and 26.5 % (22/83) as benign proliferative lesions with high risk of developing cancer (Histo 4). In the latter category, 9 out of the 22 biopsies were reported as ADH. When Manfrin and colleagues compared their results with other studies, they could apply all the four histological categories in two studies by Spencer et al. (1994) and Chew et al. (2006) which reported open biopsies in 68.7 % and 91.3 % Histo 2 categories, respectively. These two studies show very high rates of open biopsies especially in the report by Chew and colleagues because cytology is the main mode of nonsurgical assessment in the Singapore Screening Programme. Spencer and colleagues (1994) reported 22.2 % of Histo 3 lesions, which is not very different from Manfrin, and Chew et al. (2006), 8.7 %. Both Spencer and Chew had no lesions in category Histo 4 which illustrates the difficulties pathologists have in classifying atypical lesions or lesions with the potential to progress to malignancy. In fact in this study, Manfrin highlighted that it is not necessary to further classify the atypical lesions in needle core biopsies into four categories because his Histo 3 and Histo 4 lesions, which would be classified as B3 lesions (atypia of uncertain malignant potential) in the NHS BSP (2006), require surgical biopsy.

Meyer et al. (1998) reviewed 112 non-palpable, mammographically detected lesions, which had been reported as benign on needle core biopsy. Ninety-six of the patients underwent surgical excision, and 16 had repeat needle core biopsies. This additional evaluation was indicated for suspicious mammographic or ultrasound appearances that were discordant with a benign pathological report (24 patients); the lesions were probably missed because the biopsy showed normal breast tissue, non-specific changes or absence of calcification in biopsy (41 patients); pathologist recommendation due to presence of atypical features (31 patients); increased cellularity in a fibroadenoma, suspicious of a phyllodes tumour (nine patients); and five patients with a benign diagnosis at needle core biopsy underwent surgical excision because of history of cancer in the ipsilateral breast. Only two patients requested excision of benign lesions. None of the lesions excised for radiological–pathological discordance were malignant. Of the possibly missed lesions, two invasive carcinomas were identified, one on excision and the other on repeat biopsy. Eleven DCIS, three invasive carcinomas and two phyllodes tumours were identified among the lesions the pathologist recommended for local excision. This study highlights that, despite the high sensitivity and specificity of needle core biopsies in the diagnosis of cancer, in benign disease, there are situations where surgery is unavoidable.

Although the main indication for excising a possibly benign lesion is to exclude malignancy, in some instances patients request excision of radiologically and pathologically benign lesions for psychological peace of mind. In a large multicentre study in Italy, Ciatto et al. (1998) retrospectively reviewed 754 consecutive benign breast biopsies to determine the main indication for surgical excision. The main indication was to exclude cancer in 66.7 % of the patients, followed by an increase in growth of the mammographic lesion in 11.3 % and for cosmetic (3 %) and psychological reasons (8.2 %). Other indications included previous history of breast cancer,

family history of breast cancer or contralateral breast cancer. In one centre included in the study, there was a high rate of excision for psychological or cosmetic reasons in 47 % of the patients.

In a separate study, Cant and colleagues (1987) retrospectively questioned 124 women who had undergone surgery for symptomatic, cytologically proven fibroadenoma as to whether they would prefer surgery or conservative treatment for the same diagnosis in future. Twenty-one per cent (26) indicated that they would opt for conservative management for the same problem in the future. When asked whether they would have preferred conservative management for their previously excised masses, only 7 % (8) indicated that they would have opted for nonoperative management. The women assessed in this series had presented symptomatically with a lump, and psychologically it was reassuring to the patient to have the lump removed. Although the numbers are small, these results are similar to the Italian multicentre study, where 8.2 % (62/754) of the women with mammographically and biopsy-proven benign breast lesions requested excisional biopsies for psychological reasons (Ciatto et al. 1998).

4.5 Indeterminate Lesions Excised to Exclude Malignancy

The category of indeterminate B3 lesions can be assigned to both symptomatic and screen-detected breast lesions but with a higher prevalence in the latter where approximately 5 % of the lesions are classified as B3 (El-Sayed et al. 2008; Lieske et al. 2008).

Although the use of directional vacuum-assisted core biopsies may clarify the diagnosis of pathologically indeterminate lesions usually classified as B3 in needle core biopsies (NHS BSP Publication 58, Darling et al. 2000), definitive management of the patient would invariably require an open biopsy. The open biopsy approach raises further questions as to whether the B3 category unnecessarily increases the surgical benign biopsy rate and whether the yield of cancer in the open biopsies justifies the surgery. To determine whether the B3 category increased surgery for benign lesions, Hunt and colleagues (2011) reviewed needle core biopsies from 235 women which had been classified as B3. Twenty-seven (11 %) of the women did not undergo surgery and the remainder, 89 % (208), had open biopsies, and nine of the women who had repeat core biopsies were excluded from the study. This left 199 women who had B3 diagnosis based solely on the original core biopsy. Seventy-three (37 %) of the women were in the prevalent screening round and 126 (63 %) in the incident round. The open biopsy results identified malignancy (invasive and in situ) in 15/73 (21 %) in the prevalent round and 42/126 (33 %) in the incident round (Fisher's exact test $p = 0.038$), collectively 29 % (57/199) malignant lesions in B3 reported lesions. There were non-malignant lesions in the remaining 142 (71 %) women with a predominance of radial scars and other benign lesions. In other studies the rates of malignancy in excision biopsies of B3 category were reported as 21 % (Dillon et al. 2007) and 34 % (Lieske et al. 2008). The majority of the cancers in the open biopsies were in situ. The study by Hunt and colleagues (2011) demonstrated the following:

(i) Excision biopsies in B3 lesions identify malignant lesions in nearly 30 % of the patients.
(ii) The yield is higher in the incident round as the women are older than the prevalent round.
(iii) Needle core biopsies underestimate the presence of malignant disease in the presence of atypical proliferations such as ADH and ALH.
(iv) Where there is uncertainty of the definitive diagnosis of the breast abnormality, excision is justified following multidisciplinary team discussion.

These results are in contrast to those reported by Carder and Liston (2003) who only identified four cancers out of 36 (11 %) B3 category biopsies and the remaining 22 yielded benign lesions in the excision biopsies. Furthermore, BI-RADS Category 3 only yields on 2 % cancers in the excision biopsies (Eberl et al. 2006). The high yield of cancers in the excision biopsies of B3

lesions in the above studies could be explained by a low threshold of reporting B3 lesions in needle core biopsies instead of classifying them as B4. Overall the risk of an open biopsy for a B3 lesion outweighs the need to minimise the number of excised benign lesions as there is evidence that at least 30 % of B3 lesions on biopsy yield cancer on open biopsy.

Jacobs and colleagues (2002) performed a literature review to provide guidelines on which lesions should be excised following an indeterminate diagnosis of a needle core biopsy. The authors recommended surgical excision for ADH, lobular neoplasia (ALH and LCIS), papillary lesions, radial scars, fibroepithelial lesions, mucocoele-like lesions and columnar cell lesions. This section briefly outlines justification for surgical excision in these indeterminate lesions. Berg (2004) advocates a similar approach to the management of these lesions. The radiological and pathological features and any related risk will be discussed in the appropriate chapters.

4.5.1 Atypical Ductal Hyperplasia (ADH)

It is well known that patients with ADH have a 4–5 times risk of developing malignancy in both breasts compared to the general population (Dupont and Page 1985). The rationale for excising ADH when diagnosed in a needle core biopsy includes the following:

(i) The difficulties in distinguishing ADH from low-grade DCIS in a small needle core biopsy can be difficult compared to an excision biopsy.

(ii) ADH is usually present at the periphery of DCIS, and therefore, diagnosis of ADH in a needle core biopsy is not always representative (Lennington et al (1994).

(iii) Studies using automated gun biopsies with 14 gauge needles reported that ADH represents an under-diagnosis in many patients as carcinoma was found in 33–87 % of patients who underwent excision biopsy (Dahlstrom et al 1996; Jackman et al. 1999, 1994; Liberman et al. 1995).

(iv) Under-diagnosis of cancer with the diagnosis of ADH is more likely if the target lesion has microcalcification than a lesional mass with a 30 % and 5 % carcinoma identified in excision specimens, respectively (Liberman et al. 1997).

(v) The likelihood of finding carcinoma in the excision biopsy depended on the extent of the ADH in the needle core, with a higher yield of carcinoma if the biopsy had four or more foci of ADH (Ely et al 2001).

Based on these observations, the joint task of the American College of Radiology, American College of Surgeons and College of American Pathologists (Basset et al. 1997) recommended surgical excision on all cases with the diagnosis of ADH on needle core. The same approach is advocated by the UK NHS Breast Screening Programme (2005). However, with the use of the vacuum-assisted biopsies, there are reports of complete removal of small areas of microcalcification with no evidence of a high-risk lesion in the excision biopsies (Villa et al. 2011). Follow-up studies are required to determine whether vacuum-assisted device could be used for therapeutic purposes rather than diagnostic.

4.5.2 Lobular Neoplasia

The term neoplasia is used collectively for atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). This is because phenotypically and genetically, ALH is identical to LCIS. However, this pathological combination of the terms fails to address the differences in risk associated with malignancy which is 4–5 times and 11 times for ALH and LCIS, respectively (Dupont and Page 1985). Unlike ADH, the management of lobular neoplasia is more controversial because ALH and LCIS are usually identified as incidental findings in the needle core biopsy or excision biopsy during investigation of another lesion such as radial scar, calcifying ADH or DCIS. The incidence of LCIS in needle core biopsies is less than 2 % in most series (Berg et al. 2001b; Liberman et al. 1999a). Local excision of lobular neoplasia is recommended if

associated with other high-risk lesions such as radial scar or ADH (Liberman et al. 1999b). The presence of LCIS or ALH in a needle core biopsy that is inconsistent with the radiological findings is also an indication for local excision. Sometimes it is difficult to distinguish ALH and LCIS from low-grade solid DCIS, and local excision would be prudent in these circumstances. E-cadherin immunocytochemistry is a useful adjunct to morphological assessment as this is positive in DCIS and negative in ALH and LCIS (Acs et al. 2001). Amorphous calcification associated with ALH and LCIS has been reported in mammographic lesions diagnosed at needle core biopsy (Berg et al. 2001a). This should prompt an excision biopsy to exclude high-grade DCIS. The current recommendation is that if lobular neoplasia is present in a needle core biopsy, this should be managed by an excision biopsy; but if present in an excision biopsy, no further surgical intervention is necessary (Walker et al. 2012).

4.5.3 Radial Scar

Radial scars are radiologically indistinguishable from a stellate invasive cancer. Previously it was debatable as to whether radial scars were a risk factor for cancer or not. There is now a body of evidence that women with radial scars have a twofold increase in cancer risk in both breasts (Jacobs et al. 1999) and the risk of cancer is higher in larger radial scars (Sloane and Mayer 1993). In the later study, Sloane and Mayer reported a 30 % prevalence of carcinoma in radial scars more than 6 mm in size. Of significance in the series reported by Sloane and Mayers was that the carcinomas were present at the periphery of the radial scars and therefore invariably not sampled in the needle core biopsies which target the fibro-elastotic core of the radial scar. In a separate study of 40 women with lesions mammographically suggestive of radial scars, Frouge and Colleagues (1995) reported the presence of carcinoma in 8 (28.6 %) of 28 pathologically confirmed radial scars. Based on these findings, it is doubtful that any multidisciplinary team looking after women with lesions radiologically and pathologically suggestive of a radial scar will have alternative management but recommend excision biopsies. However, Brenner and colleagues (2002) advocate conservative management with the use of a directional vacuum-assisted device, if the diagnosis of a radial scar can be made in needle core biopsies in at least 12 specimens. This only applies if there is no associated ADH or if the pathological features are in keeping with the radiological features.

4.5.4 Columnar Cell Lesions (CLLs)

When the first edition of the book was written, there was little information regarding the cancer risk associated with columnar cell lesions and how to manage if identified in a needle core biopsy. There is also a better understanding of the terminology than it was in the first edition of this book. The pathologists are also becoming aware of this lesion, and more information is now available in the literature regarding the biological nature of these lesions.

Columnar cell lesions are a spectrum of lesions characterised by architectural and cytological alteration of the terminal duct of lobular units which becomes irregular or mildly dilated and lined by a layer of epithelium with apical snouts. The lesions are usually detected mammographically due to the presence of microcalcification but are also invariably present in biopsies sampled for investigation for other breast lesions, benign or malignant.

Columnar cell lesions have been reported in the literature under different names (Chap. 11), but there is now an acceptable unifying terminology based on the classification by Schnitt and Vincent-Salomon (2003). The spectrum of the lesions is classified into columnar change (CCC), columnar cell change with hyperplasia, columnar cell change with atypia and columnar cell hyperplasia with atypia with the advanced end of the spectrum being DCIS. Columnar cell change with atypia and columnar cell hyperplasia with atypia were collectively classified as flat epithelial atypia (FEA) by the WHO (Tavassoli and Devilec 2003). When there is prominent architectural alteration, the designation of atypical ductal hyperplasia applies (CCL-ADH). CCC with atypia and

columnar cell hyperplasia with atypia, if present in a needle core biopsy, will fall into the B3 category, i.e. atypia of uncertain malignant potential (Walker et al. 2012). Evaluation of the published results of the excision biopsies following the diagnosis of FEA on needle core biopsies reported the presence of DCIS and lobular neoplasia up to 22 % and 36 % of cases, respectively (Jar-Lazaro et al. 2009). DCIS or invasive carcinoma was reported in other studies where excision biopsies were undertaken following the diagnosis of FEA on needle core biopsy (Brogi and Tan 2002; Bonnet et al. 2003; Martel et al. 2007).

The biological significance of columnar cell lesions is still evolving, and further information is required on long-term follow-up of these lesions. Based on the currently available data, the following management is advocated on finding CCL in needle core biopsies:

(i) CCCs and columnar cell hyperplasia without atypia should be classified as B2 lesions in the same category as fibrocystic change following examination of multiple levels (Walker et al. 2012).
(ii) CCLs with atypia (FEA) and more complex lesions (ADH) should be classified as atypical proliferations of uncertain malignant potential (B3) and, following multidisciplinary team discussion, recommend surgical excision (Jar-Lazaro et al. 2009).
(iii) When columnar cell lesions are present in excision biopsy in association with DCIS or invasive carcinoma, the patient should be managed according to conventional criteria of the high-grade lesion (Walker et al. 2012).
(iv) There is a dearth of information regarding the management of columnar cell lesions amounting to ADH and FEA in an excision biopsy. Following an excision biopsy when there is no DCIS or invasive carcinoma, it would be prudent to follow these patients up as per conventional ADH as per local multidisciplinary team recommendations, taking into account other factors such as age of the patient and family history of breast cancer (Vincent-Salomon 2006). Patients with ADH are followed up 6-monthly with clinical examination plus annual mammography (Kiluk et al. 2007).

4.5.5 Mucocoele-Like Lesions (MLLs)

Although in the original description of a mucocoele-like lesion (MLL) described by Dr Rosen in 1986 (Rosen 1986) the patients had presented symptomatically, MLLs are frequently detected mammographically as an indeterminate microcalcification or mass lesion which will lead to a needle core biopsy (Ramsaroop et al. 2005). Like the columnar cell lesion, the MLL is histologically heterogenous. The histological features of an MLL in a needle core biopsy include mucin-filled ducts lined by benign epithelium, extravasated mucin containing benign epithelium or extravasated mucin without epithelium. In a retrospective study of MLLs, Chinyama and Davis (1996) reported association of MLL with ADH, DCIS and mucinous carcinoma. Further studies on screen-detected MLLs which were excised following diagnosis on needle core biopsies reported the association of MLL with ADH, DCIS and mucinous carcinoma (Carder et al. 2004). Carder and colleagues recommended excisional biopsy on diagnosis of the MLL on core biopsy. This is the general consensus of other clinicians (Ramsaroop et al. 2005; Carkaci et al. 2011). However, in a review of 54 core biopsies of MLL without atypia which were managed as B3 lesions, Rakha et al. (2013) identified only two low-grade cancer (4 %); and review of the literature in the same publication identifies four cancers out of 106 MLLs without atypia. If there is atypia in the MLL, the yield of malignancy is up to 21 %. The authors concluded that the risk of malignancy is low after a core biopsy showing MLL without atypia, but much higher if there is atypia. They emphasise the importance to search for atypia by examination of multiple levels. The authors suggested that if no atypia is present, excision with a vacuum-assisted device after multidisciplinary team discussion may be a reasonable to surgical excision.

4.5.6 Microglandular Adenosis

Microglandular adenosis is notoriously difficult to exclude from tubular carcinoma in a needle core biopsy. This is because both lesions lack the

myoepithelial layer (Eusebi et al. 1993). Definitive diagnosis of microglandular adenosis can be confirmed only on excision biopsy. Furthermore, there is evidence that microglandular adenosis may be a precursor for carcinoma with atypical microglandular adenosis as an intermediate lesion (Salareih and Sneige 2007). As a needle core biopsy only samples a fraction of the lesion, definitive diagnosis can only be achieved in an excisional biopsy.

4.5.7 Papillary Lesions

Papillary lesions present as isolated central intraductal papillomas or multiple peripheral papillomas. The central lesions present with bloodstained discharge or serous discharge. Cells may be present on cytological evaluation of the nipple discharge. Duct ectasia invariably presents with nipple discharge. It is not always possible to distinguish duct ectasia from a central papilloma because imaging is usually normal. Furthermore, there is a slight increased risk of 1.3–2 of developing cancer with central intraductal papillomas (Lewis et al. 2006). Although the presence of an intraductal lesion can be confirmed or excluded by galactography (Van Zee et al. 1998; Hou et al. 2001), this procedure is not routinely carried out in most institutions, and local excision is usually performed to treat the discharge (Vargas et al. 2002; Cabioglu et al. 2003).

The presence of a papillary lesion in the needle core biopsy of a symptomatic or screen-detected lesion gives rise to three possible diagnoses: benign intraductal papilloma, atypical intraductal papilloma or intracystic papillary carcinoma. There is no debate with regard to the management of atypical papilloma and intracystic papillary carcinoma as these require surgical excision (Page et al. 1996; Renshaw et al. 2004; Ivan et al. 2004). It is the management of the benign intraductal papilloma which is controversial.

Peripheral papillomas tend to be multiple, and there is higher risk of progressing to malignancy than the central papillomas (Page et al. 1996; Ohuchi et al. 1984). The UK NHS Breast Screening Programme classifies all benign papillomas and atypical papillomas in a needle core biopsy as papillary lesions and is assigned the B3 category of proliferation of uncertain malignant potential (Ellis et al. 2004); and following a multidisciplinary team discussion, the patients are referred for surgical excision. Although this approach may be valid for atypical papilloma/atypical papillary lesions, there are cases where the pathology of the papillary lesion is clearly a benign papilloma, and the question is whether these papillomas should be excised if the radiological features support a benign diagnosis. In addition to the risk of progression to malignancy, separate studies reported the presence of high-risk lesions such as ADH, DCIS and invasive carcinoma in the excision specimens when the original diagnosis on needle core biopsy was a benign papilloma. In a study of 104 patients with pure intraductal papillomas on core biopsies, Shabnam and colleagues (2009) reported the following diagnoses in the excision specimens: benign intraductal papillomas in 71 (68.3 %), no residual intraductal papillomas in 6 (5.8 %), ADH in 8 (7.7 %), DCIS in 6 (5.8 %) and invasive carcinoma in 3 (2.9 %). The high-risk lesions were identified adjacent to but not in the biopsy site. In the cases with ADH or DCIS, there was a spectrum of histological changes ranging from florid to ADH to DCIS. The overall upstage from benign papilloma on needle core biopsy to atypia or malignancy in excision biopsies was 16.4 %. Based on these findings, Shabnam and colleagues recommended excision of benign papillomas following diagnosis on needle core biopsy. This approach is supported by Rozentsvayg and colleagues (2011) who reported 19 % high-risk lesions in 54 patients with a diagnosis of papillomas on core biopsy. In a separate study, Liberman et al. (2006) identified cancer in 14 % of patients with the diagnosis of papilloma on needle core biopsy and high-risk lesions in 17 % of the patients. In this study Liberman and colleagues (2006) concluded that 'Lesions yielding a benign, concordant diagnosis of papilloma at percutaneous biopsy may warrant surgical excision'. This was obviously a precautionary statement following their earlier publication in 1999 when they

reported that surgical excision was not indicated when benign intraductal papillomas without atypia were diagnosed on large-core biopsies in seven cases. In a similar study Renshaw and colleagues (2004) did not find high-risk lesions in eight cases of benign intraductal papilloma. Of note in the follow-up paper by Liberman and colleagues (2006) where they reported five (14 %) cancers in 35 lesions with benign papilloma on needle core, the patients were under mammographic follow-up. This indicates that there was anxiety regarding the biological behaviour of benign papillomas on biopsy, otherwise, the women should have been discharged or returned to routine screening programme. The evidence available to date is in favour of excising papillomas to reduce the likelihood of missing high-risk lesions, an approach followed by the UK NHS Breast Screening Programme (Ellis 2004).

4.5.8 Fibroepithelial Tumours

Sampling of a fibroepithelial tumour in a needle core biopsy represents either a fibroadenoma or a phyllodes tumour. Cancer arising in a fibroadenoma is rare. Furthermore, fibroadenoma is the most common tumour of the breast, and indiscriminate surgical excision would put a strain on the health resources and induce unnecessary scarring. Most institutions would manage symptomatic fibroadenomas conservatively in women under the age of 35 years and by surgical excision in women over the age of 35 years because of the increased risk of cancer (Foster and Williams 1988; Wilkinson et al. 1989; Carter et al. 2001; Greenberg et al. 1998; Sainsbury et al. 1988). However, if fibroadenomas are detected through the mammographic screening programme, they tend to be atrophic and calcified, and these lesions are managed conservatively. With improved imaging techniques and use of mammotome, most institutions follow a conservative approach in managing fibroadenomas irrespective of the age of the patient and only excise if the fibroadenoma increases in size or at the request of the patient (Greenberg et al. 1998).

There is no consensus on how to manage patients with complex fibroadenoma following diagnosis in a needle core biopsy. A complex fibroadenoma was first reported by Duport et al. (1994) and contains a combination of some of these epithelial proliferations: sclerosing adenosis with or without calcification, fibrocystic change with apocrine metaplasia and cysts larger than 3 mm. There is a high risk of progression to malignancy with complex fibroadenomas. Klair-Levy and colleagues (2008) advocate conservative management of women with complex fibroadenomas, whereas other studies recommend surgical excision (Greenberg et al. 1998). As with any other breast condition, the approach to this subject is to discuss the risk factors in each individual patient at multidisciplinary team meetings, taking into account the clinical and radiological features and other risk factors such as family history, presence of other epithelial proliferations external to the fibroadenoma (Kuijper et al. 2001) or previous biopsies to allow the patient to have an informed decision as to whether the surgical approach is appropriate or not. A complex fibroadenoma with columnar cell change would, for example, persuade the multidisciplinary team to recommend a surgical excision (Petersson et al. 2010).

The other differential diagnosis of a fibroepithelial tumour in a needle core biopsy is a cellular fibroadenoma or phyllodes tumour. There is no controversy regarding the management of these patients which is surgical excision to allow proper evaluation of the stroma so as to make a definitive diagnosis of malignancy or benignity (Jacobs et al. 2002, 2005).

4.6 Guide-Wire Localisation Excision Biopsy

Impalpable, screen-detected benign or malignant lesions are difficult to identify during surgery, and these require guide-wire localisation (Fig. 4.1). Ultrasound and mammographic guide-wire localisation are routinely used in the excision of impalpable lesions. Rarely magnetic resonance (Gould et al. 1998) guidance has been used in the excision of benign lesions. Different types of localisation wires are available on the market. The advantage of guide-wire localisation

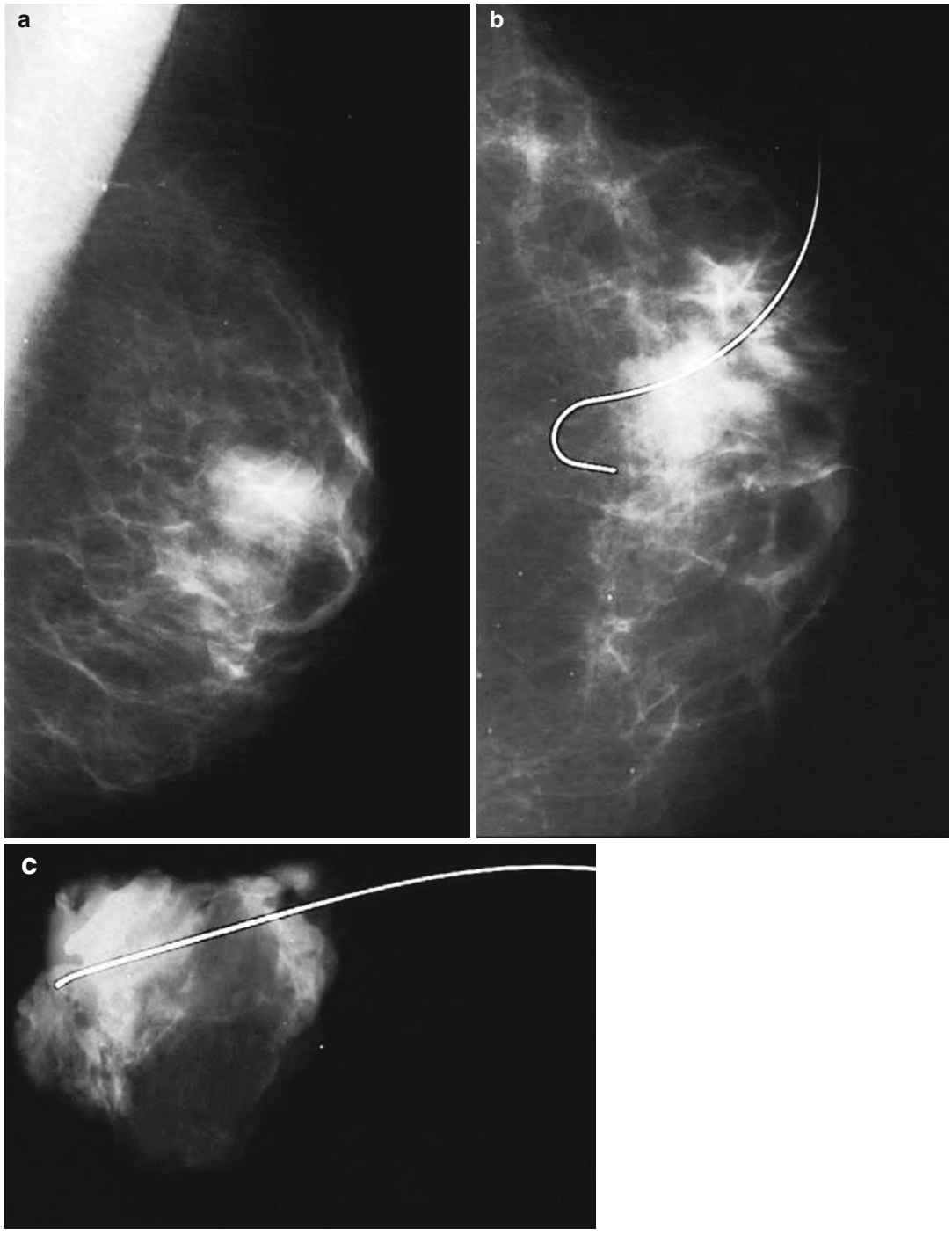

Fig. 4.1 (**a**) Mammography shows a well-circumscribed, screen-detected fibroadenoma in a 53-year-old woman. (**b**) Localisation guide-wire is in situ. (**c**) Specimen X-ray confirms the excision of the mammographic lesion. The histology showed a fibroadenoma with hyalinised stroma. (**d**) This TranSpec specimen radiography device is used for compression of excision biopsies in our department. The compression plate is available solid or perforated (With courtesy of E-Z-EM Inc., Westbury, NY, USA)

Fig. 4.1 (continued)

is that the abnormal area can be targeted for excision; this minimises loss of normal tissue, especially when excising benign (B2) or atypical lesions of uncertain malignant potential (B3). To minimise tissue loss and maintain acceptable cosmetics, the British Association of Surgical Oncology (BASO) recommends that tissue excised for benign disease for diagnostic purposes should weigh less than 20 g (UK NHSBSP 2009). After excision, the specimen should be X-rayed to confirm that the lesion is the specimen. In our department, the specimen is X-rayed in the TranSpec specimen radiography device (E-Z-EM, Westbury, NY; Fig. 4.1d). This affords the even compression required for optimal image resolution. The X–Y grid axis allows location of the lesion on the X-ray. The surgeon should resist slicing into the specimen, and whenever possible, the specimen should be orientated. The specimen X-ray and the specimen should be submitted to pathology to assist the pathologist in sampling the appropriate area (Fig. 4.1c).

Specimen X-rays not only confirm that the mammographic lesion has been excised but sometimes detect lesions that may not be apparent in the mammographs, including microscopic cancers (Bauermeister and Hall 1973). Because there is less tissue depth to be assessed in a specimen X-ray than in in vivo mammograms, the pathologist can target other abnormal areas in addition to the lesion that prompted the excision biopsy. Gallager (1975) considers specimen radiography as an obligatory investigative tool for assessing non-palpable abnormalities.

4.7 Follow-Up Versus Excision of Indeterminate Lesions

Improved imaging techniques have also resulted in the ability to detect small and indeterminate lesions. These indeterminate lesions lead to further investigations such as ultrasonography, fine needle aspiration cytology or needle core biopsy. If the above investigations fail to give a definite

diagnosis of benignity, local surgical excision is usually performed. However, surgical excision does not guarantee excision of the lesion, even with mammographic guidance. Surgical excision failure rates as high as 17 % have been reported (Norton et al. 1988).

Insufficient use of specimen X-ray by the pathologist may also result in radiological–pathological discordance. The alternative to surgical operation of a mammographically indeterminate lesion with indeterminate cytological (C3) or pathological (B3) diagnosis is mammographic follow-up. This spares the woman a surgical procedure with related complications. The difficulty in adhering to periodic follow-up for indeterminate lesions lies in the inability to reassure the woman that the lesion is definitely benign and the risk of missing an early potential cancer. Other factors related to follow-up include anxiety for the woman, who does not know whether she has a benign or malignant lesion in her breast. The physician looking after the patient may be anxious as to whether or not the right decision has been taken by advising follow-up (Adler et al. 1990). Another matter raised by Adler and colleagues, which may negate the effects of periodic follow-up, is the reduction in compliance with time. They recommended that for mammographic follow-up to be successful, there must be compliance between the physician and the patient. The physician has to educate the woman as to why periodic follow-up is necessary. Another matter to be considered is whether the classification of indeterminate lesions as B3, prompting an excision biopsy, will increase the benign biopsy rate (Carder and Liston 2003). Carder and Liston reported 22 benign lesions (61 %) in 36 cases which had been classified as B3 on needle core biopsy, a relatively high benign rate. However, Moskowitz (1989) argued that the excised benign:malignant ratio should be as high as 10:1 if screening is to affect mortality due to breast cancer. This was in response to Brenner and Sickle's (1989) statement that 'majority of benign breast lesions detected with mammography do not have a pathognomonic appearance', and therefore, biopsies should not be done for mammographic findings with a low predictive value for cancer, but the patients should be followed up. Moskowitz challenged this approach and questioned how often are the women to be followed up and at what interval; would the follow-up be age-dependent? He therefore advocates excision biopsy of the benign lesions.

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Pathology of Benign Breast Lesions

5

Learning Points

- FNAC is useful for diagnosis of fibroadenomas, apocrine cysts and lymph nodes.
- Needle core biopsies may provide a definite diagnosis when compared to FNAC for fibrotic and calcified lesions.
- The higher the number of needle core biopsies, the higher the diagnostic accuracy.
- B3 lesions in needle core biopsies underestimate the presence of a high-grade lesion in a significant number of cases.
- Specimen X-ray is important to confirm excision of screen-detected abnormality.
- Ancillary immunocytochemistry such as CK5/6 may assist in confirming benignity.

5.1 Diagnostic Specimens in Benign Breast Lesions

Nonoperative diagnostic procedures such as needle core biopsy or fine needle aspiration cytology (FNAC) are essential for appropriate decision-making in the management of the patient with benign or malignant breast disease. A conclusive radiological and histological diagnosis of benign breast disease allays anxiety in the woman concerned, especially if this can be achieved without surgical operation. Inadequate sampling from fibrotic lesions, such as lobular carcinoma, hyalinised fibroadenomas and scattered microcalcification, now limits the use of FNAC, which was once a popular diagnostic modality. Consequently more and more units are using stereotactic needle core biopsies in combination or as an adjunct to FNAC as a diagnostic tool. Needle core biopsies benefit from a higher sensitivity and specificity than FNAC (Britton 1999). More sections can be cut, and immunocytochemistry stains carried out on a needle core biopsy which may assist in reaching a diagnosis in equivocal cases. Needle core biopsies are also preferred to localised excision biopsies as they potentially spare patients with benign lesions from unnecessary surgery.

Frozen section examination is not recommended in screen-detected lesions because of the risk of a false-positive diagnosis with lesions such as radial scars and sclerosing adenosis (Nielsen 1987). If one is faced with an equivocal FNAC or needle core biopsy diagnosis, it is preferable to perform an excisional biopsy and confirm the diagnosis on the paraffin-embedded tissue rather than risk a misdiagnosis on frozen section. Screen-detected lesions are usually small, and it is preferable to assess the whole lesion after appropriate fixation. Partly sampling the lesion for frozen section may distort the specimen, which could interfere with the final diagnosis. Even with a palpable lump, there is no justification for using frozen section for primary diagnosis.

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_5, © Springer-Verlag Berlin Heidelberg 2014

5.2 Reporting Fine Needle Aspiration Cytology

Meaningful cytology results, especially in impalpable lesions, depend on the experience of the aspirator (usually the radiologist), the quality of the prepared slides (radiologist, pathologist or laboratory biomedical scientist), the quality of the staining (laboratory biomedical scientist) and the experience of the reporting pathologist or cytopathologist. The experience of the cytopathologist is enhanced by the volume of different cases reported in each unit, complimented by multidisciplinary team discussion of these cases. The UK National Health Service Breast Screening Programme (NHSBSP 1993) devised a standardised format for reporting cytology similar to the radiological criteria. The criteria were updated in NHBSP Publication 50 (2001) which provides guidelines on nonoperative diagnostic procedures and reporting. The European Society of Mastology (EUSOMA) also applies similar reporting criteria (Perry et al. 2001).

5.2.1 Cytology Reporting Categories

C1 denotes an inadequate aspirate where there are no cells to represent the radiological or clinical lesion. With impalpable lesions, apparent inadequate sampling can occur with hypocellular fibrotic lesions, which would benefit from needle core biopsies. Scattered microcalcification can also produce an inadequate aspirate. The lack of epithelial cells in lipomas, cysts or fat necrosis should be reported in conjunction with radiological images to ensure that the appropriate lesion has been sampled. Again a needle core may assist with the diagnosis. Heavily bloodstained smears and poorly spread and stained smears, which preclude accurate cytological assessment, should be reported as inadequate. Repeat fine needle aspiration or core biopsy is recommended after the bleeding has settled, usually in 4–6 weeks.

C2 indicates a benign aspirate containing uniform cells arranged in monolayers. The background is usually ‘clean’ as opposed to the dirty background of a malignant aspirate. A mixture of myoepithelial and epithelial cells gives the ‘two-cell-type’ appearance because the myoepithelial cells take up more stain and appear darker than the ordinary epithelial cells. Fibroadenomas typically give this two-cell-type appearance. The presence of apocrine cells also indicates benignity (Fig. 5.1) in aspirates from fibrocystic change. Lipid-laden foamy macrophages from cysts or duct ectasia may also be present (Fig. 5.2).

C3 cytology is reported in lesions where the aspirate shows a mixture of benign cells and atypical forms. The aspirate may contain monolayer cells with two cell types as well as pleomorphic cells with an increase in nuclear:cytoplasmic ratio; loss of cohesiveness may be present. These features occur in atypical ductal hyperplasia (ADH) and some cellular fibroadenomas or may be secondary features of hormone replacement therapy. Depending on the mammographic appearance, lesions with C3 cytology should be followed up by short-interval mammography, needle core biopsy or excision biopsy.

C4 is designated to an aspirate containing atypical cells suspicious of malignancy, but there are other features preventing a definite diagnosis such as pauci-cellular material, poorly preserved cells or a mixture of benign and atypical cells, more pleomorphic than C3 cells. A core biopsy should be performed to confirm the diagnosis before definitive surgical treatment.

C5 is reported in the presence of overtly malignant cells, which are pleomorphic and dissociated. Due to the widespread use of core biopsies, definitive surgical treatment is rarely made on C5 cytology. However, C5 cytology in an aspirate from metastatic carcinoma in a lymph node assists in appropriate management of the patient.

FNAC is the cheapest form of making a pathological diagnosis. The procedure is carried out in outpatient or radiology departments, and the patient can have the results on the same day. While FNAC is useful in the diagnosis of apocrine cysts, fibroadenomas and lymph nodes, due to the high risk of false-positive diagnosis, surgery for cancer should not be performed based on cytological diagnosis of C5 (Makunura et al. 1994).

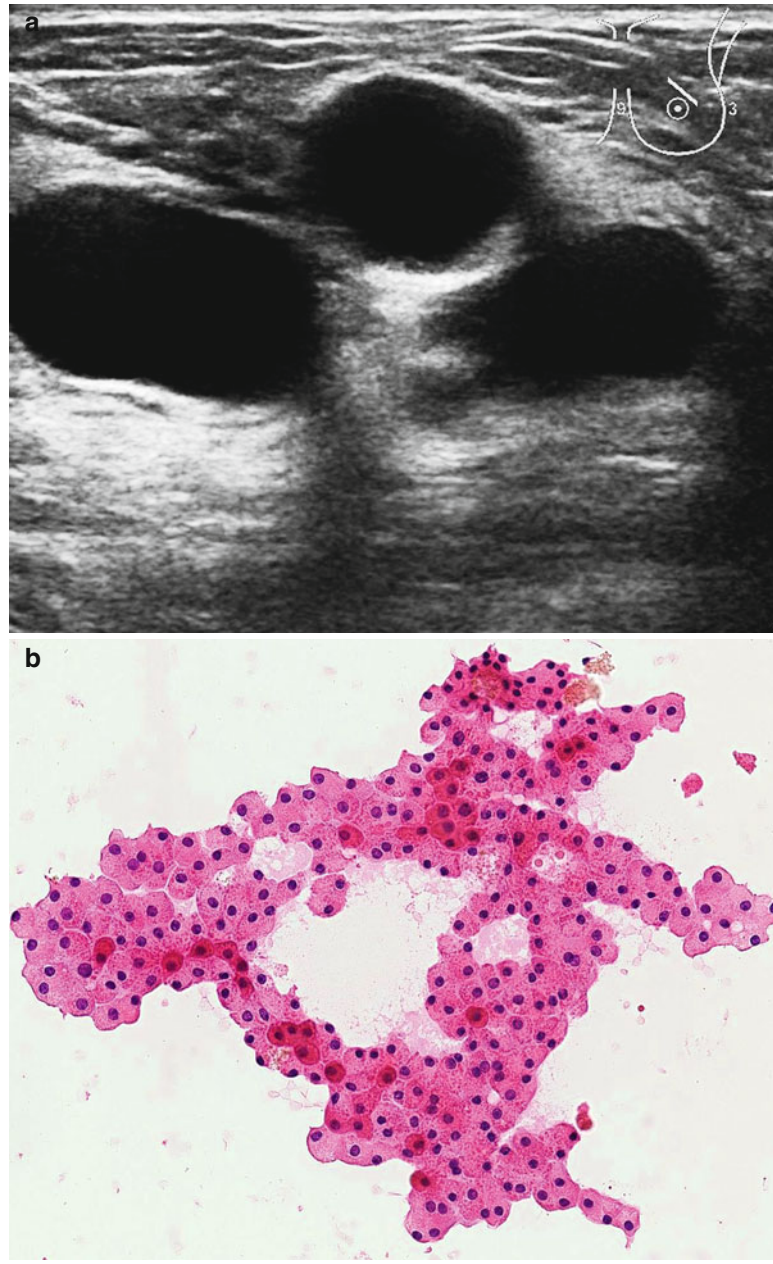


Fig. 5.1 (**a**) The ultrasound showed multiple cysts (U2). (**b**) The cytology showed layers benign apocrine cells; no malignant cell seen (C2). The haematoxylin and eosin (H&E) highlights the granular cytoplasm

5.3 Reporting Needle Core Biopsies

Needle core biopsies can be sampled under ultrasound or stereotactic guidance. Larger and high-volume needle core biopsies can be obtained by a vacuum-assisted device (mammotome). If the target abnormality is mammographic calcification, the needle core biopsies can be placed in a small cassette and X-rayed to confirm the presence of calcification. The cassette will then be submitted to the laboratory for processing.

At least three levels should be examined histologically to obtain an adequate diagnosis on needle core biopsies. The greater the number of needle core biopsies, the easier it is for the pathologist to make a diagnosis. Brenner et al. (1996) reported increased diagnostic accuracy

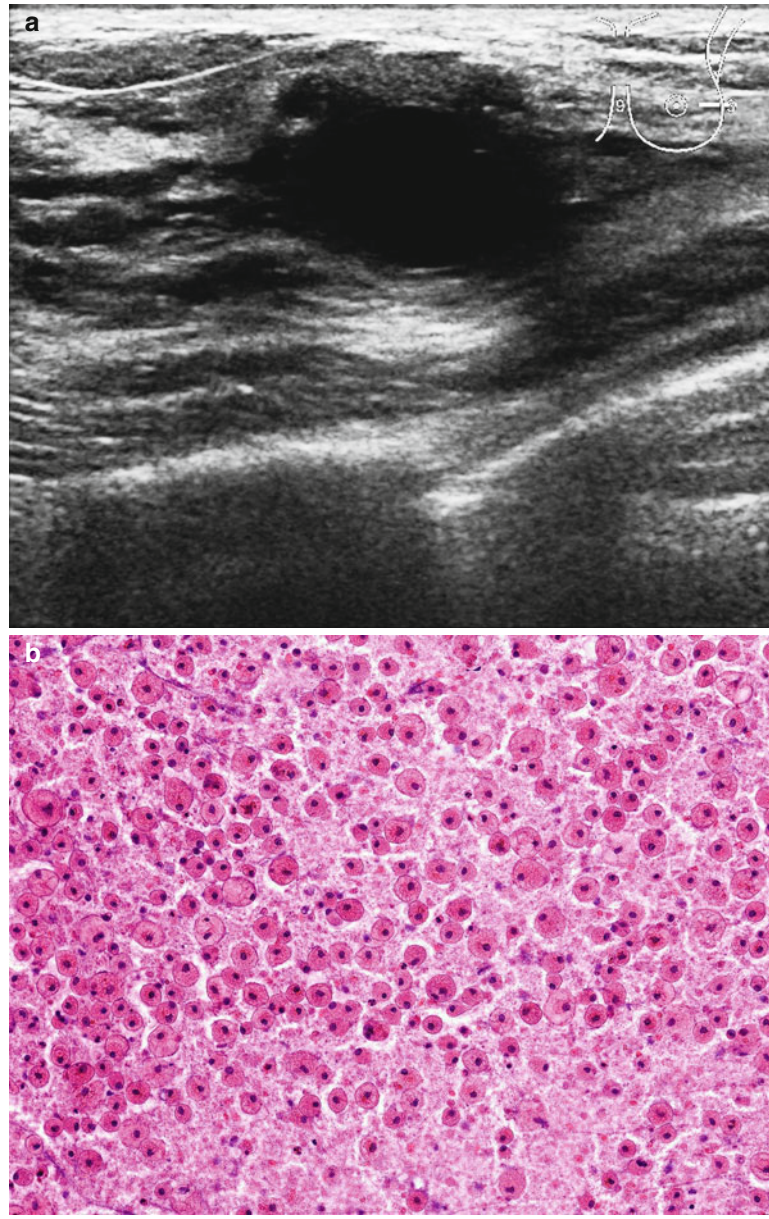


Fig. 5.2 (**a**) This ultrasound showed irregular cyst with contents (U3). The aspirate consisted of thick material resembling pus. (**b**) The cytology showed numerous macrophages in an amorphous background. No epithelial cells or malignant cell is seen (C2)

with increasing number of needle core biopsies. With five biopsies, diagnostic accuracy was 98 % for masses, 91 % for calcifications, 100 % for masses with calcification, 100 % for focal asymmetries and 86 % for architectural distortions. Bagnall et al. (2000) reached a similar conclusion when they assessed 57 consecutive stereotactic needle core biopsies. The authors reported that the presence of calcification in the specimen X-ray was associated with a high sensitivity. The presence of five or more flecks in three or more needle core biopsies gave an absolute sensitivity of 100 % for carcinoma. The use of a vacuum-assisted device also reduces the rate of false-negative biopsies (Burbank 1997). If microcalcification is being sought, further levels should be examined before rendering an inadequate specimen. The pathologist should also be aware of calcium oxalate (weddellite) which can be present in the specimen X-ray but absent

in the tissue unless examined under polarising light. Renshaw (2001) found out that at least five sections of the needle core biopsy are required in order to identify atypical small acinar proliferations or ADH.

The UK NHSBSP (2001) devised criteria for reporting needle core biopsies, which were later adopted by EUSOMA (Perry 2001). Although the needle core biopsy reporting categories are similar to those of radiological and cytological reports, the B3 category does not strictly follow the same criteria applied to radiology and cytology features (NHSBSP 2001).

5.4 Needle Core Biopsy Reporting Categories

B1 is applied to a needle core biopsy that contains normal breast tissue or adipose tissue. The presence of normal breast tissue in needle core biopsies should not be reported as benign in the presence of a radiological lesion, unless this has been discussed at a multidisciplinary team meeting. Lipomas or hamartomas can give a B1 report; therefore, the clinical and radiological features should be taken into account when these lesions are suspected. Involuting lobules may contain microcalcification on histology, which was not apparent mammographically or on specimen X-rays. This microcalcification may not be representative of the radiological lesion, and a B1 report may be appropriate following multidisciplinary team discussion.

B2 confirms benignity in breast lesions such as fibroadenoma, fibrocystic change, sclerosing adenosis (Fig. 5.3) or fibrosis, with radiological evidence that the pathological lesion was sampled. Depending on the radiological features, the patient may return to routine screening.

B3 does not correspond to the cytological diagnosis of atypia that is probably benign. B3 is applied to needle core biopsies that contain epithelial proliferation of uncertain malignant potential. It is difficult to confirm benignity in these lesions in small-needle core biopsies; excision biopsies are required to exclude malignancy. These lesions include radial scars, papillary tumours (Fig. 5.4), ADH (Fig. 5.5), microglandular adenosis, phyllodes tumours, lobular neoplasia, mucocoele-like lesions and columnar cell lesions.

B4 is applied to biopsies suspicious of malignancy; these lesions require surgical excisional biopsy.

B5 is applied to lesions that are malignant, either in situ or invasive; definitive surgical treatment is required.

5.5 Pathological and Radiological Correlations

In most units needle core biopsies are now replacing FNAC as a diagnostic tool. With appropriate sampling, the diagnosis of most overtly malignant or benign lesions can be made on needle core biopsies. True false-negative biopsies are low and ranges of 0.3–1.2 % have been reported (Acheson et al. 2002; Jackman et al. 1999). There are a few reports of benign diagnosis on needle core biopsies with a diagnosis of DCIS or invasive carcinoma on repeat or excision biopsy. False-positive results are equally low with reported levels of 0.4 % (White et al. 2001). These figures are reassuring as they indicate that the needle core biopsy is a reliable preoperative diagnostic method.

A minor setback with needle core biopsies arises with the diagnosis of ADH, when there is a risk of underestimation of a high-grade lesion such as DCIS or invasive carcinoma. Underestimation of high-grade lesions in needle cores with a diagnosis of ADH ranges from 0 % to 38 % (Burbank 1997; White et al. 2001; Meyer et al. 1999). Darling et al. (2000) retrospectively reviewed 139 needle core biopsies, which had been reported as ADH, and the subsequent excisional biopsies. Thirty-eight (27 %) of the biopsies revealed either DCIS (27 lesions) or invasive carcinoma (11 lesions). Underestimation of carcinoma was more frequent in biopsies performed using the 14 gauge automated needle than in those using the 11 gauge directional vacuum-assisted device.

In an attempt to predict the outcome of excision biopsies following the diagnosis of ADH in

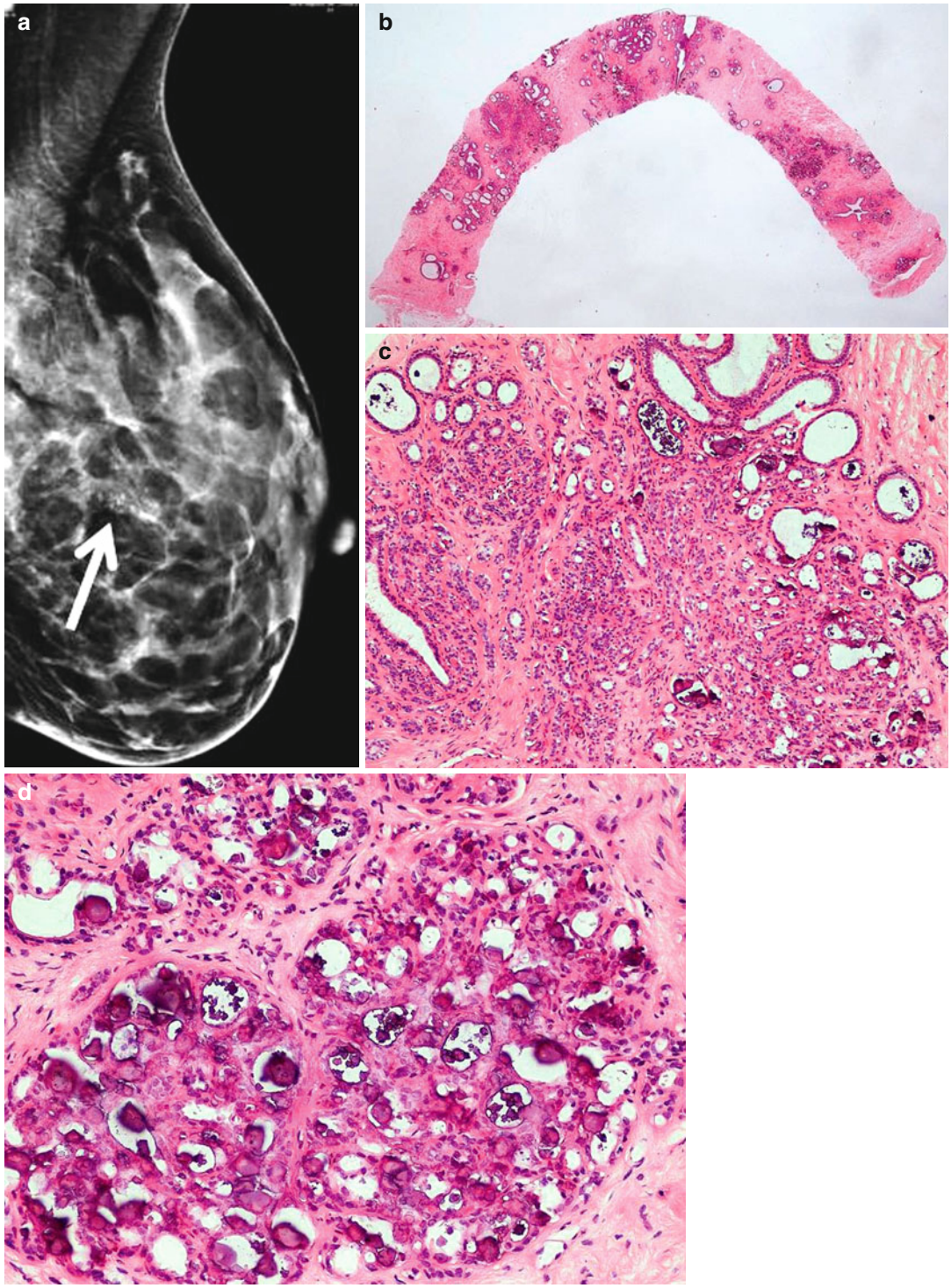


Fig. 5.3 (**a**) Symptomatic lump graded as benign, but mammogram revealed abnormal coarse calcification graded as R4. (**b**, **c**) The needle core biopsy showed sclerosing adenosis with coarse microcalcification (B2). (**d**) The lesion was excised because of radiological–pathological discordance. The excision specimen contained widespread calcifying sclerosing adenosis and other benign lesions

needle core biopsies, Ely et al. (2001) assessed the number of ducts or duct–lobular units involved with the atypical cells. One involved duct was assessed as one focus, one terminal duct–lobular unit as two foci, etc. Using this method, the authors noted that when a needle core biopsy contained four or more foci of ADH, the excision biopsy was more likely to contain an

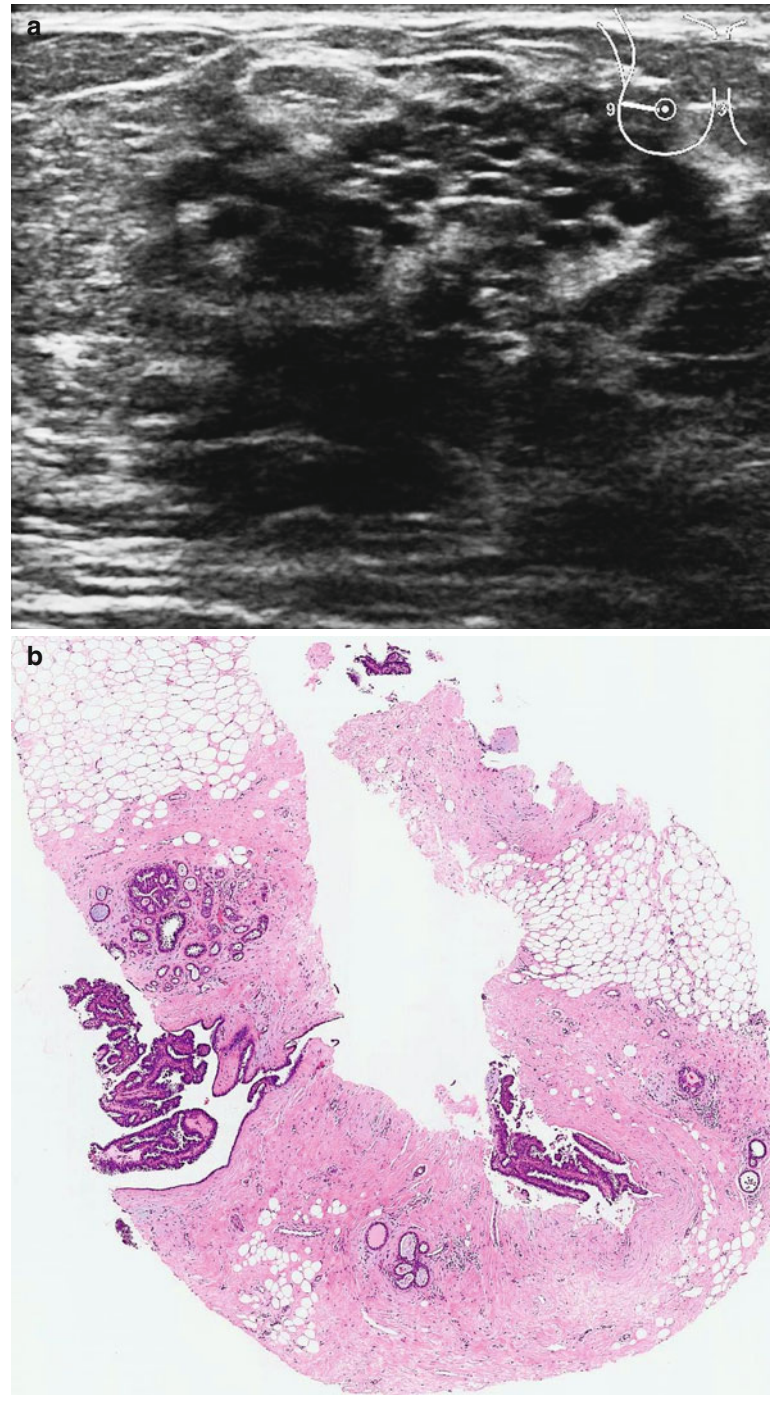
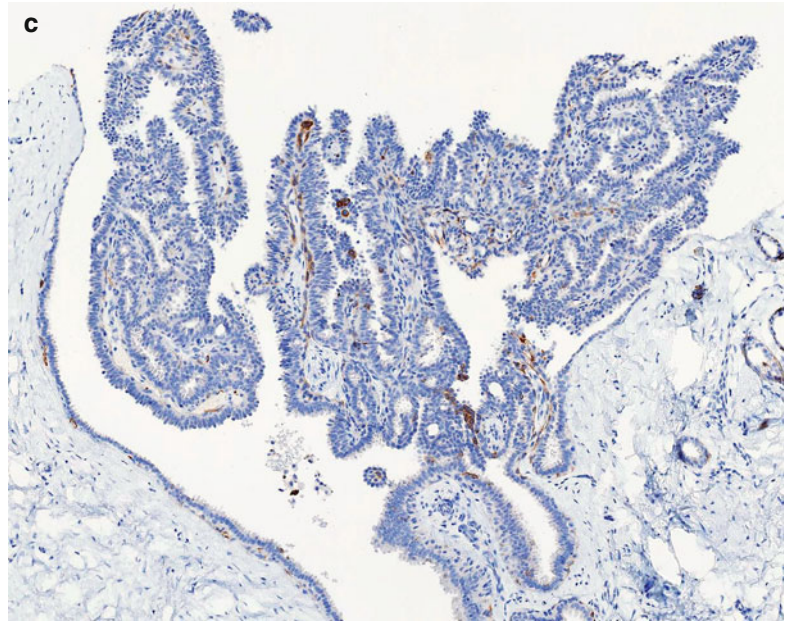


Fig. 5.4 (**a**) Ultrasound assessment for history of trauma showed features suggestive of fibrocystic change (U2). (**b**) The needle core biopsy showed a papillary lesion (B3). (**c**) There are only occasional myoepithelial cells on staining with CK5/6 immunocytochemistry. Excision biopsy showed multiple peripheral intraductal papillomas (Fig. 10.6)

Fig. 5.4 (continued)



advanced lesion, usually DCIS ($P<0.0001$). Sneige et al. (2003) applied the same method on directional vacuum-assisted stereotactic biopsies of microcalcifications and reported complete removal of ADH with no residual lesion in 24/42 cases. The ADH was present in three or fewer lobules and the number of biopsies ranged from 6 to 22. The authors advise adequate radiological–pathological correlation, as the low volume of ADH in directional vacuum-assisted stereotactic biopsies may not require excisional biopsy.

In a separate study, the Nottingham group (Spencer et al. 1994) reviewed the mammographic features of 108 benign lesions detected in a screening programme. The most common mammographic abnormalities reported as benign on excision biopsy were non-comedo-type suspicious calcification (29 %), poorly defined mass (21 %), architectural distortion (19 %) and well-defined mass (18 %). Non-comedo calcification was associated with fibrocystic change (6 %), sclerosing adenosis (35 %) and radial scar/complex sclerosing lesion (13 %). Poorly defined masses revealed fibrocystic change (37 %), fibroadenoma (37 %) and sclerosing adenosis (25 %). Radial scar/complex sclerosis lesions (61 %) and fibrocystic change (26 %) were associated with architectural distortion. The authors concluded that the high number of benign excision biopsies in the screening programme was associated with high psychological and screening costs, so attempts should be made to reduce the number of benign biopsies. A similar review of 137 benign biopsies in the prevalent round of breast screening also revealed that the most common diagnostic problems were clustered and variable microcalcification, radial scar/complex sclerosing lesion and atypical ductal hyperplasia (Burnett et al. 1995).

The B3 category of epithelial proliferation of uncertain malignant potential has the potential to increase the number of surgical biopsies (Carder and Liston 2003). Previously, Harvey et al. (2002) reviewed the excision biopsies from patients whose needle core biopsies had been classified as ADH or intraductal atypia of uncertain significance ($N=52$), and this constituted 5 % of 1,048 core biopsies. Forty-six of the fifty-two biopsies were excised, and seven invasive carcinomas, fifteen DCIS, eleven ADH, two LCIS, nine fibrocystic changes, one mucocoele-like lesion and one fibroadenoma were identified. This rather high prevalence of carcinoma (22/46, 47.8 %) may be due to the lack of strict criteria in

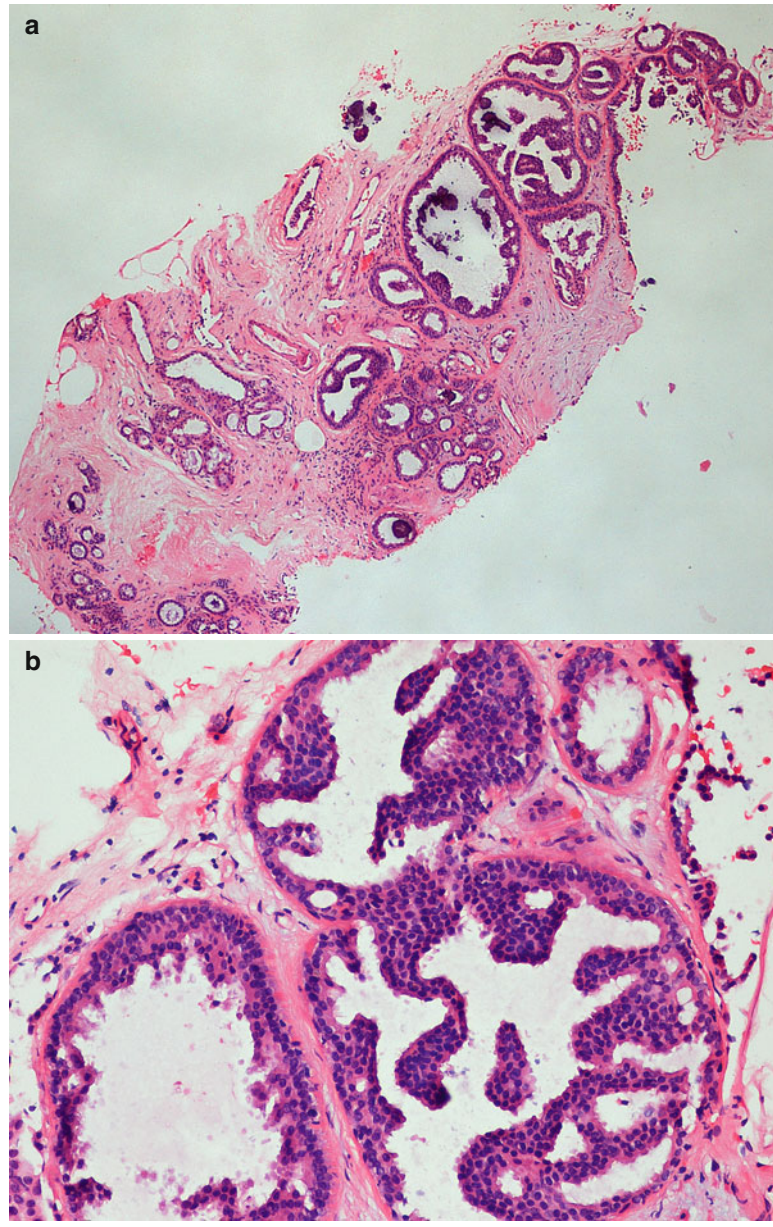


Fig. 5.5 Needle core biopsy performed for indeterminate calcification (R3). (**a**) The histology shows ADH with calcification. (**b**) ADH with atypical cells forming arcades which is difficult to exclude low-grade DCIS. There was no DCIS in the excision specimen

differentiating DCIS, ADH and atypia of uncertain significance on needle core biopsies. A columnar cell lesion with atypia is another radiological abnormality associated with a high yield of DCIS or invasive carcinoma on excision biopsy (Verschuur-Maes et al. 2012).

In a review of the mammographic–histopathological correlation of large-core needle biopsies, Berg et al. (1996) emphasised that radiologists and pathologists need experience in identifying benign processes that can manifest as discrete masses at mammography such as focal fibrosis, apocrine metaplasia, sclerosing adenosis and fat necrosis. When these features are present in a needle core biopsy, the diagnosis should be accepted. Pathologists should avoid non-specific diagnoses such as 'benign breast tissue' without the confirmation of the mammographic lesion. In these circumstances, repeat core or excisional biopsy is advisable.

5.6 Processing Localisation Excision Biopsies

Excision biopsies for benign breast disease are usually performed when there is a radiological–pathological discordance, clinical–radiological–pathological discordance or report of an indeterminate lesion as B3 category in the needle core biopsy. Sometimes a benign lesion is excised on patient's request. Non-palpable lesions are excised under ultrasound or guide-wire localisation. Although it is preferable to submit the specimen fresh to the laboratory, this is not always possible, especially if surgery is performed after the laboratories have closed. To prevent autolysis, the specimen should be immersed in formalin, ten times the volume of the specimen, and covered with a sheet of paper to prevent floating specimens from surface drying. The specimen is fixed for 24 hours, measured and weighed. The margins are painted appropriately. In our department, we use six different paints for the six surfaces (posterior, anterior, medial, lateral, inferior and superior), provided the surgeon has orientated the specimen. Non-palpable lesions should be submitted to the laboratory with specimen X-ray to assist the pathologist to localise the lesion (Fig. 5.6) The presence of the lesion in the specimen X-ray should be confirmed by the radiologist to the surgeon prior to submitting the specimen to the laboratory. If the lesion is not in the specimen X-ray or has been partially excised, the surgeon can sample further tissue immediately and will spare the patient a second surgical procedure, which would be the case if the surgeon has to wait for the pathology report to be informed of an inadequate excision. If, on slicing the specimen, the lesion is not identified macroscopically, especially with microcalcification, the slices are X-rayed individually to further characterise the lesion. In macroscopically ill-defined lesions, such as microcalcification, the specimen X-ray may provide an accurate size, and this should be measured on the specimen radiograph. Small specimens, less than 30 mm maximum dimension, should be processed in their entirety. Where possible, a section of lesion with the nearest excision margin should be included.

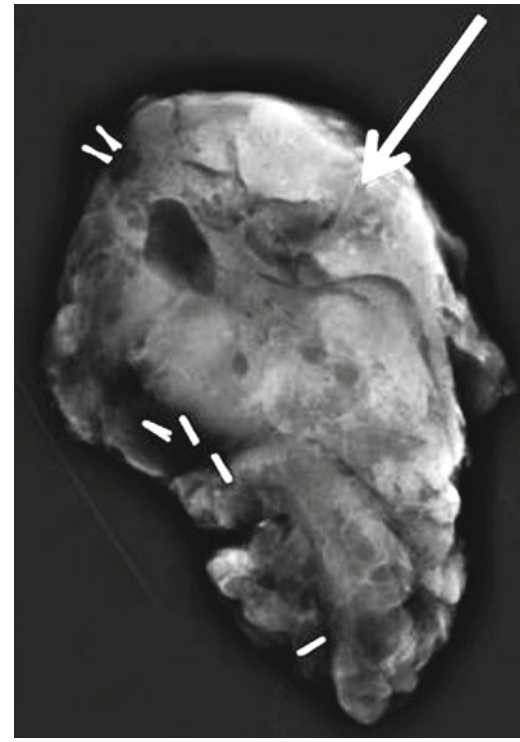


Fig. 5.6 The specimen X-ray of patient in Fig. 5.3 confirming that the mammographic calcification had been excised. The margins are identified with metallic staples

To determine how much tissue should be sampled for pathological examination from localisation excision biopsies, Owings and colleagues (1990) performed a prospective study on 157 consecutive needle localisation breast biopsies to investigate the relationship between mammographic calcifications and pathological extent of the lesions. The specimens were measured, X-rayed with localisation needle wire biopsy in situ, inked and sliced at 3 mm intervals. If, on macroscopic examination, there was an obvious lesion, the specimen was excluded from the study. If there was no gross lesion, the slices were X-rayed and the tissue specimens processed in their entirety. The number of blocks containing

fibrous parenchyma in each case was also determined. The sampled specimen blocks were considered to contain fibrous tissue if 25 % or more of the specimen showed fibrous tissue with mammary ducts and lobules. The actual dimensions of the specimens were not indicated in this study. However, the size of the specimen was determined by the number of blocks submitted. In 4 % of the specimens, 1–5 blocks were required to adequately assess the radiological calcification; in 37 %, 6–10 blocks; in 29 %, 16–20 blocks and the remaining 15 % of cases required more than 20 blocks. Microscopic examination revealed carcinoma in 32 % of the specimens, atypical hyperplasia in 12 % and benign disease in 56 %. The likelihood of identifying carcinoma or atypical hyperplasia was not related to the size of the biopsy. There was no difference in the number of blocks submitted for specimens with carcinoma (mean 14.1 blocks per case), atypical hyperplasia (mean 14.5 blocks per case) and benign breast disease (mean 13.6 blocks per case). In 49 out of 50 carcinomas (98 %) and in 14 out of 19 atypical hyperplasias (74 %), at least a part of the lesion was present in the tissue block that contained the mammographic lesion. Owings and colleagues concluded that if microscopic examination had been restricted to the tissue slices containing the mammographically detected calcification, only 34 % of the total number of blocks actually submitted would have been processed. However, 1 out of 50 carcinomas (non-comedo DCIS) and 5 out of 19 atypical hyperplasias would have been missed. The authors considered another method of submitting the slices with the mammographic calcification and the remaining tissue in the cases where carcinoma or atypical hyperplasia was identified. By applying this method, 62 % of the total number of blocks actually submitted will have to be processed with the same detection of carcinoma and hyperplasia. Previously Schnitt and Wang (1989) noted that when carcinoma and atypical hyperplasia are identified in grossly benign tissue, they are usually present in the fibrous parenchymal component. Therefore, submitting the area of microcalcification, areas of fibrous parenchyma and the remaining tissue in cases of carcinoma and atypical hyperplasia, Owings and colleagues processed 80 % of the tissue submitted. This identified all 50 carcinomas and 17 out of 19 atypical hyperplasias. As processing of all specimens is both expensive and labour-intensive, Owings and colleagues recommend submitting the mammographic calcification and the associated fibrous parenchyma as the initial screening stage and processing further tissue if carcinoma or hyperplasia are present.

5.7 Ancillary Stains in Benign Breast Disease

Routine haematoxylin and eosin stains are usually adequate for diagnosis of most benign lesions. Immunocytochemistry markers such as smooth muscle actin, which highlights myoepithelial cells and basement membrane stains (laminin and collagen IV), may assist in confirming benignity. These ancillary stains are important in confirming benign lesions such as radial scars, sclerosing adenosis and epithelial hyperplasia. Immunocytochemistry staining with cytokeratin 5/6 (CK 5/6) has been found to be more useful in differentiating benign epithelial proliferation from DCIS. Lesions such as ductal hyperplasia of usual type, papillomas, tubular adenosis and sclerosing adenosis contain a subpopulation of cells that express CK 5/6, but this is not present in DCIS (Otterbach et al. 2000). Distortion of lobules in sclerosing adenosis can mimic invasive carcinoma, but positive staining with CK5/6 confirms benign glands with a myoepithelial layer (Fig. 5.7). E-cadherin immunocytochemistry staining can assist in differentiating lobular neoplasia from DCIS with a solid growth pattern (Acs et al. 2001). Lobular neoplasia shows complete lack of membrane expression of E-cadherin which is preserved in normal epithelium and ductal neoplasia (Fig. 5.8).

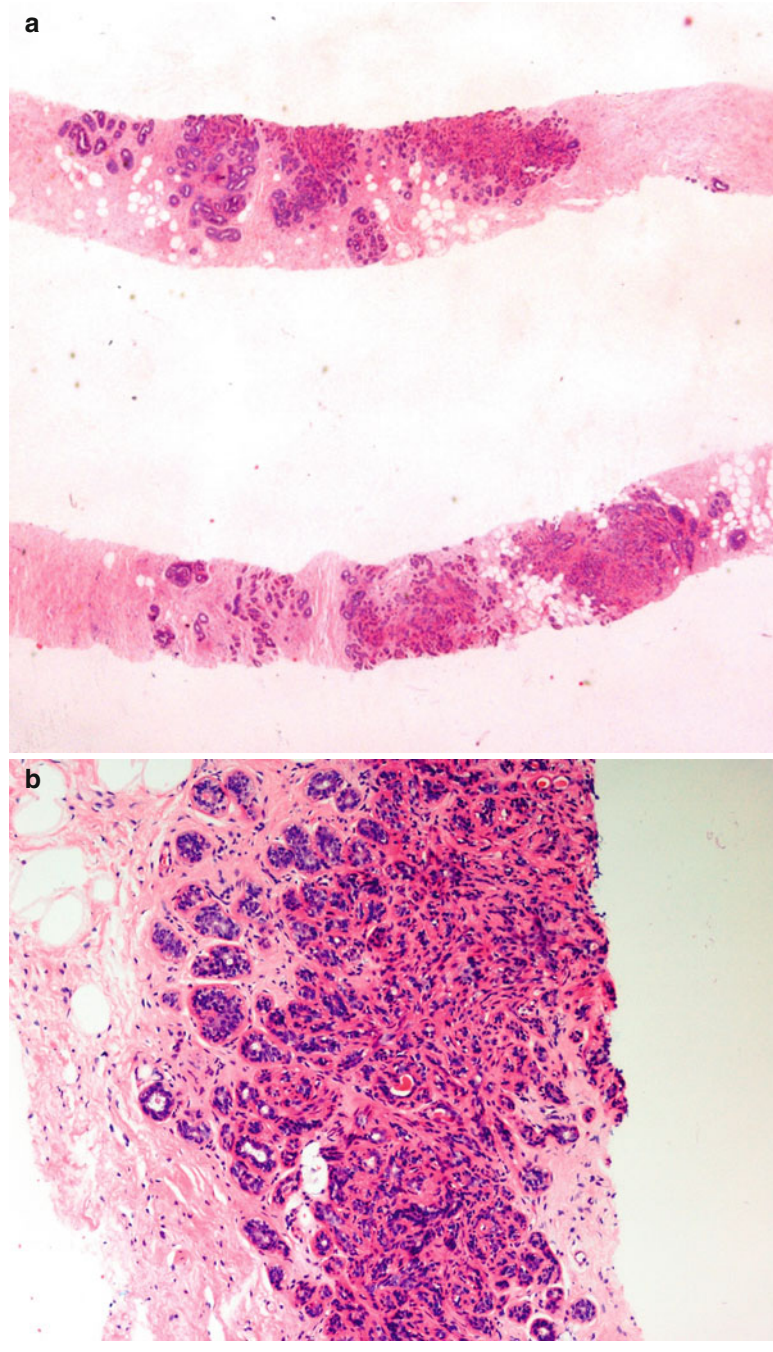


Fig. 5.7 (**a**) Sclerosing adenosis in a needle core biopsy. (**b**) Sclerosing adenosis consists of an expanded lobule due to myoepithelial cells epithelial cells and fibrous tissue. (**c**) High magnification shows tubular structures in the stroma. (**d**) The myoepithelial cells are positive with CK5/6 which excludes invasive carcinoma

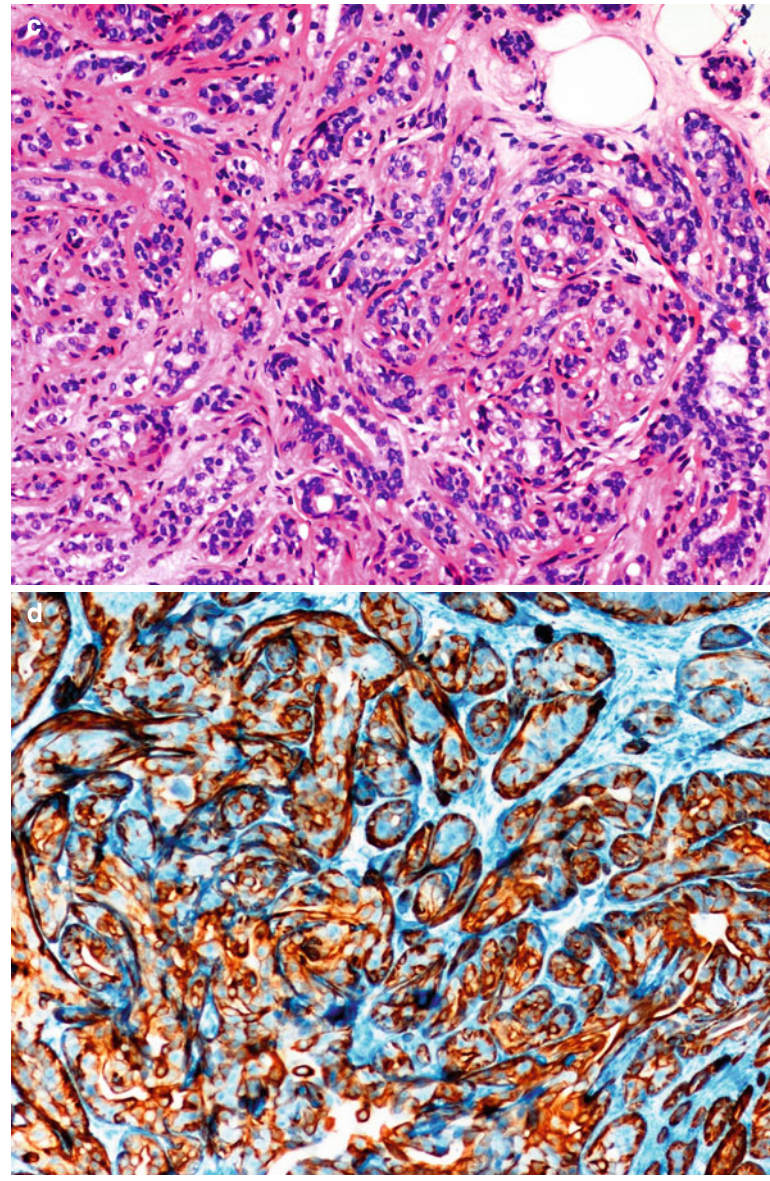


Fig. 5.7 (continued)

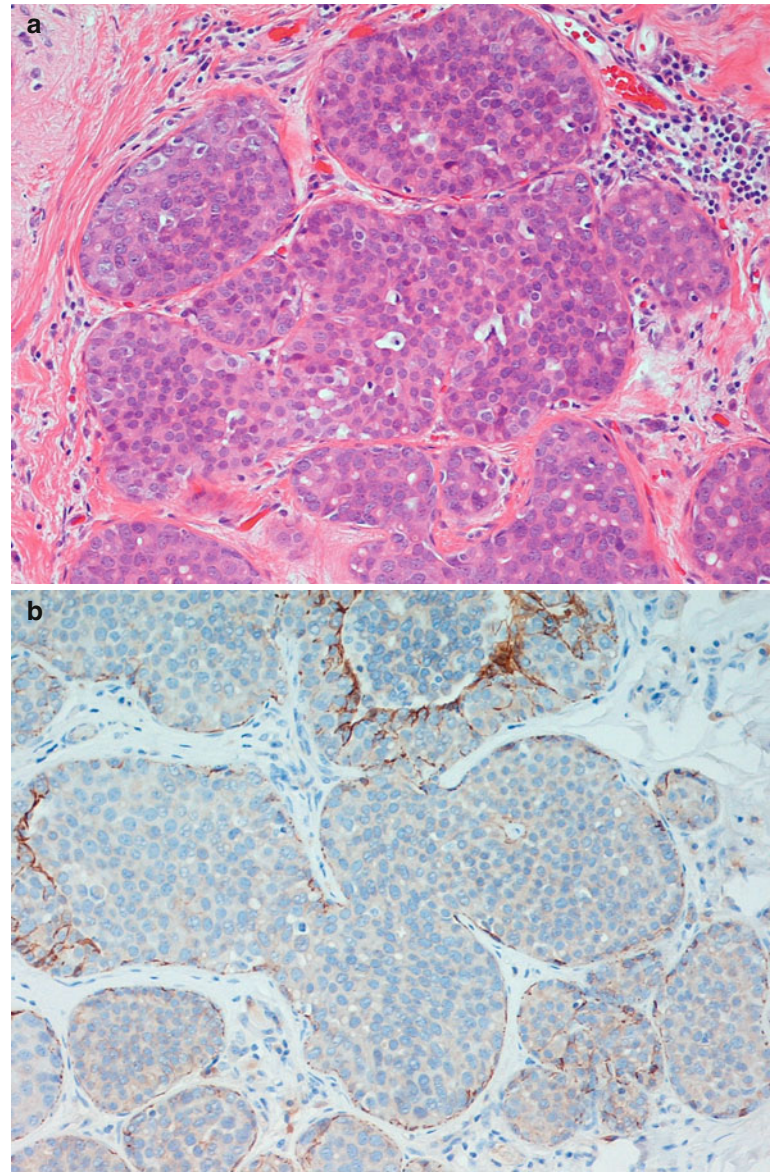


Fig. 5.8 (**a**) LCIS found incidentally in a specimen excised for another abnormality and solid-type DCIS could not be excluded. (**b**) The cells are negative for E-cadherin confirming LCIS

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Inflammatory Lesions

6

Learning Points

- Milk stasis is the main predisposing factor of lactational mastitis.
- Lactational breast abscesses are initially treated conservatively with aspiration and antibiotics and refered for surgery if conservative management fails.
- If not treated appropriately, lactational breast abscesses can recur and may be complicated by a fistulous tract.
- Duct ectasia is characterised by inflammation and dilation of the major ducts.
- Possible aetiological factors of duct ectasia include infections and cigarette smoking.
- Complications of duct ectasia include abscess formation, fistulous tract and nipple retraction.
- Associated fibrosis and calcification in duct ectasia can simulate breast cancer.
- Diabetic mastopathy is a rare condition mostly reported in women with Type 1 diabetes mellitus.
- Diabetic mastopathy is thought to be an autoimmune disease characterised by keloid-type fibrosis and lymphocytic lobulitis.
- There is no risk of progression to malignant lymphoma in patients with diabetic mastopathy.
- Diabetic mastopathy has a tendency to recur in the ipsilateral or contralateral breast.
- Idiopathic granulomatous mastitis (IGM) can mimic an abscess and should be considered if treatment for breast abscess fails.
- IGM simulates cancer clinically and radiologically.
- Preoperative pathological diagnosis of IGM is essential to avoid unnecessary mastectomy.

6.1 Mastitis and Breast Abscess

6.1.1 Mastitis

Mastitis is an inflammatory condition of the breast, which may or may not be accompanied by infection (WHO 2000). The condition is usually associated with lactation, the so-called lactational mastitis (Kvist et al. 2008; Scott et al. 2008) but can also arise in non-lactating women. Mastitis is defined as a red, tender, hot, swollen area of the breast, accompanied by one or more of the following:

(i) An elevated temperature (either estimated or measured as being over ≥ 38 °C)

(ii) One or more of the constitutional symptoms of fever, body aches, headaches and chills

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_6, © Springer-Verlag Berlin Heidelberg 2014

(iii) Diagnosis of mastitis from a medical practitioner (Kinlay et al. 1998)
(iv) Symptoms had to have been present for a minimum of 24 h (Fetherston 1998)

Although mastitis can occur any time during lactation, the condition is most common during the second and third weeks postpartum with 75–95 % of the cases occurring before the infant is 3 months of age (WHO 2000). Lactational mastitis affects the left and right breast equally (Wambach 2003).

6.1.2 Incidence of Lactational Mastitis

The incidence of mastitis varies in each country and the publications tend to be on selected cases. In population-based studies in Australia where breastfeeding initiation is over 80 % and approximately 50 % of women breastfeed for 6 months (Donath and Amir 2005), the incidence of mastitis is reported to be 15–20 %, 6 months postpartum (Kinlay et al. 1998; Brown and Lumley 1998). In a large cohort study from Australia, 1,193 women were assessed 6 months postpartum and 217 (17 %) reported mastitis and five developed an abscess (Amir et al. 2004). Approximately 10 % of women experience postpartum mastitis in the USA (Foxman et al. 2002). In a prospective cohort study in Glasgow UK, the authors reported lactational mastitis in 74 (18 %) out of 420 breastfeeding women (Scott et al. 2008).

6.1.3 Causes of Lactational Mastitis

Milk stasis and infection are the main causes of lactational mastitis. Milk stasis is a significant factor in initiating mastitis. Thomsen and colleagues (1984) reported that a raised white cell count and bacteria in the milk of infectious mastitis improved with removal of milk than with antibiotics. Milk stasis occurs when the breasts are engorged soon after delivery or when the infant does not breastfeed effectively due to ineffective suckling, restriction of the frequency or duration of feeds and blockage of milk ducts (WHO 2000). The baby should be well attached to the breast for effective removal of milk. Poor attachment to the breast causes fissured nipples and pain (Woolridge 1986). Sore nipples and pain leads to avoidance of breastfeeding with further milk stasis (Fetherston 1998). A short frenulum (tongue-tie) in the infant causes sore and fissured nipple reduces the efficiency of milk removal (Marmet et al. 1990).

Maternal fatigue, stress, anaemia, poor nutrition and maternal or infant illness have all been associated with mastitis (WHO 2000). The main cause of infectious mastitis is coagulase negative *S. aureus*, which are the bacteria frequently cultured in milk (WHO 2000). *S. albus*, *E. coli* and *Streptococci* have all been isolated from milk (WHO 2000). A nipple fissure is the most likely port of entry (Masaitis and Kaempf 1996). Many lactating women have potentially pathogenic bacteria on their skin or in their milk, but many women who do develop mastitis do not have pathogenic organisms in their milk (WHO 2000).

Mastitis should be treated urgently and the focus is on reversing milk stasis, maintaining milk supply, continuing breastfeeding and ensuring maternal comfort (WHO 2000). Mothers with acute pain, severe symptoms and/or fever need prompt antibiotic treatment, irrespective of whether the mastitis is presumed infectious or not (Betzold 2007).

6.1.4 Lactational Breast Abscess

If lactational mastitis is not treated promptly, this will lead to a breast abscess. Breast abscesses develop as a complication of mastitis in 5–11 % of the patients (Amir et al. 2004). The most common causative organism is *S. aureus* (Trop et al. 2011). This type of abscess affects up to 65 % of primiparous mothers and responds well to drainage and antibiotics (Ulitzsch et al. 2004; Dener and Inana 2003).

6.1.5 Non-lactational Breast Abscess

Breast abscesses that occur outside the breastfeeding period are classified according to location,

either central (peri-areolar) or peripheral (Trop et al. 2011). Non-lactational abscesses affect more black women than white (Benson 1989). Other risk factors include obesity, cigarette smoking and diabetes mellitus (Benson 1989; Rizzo et al. 2010).

Central (peri-areolar) non-lactational abscesses are the most common form of abscesses that develop outside the breastfeeding period (Trop et al. 2011). They affect mostly young women who smoke (Bharat et al. 2009). The abscesses arise as a complication of periductal mastitis. Initially there is squamous metaplasia of the cuboidal epithelium of the lactiferous ducts which leads to formation of keratin plugs followed by acute inflammation and cellular debris which distend and obstruct the ducts, leading to dilatation. Stagnation predisposes to secondary infection leading to development of an abscess (Fig. 6.1) which may be complicated by a fistula as a way of releasing the pressure from the pus distending the ducts. It is postulated that smoking may have a direct toxic effect on the retro-areolar epithelial ducts (Versluijs-Ossewaarde et al. 2005). Central non-lactational breast abscesses have a high recurrence rate in 25–40 % of women with formation of cutaneous fistulas in a third of the women (Bharat et al. 2009; Lannin 2004). Microbiological analysis reveals mixed

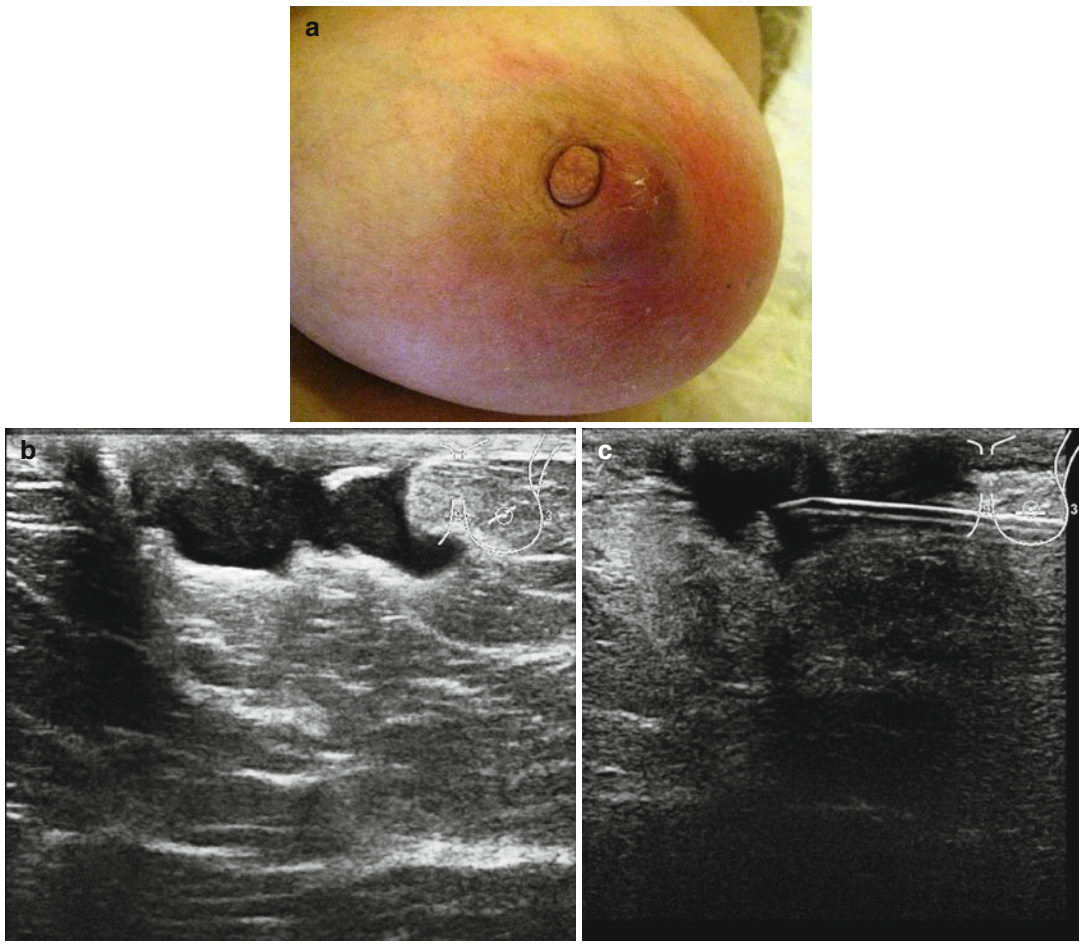


Fig. 6.1 (**a**) Central non-lactational abscess in a 52-year-old woman who presented with an abscess of the left breast. The skin is red and the abscess is 'pointing' as if it would burst at any time. (**b**) The ultrasound showed an irregular abscess. (**c**) The abscess was aspirated and reduced in size. The aspirated pus grew mixed flora and the patient was treated with Metronidazole. The abscess did not resolve and had to be excised

infection with staphylococcus, streptococcus and anaerobes (Benson 1989).

Peripheral non-lactational breast abscesses are less common than the central abscesses. They occur in older women with underlying chronic medical conditions such as diabetes mellitus and rheumatoid arthritis (Trop et al. 2011). Other risk factors include steroid therapy, recent surgical intervention or post-radiation therapy. The most common pathogens are *S. aureus* and *Streptococcus* (Trop et al. 2011). Peripheral non-lactational abscesses respond well to drainage and antibiotics and recurrences are rare (Trop et al. 2011).

6.1.6 Radiological Features of Mastitis and Abscess

Since the conventional incision and drainage of abscesses is no longer recommended, patients with mastitis and breast abscesses are mostly managed by radiologists. Ultrasound is the first line of investigation because it is relatively painless, allows assessment of the breast during treatment and provides guidance for percutaneous drainage (Trop et al. 2011). On ultrasound imaging, mastitis appears as an ill-defined area of altered echo texture with increased echogenicity in the infiltrated and inflamed fat lobules, hypoechoic areas in the glandular parenchyma and associated mild skin thickening with occasional distended lymphatic vessels (Trop et al. 2011; Ulitzsch et al. 2004). The ipsilateral axillary lymph nodes may exhibit inflammatory features. The diagnosis of an abscess requires identification of hypoechoic collection of variable shape and size with multiloculation in the majority of the cases. There is often a thick echogenic periphery with increased vascularity. There is no vascularity in the collection but acoustic enhancement is present due to fluid content (Trop et al. 2011; Karstrup et al. 1993). The patient in Fig. 6.1a had ultrasound examination which confirmed an irregular abscess (Fig. 6.1b). The abscess was aspirated under ultrasound guidance. She did not undergo mammography.

Mammography is recommended in women with breast abscesses outside the peripartum period, with some authorities advocating mammography in all women older than 30 years (Berna-Serna et al. 2004; Eryilmaz et al. 2005). However, mammography should be delayed until after the acute episode for the patient's comfort. Mammography can show skin thickening, asymmetric density, a mass (Fig. 6.2a) or distortion which reflect the underlying inflammation and breast abscess. The ultrasound showed irregular shadowing suspicious of cancer (Fig. 6.2b). The main differential diagnosis of mastitis or abscess in an older non-lactating woman is an inflammatory carcinoma (Trop et al. 2011).

6.1.7 Surgical Management of Breast Abscesses

Abscesses that fail to resolve after several attempts at percutaneous drainage are referred for surgery. Referral for surgery is indicated after several attempts (at least three to five) at ultrasound-guided drainage, although management decisions depend on the clinical context (Trop et al. 2011; Lannin 2004). Multiloculated and large abscesses (larger than 3 cm) are difficult to treat and are associated with an approximately 50 % rate of failure to cure with aspiration (Elagili et al. 2007; Schwarz and Shrestha 2001). Schwarz and Shreestha (2001) reported late presentation as a major factor associated with failure of percutaneous drainage in 33 women with breast abscesses, with a 100 % success rate reported in women treated within six of onset of symptoms.

Surgery is also indicated for recurrent central non-lactational abscesses. Lannin (2004) reported that medical nonsurgical management of recurring subareolar non-lactational abscesses was

successful in 50 % in 67 of patients with the remainder requiring duct excision to control symptoms. In a separate study, Versluijs-Ossewaarde et al. (2005) reported that surgical excision of the inflamed ducts is not always curative in non-lactational abscesses with recurrence rate of 28 % (11 out of 39 patients).

6.1.8 Pathology of Breast Abscess

A breast abscess is like any other abscess occurring anywhere in the body. If aspirated the cytological material contains numerous polymorphs in the background of necrotic debris. Any epithelial cells sampled during the procedure will appear atypical due to inflammation and it may not be possible to exclude malignancy. The aspirate from the 62-year-old woman contained pus and atypical cells suspicious of malignancy (Fig. 6.2c), which lead to an excision biopsy.

An excised abscess will consist of a central irregular cavity containing numerous polymorphs admixed with necrotic debris (Fig. 6.2d). The cavity is surrounded by necrotic tissue and walled off by fibrous tissue to indicate chronicity as the patient would have had prior conservative management (Fig. 6.2). If the inflammation does not resolve despite surgery and antibiotics, this may complicate into sinus tract (Fig. 6.3). This is a sinus excised from a different patient.

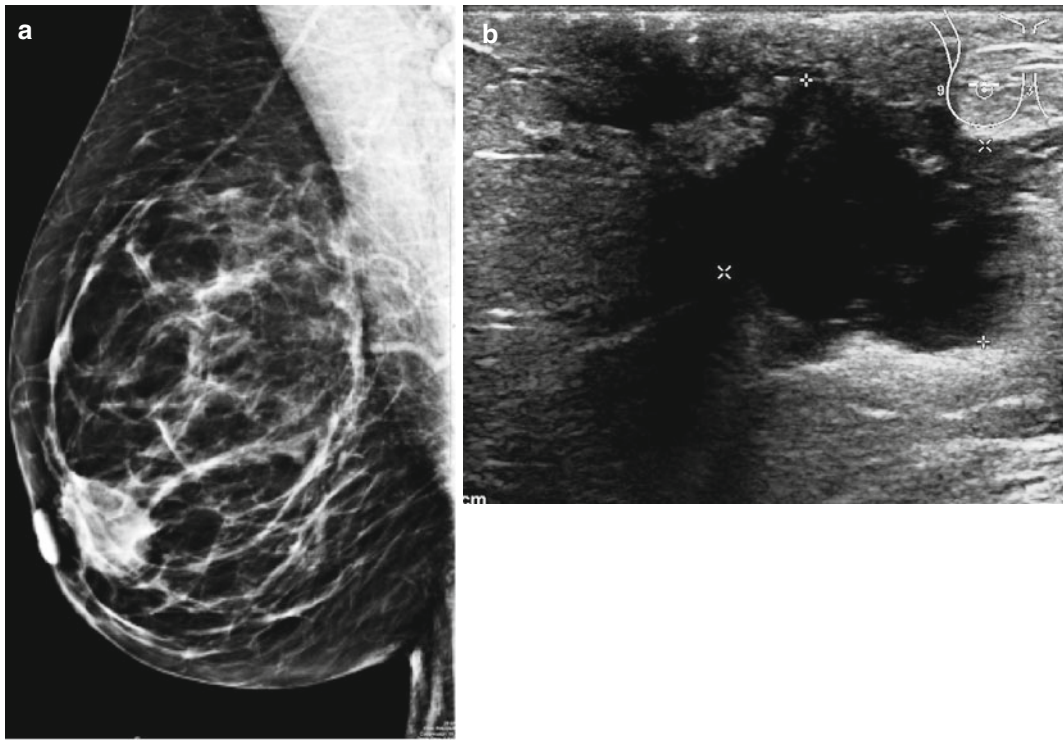


Fig. 6.2 (**a**) Mammography in a 61-year-old woman shows subareolar mass. She presented with retracted nipple suspicious of cancer (R4). (**b**) The ultrasound showed an irregular shadow suspicious of cancer. (**c**) The aspirate contained pus cells and atypical cell suspicious of malignancy, H & E stain (C4). (**d**) The excision specimen showed an abscess cavity containing pus. The abscess is surrounded by a fibrous wall indicating chronicity. There is periductal mastitis in the surrounding tissue

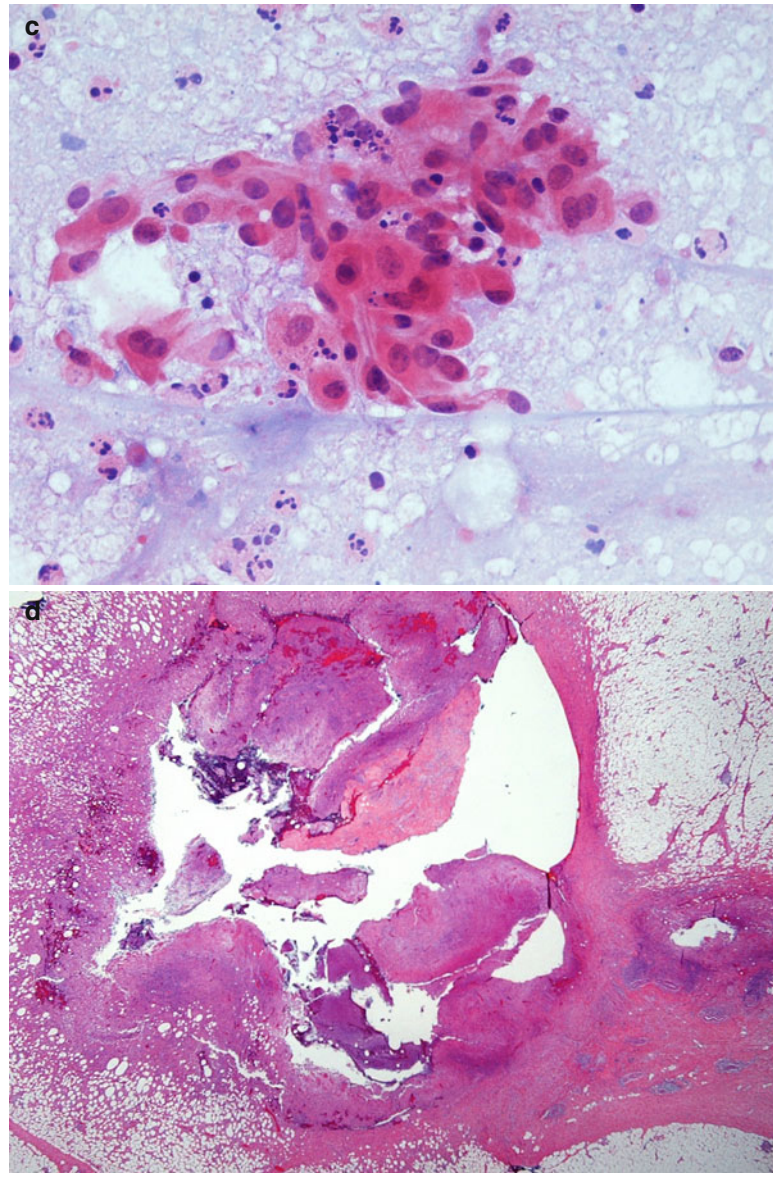


Fig. 6.2 (continued)

6.2 Duct Ectasia

6.2.1 Possible Aetiological Factors and Pathogenesis of Duct Ectasia

Haagensen (1951) applied the term mammary duct ectasia to a condition, which is characterised by dilated ducts and chronic inflammation. Duct ectasia had been known previously by other names such as 'varicocele' tumour (Bloodgood 1923), plasma cell mastitis (Adair 1933), comedo mastitis (Tice et al. 1948) and mastitis obliterans (Payne et al. 1943). These terms intended to portray the morphology as well as the possible aetiology of the disease process. Based on a clinico-pathological study of 20 women with duct ectasia, which clinically simulated carcinoma, Haagensen (1951) concluded that duct ectasia was an involutional condition that commenced with dilation of the nipple major ducts, followed by inflammation and fibrosis.

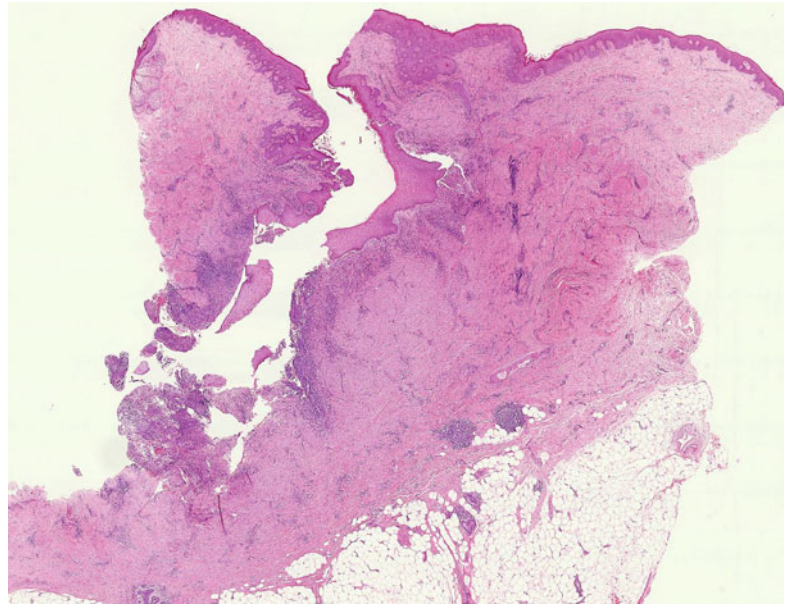


Fig. 6.3 A fistulous tract in a different patient, complicating a breast abscess

Duct ectasia usually coexists with periductal mastitis and the terms are sometimes used interchangeably. There is no agreement among investigators regarding the pathogenesis of this condition. Multiple birth and lactation have been implicated as aetiological factors of the condition (Bonser et al. 1961). However, the role of pregnancy and lactation is not universally accepted as a possible aetiological factor in duct ectasia, as the condition also occurs in nulliparous women. Some authorities believe that stasis of luminal contents leads to duct ectasia and inflammation is a secondary process due to leakage of luminal contents (Tice et al. 1948; Haagensen 1951). In an earlier study, Foote and Stewart (1945) investigated the presence of periductal mastitis in cancerous and non-cancerous breasts. They observed that the most common histological feature of periductal mastitis was a predominant lymphocytic infiltrate around the mammary ducts. Although they did not apply the term duct ectasia, they noted that the appearances of the inflammatory cells were nearly in every case preceded by other changes, such as stasis of amorphous acellular and cellular duct contents, dilation of the duct wall and varying degrees of atrophy of periductal myoid tissue. It is not clear from this paper how the authors came to the conclusion that the duct dilation preceded the inflammatory process.

When Dixon et al. (1983) reviewed 88 biopsies from patients with duct ectasia, they noted that biopsies from younger women showed severe periductal inflammation around non-dilated ducts and the patients had presented with mastalgia or a symptomatic lump. In contrast, biopsies from older patients showed duct dilation as the main pathological feature and these patients had presented with nipple retraction. Based on these observations, Dixon and colleagues postulated that the sequence of events is more likely to be periductal inflammation followed by resolution of the inflammatory process, leading to periductal fibrosis and duct dilation. These pathological features can be correlated with the clinical presentation: thus breast pain and lump in the younger women, which pathologically is consistent with periductal inflammation, and nipple retraction in the older women due to resolution of inflammation is associated with fibrosis and dilation of ducts. The authors felt that the term duct ectasia described the outcome of the inflammatory process but not the primary lesion and suggested that the appropriate term should be periductal mastitis.

Previously Bonser et al. (1961) reached a similar conclusion to Dixon et al. (1983) as the inflammatory process was more prevalent in younger than older women. However, Dixon

could not confirm the association of duct ectasia with parity and lactation. Anaerobic organisms have been isolated in some patients with duct ectasia and some patients benefit from antibiotic therapy (Dixon 1989). Most studies reported sterile secretions, including lack of mycobacterial infection. The process of periductal mastitis/duct ectasia progresses to duct fibrosis with obliteration of ductal lumina and this was termed mastitis obliterans (Payne et al. 1943). Granulomatous inflammation with giant cells is not uncommon in duct ectasia. Trop et al. (2011) advocates a squamous metaplasia of the cuboidal epithelium of the lactiferous ducts as the initiating factor which leads to formation of keratin plugs followed by acute inflammation, obstruction of ducts leading to dilatation. Stagnation predisposes to secondary inflammation.

Smoking has also been implicated as an aetiological factor in duct ectasia and this appears to be due to the direct toxic effects on the breast epithelium (Furlong et al. 1994). Younger women who smoked more than ten cigarettes a day had more periductal inflammation than those who did not smoke. Duct ectasia was more prevalent in older than younger women. In a later study, Dixon et al. (1996) also confirmed that periductal mastitis was more prevalent in young women who smoked, whereas duct ectasia tended to affect older women who did not smoke. The earlier suggestion that periductal mastitis preceded duct ectasia (Dixon et al. 1983) was contradicted in the 1996 publication by the same authors who suggested periductal mastitis and duct ectasia should be regarded as two different conditions affecting different age groups due to different aetiological factors. Despite the conflicting reports on the possible pathogenesis of periductal mastitis/duct ectasia, and whether they are two different diseases or the same disease process, in routine surgical pathology, periductal mastitis and duct ectasia are invariably present in the same breast biopsy or histological slide suggesting a continuum of the same disease process, without resorting to the dilemma of which came first.

6.2.2 Clinical Features of Duct Ectasia

Duct ectasia can be unilateral or bilateral. Although the condition is prevalent in women, it can also occur in men (Al-Masad 2001). In the early stages the women present with nipple discharge. The discharge can be off-white, creamy, brown, grey or green and can be thick as toothpaste (Mansel et al. 2009). Bloodstained nipple is less common but duct ectasia causes bloodstained nipple discharge more so than duct papilloma. Patients who present with nipple discharge tend to be perimenopausal or postmenopausal. Mansel et al. (2009) describes four types of masses associated with duct ectasia:

(a) The evanescent mass which is a small, slightly tender subareolar lesion which appears and resolves spontaneously, usually without treatment.
(b) The recurrent mass which represents the evanescent mass occurring in the subareolar region at intervals of a few months to 10 years. The condition has a tendency to become more severe with each recurrence and can be bilateral.
(c) The persistent mass which is present for some weeks is usually firm and well-defined. Fine needle aspiration cytology shows foamy macrophages and inflammatory cells. As cancer cannot be excluded, an excisional biopsy is usually warranted.
(d) The chronic mass which is hard, oedematous and fixed to the skin with associated nipple retraction and has all the hallmarks of cancer, especially if associated with axillary lymphadenopathy. A formal excision biopsy with antibiotic cover is advocated.

Other clinical presentations or complications of duct ectasia are breast abscess and mammary duct fistula. The fistula can be due to an abscess discharging spontaneously or a complication of surgical drainage of the abscess. This is associated with scarring of the areola and nipple inversion. Mansel et al. (2009) emphasises the need for caution when advising women about duct excision.

The clinical features of duct ectasia invariably mimic carcinoma. Screening mammography now frequently detects carcinoma in the background of calcified duct ectasia. This is a coincidental finding in older women rather than a causal relationship.

In Haagensen's (1951) series of patients with duct ectasia, the average age was 55.4 years. This would support the theory that duct ectasia is the end product of periductal mastitis, although Haagensen believed that duct ectasia preceded mastitis. Foote and Stewart (1945) reported ductal stasis and distension to be more prevalent in women over 50 years, but there was no difference in the presence of these lesions in cancerous and non-cancerous breasts.

There are no reports to date indicating that periductal mastitis or duct ectasia is associated with an increased risk of breast cancer. Bonser and colleagues (1961) reported 82 cases of duct ectasia in association with 220 specimens containing breast cancer. In 14 patients, the cancer was arising in ectatic ducts; in 30 patients, cancer was present in the same segment as duct ectasia but outside the ducts, and in 38 patients, cancer was in the segment without duct ectasia. This association was considered coincidental rather than causal. The investigators asserted that if duct ectasia were premalignant, there would be a high prevalence of cancers arising in dilated ducts in women over 50 years of age. The low prevalence of cancer arising in duct ectasia is most likely due to the fact that in periductal mastitis/duct ectasia there is destruction rather than hyperplasia of the ductal epithelium. However, some ducts exhibit squamous metaplasia and this raises the possibility of whether this metaplastic epithelium may predispose to primary squamous cell carcinoma of the breast.

Despite the characteristic pattern of calcification in duct ectasia, there are occasions in which duct ectasia mammographically mimics carcinoma and this requires diagnostic biopsy to exclude malignancy. Sweeney and Wylie (1995) reported 12 cases of duct ectasia that were mammographically suspicious of carcinoma. Eight cases showed clusters of microcalcification, three spiculated masses and three lobulated masses. These cases required fine needle aspiration cytology and biopsies to exclude malignancy. Duct ectasia simulating carcinoma previously led to mastectomies in a period when preoperative biopsies and multidisciplinary team meetings were not routine (Adair 1933; Haagensen 1951).

6.2.3 Radiological Features of Duct Ectasia

In postmenopausal women, duct ectasia is usually asymptomatic and detected mammographically due to the presence of calcification with variable morphology. Periductal dystrophic calcification results in calcified rings (Fig. 6.4), oval shapes or elongated, very dense calcification with central lucency. This represents the dilated ducts and intraductal calcification of inspissated luminal contents. Needle-like forms with branching patterns usually maintain polarity towards the nipple (Sweeney and Wylie 1995). Ring or tubular calcifications on mammography, depends on whether the ducts are assessed, end on or from the side. Calcification of duct ectasia is of high density and wider calibre than malignant-type casting calcifications of intraductal carcinoma (Tabár and Dean 1985). Calcified duct ectasia can be bilateral, which assists in confirming benignity (Fig. 6.4). Calcification in duct ectasia can be course and malignancy cannot be readily excluded especially if associated with soft tissue density (Fig. 6.5).

Non-calcifying duct ectasia in patients with nipple discharge is better assessed by galactography. Ultrasonography would detect architectural changes within the parenchyma, dilated ducts with hypoechoic contents or acoustic shadowing with increased fibrosis (Fig. 6.6).

6.2.4 Pathological Features of Duct Ectasia

In a patient with nipple discharge examination of the discharge on a smeared slide reveals foamy macrophages in an amorphous background

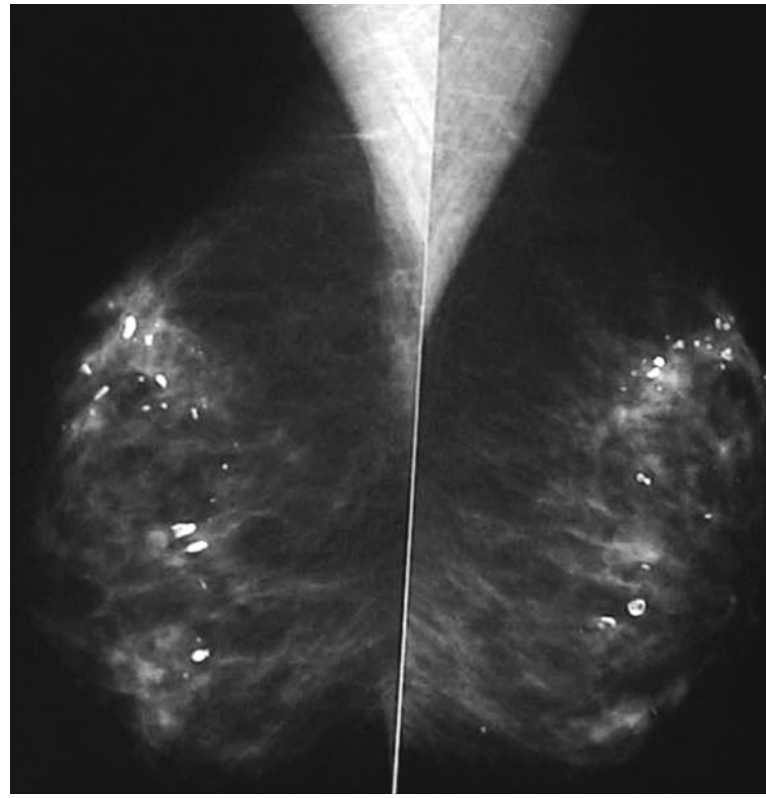


Fig. 6.4 Bilateral mammographic calcification consisting of ring and needle-shaped forms in 68-year-old woman which progressively increased over the years, typical of duct ectasia

(Fig. 6.7). Sometimes epithelial cells are present which will raise the possibility of a papillary neoplasm.

The histological features vary according to the stage of the condition. In the early stages the ducts are dilated and contain eosinophilic proteinaceous material with minimal periductal inflammation (Fig. 6.8). This was an incidental duct ectasia in a mastectomy specimen for carcinoma. The ducts contained toothpaste-like simulating comedo DCIS. There is marked tortuous dilation and minimal inflammation which tends to support that obstruction precedes the inflammation. Chronic periductal mastitis is characterised by a prominent lymphocytic infiltrate around the duct with attenuated epithelium and fibrosis (Fig. 6.6). In later stages the ducts are obliterated by the inflammatory process with associated fibrosis, cholesterol cleft due to cellular lipid accumulation (mastitis obliterans). Dystrophic calcification is invariably present which radiologically can simulate malignancy (Fig. 6.5).

6.3 Diabetic Mastopathy

6.3.1 Aetiological Factors of Diabetic Mastopathy

Diabetic mastopathy, also termed sclerosing lymphocytic lobulitis or lymphocytic mastitis, is a rare condition which was first described by Soler and Khardori (1984) as fibrous disease of the breast. The authors reported 12 patients with long-standing Type 1 diabetes mellitus with multiple complications and breast masses. Byrd and colleague (1987) applied the term diabetic mastopathy when they reported the condition in eight women with insulin-dependent diabetes mellitus who presented with breast lumps. Soler and Khardori (1984) suggested an autoimmune reaction as a possible aetiological factor. An autoimmune process was also suggested by other authors (Schwartz and Strauchen 1990; Lammie et al. 1991) because lymphoepithelial lesions seen in diabetic mastopathy are also present in other autoimmune diseases

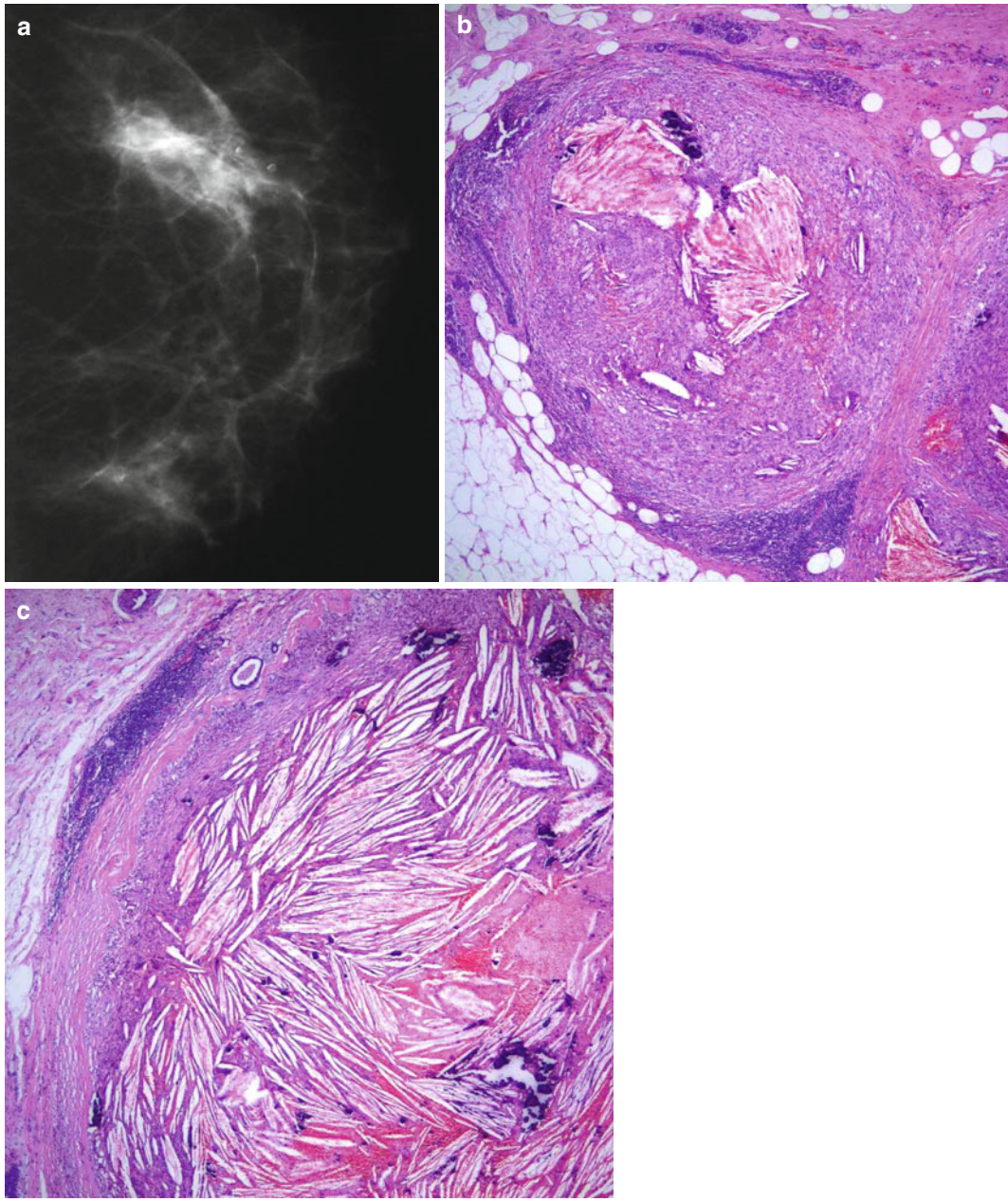


Fig. 6.5 (**a**) Calcifying duct ectasia with background soft tissue density suspicious of malignancy (R4). (**b**) The histology shows periductal mastitis with amorphous microcalcification. The duct wall is fibrotic and the lumen is occluded by cholesterol crystals and foamy macrophages, previously termed mastitis obliterans. (**c**) The cholesterol crystals are due to lipids leaked from the cells during the inflammation

such as Hashimoto's thyroiditis and Sjogren's syndrome. In a large study of patients enrolled in the Rochester Diabetic Nephropathy study, Kudva and colleagues (2005) investigated the presence of diabetic mastopathy in 24 patients with Type 1 diabetes mellitus (Group 1), 55 patients with Type 2 diabetes mellitus (Group 2), 55 patients with autoimmune thyroiditis (Group 3) and 55 patients with proven benign breast disease (Group 4). Histological features of diabetic mastopathy were

reported in 17 (69 %) out of 24 patients with Type 1 diabetes mellitus. None of the patients in Groups 2–4 had histological features of diabetic mastopathy. The condition did not occur even in patients with Type 2 diabetes treated with insulin. The authors concluded that diabetic mastopathy was strongly associated with Type 1 diabetes mellitus ($p<0.001$).

As lymphoepithelial lesions are also present in extranodal marginal zone B cell lymphoma, Valdez and colleagues (2003) studied the clonality of the lymphocytic infiltrate in 11 patients with diabetic mastopathy by assessing immunoglobulin heavy chain gene rearrangement. Seven patients had long-standing Type 1 diabetes mellitus, one patient had history of Sjogren's syndrome, and three patients had no history of diabetes mellitus or autoimmune disease. On immunostaining all the 11 cases showed a predominance of B cells in the lymphocytic infiltrate, and there was no evidence of immunoglobulin heavy chain gene rearrangement on polymerase

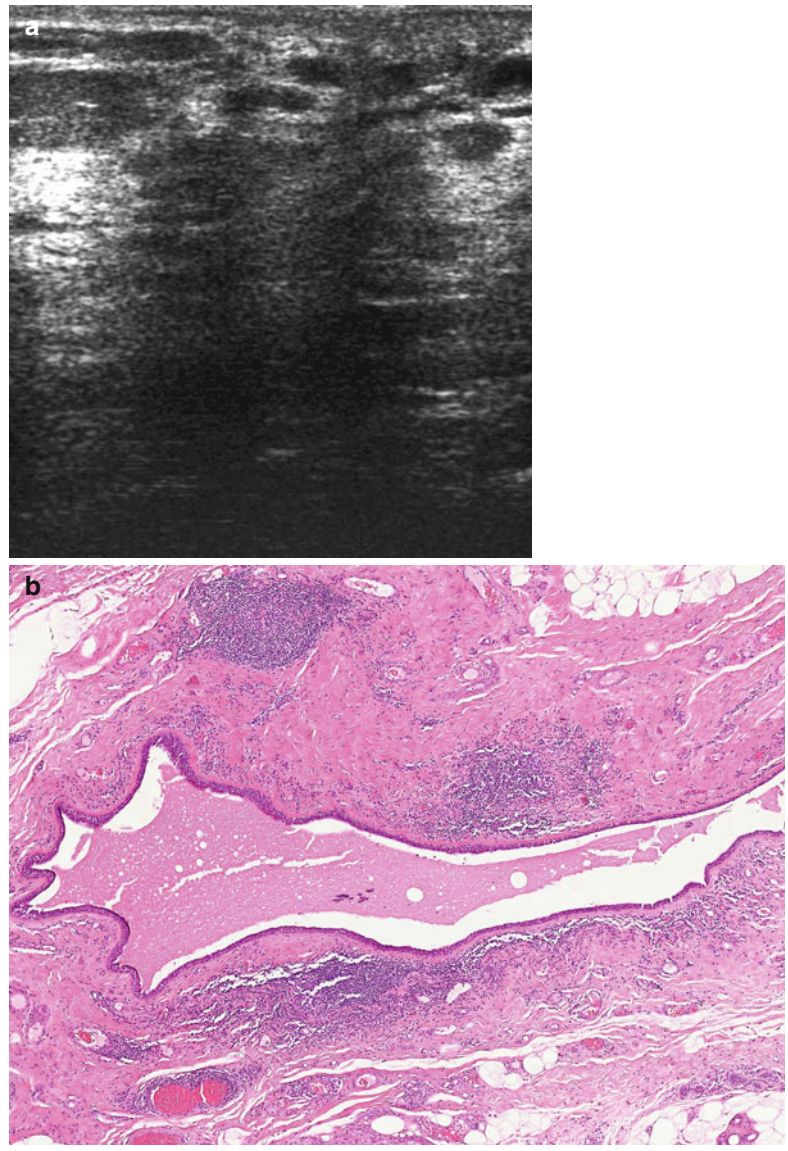


Fig. 6.6 (**a**) Ultrasound scan of duct ectasia demonstrating dilated ducts in a 51-year-old woman. (**b**) The histology of the subareolar resection of the duct ectasia with periductal fibrosis and periductal inflammation. (**c**) Transverse section of the duct ectasia showing prominent luminal fibrosis

Fig. 6.6 (continued)

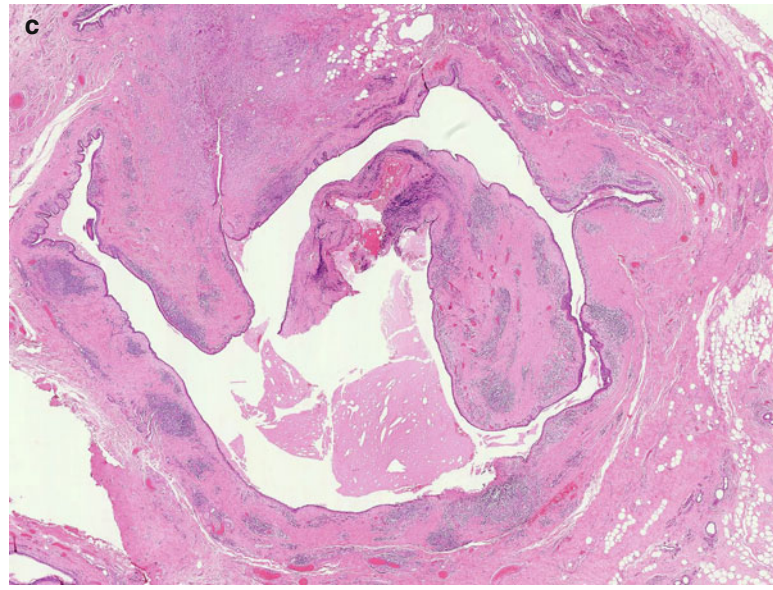
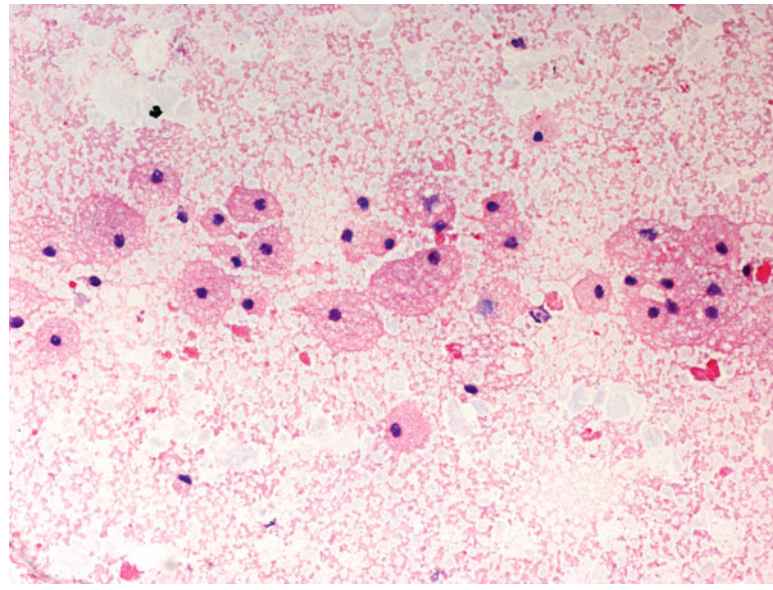


Fig. 6.7 The nipple discharge from duct ectasia contains of foamy macrophages in an amorphous background in a cytological smear. There were no epithelial cells, H & E stain



chain reaction (PCR)-based studies. Although previous studies had reported a relationship between diabetic mastopathy and non-Hodgkin's lymphoma (Aozasa et al. 1992; Lee et al. 1994), Valdez and colleagues concluded that there was no association between diabetic mastopathy and B cell lymphoma as there was no evidence of clonality in the lymphocytic infiltrate in the patients they studied.

6.3.2 Clinical Features of Diabetic Mastopathy

As diabetic mastopathy is associated with Type 1 diabetes mellitus, the mean age of patients at the time of diagnosis ranges from 32.2 to 62.0 years (Camuto et al. 2000), with duration of diabetes mellitus ranging from 4 to 43 years. The condition affects mostly women but has also been

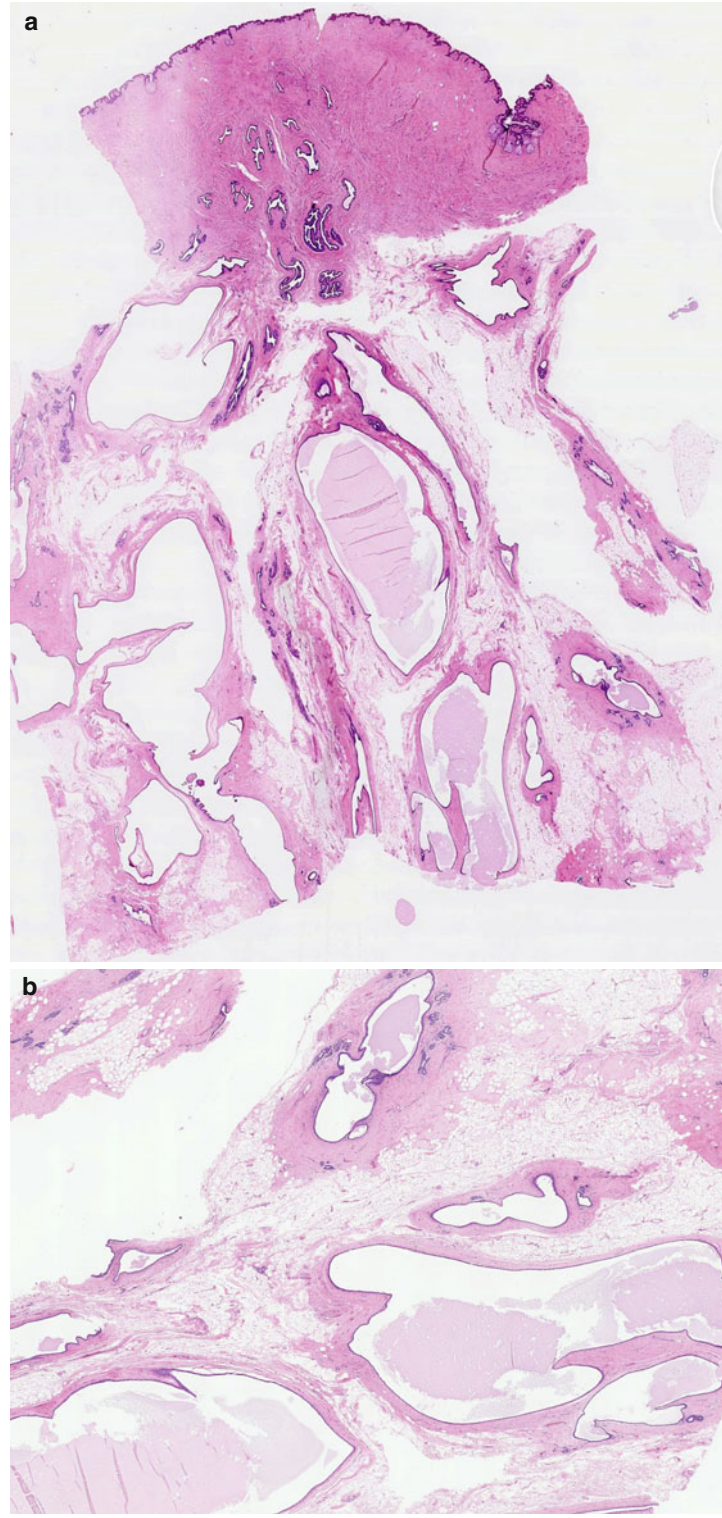


Fig. 6.8 (**a**) This incidental duct ectasia in a mastectomy specimen for carcinoma. There is marked tortuous dilation of the ducts and minimal inflammation which tends to support that obstruction precedes the inflammation. Macroscopically thick luminal secretions were apparent simulating comedo DCIS. (**b**) At higher power the ducts contain luminal secretions, but no inflammation

reported in men (Cavazza et al. 1997). When Byrd et al. (1987) applied the term diabetic mastopathy in eight women with Type 1 diabetes mellitus, five of them had severe retinopathy. In this cohort diabetes mellitus had been diagnosed between the age of 4 and 19. The women presented with firm hard palpable masses which were confirmed on mammography. Breast cancer was the main differential diagnosis.

In a separate study Ely and colleagues (2000) reviewed 19 patients with histological diagnosis of diabetic mastopathy, there were 17 women and two men with an age range of 27–75 years (mean 39 ± 12). Fifteen patients had a single mammary lesion and four patients had bilateral disease. In 17 patients the breast lesions were palpable discrete masses and diffuse nodularity was noted in one patient. In seven patients the lesions were localised to the subareolar region. One patient had the diagnosis made on reduction mammoplasty. Fourteen patients had Type 1 diabetes mellitus; one had Type 2 diabetes mellitus which required insulin; and two had non-insulin dependent diabetes mellitus. Three patients had no history of diabetes mellitus.

Kudva et al. (2002) noted that there is no association of diabetic mastopathy with the duration of the diabetes mellitus or glycaemic control, although the patients tend to have higher prevalence of retinopathy and nephropathy. Furthermore, insulin treatment is not a risk factor as the condition is reported infrequently in patients with Type 2 diabetes mellitus treated with insulin. There is no increased risk of breast cancer in patients with diabetic mastopathy (Kudva et al. 2002). The condition can be bilateral and recurrent disease, and recognition of this will negate the need for repeated breast biopsies (Ely et al. 2000).

6.3.3 Radiological Features of Diabetic Mastopathy

The most common mammographic findings in diabetic mastopathy are ill-defined masses or asymmetric densities, invariably masked by dense glandular tissue which makes evaluation difficult (Sabate et al. 2005). The mammogram in Fig. 6.9 is from a patient who initially presented with non-insulin dependent diabetes mellitus which went out of control and required in insulin in the later stages of the disease. She presented with a palpable mass, clinically suspicious of malignancy. The mammogram shows a soft tissue density which was graded as R5. The mammographic features were confirmed on ultrasound. Ultrasound images are characterised by irregular hypoechoic masses with marked posterior acoustic shadowing (Sabate et al. 2005). Well-circumscribed masses without acoustic shadowing are less common (Dipiro et al. 1999).

Very few cases report MRI features of diabetic mastopathy. Sakuhara et al. (2002) described poor enhancement in the early phase of contrast injection on MR imaging in a 60-year-old woman with Type 2 diabetes mellitus. The degree of enhancement increased gradually and the mass showed heterogenous spotty enhancement in the delayed phase. The radiological differential diagnosis of diabetic mastopathy include invasive lobular carcinoma, simple fibrosis of the breast, fibroadenomas with marked fibrosis, mammary fibromatosis, leiomyomas and desmoid tumours (Bayer et al. 1998).

6.3.4 Pathological Features of Diabetic Mastopathy

The gross examination of specimens excised from patients with diabetic mastopathy show firm homogeneous white tissue ranging in size from 3.0 to 6 cm in maximum dimensions (Camuto et al. 2000). Microscopic examination is characterised by dense keloid-like fibrosis associated with perivascular, periductal and perilobular lymphocytic infiltrate termed lymphocytic lobulitis (Fig. 6.9). Tomaszewski et al. (1992) described the presence of ‘epithelioid fibroblasts’ which the authors considered to be unique to the diabetic mastopathy. Ely and colleagues (2000) identified epithelioid fibroblasts in 15 out of 19 patients.

Sclerosing lymphocytic lobulitis can occur in women with no history of Type 1 diabetes mellitus as in this 45-year-old woman presented with a subareolar mass in the right breast (Fig. 6.10) clinically and radiologically graded as suspicious of

malignancy (R4). The needle core biopsy showed benign breast tissue and was therefore was not representative (B1). The patient underwent an excision biopsy and the histology showed hyalinised fibrous tissue containing benign ducts and lobular units with associated lymphocytic infiltrate. The lymphocytic infiltrate was quite prominent around the lobules and with associated fibrosis qualified for the diagnosis of sclerosing lymphocytic lobulitis.

6.4 Idiopathic Granulomatous Mastitis

6.4.1 Prevalence of Granulomatous Mastitis

Idiopathic granulomatous lobular mastitis or idiopathic granulomatous mastitis (IGM) is an inflammatory condition of unknown aetiology which affects the breast in the absence of mycobacterial infection, fungal infection, parasite infection or other common known granulomatous inflammations such as sarcoidosis or silicone granuloma. This is a rare inflammatory condition of the breast which was first described by Kessler and Wollock in 1972. The authors reported breast masses in five women which were characterised by florid non-caseating granulomatous inflammation not associated with trauma, specific infection or exogenous materials. The significance of IGM is its ability to mimic breast cancer both clinically and radiologically (Hovanessian Larsen et al. 2009).

IGM affects women of childbearing age with a median age of 36.5 years (Fletcher et al. 1982; Azlina et al. 2003; Hovanessian Larsen et al. 2009) but can also occur in older women (Verfaille et al. 2006). Isolated case reports and relatively large-case studies tend to suggest that IGM is more prevalent in non-Caucasian women. Ebrahimi-Fara et al. (2010) reported

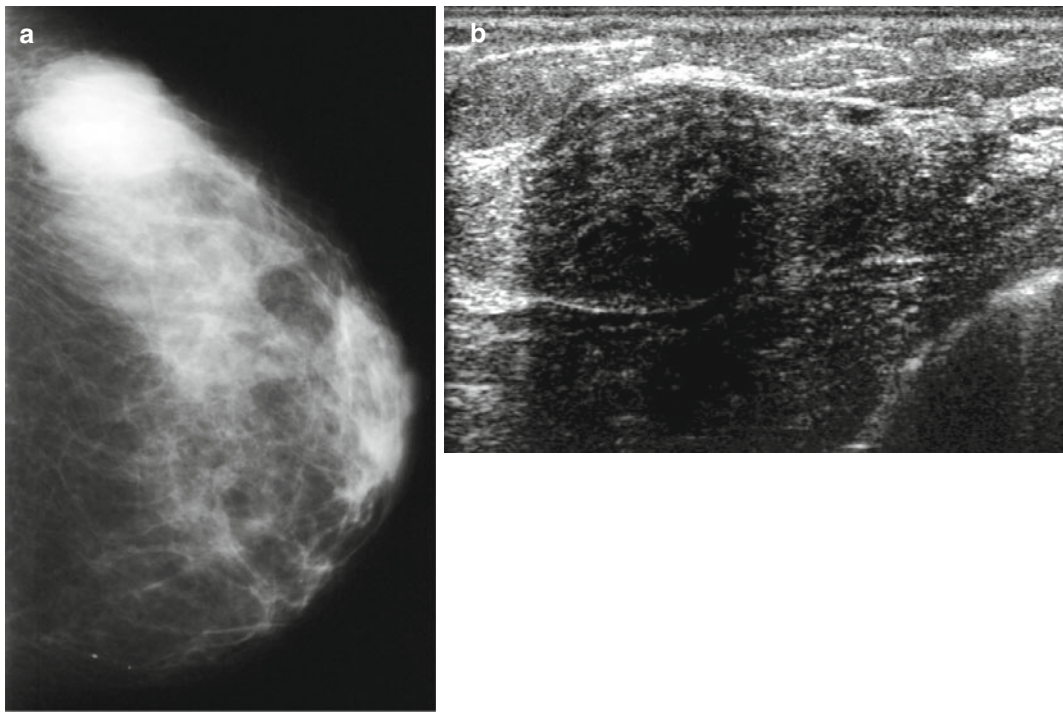
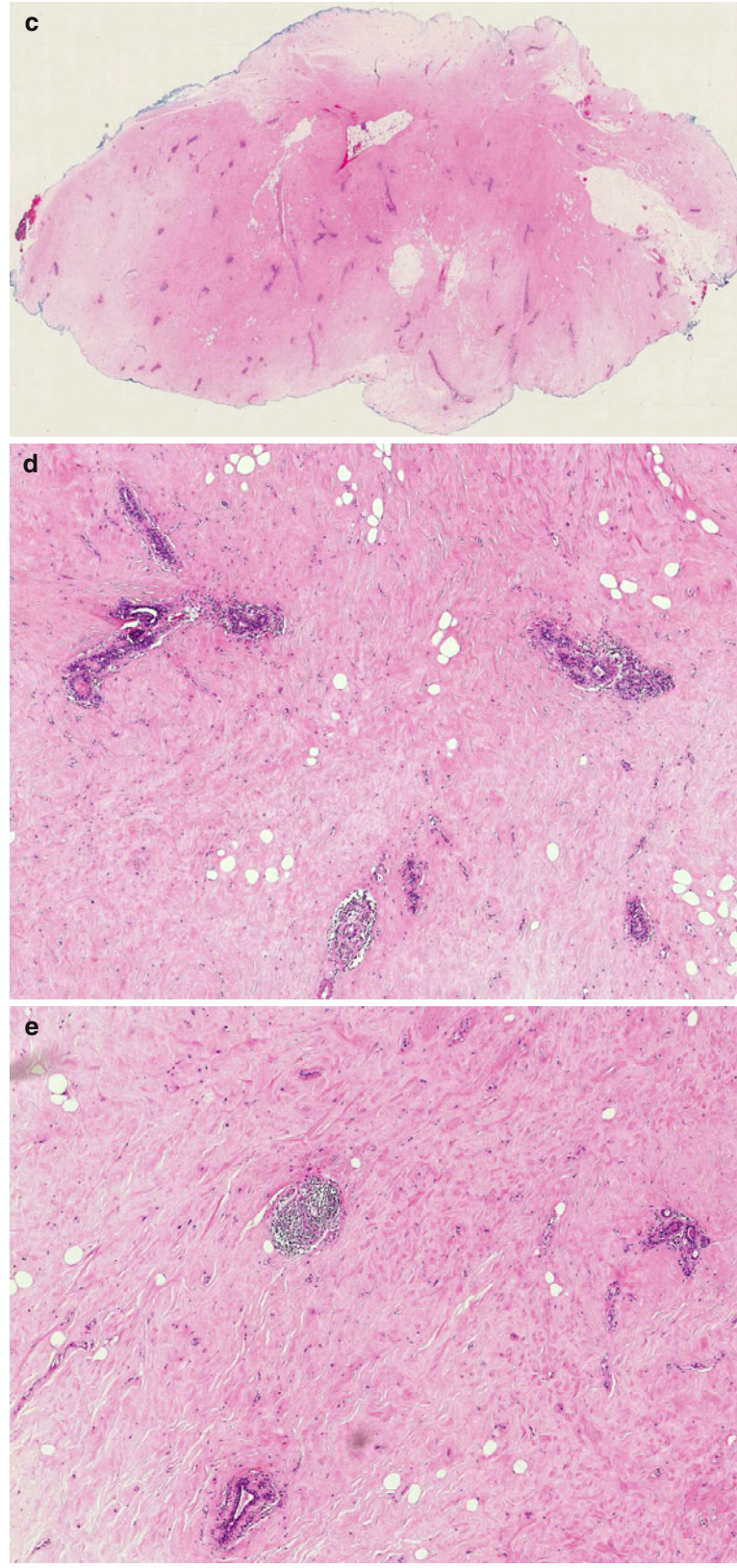


Fig. 6.9 (**a**) The mammogram of diabetic mastopathy showing an ill-defined soft tissue mass graded as R5 in a patient with non-insulin-dependent diabetes mellitus. (**b**) Mass is confirmed on ultrasound. The needle core biopsy was reported as fibrosis (B2). Because there was clinical, radiological and pathological discordance, the patient had an excision biopsy which macroscopically showed a solid white cut surface. (**c**) The histology shows extensive scarring, atrophic ducts and lobular units. (**d**) High magnification highlights periductal lymphocytic inflammation and lymphocytic lobulitis. (**e**) The fibrosis exhibits scar-tissue-like appearances

Fig. 6.9 (continuted)



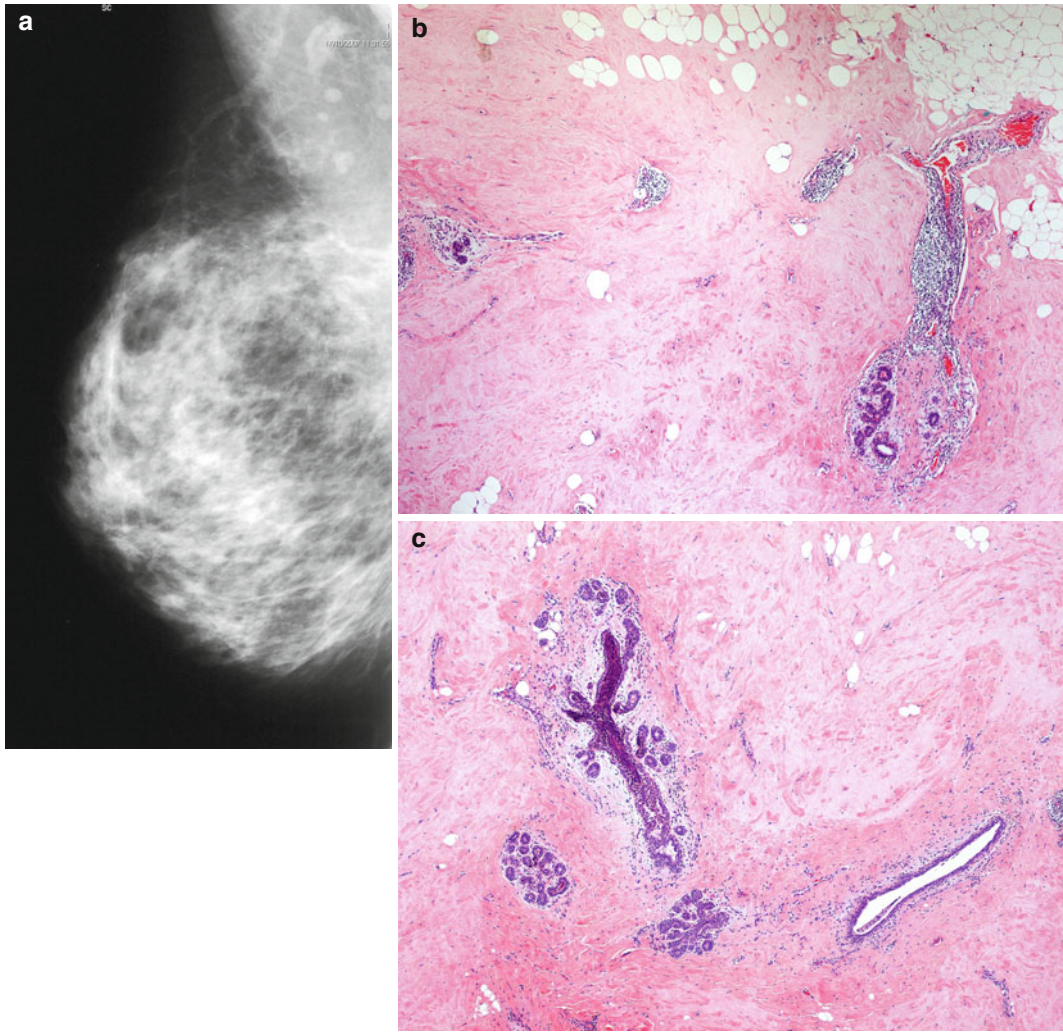


Fig. 6.10 (**a**) Dense breast showing a subareolar soft tissue density graded as R4. The needle core biopsy was graded as in adequate (B1). (**b**) The excision specimen showed features of sclerosing lymphocytic lobulitis in a non-diabetic patient. (**c**) The lymphocytic lobulitis is in the background hyalinised scar-like tissue

three cases in 41, 34 and 24-year-old women with this condition in Iran. On reviewing the literature, the authors reported that IGM was more prevalent in Eastern countries such as China and Turkey. Akyildiz E et al. (2010) reported 30 patients with IGM treated at Istanbul University Cerrahpasa Medical School between 2000 and 2008. Isolated case reports on this condition are on non-Caucasian women (Imoto et al. 1997; Bakaris et al. 2006; Olsen and Dilaveri 2011). Azlina et al. (2003) reported the condition in 25 Malaysian women, and the Centre for Disease Control and Prevention reported that a physician in Indianapolis (USA) recorded a cluster of IGM in seven Hispanic women between 2006 and 2008 (MMWR 2009). Further investigations to determine the prevalence of IGM in Indianapolis between 2006 and 2008 reported that eight of the patients including seven from the cluster were Hispanic women and only one woman was Caucasian. The largest study on this condition which morbidity and mortality weekly report investigated 54 women did not specify ethnicity (Hovanessian Larsen et al. 2009).

6.4.2 Possible Causes of IGM

The cause of IGM is not known but is thought to be an autoimmune cellular reaction to secretions extravasated into the perilobular connective tissue secondary to epithelial damage as a result of infection, trauma or a chemical event. However, a specific antigen has yet to be found (Kessler and Wolloch 1972; Bani-Hari et al. 2004). Whatever the aetiological antigen is, this elicits an inflammatory response consisting of lymphocytes, polymorphs and granulomas. Use of oral contraception, lactation and hyperprolactinaemia have been implicated as possible causal agents. In a review of seven patients, Fletcher and colleagues (1982) did not find any relationship between the use of contraceptive pill and IGM. However, Imoto and colleagues (1997) carried out a literature review of 49 cases and reported that a third of the patients had used oral contraception and two women had been treated with oestrogen to suppress lactation. The authors suggested 'hormonal perturbation' as a possible cause of IGM. Hormonal abnormality as a possible aetiological cause of IGM is supported by detection hyperprolactinaemia in patients who presented with granulomatous mastitis (Cserni and Szajki (1999); Lin et al. 2012).

6.4.3 Clinical Features of IGM

Except in a few cases where the condition was reported in women of over 50 years of age, the majority of the women are of childbearing age. IGM may present with unilateral signs of infectious mastitis with features of an underlying abscess (Fig. 6.11a), and patients are invariably treated with antibiotics and, if this fails, incision and attempted drainage (Olsen and Dilaveri 2011). More importantly IGM presents with a painful palpable with clinical and radiological features of breast cancer (Hovanessian Larsen et al. 2009; Azlina et al. 2003).

In a study of 25 patients with IGM, Azlina and colleagues (2003) reported that 13 of the patients had clinical features of malignancy. Diagnosis of IGM was made on FNAC in three patients, needle core biopsies in nine patients and excisional biopsies in the remainder. Nonoperative diagnosis will avoid unnecessary mastectomy (Bani-Hani et al. 2004). Imoto and colleagues (1997) reported a case where a modified mastectomy was performed in a 35-year-old woman who presented with a mass, clinically assessed as stage II breast cancer. The radiology was suspicious of breast cancer. However, the cytology was only suspicious of cancer (C4). There was no needle core biopsy performed.

Other presenting features of IGM include nipple discharge, nipple retraction, ulceration and complicated sinus discharges due to previous drainage (Fig. 6.11b).

6.4.4 Radiological Features of IGM

It is important to be aware of the radiological features of IGM because this is the second line of investigation after clinical assessment and will make a difference between the diagnosis of cancer and benign lesion. In probably one of the largest studies of patients with IGM, Hovanessian Larsen et al. (2009) reviewed 54 patients with IGM with an age range of 22–44 years (mean 33.1 years). The authors correlated the clinical, radiological and pathological features. All 54 women had ultrasonographic examination. In 32 (59 %) women, there was a large hypoechoic mass with multiple tubular extensions. A lobulated or irregular mass was identified in 18 (33 %) women. All masses were heterogeneously hypoechoic. Parenchymal distortion with acoustic shadowing and no discrete mass was noted in four women (7 %). Skin thickening was noted in 28 (52 %) women and axillary adenopathy in 15 (28 %) women. The ultrasonographic features of IGM are illustrated in Fig. 6.11 consisting of irregular cavities interpreted as abscess and was treated with aspiration.

In the same study (Hovanessian Larsen et al. 2009) 45 women had mammographic examination, and 25 (56 %) patients showed a heterogeneous dense or extremely dense parenchymal breast pattern. Twenty women showed large focal asymmetric density and seven women had

irregular or lobulated mass. Three women had diffusely increased density in the affected breasts. Skin thickening and axillary lymphadenopathy was seen in 11 women. Although mammographic features of IGM are considered to be non-specific (Han et al. 1999), the study by Hovanessian Larsen and colleagues (2009) demonstrated that the most common mammographic presentation of IGM was focal asymmetric density with no distinct margins in 20 out of 45 women and was not easily identified when compared with the contralateral breast. The authors also noted that IGM was mainly unilateral and most often present at the periphery of the breast. Less common mammographic findings included lobulated or irregular mass (7/45) and diffusely dense breast (3/45). Lesions were mammographically occult in 15 out of 45 women, possibly because of an underlying dense breast pattern present in 36 of the 45 women. The authors suggested that the presence

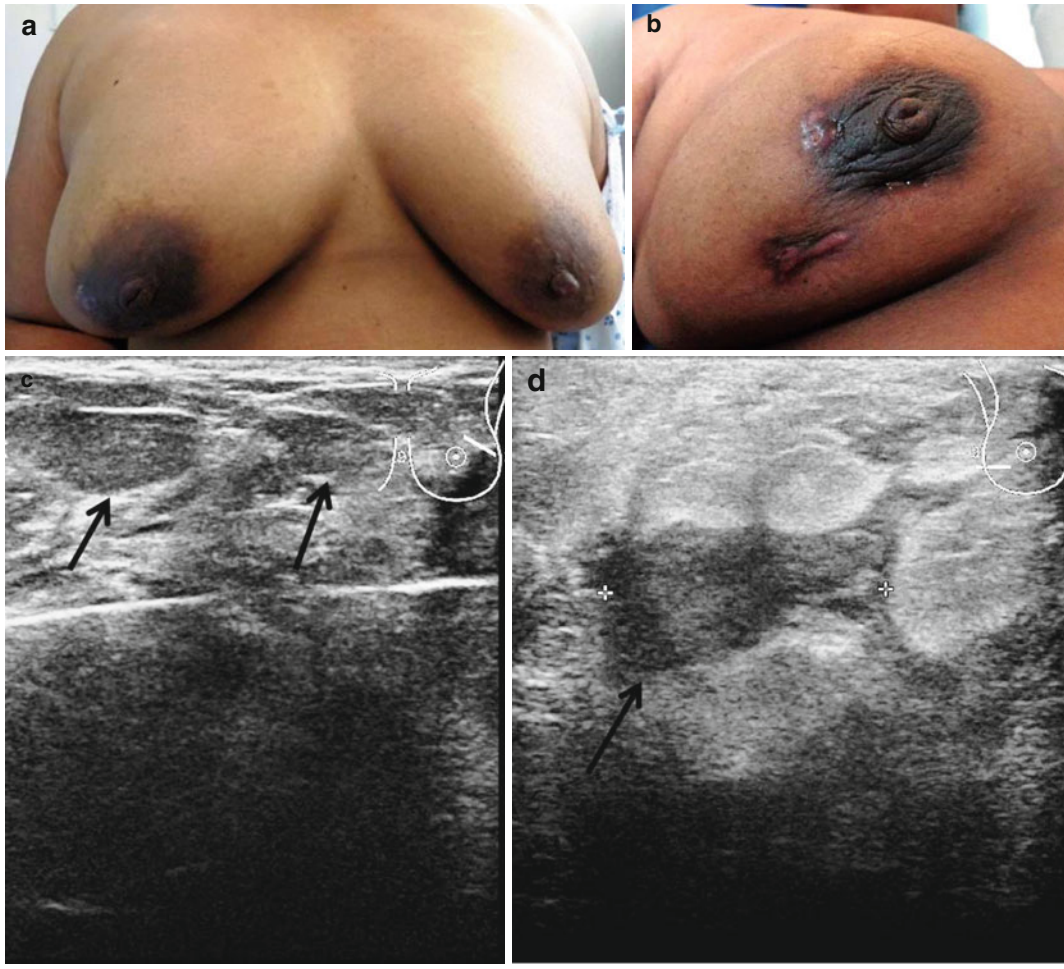
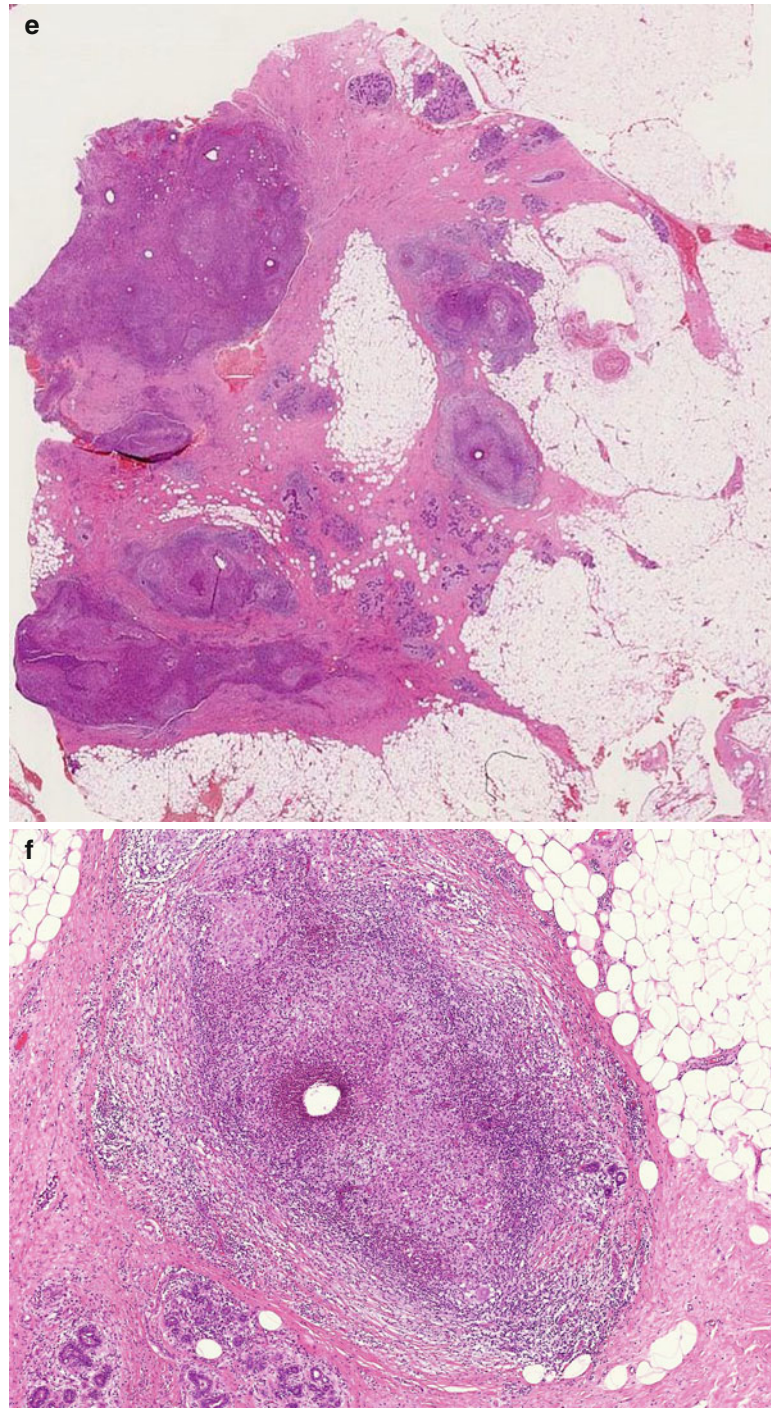


Fig. 6.11 (**a**) A 31-year-old woman presented with bilateral breast abscesses, not responding to aspiration or antibiotics, 18 months postpartum. (**b**) The abscess was complicated by a discharging sinuses in the right breast. (**c**) Ultrasound confirmed the presence of abscess in the left breast undergoing needle aspiration. (**d**) The ultrasound of right breast shows an irregular abscess. (**e**) The right breast sinus was excised and this showed an area of mixed inflammation. (**f**) At higher magnification there was abscess formation. (**g**) The inflammatory infiltrate consisted of polymorphs, lymphocytes, eosinophils and granulomas. (**h**) Granulomas and giant cells were present in other fields. IGM in the left breast was confirmed on needle core biopsy

Fig. 6.11 (continued)



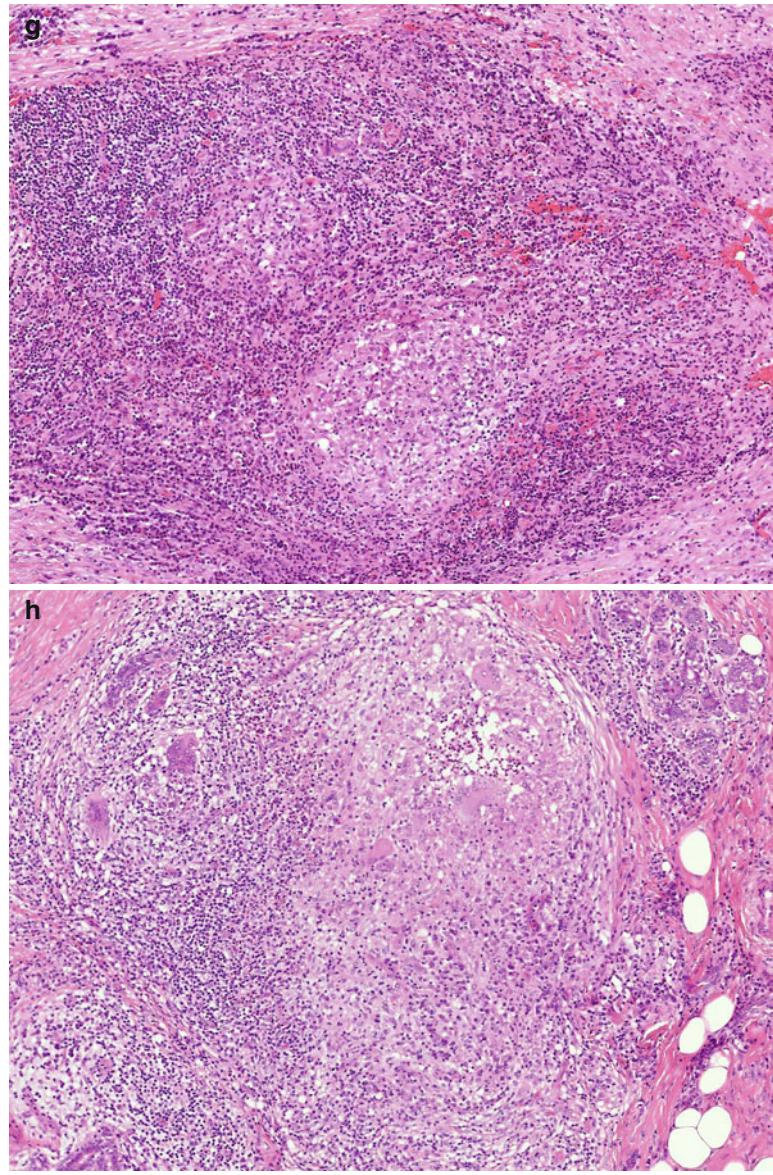


Fig. 6.11 (continued)

of irregular hypoechoic mass with multiple tubular extensions on sonography suggest IGM. However, the final diagnosis should be made on biopsy.

6.4.5 Pathological Features of IGM

The diagnosis of IGM can readily be made on needle core biopsy. In an excision specimen IGM consists of mixed inflammation with a lobular pattern (Fig. 6.11e). The inflammatory infiltrate consists of lymphocytes, polymorphs macrophages, granulomas, giant cells and foci of abscess formation. Caseating necrosis, fungal organisms or acid-fast bacilli should be absent.

6.4.6 Management of IGM

Treatment depends on the severity of the disease and may include observation, systemic steroids, methotrexate or surgery (Olsen and Dilaveri

2011). Approximately half of the women have spontaneous resolution without specific therapy (Lai et al. 2005).

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Cystic Lesions

7

Learning Points

- Fibrocystic change replaced the term fibrocystic disease.
- Fibrocystic change consists of cysts lined by attenuated cells or apocrine epithelium.
- Fibrocystic change with apocrine epithelium is a common abnormality present in benign and cancerous breast.
- The cause of fibrocystic change is unknown but may be related to hormonal abnormality or dietary factors.
- Simple cysts are adequately managed by aspiration under ultrasound guidance.
- Cytological assessment of cyst contents is only necessary if the contents are bloodstained.
- Complex cysts are thick walled and have thick septae, intracystic masses or other solid component.
- Recurrent cysts can be managed by aspiration but will require needle core biopsy or excision if bloodstained or if there is a persistent mass.
- There is no consensus regarding the risk of breast cancer in patients with fibrocystic change but generally considered to be very low.
- Chromosomal abnormalities in apocrine epithelium suggest possible precursor of apocrine carcinoma.

7.1 Fibrocystic Change

7.1.1 Background and Clinical Features of Fibrocystic Change

Several terms have been applied to the condition of fibrocystic change, including mammary dysplasia, fibrocystic disease, cystic mastopathy and cystic hyperplasia.

The term fibrocystic disease was laid to rest in 1985 at a consensus meeting held by the Cancer Committee of the College of American Pathologists in favour of fibrocystic change (Hutter et al. 1986). This meeting was prompted by complaints from women who were paying high insurance premiums following the diagnosis of fibrocystic disease. The participants at the meeting agreed that if the term fibrocystic change was used, the associated benign epithelial proliferations should be stated to assist in assessing individual risk. In 1998, Fitzgibbons et al. published the updated version of the consensus definitions which included categories of risk based on pathologic diagnosis (Fitzgibbons et al. 1998). In this book, the term fibrocystic change is applied to lesions consisting of cysts, some of which are lined apocrine epithelium, with or without associated fibrosis. Although fibrocystic change can be present as the dominant disease process, in the majority of cases the proliferation is identified in breast tissue excised for other benign or malignant disease (Foote and Stewart 1945; Wellings

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_7, © Springer-Verlag Berlin Heidelberg 2014

and Alpers 1987). Benign epithelial proliferations associated with fibrocystic change include intraductal papillomas, fibroadenoma, duct ectasia, radial scar, sclerosing adenosis (apocrine adenosis) epithelial hyperplasia of usual type and many more. Fibrocystic change is also present in 'normal' breast tissue (Frantz et al. 1951), is rare before the age of 20, becomes more prevalent in perimenopausal women and the microscopic lesion persists in postmenopausal women (Wellings and Alpers 1987). Fibrocystic change can present symptomatically with palpable mass or detected during mammographic screening.

7.1.2 Possible Aetiological Factors and Pathogenesis of Fibrocystic Change

Because of the distinct appearance of the apocrine epithelium which makes it prominent among other proliferations, theories abound as to the possible aetiological factors of fibrocystic change. There is no consensus as to whether the characteristic 'pink epithelium' of Lendrum (1945), which microscopically and ultrastructurally resembles the apocrine sweat glands (Ozzello 1971), originates from the sweat gland (Haagensen 1986), is native to the breast and metaplastic (Ahmed 1975) or represents epithelial degeneration (Dawson 1932). The eosinophilic appearance of apocrine epithelium is due to the presence of excess mitochondria (Ahmed 1975). Although the metaplastic theory is generally accepted, this has been challenged by the detection of cells that are positive for gross cystic disease fluid protein-15 (GCDFP-15), a marker of apocrine cells, in developing fetal breast tissue (Viacava et al. 1997).

In addition to GCDFP-15, GCDFP-24 has been identified in fibrocystic change. These proteins are significant constituents of the proteins present in the fluid aspirated from the cysts in fibrocystic change (Haagensen et al. 1979). GCDFPs can be detected by immunohistochemistry in apocrine epithelium but not in normal breast tissue. GCDFP-15 has the highest concentration in the cystic fluid and this protein has been extensively investigated in several tumours to assess its specificity for apocrine epithelium. The initial study by Mazoujian et al. (1983), which was later followed by a publication from Wick and colleagues (1989), confirmed GCDFP-15 as a specific marker for apocrine differentiation.

Simard and colleagues (1989, 1990) demonstrated that androgens stimulate GCDFP-15 and GCDFP-24 production in breast cancer cell lines, whereas oestrogens inhibit the production of these proteins. Based on these observations, Haagensen (1991) postulated that the selector genes that control apocrine metaplasia may, as part of this process, also govern co-ordinated expression of GCDFPs, and the hormonal modulation of these proteins appears to be under similar mechanisms, with androgens enhancing synthesis and oestrogens having an inhibitory effect. The results of these hormonal effects can be illustrated by immunohistochemical staining. Apocrine epithelium expresses androgen receptors, but lacks oestrogen and progesterone receptors (Gatalica 1997; Selim and Wells 1999). Although apocrine epithelium lacks oestrogen-α receptor, Shaaban et al. (2003) demonstrated expression of oestrogen-β receptor in apocrine metaplasia and other benign breast epithelium, which may have a bearing on carcinogenesis. Apocrine carcinomas are oestrogen and progesterone receptors negative.

Because the condition peaks during the perimenopausal period, several hormonal abnormalities have been implicated in the pathogenesis of fibrocystic change, including hyperprolactinaemia, increased oestrogen levels, reduced progesterone levels and excess thyroid hormone activity (Drukker and deMendonca 1987). However, the changes in the hormonal levels have not been constant in all patients to make this a definite aetiological factor.

Ingestion of excess tea, coffee, chocolates and certain cola drinks, which produce methylxanthines, has been implicated in the development or exacerbation of fibrocystic change. Minton et al. (1979a) proposed that methylxanthines inhibit cyclic adenosine monophosphate phosphodiesterase and cyclic guanosine monophosphate phosphodiesterase action, thereby increasing tissue levels of adenosine monophosphate and

guanosine monophosphate compounds, which were reported to be present in women with fibrocystic change. As a follow-on study, Minton and colleagues (1979b) reported disappearance of symptoms in 65 % of 20 women who abstained from taking methylxanthines for 1 to 6 months. A separate case-controlled study, which included 634 women with fibrocystic change and 1,066 controls, also reported a positive association of fibrocystic change with caffeine consumption (Boyle et al. 1984). Women who consumed 31–250 mg of caffeine a day had a 1.5-fold increased risk of developing fibrocystic change and those who drank more than 500 mg a day had a 2.3-fold increased risk. This study also reports high caffeine consumption in women with atypical lobular hyperplasia, sclerosing adenosis and 'papillomatosis', lesions that were part and parcel of 'fibrocystic disease' prior to the 1985 consensus meeting. Inclusion of these confounding factors does not give a true effect of caffeine, if any, on the pathogenesis of fibrocystic change.

Haagensen (1991) postulated that the microscopic lesion that is the progenitor of gross cystic disease of the breast is apocrine metaplastic change of the epithelium in the terminal duct–lobular units. Secretions from the apocrine cells expand the lobules and this progresses into apocrine-lined microcysts, which further expand into grossly apparent cysts. This process was succinctly illustrated by Warner and colleagues (Fig. 7.1). Warner et al. (1998) further expanded this theory and indicated that the microcysts were caused by unfolding of lobules, based on the previous work by Wellings and Alpers (1987). Wellings and Alpers performed subgross analysis of fibrocystic change on 186 postmortem breasts and 107 breasts with cancer. The investigators observed that fibrocystic change with apocrine metaplasia arose in terminal duct–lobular units and hypothesised that the cysts are created by 'unfolding of the lobules'. As time progresses, the small cysts coalesce to create larger cysts. In the older women the cysts were larger and lined by flat epithelium, and the luminal contents were more voluminous, indicating an aging process.

7.2 What Is the Stimulus that Evokes the Metaplastic Process?

Slack (1986) believed that epithelial metaplasia is a single-step process without an intermediate stage. He hypothesised that metaplasia is caused by a master selector gene that distinguishes between various tissues and co-ordinates changes in cell kinetics, responses to growth factors and hormones. Haagensen (1991) expanded this theory further and formulated a model of the possible interacting processes, which eventually lead to breast cancer with apocrine features as illustrated in Fig. 7.2.

7.3 Molecular Pathology of Fibrocystic Change

Apocrine epithelium is an inherent feature of fibrocystic change and the presence of apocrine cells in a breast biopsy is generally considered by pathologists to be a reassuring feature of benignity. However, this view is changing with time due to detailed study of this lesion and application of molecular markers. There is molecular evidence that some benign forms of apocrine epithelium may be potentially neoplastic.

Expression of C-myc and ras proteins has been reported with a high prevalence in apocrine epithelium with papillary proliferation (Agnantis et al. 1992). As both C-myc and ras oncoproteins are expressed in several cancers, their presence in papillary apocrine epithelium suggests possible indicators of malignant change.

One of the major changes that occur in carcinogenesis is loss of heterozygosity (LOH), and this was assessed by Washington et al. (2000) on 32 breast specimens with fibrocystic change. Twenty of the patients were postmenopausal. Fourteen lesions of apocrine metaplasia adjacent to cancer were also assessed for LOH. LOH was assessed on 9p, 11p, 13q, 16q, 17p and 17q because these chromosomal loci show a high frequency of LOH in breast tumours. LOH was detected in 6/27 normal terminal duct–lobular units, 4/23 adenosis, 4/21 ductal hyperplasia and

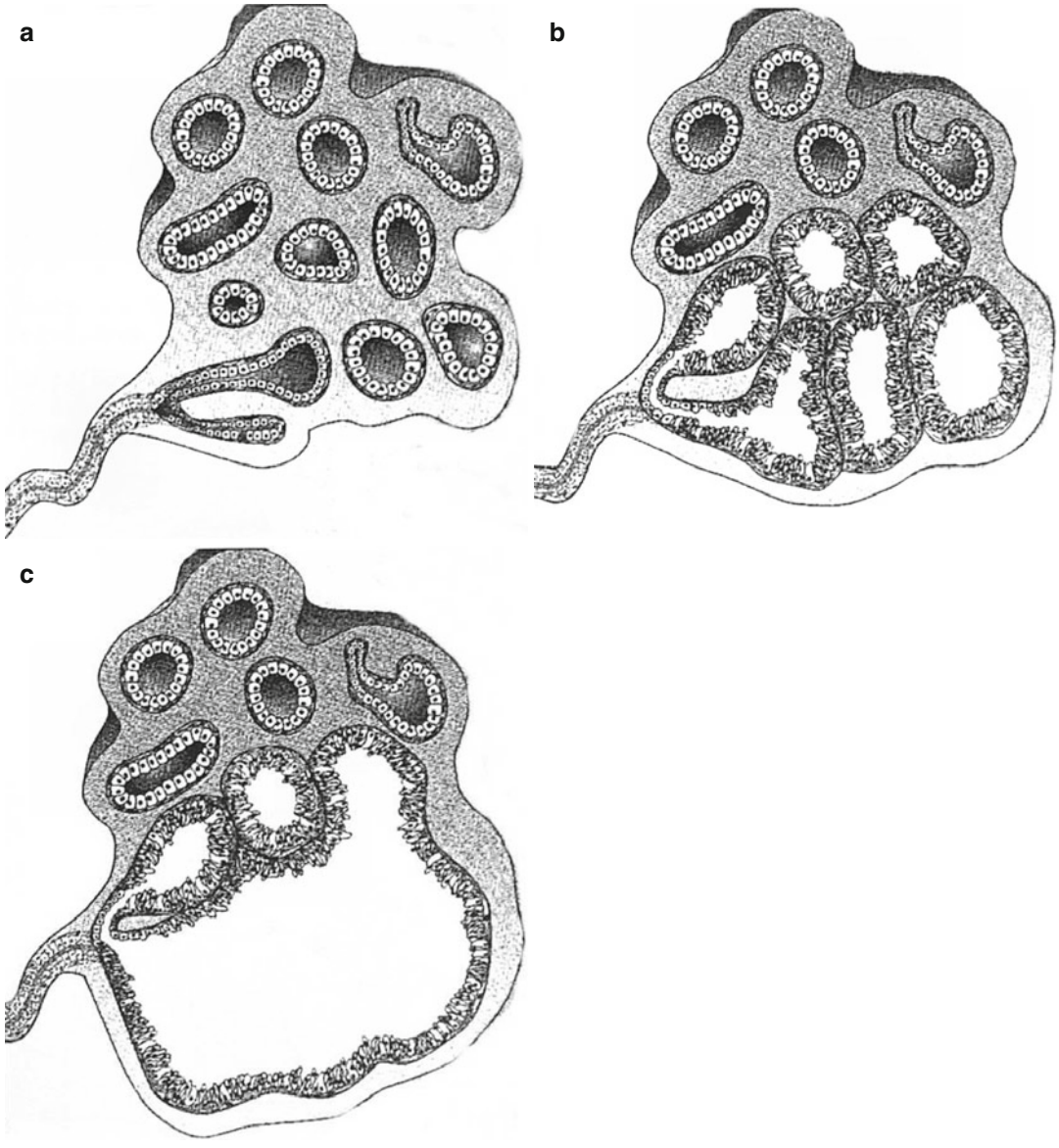


Fig. 7.1 Schematic drawings of apocrine metaplastic change in terminal duct–lobular unit. (**a**) Normal terminal duct–lobular unit shows acini lined by cuboidal epithelium. (**b**) Many acini within the terminal duct–lobular unit are now lined by columnar epithelium and are dilating, presumably because of fluid production by this apocrine metaplastic epithelium. (**c**) Several adjacent acini have fused to form a larger cystic space (From Warner JK, Kumar D, Berg WA (1998) Apocrine metaplasia: mammographic and sonographic appearances. Am J Roentgenol 170: 1375–1379, Fig. 4A, B, C. Reprinted with permission from the *American Journal of Roentgenology*)

10/19 apocrine metaplasia. Seven out of 14 specimens of apocrine metaplasia adjacent to carcinoma also showed LOH. In all seven cases the carcinoma and apocrine epithelium shared LOH at one or more loci. Because of the high frequency of LOH in apocrine metaplasia in non-neoplastic cases, the authors hypothesised that apocrine epithelium could be derived from genetically altered cells, which also give rise to an adjacent carcinoma. LOH in some apocrine metaplasia and adjacent carcinoma also suggested a common clonal precursor.

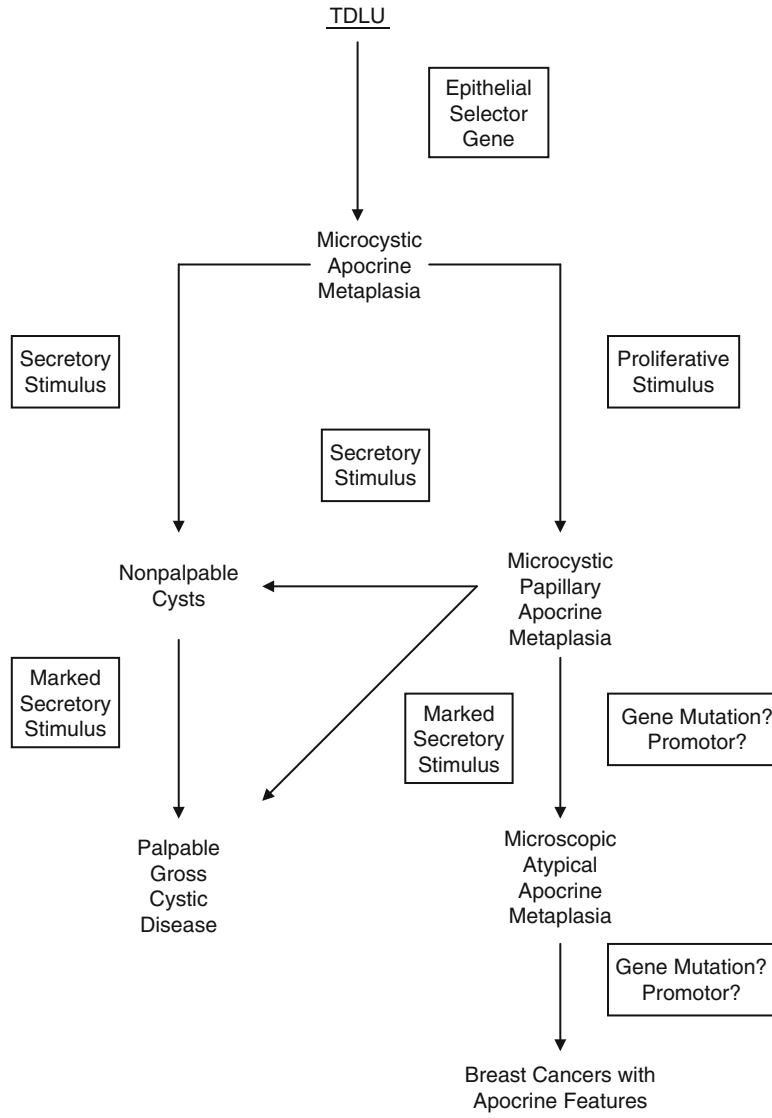


Fig. 7.2 Diagram of possible pathways for breast epithelial changes that result in breast gross cystic disease or in breast carcinoma with apocrine features. TDLU terminal duct–lobular unit (Reproduced with permission from Lippincott Williams & Wilkins)

In a separate study, comparative genomic hybridisation (CGH) was applied to benign apocrine hyperplasia, apocrine ductal carcinoma in situ (DCIS) and apocrine invasive carcinoma to assess the presence of genetic alterations in these lesions (Jones et al. 2001). The mean number of genetic alterations (chromosomal gains and losses) in apocrine hyperplasia was 4.1 ($n=10$), apocrine DCIS, 10.2 ($n=10$) and invasive apocrine carcinoma, 14.8 ($n=4$). There was overlap in the genetic alterations in apocrine papillary hyperplasia, DCIS and invasive carcinoma. Losses at 1p, 16q and 17q and gains at 2p and 13q were detected in multiple cases of all three types of proliferations (hyperplasia, in situ and invasive carcinoma). Based on the widely held view that there is progression from hyperplasia through in situ change to invasive carcinoma, the authors suggested that the chromosomal alterations might be early changes in the carcinogenesis of apocrine breast cancer. The detection of genetic alterations in papillary apocrine proliferation also implied that a proportion of these lesions might be clonal neoplasms. The overlap of some chromosomal abnormalities with apocrine DCIS and invasive carcinoma proposed apocrine papillary hyperplasia as a putative non-obligate precursor of apocrine carcinoma.

7.4 Radiological Features of Fibrocystic Change

7.4.1 Mammography

Although cysts are usually present in association with other symptomatic or screen-detected lesions, they can be the main pathological abnormality at symptomatic presentation or as a screen-detected lesion. Cysts can appear as round, oval or well-circumscribed masses (Fig. 7.3). If present in dense breasts, cysts may be partially obscured or mammographically invisible (Heywang-Köbrunner et al. 2001), and in fatty breasts, the cysts can exhibit the halo sign (Tabár and Dean 1985). Warner and colleagues (1998) carried out a retrospective study on mammographic and sonographic features of 17 lesions

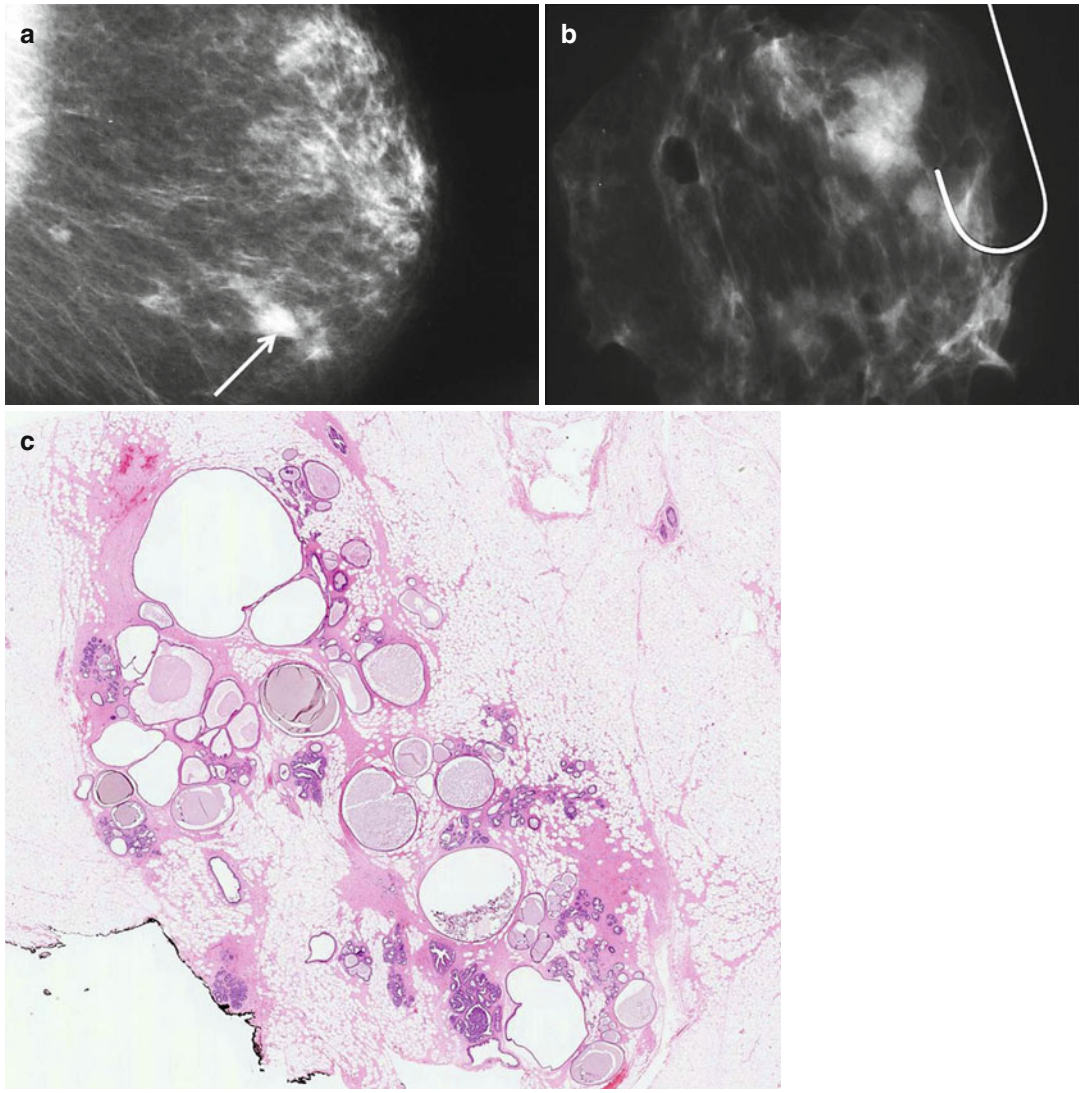


Fig. 7.3 (**a**) The mammogram shows a new, irregular, soft tissue density in a 57-year-old woman graded as R3 (*arrow*). Ultrasonography showed multiple cystic spaces with associated fibrous tethering. The needle core biopsy was not representative and the lesion was excised. (**b**) The specimen X-ray shows an ill-defined soft tissue density with no calcification. (**c**) Whole mount section of the excised lesion shows fibrocystic change consisting of multiple cystically dilated duct–lobular units, some containing featureless eosinophilic secretions

in which apocrine metaplasia constituted 50 % of the lesions. The diagnosis was made on needle core biopsies in 13 patients and on fine needle aspiration cytology in the remaining four. The mean age of the patients was 57 years (range 37–95 years). Nine of the lesions were screen-detected. The average size of the lesions was 12.8 mm (range 6–24 mm). Fifteen lesions were mammographically of equal density to the surrounding breast tissue. Two lesions had lower density than the surrounding parenchyma and none of the lesions was of higher density than the adjacent breast tissue. Calcification was not a common feature and this was only present in a single lesion. Ten lesions exhibited microlobulated borders, five had macrolobulated borders and two had circumscribed oval borders. Eleven of the 17 lesions decreased in size at the time of needle core or fine needle aspiration, confirming their cystic nature. Most of the lesions showed variable resolution or decrease in size on follow-up mammography. On histological examination, 9/17 lesions had isolated focal apocrine metaplasia and predominantly apocrine metaplasia in 8/17 cases. The latter cases had associated fibrosis (four cases), sclerosing adenosis (three cases) and intraductal epithelial hyperplasia (single case).

When Warner et al. (1998) compared the radiological and histological features, they noted that the mammographic microlobulated and macrolobulated pattern corresponded with lobulated margins of a dilated terminal duct–lobular unit on histology. Despite the correlation of mammographic and sonographic features with the histological appearances, the authors were reluctant to recommend the diagnosis of apocrine metaplasia on radiological appearances alone, due to the small size of the sample. Moreover fibrocystic change is invariably associated with other disease processes and a radiological diagnosis without a biopsy may not be safe. Kushwaha et al. (2003) did not find the mammographic features of fibrocystic change to be diagnostic when they performed a mammographic–pathologic correlation of apocrine metaplasia diagnosed using vacuum-assisted stereotactic needle core biopsy. The pattern of calcification was heterogeneous, as were the soft tissue abnormalities. However, Lanyi (2003) describes a 'tea cup phenomenon' as pattern of calcification unique to cystic lesions. This mammographic abnormality occurs in 90° lateral views due to sedimentation of the calcification which is heavier than the fluid in the cyst.

7.4.2 Ultrasonography

Ultrasonography is the most accurate diagnostic modality in assessing cysts. A chronically distended simple cyst exhibits a thin wall and lacks internal echoes and distal enhancement (Heywang-Köbrunner et al. 2001; Fig. 7.4). The presence of calcification within the wall, anechoic cyst contents and lack of enhancement behind the cyst are all features of a complicated cyst and malignancy should be excluded. Echoes within the cyst could be due to sediment as a result of inflammation and increased protein content, blood clots or tumour (benign or malignant).

When Warner et al. (1998) reviewed the sonographic features of the 13 patients with a pathological diagnosis of apocrine metaplasia on needle core biopsy or fine needle aspiration, ten lesions consisted of lobulated masses composed of small (2–5 mm) anechoic foci with intervening septae. The remaining three lesions were lobulated with small anechoic foci as well as a discrete hypoechoic solid component. Eleven of the 13 lesions had posterior acoustic enhancement. The

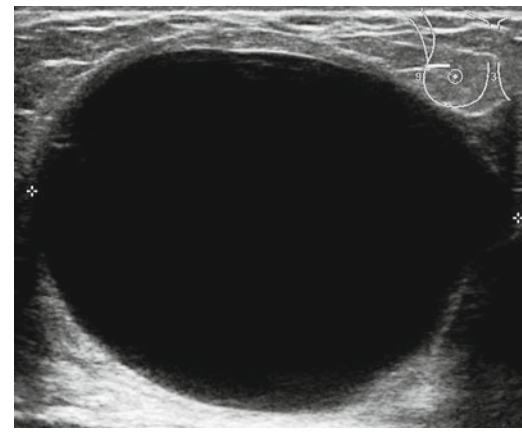


Fig. 7.4 Ultrasound is the best mode of investigation to assess cysts. This is an uncomplicated simple cyst with no internal echoes

sonographic anechoic foci also corresponded with the histologically dilated acini and the intervening septae corresponded with the adjacent walls of the acini with or without associated fibrosis.

7.4.3 Pneumocystography

Pneumocystography is an adjunct mammography performed when a cyst has been aspirated and infused with air. This enhances resolution of the cyst wall to ascertain the internal structures and exclude malignancy (Tabár et al. 1981). Although the use of pneumocystography is becoming obsolete due to the use of ultrasound, Lanyi (2003) advocates there is a place for this procedure in evaluating cysts. He states that if a lesion displays the classic sonographic criteria of a simple uncomplicated cyst, i.e. round or oval in shape with a thin smooth wall and no internal echoes or posterior acoustic enhancement, the cyst should be aspirated and imaged by pneumocystography after air inflation. Lanyi (2003) also states that there is a therapeutic benefit in use of pneumocystography as 95 % of the cysts regress after this procedure.

7.4.4 Magnetic Resonance

Because of the accuracy of ultrasonography in assessing cysts, magnetic resonance (MR) imaging is not used routinely. Where cysts are identified during investigations for other breast conditions, MR images exhibit a smooth contour and low signal intensity. Enhancement within a cyst should be investigated to exclude malignancy (Heywang-Köbrunner et al. 2001).

7.5 Management of Cysts

Cysts should be aspirated under ultrasound guidance. There is no consensus as to whether the cyst fluid aspirated by the radiologist should be submitted for cytological examination (Ciatto et al. 1987; Forrest et al. 1975). Although practices vary in different units, it should be left to the discretion of the radiologist, based on the appearance of the cyst pre- and post-aspiration, to decide whether the fluid should be submitted for cytological examination. Non-bloodstained fluid should be discarded and this invariably contains degenerate epithelial cells which will be reported as atypical on cytology, causing patient anxiety and unnecessary further investigations. Simple cysts usually disappear after aspiration under ultrasound guidance (Fig. 7.5).

Patients with multiple symptomatic cysts at first presentation have a tendency to recur, requiring multiple aspirations (Jones and Bradbeer 1980). Persistent mass and bloodstained aspirate are the main indications for surgical excision (Mansel et al. 2009). All bloodstained fluid (unless iatrogenic) should be submitted for cytological examination to exclude

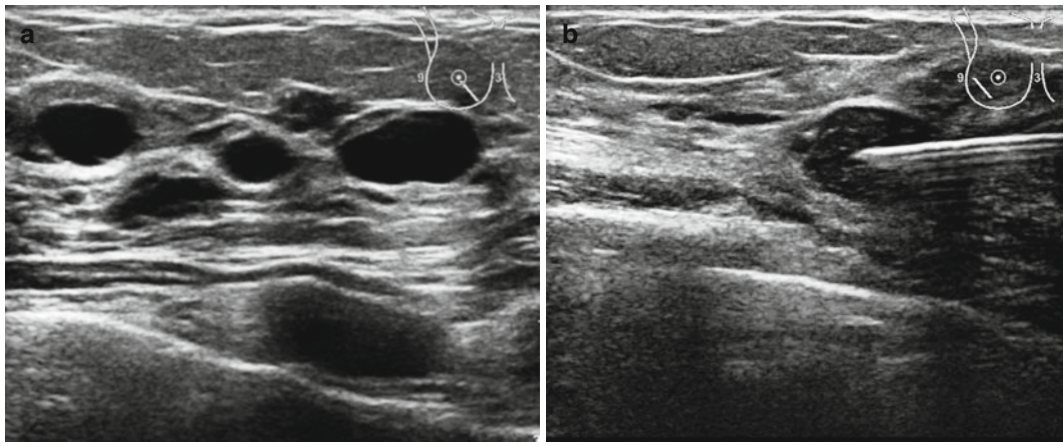


Fig. 7.5 (**a**) Multiple cysts in a patient with recurrent cysts. (**b**) The cysts disappeared on aspiration

intraduct papilloma or intracystic carcinoma. After aspiration of a cyst, follow-up ultrasonography with or without mammography should be performed within a period of 4–6 weeks. A needle core biopsy should be performed if there is a solid lesion on aspiration of bloodstained fluid. Differential diagnoses of complex cysts include fibrocystic change, intraduct papilloma with or without atypia, fibroadenomas, duct ectasia, DCIS and intracystic papillary carcinoma and invasive carcinoma (Doshi et al. 2007). Complex cysts require diagnostic biopsies and discussion at multidisciplinary team meetings to ensure radiological–pathological concordance.

7.6 Pathology of Fibrocystic Change

The main specimens submitted for pathological evaluation are aspirates from cyst contents, needle core biopsies and excision biopsies. The fluid from breast cysts is variable in colour from clear, straw-colour turbid, dark brown to bloodstained. On cytological analysis, the contents can be acellular and just contains proteinaceous material. Although technically this should be graded as inadequate for diagnosis (C1 category), the patient should be discussed at a multidisciplinary team meeting to compare the radiological and pathological features. The fluid can also contain numerous foamy macrophages in the background of proteinaceous material (Fig. 5.2b). Diagnosis of benign apocrine cells in the cyst fluid can also be made confidently on cytology (Fig. 5.1b).

If on aspiration of the cyst, it does on disappear or exhibit abnormal echoes, the Radiologist will perform a needle core biopsy for pathological assessment and the presence of part of the cyst wall lined by apocrine cells will confirm benignity (Fig. 7.6). In excisional biopsies, fibrocystic change usually consists of a collection of multiple connected cysts which confirms the origin from the terminal duct lobular units

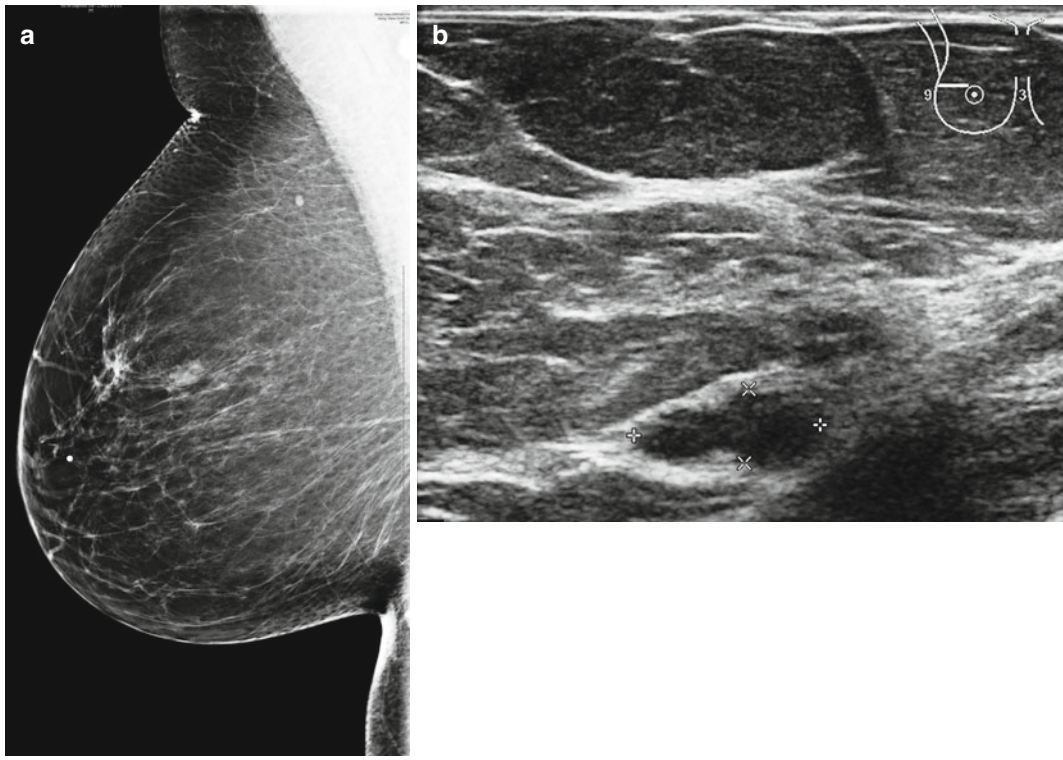


Fig. 7.6 (**a**) Lobulated soft tissue mass in a 47-year-old woman was graded as R3. (**b**) The ultrasound confirmed a lobulated cyst which did not disappear on aspiration. (**c**) The needle core biopsy showed a multiloculated cyst with a fibrous wall lined by benign epithelium and graded as B2. (**d**) The presence of benign apocrine epithelium is confirmed on higher magnification

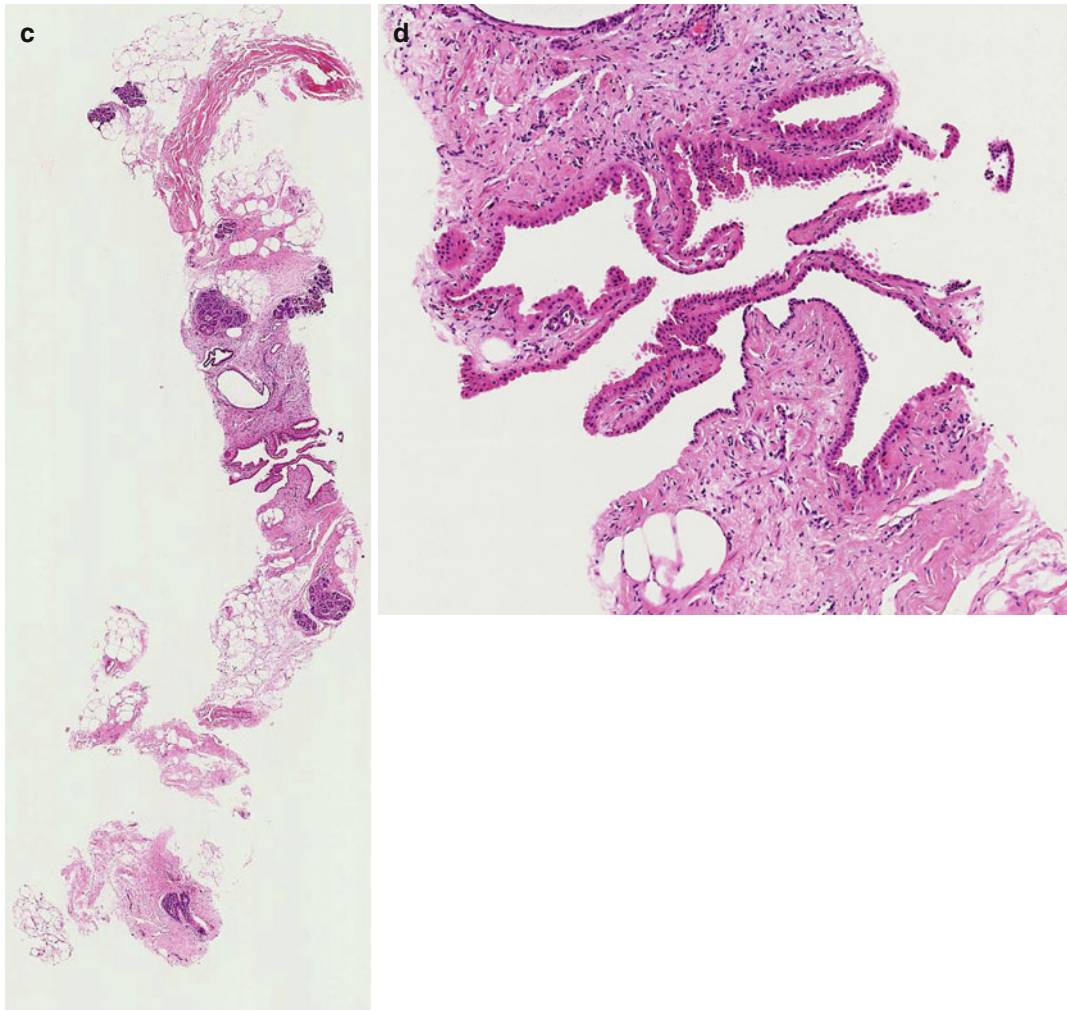


Fig. 7.6 (continued)

(Fig. 7.7a). The intervening walls show variable thickness. The lining epithelium can be attenuated (Fig. 7.7b), hyperplastic with or without papillary proliferation (Fig. 7.7c). The cells contain granular cystoplasm and the nuclei shows prominent nucleoli (Fig. 7.7d). Inflammation is minimal unless the cyst was previously aspirated.

Isolated cysts or fibrocystic change must be distinguished from duct ectasia. Although the two pathological processes can exist in the same breast (Fig. 7.8) the aetiological factors, pathogenesis, clinical presentation and pathological features are different. These differences between cysts and duct ectasia are documented in Table 7.1.

7.7 Clinical Significance of Fibrocystic Change

One of the main factors that affect the accurate assessment of the risk related to fibrocystic change is that, for a long time, the term 'fibrocystic disease' was used as both a clinical and pathological diagnosis. In their review entitled 'Fibrocystic disease of the breast – a nondisease', Love et al. (1982) highlighted how different authorities in the field of breast disease viewed the term fibrocystic disease. Clinically the term fibrocystic disease was applied when the breasts were lumpy and this was associated with pain and tenderness. These changes were related to

the menstrual cycle and disappeared at menopause. Other terms applied to this condition were cyclical mastalgia and chronic cystic mastitis. The pathological diagnosis of fibrocystic disease or chronic cystic mastitis included the presence of macrocysts, microcysts, adenosis, apocrine change, fibrosis, fibroadenoma and ductal hyperplasia. The combination of these epithelial proliferations with different risk factors certainly overshadowed the accurate assessment of risk of cancer associated with fibrocystic change. A detailed review of the literature on this subject is summarised in the paper by Love and colleagues (1982).

When Dawson (1932) examined 120 cases of breast cancer, which included 700 large sections, she identified the 'pale epithelium' (the term she applied to apocrine epithelium) in association with 116 malignant breasts. The study did not demonstrate cancer arising directly from the apocrine epithelium and Dawson did not consider the apocrine epithelium to be premalignant.

Subsequently, Foote and Stewart (1945) carried out a comparative study on 300 breast cancer

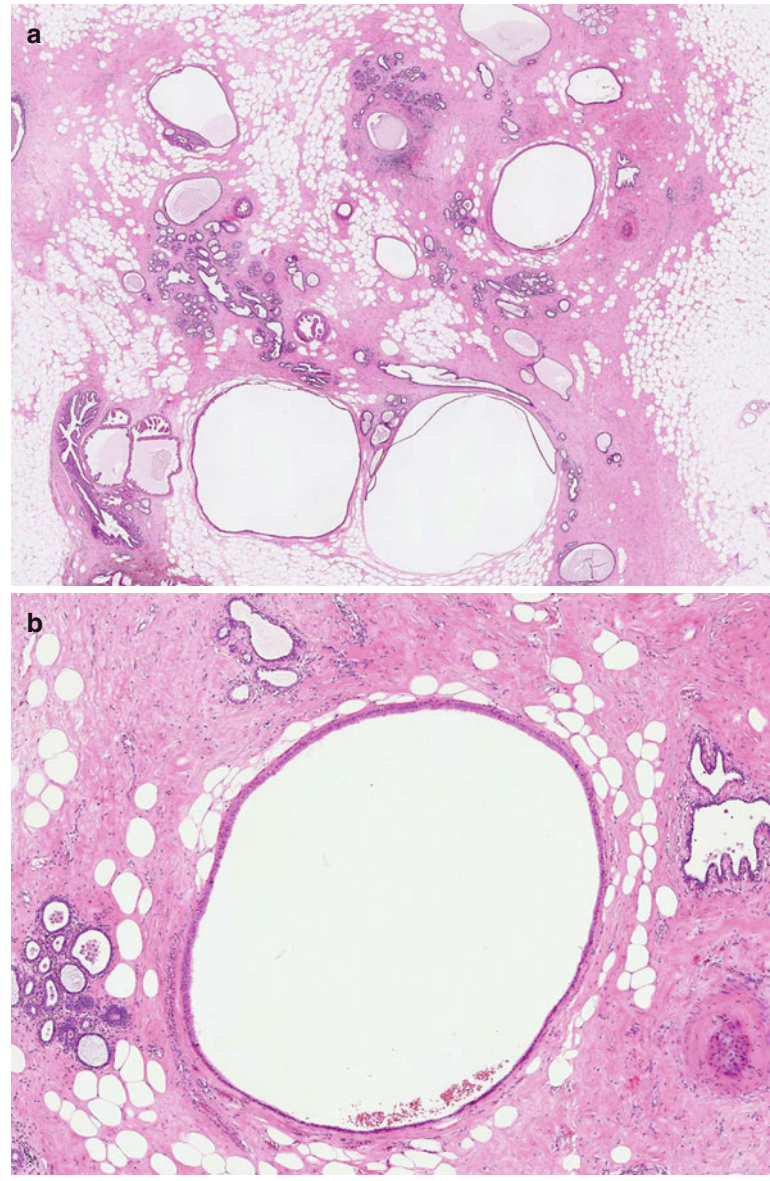
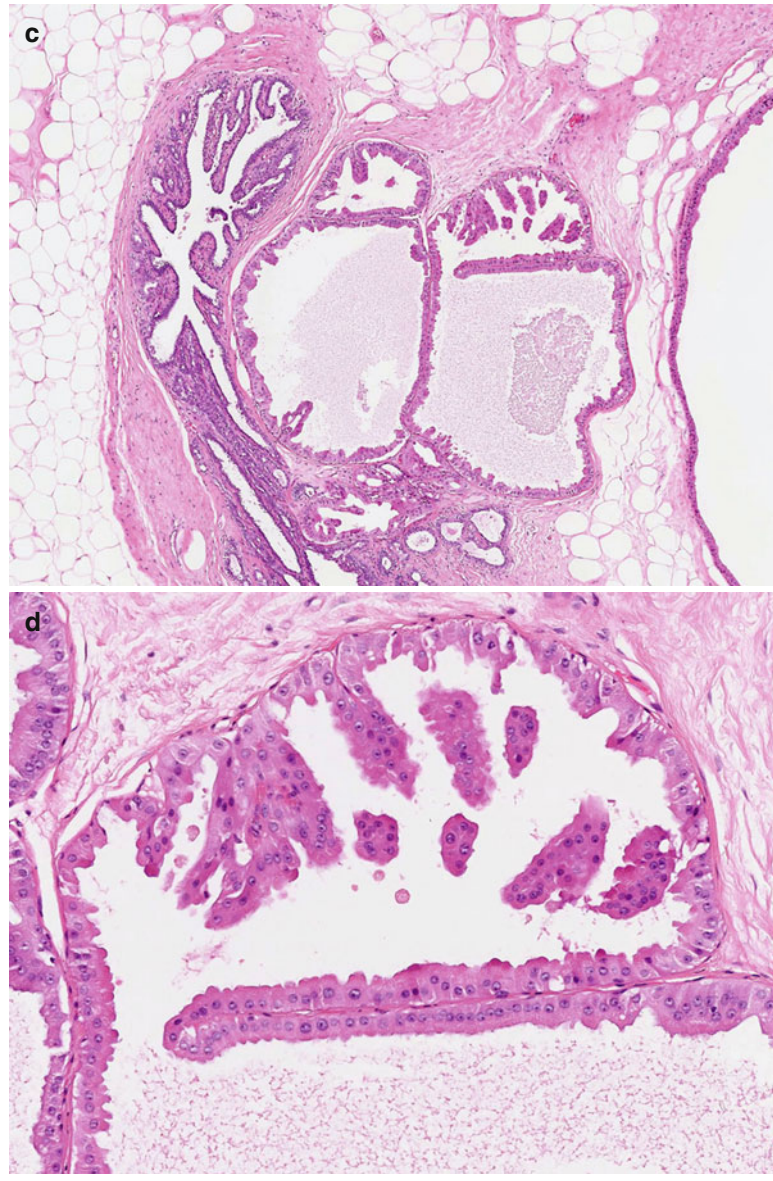


Fig. 7.7 (**a**) In excisional biopsies fibrocystic change consist of dilated ducts and lobular units. (**b**) Some cysts are lined by attenuated epithelium. (**c**) Other cysts are lined by hyperplastic apocrine epithelium. (**d**) At high magnification there is apocrine papillary hyperplasia, the apocrine cells show large amounts of eosinophilic cytoplasm with ill-defined cell borders. The nuclei are large with prominent nucleoli. There is no cytological atypia

Fig. 7.7 (continued)



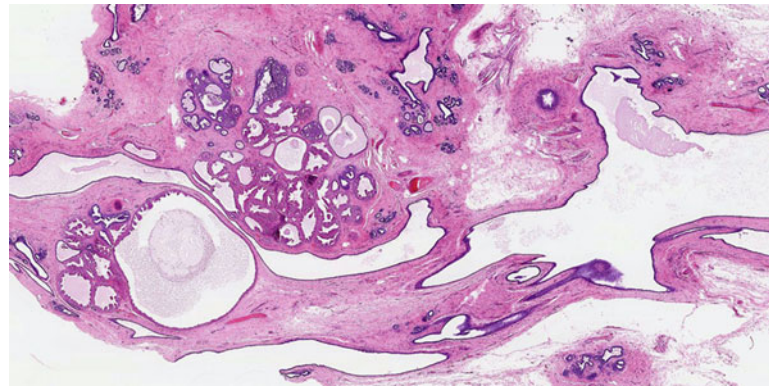


Fig. 7.8 Incidental duct ectasia and fibrocystic change with apocrine metaplasia from a mastectomy specimen for breast cancer

Table 7.1 Comparison of fibrocystic change and duct ectasia

Fibrocystic change	Duct ectasia
1. Mammographic calcification rare, when present has an amorphous pattern and may exhibit 'tea cup phenomenon'	Calcification common in the duct wall or lumen, usually dense with ring forms, needle-like and branching patterns
2. A disease of the terminal duct–lobular units	Disease of the ducts, lobules mainly affected by involution
3. Involves any part of the breast	Affects mostly the major subareolar ducts, spreads centrifugally, often segmental
4. No nipple discharge	Nipple discharge present in 20 % of patients with clinical disease
5. No nipple inversion	Nipple inversion may be present due to periductal fibrosis and traction on nipple summit
6. Inflammation uncommon, unless secondary to ruptured cysts	An inflammatory disease process, periductal mastitis usually present, +/– granulomas
7. Cysts round and ovoid with watery contents	Irregular dilated ducts containing thin contents initially and later thick creamy secretions
8. There is no elastin in the wall	Dilated ducts contain elastin in the wall
9. Cystic epithelial lining mostly apocrine, but becomes attenuated in chronically distended cysts. Epithelial hyperplasia with papillary features not uncommon	Apocrine metaplasia rare. Epithelium usually destroyed by inflammation, squamous metaplasia occasionally present
10. Lobular lumina empty or contain amorphous secretions with pale eosinophilia	Ductal lumina contain eosinophilic amorphous material, foamy macrophages +/– luminal occlusion due to fibrosis – 'mastitis obliterans'

Part of the text in this table was obtained from Cystic disease, duct ectasia, fat necrosis. 'Fibrous disease of the breast', Table 5-1. In: Problems in breast pathology, by J.G. Azzopardi (1979), pp 58–59, by the permission of the publisher, W.B. Saunders

specimens (average age 49.5 years) and on 200 non-cancerous specimens (average age 39 years). The study was to determine the composition of epithelial proliferations in the breast tissue. The authors identified apocrine epithelium with similar frequency in the non-cancerous and cancerous groups as follows: 30–40 years, 33 % and 25 %; 40–50 years, 47 % and 44 %; 50–60 years, 40 % and 31 %, with the first percentage representing non-cancerous specimens and the second cancerous specimens, respectively. Among the 300 cancers, Foote and Stewart identified only three cancers with apocrine features and only two cases had associated apocrine atypia. Based on these findings the authors did not believe apocrine metaplasia was a precursor of cancer, considering the prevalent nature of the lesion, a belief previously held by Dawson (1932). Similarly, Wellings and Alpers (1987) failed to demonstrate 'a continuous spectrum of lesions of apocrine metaplasia ranging from unequivocally benign through progressive stages of atypia to overt carcinoma . . .' when they performed subgross analysis of 186 autopsy breast tissue specimens and 107 breast cancer specimens.

Despite the above results, Haagensen (1986) reported the highest number of patients who developed carcinoma in association with apocrine epithelium. He reported that patients with apocrine epithelium were three times more likely to develop carcinoma than those without this type of epithelium. The majority of the cancers (85 %) in his study had apocrine features. In this series of more than 1,000 patients, Haagensen compared patients with gross cystic disease and apocrine epithelium with those without apocrine epithelium on biopsy. Five out of 225 (2 %) patients without apocrine epithelium, compared with 99 out of 957 (10.3 %) patients with apocrine epithelium, developed carcinoma. However, 76 of the 99 patients had biopsies with apocrine epithelium associated with other benign epithelial proliferations. In spite of this, Haagensen asserted that the evidence was not that of 'guilty by association' as apocrine epithelium was quite common in most breast tissue. In this dissertation

he illustrated progressive changes of benign apocrine epithelium through papillary epithelial proliferations and associated nuclear atypia and subsequent transformation to malignancy. The prevalence of carcinoma with apocrine features in this study appears quite high if one considers how infrequent apocrine carcinoma is in routine breast cancer pathology. However, with use of GCDFP-15 immunocytochemistry, more cancers with apocrine features can be identified (Eusebi et al. 1986; Mazoujian et al. 1983).

In a separate study Page and colleagues (1978) followed up patients with 'fibrocystic disease' over a period of 15–24 years. Although in this study, the term fibrocystic disease was applied loosely to include other benign lesions such as duct ectasia, ductal epithelial hyperplasia with atypia, atypical lobular hyperplasia, sclerosing adenosis and cysts, the authors separately analysed the risk associated with individual epithelial proliferations. Thirty-one out of 925 women developed cancer, most of them within a period of 10 years. Women with biopsies containing papillary apocrine epithelium had a similar risk of developing cancer to those with ductal hyperplasia without atypia. The RR for women over the age of 45 with papillary apocrine metaplasia was 2.71 and 2.65 for ductal hyperplasia without atypia. In a study of lower-category risk benign breast disease in women participating in Breast Cancer Prevention Trial in the National Surgical Adjuvant Breast and Bowel Project, Wang and colleagues (2004) identified 11,307 women's benign breast disease diagnosed on biopsy but without atypia or in situ carcinoma. 1,376 women had lower-category risk benign disease (LC-BBD) and 47 of them developed breast cancer. 674 women out of 1,376 had cysts and 26 of them developed invasive breast cancer. In this study Wang and colleagues took into account confounding effects of other epidemiological factors affecting breast cancer risk. The authors concluded that a diagnosis of cyst was an independent risk factor for breast cancer; the risk of breast cancer in patients with cysts was 60 % higher than the risk in those who have no form of breast disease with a RR of 1.60 (95 % CI = 1.07–2.40).

In a follow-up study, Page and colleagues (1996) identified 2,876 cases with apocrine epithelium among 10,357 benign biopsies. The papillary apocrine change was stratified according to the complexity of cytological and architectural features; 1,613 women with papillary apocrine change were followed-up for a median of 20 years. When women with concurrent atypical hyperplasia were excluded, the overall RR associated with papillary apocrine change was 1.2. Only 1 % of the biopsies exhibited highly complex patterns and 20 % of these had coexisting atypical hyperplasia. Women with highly complex patterns of apocrine change without atypical hyperplasia had a slightly increased relative risk of 2.4 (95 % CI = 0.77–7.04), but this was not statistically significant. Previously Dupont and Page (1985) reported a RR of 3.0 times that of the general population in women with cysts and a family history of cancer.

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Fibroepithelial Lesions

8

Learning Points

- Fibroadenomas and phyllodes tumour are collectively referred to as fibroepithelial tumours.
- Due to increased stromal cellularity, it is not always possible to differentiate a cellular fibroadenoma from a phyllodes tumour on needle core biopsy.
- Complex fibroadenomas are associated with an increased risk of subsequent breast cancer.
- Molecular evidence suggests that fibroadenomas are polyclonal therefore hyperplastic lesions and not neoplastic.
- Observational and molecular studies suggest fibroadenomas can transform into phyllodes tumours.
- Genetic abnormalities in both the stromal and epithelial components of fibroadenomas suggest the epithelium is potentially neoplastic.
- Phyllodes tumours are graded as benign, borderline and malignant.
- Fibroadenomatoid hyperplasia may be a precursor of multiple fibroadenomas.
- As there are no pathognomonic features of a hamartoma, the final diagnosis may be made on needle core biopsy.

8.1 Fibroadenoma

8.1.1 Clinical Features of a Fibroadenoma

The fibroadenoma is a benign tumour occurring most commonly in the second and third decades (Foster et al. 1988), becoming infrequent in postmenopausal women. In young patients, fibroadenomas tend to be cellular and the cellularity declines with age. Increase in cellularity can also be present in postmenopausal women, which has been attributed to a response to the unopposed action of oestrogens (Foster et al. 1988). Fibroadenomas commonly present as palpable lesions, but some tumours regress with age, and in postmenopausal women, they can be detected mammographically with or without associated calcification.

Hunter et al. (1996) reviewed the occurrence of fibroadenomas in postmenopausal women who were referred for biopsies at the Tucson Breast Center, Arizona. A total of 100 fibroadenomas were reported in 709 breast biopsies. Fifty-two of the fibroadenomas were in premenopausal women and 44 in postmenopausal women. Eleven of the 44 postmenopausal women reported hormone use. Fibroadenomas constituted 20 % (39/195) of benign masses and 12 % (39/339) of all masses in postmenopausal women and 10 %

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_8, © Springer-Verlag Berlin Heidelberg 2014

of all the biopsies (44/447) in postmenopausal women, which included abnormal calcifications or other lesions. Not all fibroadenomas in postmenopausal women were calcified. This study highlights the fact that fibroadenomas are common breast lesions in postmenopausal women who also fall into the screening age group. The importance of accurate radiological assessment of fibroadenoma is to exclude well-circumscribed malignant tumours such as mucinous carcinoma, medullary carcinoma, intracystic papillary carcinoma, sarcoma, phyllodes tumours, metastatic deposits, or lymphoma.

The incidence of fibroadenomas is variable depending on the publication. Dent et al. (1988) reported the prevalence of fibroadenoma to be 7–13 % in women attending breast clinics. Franyz et al. (1951) reported the occurrence of fibroadenoma in 9 % at post-mortem examination. Overall fibroadenomas comprise 50 % of all breast biopsies and the rate increases to 75 % for biopsies in women under the age of 20 (Dent and Cant 1989). Fibroadenomas are more common in black than Caucasian women (Funderburk et al. 1972). Yu and colleagues (1992) assessed the risk factors of fibroadenoma in a case–control study involving 117 fibroadenomas in Adelaide, (Australia) in patients seen between 1983 and 1985. A high Quetelet index (body mass index [BMI]) was associated with reduced risk of developing a fibroadenoma. Age at menarche and age at menopause had no effect on the occurrence of fibroadenomas. The risk of fibroadenomas decreased with the number of full term pregnancies but was increased with use of oral contraceptives at an early age (under 20 years). Alcohol intake and dietary fat intake were not associated with risk increased of fibroadenomas, whereas cigarette smoking and daily vitamin C intake reduced the risk of fibroadenomas.

A fibroadenoma usually presents as a discrete, non-tender mobile lump, (breast mouse) 1–2 cm in diameter and can arise anywhere in the breast. In 10–20 % of the patients, they have two to four tumours in the same breast. These multiple fibroadenomas can present simultaneously or present at different stages over a period of months to years (Williamson et al. 1993). Multiple fibroadenomas have been reported in families raising the possibility of familial predisposition (Haagensen 1971; Nigro and Orgen 1976; Naraynsingh and Raju 1985). Carney's syndrome is characterised by the presence of cardiac myxomas, spotty pigmentation, endocrine psammomatous melanotic schwannomas and myxoid fibroadenomas (Carney and Toorkey 1991). When Carney and Tooley reported this condition in 145 patients, 31 (21 %) had breast lesions. The breast lesions consisted of accumulation of myxoid material in single lobules, a collection of lobules and in fibroadenomas (myxoid fibroadenomas). The myxoid breast lesions were multicentric and bilateral in eight patients (38 %). The breast lesions were the presenting symptoms as part of Carney's syndrome in six patients (19 %). The authors advised the clinicians to consider evaluation of the patient and family for the syndrome if a myxoid fibroadenoma is reported pathologically. Carney syndrome is inherited as an autosomal dominant condition and the gene was mapped to chromosomes 2p16 and 17q22-24 (Kischner et al. 2000a). The gene PRKAR1A encodes for type 1A regulatory subunit of protein kinase A (PKA) is a tumour suppressor gene on chromosome 17 and is mutated in Carney complex (Kischner et al. 2000b). In nonfamilial setting, myxoid degeneration causes enlargement of biopsy-proven fibroadenomas in patients on follow-up leading to excision, on suspicion of malignancy (Yamaguchi et al. 2011).

When a fibroadenoma presents as a large mass more than 5 cm in diameter or weighing ≥500 g, the term giant fibroadenoma is applied (Dent and Cant 1989). Giant fibroadenomas affect both adolescent girls and mature women. In mature women, giant fibroadenomas arise in pregnant or lactating women. Because giant fibroadenomas tend to affect adolescent girls more than mature women, the terminology giant fibroadenoma is often used synonymously with juvenile fibroadenoma. A conventional fibroadenoma can also arise in adolescent girls. However, when a giant fibroadenoma arises in an adolescent girl, the tumour grows rapidly, causing breast asymmetry and discomfort (Matz et al. 2013). This requires appropriate surgical skills to ensure satisfactory cosmesis in a young woman.

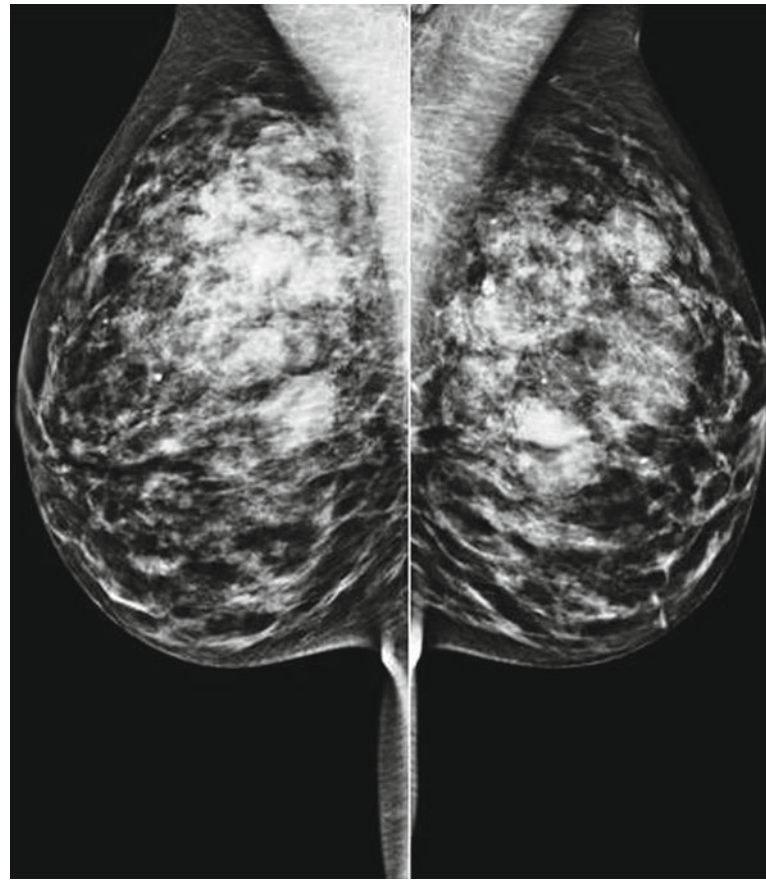


Fig. 8.1 The mammogram of a patient who presented with bilateral and multiple fibroadenomas. Despite the dense breasts, the fibroadenomas can be clearly delineated as well-circumscribed soft tissue masses. The patient also had cysts which were highlighted on ultrasound

8.1.2 Mammographic Features of Fibroadenoma

Both symptomatic (Fig. 8.1) and screen-detected fibroadenomas (Fig. 8.2) exhibit a well-circumscribed, round or oval image with or without lobulation on mammography. The mass may be characteristically demarcated from the surrounding tissue to create a halo which indicates benignity (Fig. 8.3). The halo sign is caused by a narrow radiolucent rim around the periphery of a lesion (Tabár and Dean 1985). Exceptionally, intracystic carcinoma or carcinoma arising in a fibroadenoma may give rise to a halo sign. The halo sign is reported to be present in 98 % of fibroadenomas (Sickles 1994). It can also differentiate fibroadenomas from malignant tumours such as medullary carcinoma (Lanyi 1986). Older fibroadenomas can become irregular and ill defined with or without calcification (Fig. 8.4). The calcification tends to be heterogeneous and the following patterns have all been reported in fibroadenoma: complete calcification of the fibroadenoma; coarse, popcorn-like bizarre calcification; evolving calcification, which can be linear, punctate, granular or pleomorphic (Heywang-Köbrunner et al. 2001). Partial calcification with an oyster-shell configuration and crescent-shaped appearance can be present if only part of the capsule is involved (Lanyi 1986).

8.1.3 Sonographic Features of Fibroadenoma

Ultrasound is useful in assessing well-circumscribed tumours to differentiate solid from cystic lesions. Furthermore, fibroadenomas are more prevalent in young women with dense breasts which can render the fibroadenoma

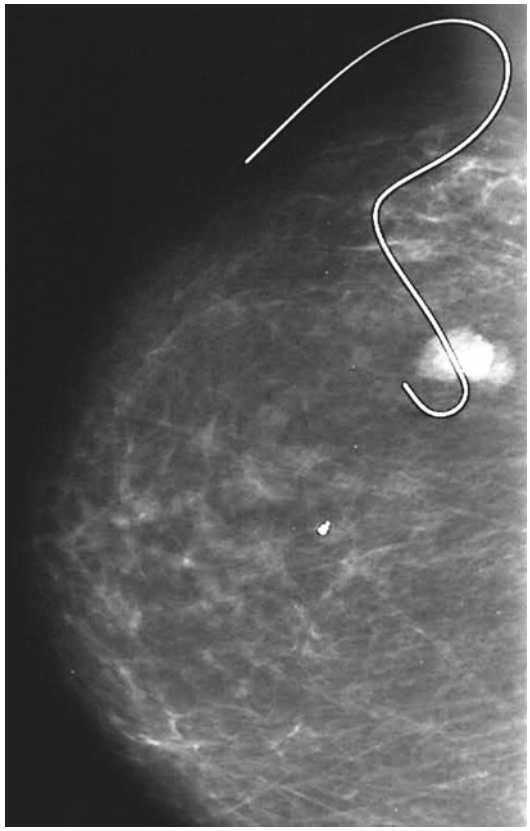


Fig. 8.2 This mammogram shows a screen-detected fibroadenoma with a guide wire in situ prior to excision

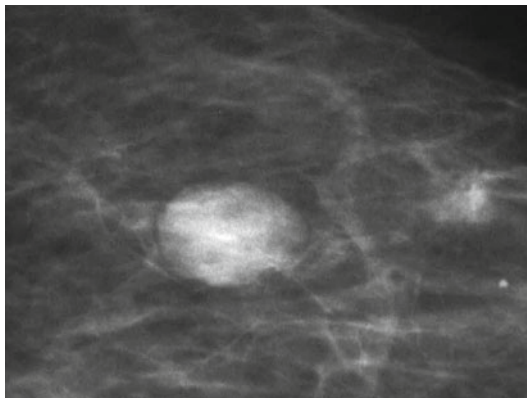


Fig. 8.3 A dark rim around this screen-detected fibroadenoma is the halo sign which indicates benignity

mammographically occult. A fibroadenoma is more easily outlined using ultrasonography in dense breast tissue than in a fatty background (Zonderland 2002). Some fibroadenomas cannot

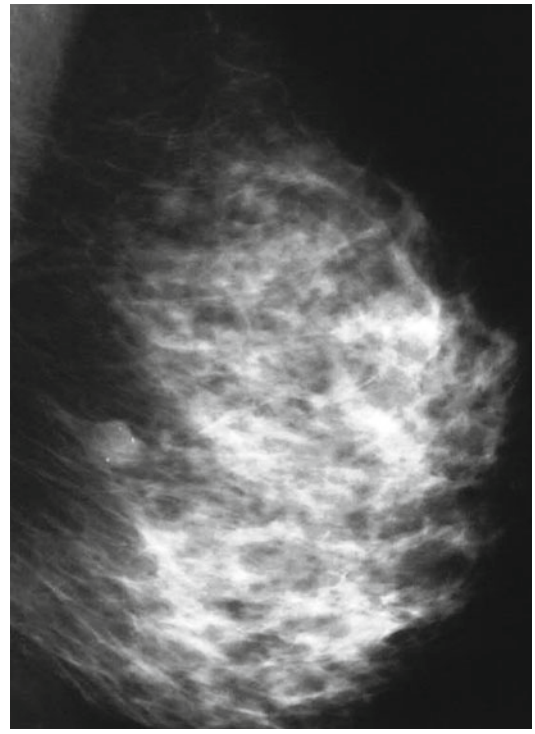


Fig. 8.4 Long-standing fibroadenomas calcify which can be detected mammographically

be detected by ultrasound because they are isoechoic with the surrounding tissue. The ultrasonographic appearances of a fibroadenoma include a well-defined round or oval lesion (Fig. 8.5) with a lobulated contour and homogeneous internal echoes (Jackson et al. 1986). In older patients the fibroadenomas tend to become hyalinised with or without calcification and this often produces a heterogeneous appearance on ultrasound (Fig. 8.6). In a hyalinised fibroadenoma, the lesion exhibits weak acoustic shadowing with partial obliteration of the posterior border. Acoustic shadowing becomes more prominent in calcified fibroadenomas.

Typical ultrasonic features of fibroadenomas are present in only 20–30 % of cases (Heywang-Köbrunner et al. 2001). Skaane and Engedal (1998) carried out a prospective study of 142 women with fibroadenomas and 194 women with invasive ductal carcinoma to determine the predictive power of sonography in differentiating fibroadenomas from invasive carcinomas. The

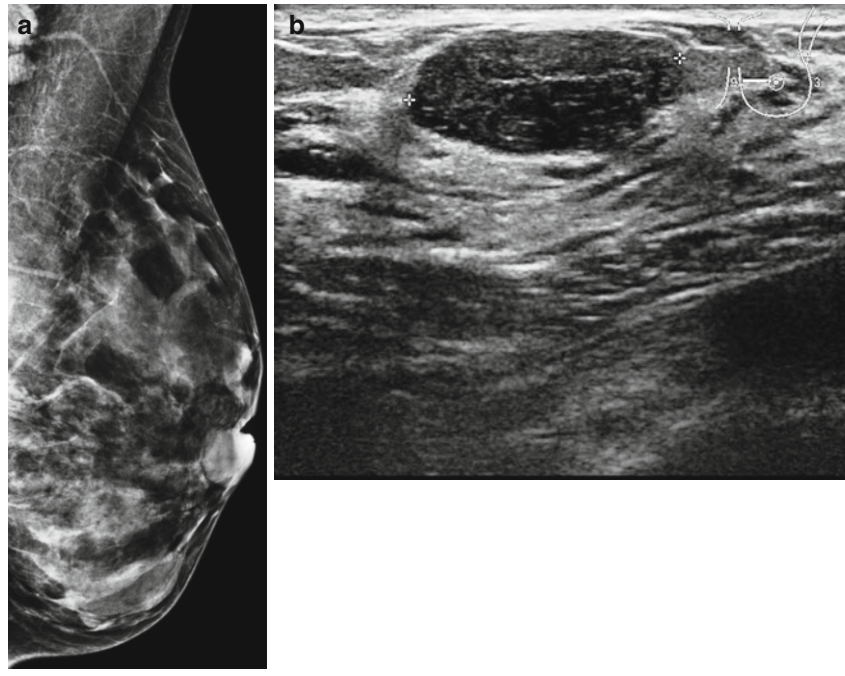


Fig. 8.5 (**a**) Dense breast in a patient who presented with lump which was mammographically occult. (**b**) Ultrasound outlined a well-circumscribed fibroadenoma confirmed on needle core biopsy

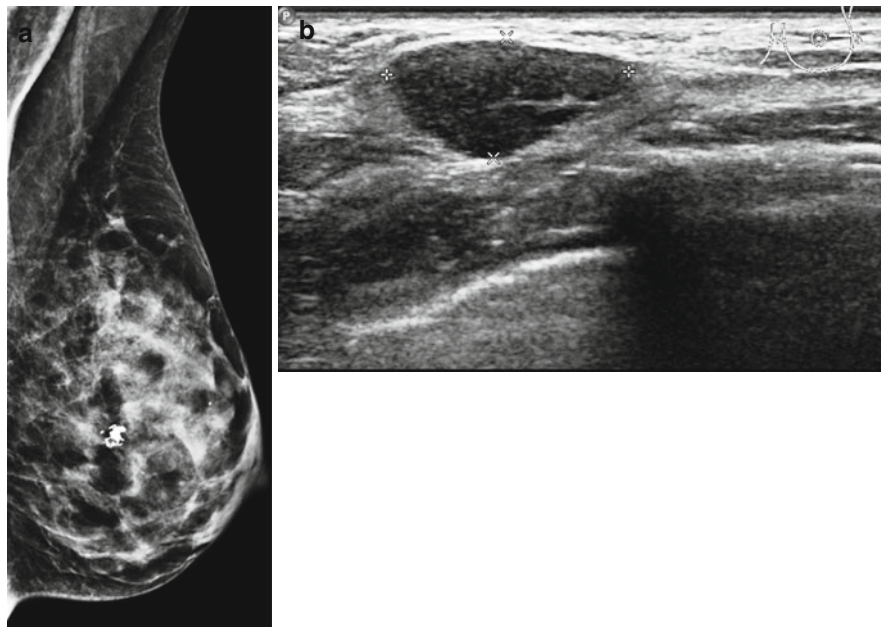


Fig. 8.6 (**a**) Screen-detected fibroadenoma with irregular calcification in a dense breast. (**b**) The ultrasound revealed a well- circumscribed lesion confirmed as fibroadenoma on biopsy

parameters studied included shape, contour, echo texture, echogenicity, sound transmission and the surrounding tissue related to the tumours. The authors reported that irregular shape and contour, extensive hypoechogenicity, shadowing, echogenic halo and distortion of surrounding tissue were features highly predictive of malignancy. A thin echogenic pseudocapsule was an important

predictive feature in benign solid masses. Echo texture was of little value in the differentiation of benign from malignant tumours. The study reported significant overlap of sonographic features in benign and malignant tumours. In an earlier study, Jackson and colleagues (1986) reported that the ultrasound diagnosis of fibroadenoma was correct in 50 out of 76 (65.8 %) histologically confirmed fibroadenomas. The classic features of fibroadenoma with smooth, round or oval mass with homogeneous internal echoes were present in only 12 fibroadenomas. Retrospective review revealed 14 fibroadenomas, which were not visible on ultrasound. The majority of the fibroadenomas had one or more atypical features such as irregular border, lobulation, inhomogeneous internal echo texture or posterior shadowing. Four masses, which were sonographically compatible with fibroadenomas, turned out to be carcinomas. This highlights the necessity of histological diagnosis in all breast masses.

8.1.4 Magnetic Resonance Imaging of Fibroadenoma

Magnetic resonance (MR) imaging is being used increasingly as an adjunct to mammography and ultrasound to differentiate benign from malignant lesions. Young fibroadenomas are highlighted by MR as well-circumscribed focal enhancement with associated non-enhancing internal septations that correspond pathologically to the fibrous bands (Heywang-Köbrunner and Boetes 2002). However, fibrotic fibroadenomas do not enhance or do so only minimally. Therefore, MR is more sensitive in differentiating fibrotic fibroadenoma from malignant lesions than young cellular fibroadenomas from malignant lesions, because of increased enhancement in the latter lesions (Heywang-Köbrunner et al. 2001). Hochman et al. (1997) investigated the histopathological features of fibroadenomas in relation to MR images. They assessed 23 fibroadenomas in 21 patients aged 23–66 years. The fibroadenomas were examined with gadolinium-enhanced MR and were graded for signal intensity, contrast material enhancement, shape and internal septations. The results were correlated with the histopathological findings. Eleven fibroadenomas demonstrated signal intensity without enhancement, and low-signal intensity without enhancement was noted in nine fibroadenomas. Low-signal intensity and lack of enhancement were associated with more sclerotic stroma and older patients. Nineteen out of 23 fibroadenomas (83 %) were lobulated, oval or round. Internal septations were identified in nine out of 14 fibroadenomas (64 %). The study demonstrated varied MR images of fibroadenoma, and this limited the ability to distinguish between benign and malignant masses on the basis of signal intensity and enhancement alone. Lobulation and internal septations, which reflect the intrinsic growth pattern of the fibroadenomas on MR, were more reliable as discriminatory features.

8.1.5 Pathology of Fibroadenoma

The diagnosis of a fibroadenoma can be made on FNAC or needle core biopsy. On FNAC, the smears contain benign epithelial cells with two cell types, i.e. dark-staining myoepithelial cells and light-staining luminal cells (Fig. 8.7). In the background there are bare nuclei without cytoplasm and these are myoepithelial cells. Cytology can be the definitive diagnosis in adolescent or young women as the fibroadenomas are invariably cellular and with a low risk of false-negative diagnosis. As fibroadenomas are known to regress, conservative management is preferable in young woman. In the older woman or screen-detected fibroadenoma, a needle core biopsy is more appropriate. The needle core biopsy can demonstrate a cellular fibroadenoma, hyalinised fibroadenoma or myxoid fibroadenoma. Needle core biopsies may assist in differentiating a fibroadenoma from a phyllodes tumour where possible. Histologically fibroadenomas have been classified as intracanalicular and pericanalicular, but this has no prognostic relevance and will not be referred to in this book.

Macroscopically fibroadenomas exhibit a well-circumscribed nodule with a vaguely lobulated pattern, white firm cut surface with no

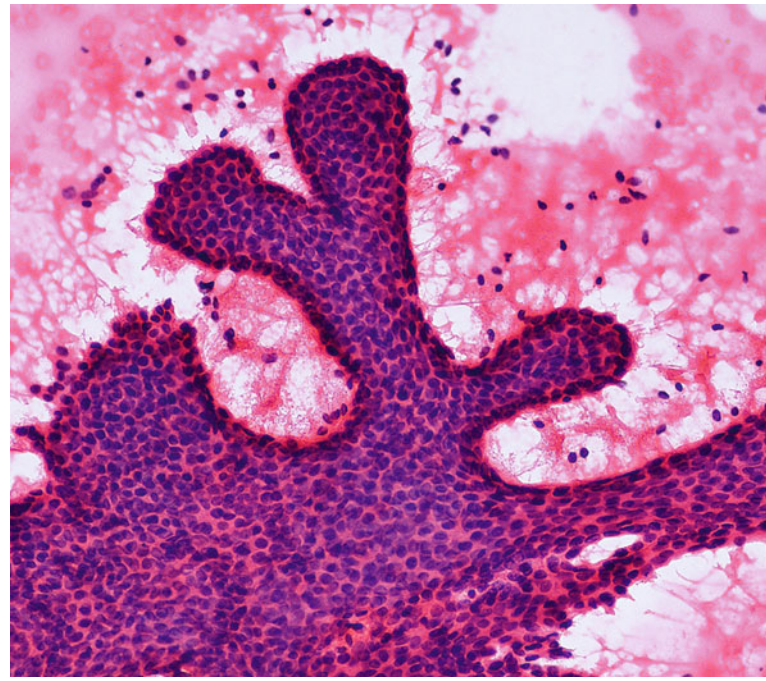


Fig. 8.7 FNAC from a fibroadenoma in an 18-year-old girl shows 'staghorn'-shaped monolayer of cell with two cell types and bare nuclei in the background (H& E stain)

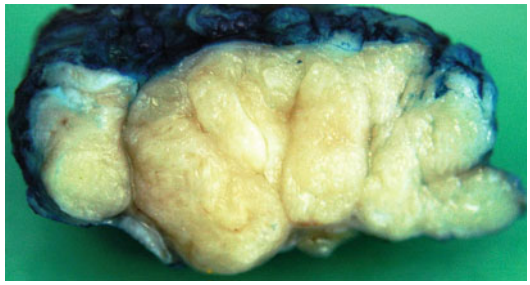


Fig. 8.8 Macroscopically a fibroadenoma has a white solid, vaguely lobulated appearance with no haemorrhage or necrosis

haemorrhage or necrosis (Fig. 8.8). The histological features of a fibroadenoma are variable depending on the age of the patient. In a young patient below the age of 40, the fibroadenoma shows a mixture of epithelium separated by viable stroma (Fig. 8.9). There is no increase in cellularity of the stroma, cytological atypia or mitotic activity. Fibroadenomas in postmenopausal women, which are usually screen-detected, show hyalinised stroma and in this case there is associated calcification (Fig. 8.10). Myxoid fibroadenomas show loose stroma due to myxoid degeneration (Fig. 8.11). Myxoid degeneration can cause the fibroadenoma to increase in size during follow-up. Rarely myxoid fibroadenoma can be part of Carney's syndrome. A complex fibroadenoma shows mixture of epithelial proliferation such as usual ductal epithelial hyperplasia, apocrine metaplasia and sclerosing adenosis, cysts with or without calcification (Fig. 8.12).

8.1.6 Heterogenous Proliferations of a Fibroadenoma

Fibroadenomas can harbour an array of epithelial proliferations including mucin-filled ducts (Fig. 8.13) and columnar cell lesions (Fig. 8.14). Kuijper and colleagues (2001) carried out a systematic examination of 396 fibroadenomas from 358 patients to determine the histological features of epithelium and stroma within and adjacent to the fibroadenomas. The mean age of the patients was 33.4 ± 12.1 years (range 12–81 years). The sizes of fibroadenomas ranged from 0.1 to 22 cm, mean 1.5 ± 1.4 cm (SD).

Multiple fibroadenomas were identified in 28 patients (78 %), which were ipsilateral in 17 (61 %) patients and bilateral in 11 (39 %) patients.

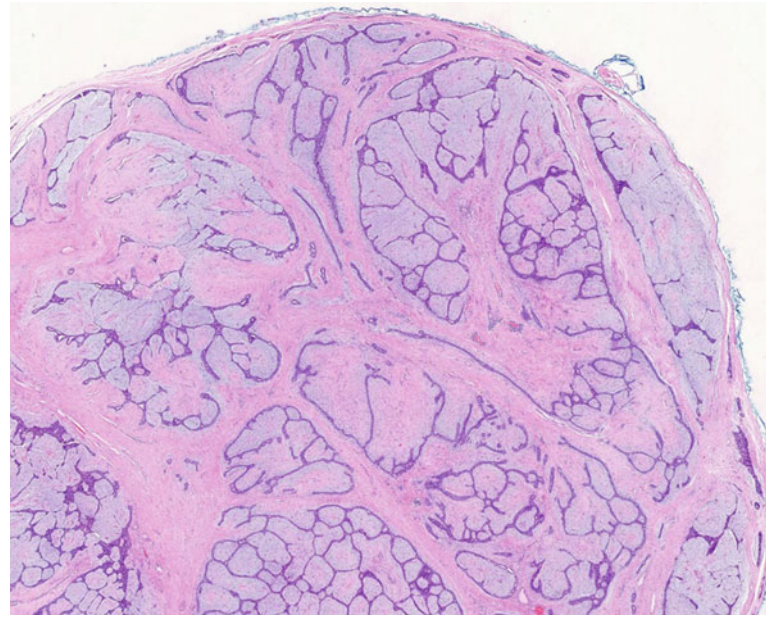


Fig. 8.9 Conventional fibroadenoma consisting mixed epithelial and fibrous proliferation to duplicate the macroscopic lobulated appearance. There is no increase in cellularity or cytological atypia

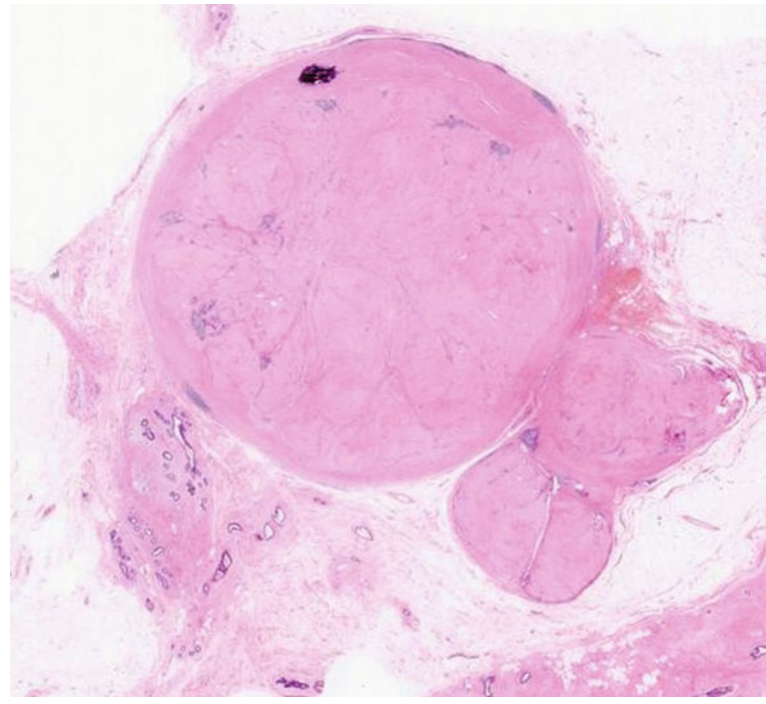


Fig. 8.10 Screen-detected fibroadenoma with a hyalinised stroma and focal calcification (From Fig. 8.2)

The main epithelial proliferations which the authors identified included mild ductal hyperplasia, 45 (11.6 %); moderate ductal hyperplasia, 106 (26.8 %); florid ductal hyperplasia, 21 (5.3 %); ADH, 1 (0.3 %) but no ALH; DCIS, 5 (1.3 %); LCIS, 3 (0.8 %) but no invasive carcinoma; fibrocystic change with apocrine metaplasia 111, (28 %); cysts, 20 (5.1 %); sclerosing adenosis, 49 (12.4 %); calcifications, 15 (3.8 %); microglandular adenosis, 1 (0.3 %); and papilloma, 7 (1.8 %).

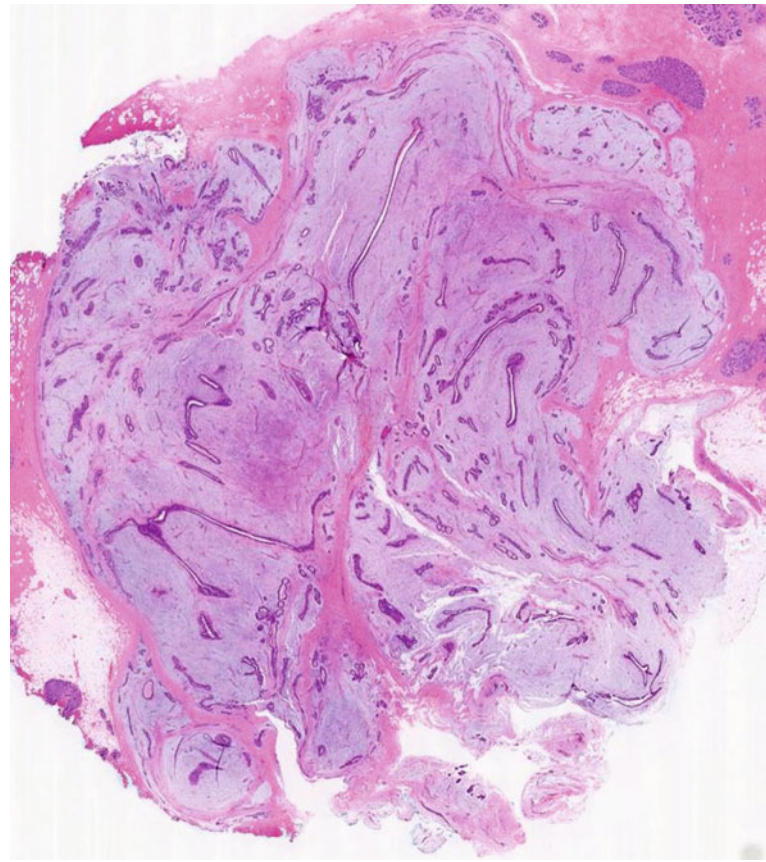


Fig. 8.11 Myxoid fibroadenoma consisting of loose stroma surrounding irregular epithelial proliferation. The border is ill-defined border. The ultrasound was reported as a heterogenous lobulated mass and graded as U3

Other minor features identified were pseudolactational changes, squamous metaplasia, stromal pseudoangiomatous changes, stromal smooth muscle changes, foci of tubular adenoma and focal phyllodes tumour. Overall 4.39 % of the fibroadenomas contained epithelial hyperplasia, and when mild hyperplasia was excluded, significant hyperplasia was present in 32.3 % of the fibroadenomas. The complexity of the fibroadenoma was associated with the presence of epithelial hyperplasia. The mean age of the patients with DCIS and LCIS was 51.7 years which was significantly older than patients without the in situ carcinoma (CIS) ($p<0.001$). CIS arising within a fibroadenoma and also present in the adjacent breast tissue was identified in three out of eight patients. 40.4 % of the fibroadenoma had complex features with 18 % of the fibroadenomas containing more than one complex feature, i.e. fibrocystic change with apocrine metaplasia, cyst, sclerosing adenosis and calcification. Complex fibroadenomas were seen more in older women (mean age: 35.4 years; $p=0.009$).

Kuijper and colleagues also evaluated the proliferation activity in the tissue surrounding the fibroadenoma and reported the following features: mild hyperplasia, 16 (5.1 %); moderate ductal hyperplasia, 22 (6.9 %); florid ductal hyperplasia, 3 (0.9 %); ADH, 2 (0.6 %); ALH, 2 (0.6 %); LCIS, 1 (0.3 %); DCIS, 6 (1.9 %); invasive carcinoma, 3 (0.9 %); fibrocystic change with apocrine metaplasia, 75 (23.7 %); cysts, 8 (2.5 %); sclerosing adenosis, 46 (14.5 %); calcifications, 11 (3.5 %); microglandular adenosis, 6 (1.9 %); papilloma, 1 (0.3 %) and pseudolactational changes, 4 (1.3 %). The authors attributed the CIS arising within the fibroadenoma to be related to the high percentage of fibroadenomas with complex proliferations in their series and they concluded this increased the risk of

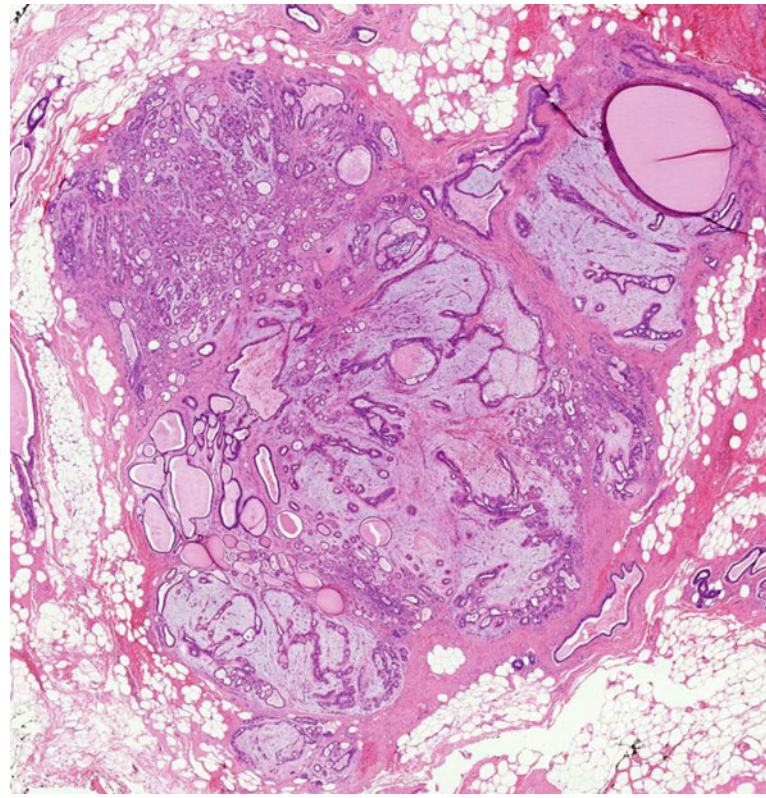


Fig. 8.12 A complex fibroadenoma in a 54-year-old woman showing myxoid stroma, sclerosing adenosis and multiple cyst

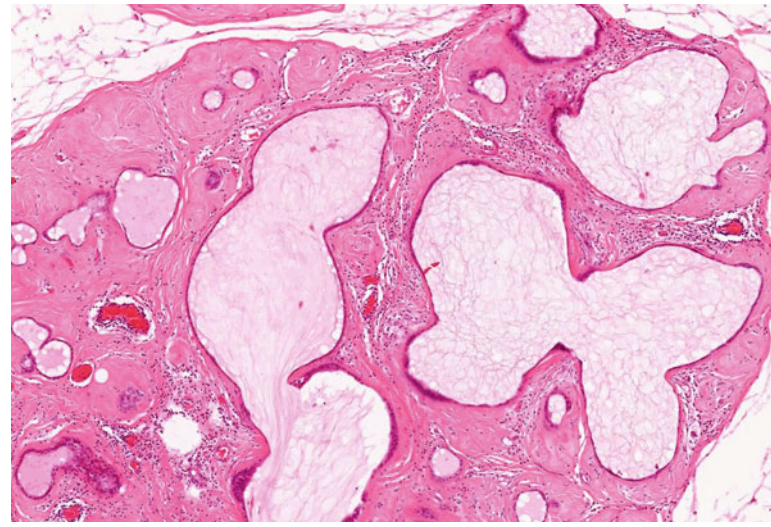


Fig. 8.13 A fibroadenoma containing multiple mucin-filled ducts or cysts in a hyalinised fibrous stroma

subsequent carcinoma. However, they considered the presence of CIS and invasive carcinoma in the adjacent epithelium as coincidental. There was overall 8.8 % of fibroadenomas with hyperplasia in the surrounding tissue. The authors did not feel this was sufficient to calculate risk of cancer conferred by this external proliferation. In a separate study, Dupont et al. (1994) reported 13.7 % occurrence of hyperplasia in the adjacent tissue with an associated RR of cancer of 3.9. Most fibroadenomas were enucleated or excised with minimal surrounding tissue because they are

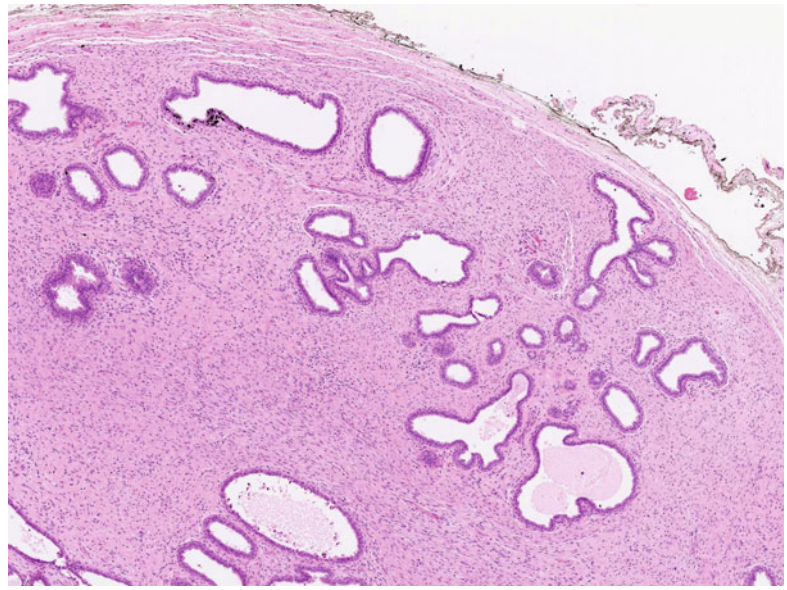


Fig. 8.14 A fibroadenoma containing columnar cell change characterised by distorted TDLU lined by columnar epithelium with apical snouts

benign lesions. Based on the findings of their study, Kuijper and colleagues advocate excision of fibroadenoma in women older than 35 years as this will remove potentially malignant lesions arising in fibroadenomas.

Sklair-Levy et al. (2008) reviewed 401 fibroadenomas and identified 63 (15.7 %) lesions which qualified as complex fibroadenomas. The average size of complex fibroadenomas was 1.3 ± 0.57 cm (range 0.5–2.6 cm) which was half the size of a simple fibroadenoma, average 2.5 ± 1.44 cm (range 0.5–7.5 cm), $p < 0.001$. On average, patients with complex lesions were 18.5 years older (median, 47 years; range, 21–69 years) than patients with simple fibroadenomas (median, 28.5 years; range 12–86 years), $p < 0.001$. Fifty-six (89 %) of complex fibroadenomas were graded as BI-RAD 3 or 4 on mammography or ultrasound and seven patients (11 %) had no imaging investigations. The diagnosis of complex fibroadenoma was made on needle core biopsy in 23 women (36.5 %), on needle core biopsy and excisional biopsy in 20 women (31.7 %), and on excisional biopsy alone in 20 women (31.7 %). Twenty-one of the 23 women with the diagnosis of complex fibroadenoma on needle core biopsy had no excisional biopsy and followed up; the masses were unchanged on mammography and ultrasound with a mean follow-up of 24.1 months (range, 10–48 months). The other two patients were lost to follow-up. Twenty patients had excisional biopsies following diagnosis of complex fibroadenoma on needle core biopsies; one patient had a diagnosis of invasive lobular carcinoma and two had phyllodes tumours. Based on these findings, the authors recommended that complex fibroadenomas are associated with a low risk of malignancy and should be managed as simple fibroadenomas if diagnosed on needle core biopsies. If there is no atypia, the lesions should be monitored on mammography and sonography biannually for 2 years and annually thereafter. This view is contradictory to Kuijper et al. 9999who attributed the presences of CIS in fibroadenomas to the presence of complex features in the fibroadenomas.

8.1.7 Is a Fibroadenoma a Hyperplastic or Neoplastic Lesion?

There is conflicting information as to whether a fibroadenoma is neoplastic or hyperplastic proliferation. Morphologically some authorities classify a fibroadenoma as hyperplastic because it is an abnormal development of lobule (Dixon 1999),

and this is supported by the following factors (Hughes et al. 1987):

(a) Use of special stains shows that each fibroadenoma develops from a single lobule.
(b) Fibroadenomas histologically closely resemble hyperplastic lobules which are common in normal breasts.
(c) Growth of most fibroadenomas stops after they reach 2–3 cm in diameter or a significant percentage of them spontaneously regress.
(d) Fibroadenomas show some hormonal dependency as the normal breast, i.e. some fibroadenomas grow rapidly during pregnancy and they lactate.

Molecular pathology has not been helpful because there are publications which report a fibroadenoma as polyclonal lesion and thus hyperplastic and others as monoclonal and therefore neoplastic. Noguchi et al. (1993) assessed the clonality of 10 fibroadenomas and five phyllodes tumours using PCR to assess the Big chromosome-linked gene PGK (phosphoglycerokinase). The stromal and epithelial elements in the fibroadenomas were polyclonal, whereas the stromal elements in phyllodes tumour were monoclonal but the epithelium was polyclonal. In a separate study Kuijper et al. (2002) also confirmed the polyclonal nature of the fibroepithelial elements in a fibroadenoma and the stroma in phyllodes tumours was monoclonal. In contrast, Cavall et al. (2001) claimed alterations in 10 cell cultures from 10 fibroadenomas in chromosomes X, 12, 14, 20 and 22, suggesting a neoplastic phenotype.

8.1.8 Fibroadenoma as Risk Factor for Malignancy

Although there are several publications, mostly as case reports (Buzanowski-Konakry et al. 1975; Pick and Iossifides 1984; Umemura et al. 1994; Tissier et al. 2000) documenting the presence of in situ or invasive cancer arising in a fibroadenoma, there is no consensus as to whether the association is coincidental in older women at risk of cancer or whether the fibroadenoma is precancerous. Fibroadenomas arise from terminal duct–lobular units, the same functional unit for lobular and ductal carcinoma. This was thought to account for the increased risk of carcinomas in fibroadenomas in the older women. Pick and Iossifides (1984) reported the presence of lobular carcinoma in situ in 65 % of the 62 cases of carcinoma arising in fibroadenoma. These authors concluded that the presence of carcinoma in the fibroadenomas was coincidental rather than the fibroadenoma being a risk factor for the carcinomas. Other studies also reported a disproportionately high prevalence of carcinoma in situ (mostly lobular) arising in fibroadenomas (Buzanowski-Konakry et al. 1975; Ozzello and Gump 1985). The authors advocated that carcinoma arising in fibroadenomas should not be treated differently from that arising de novo.

Dupont and colleagues (1994) reviewed 2,458 fibroadenomas diagnosed between 1950 and 1968, and 558 (22.1 %) were classified as complex fibroadenomas. Lesions were classified as complex fibroadenomas if they contained cysts greater than 3 mm in diameter, sclerosing adenosis, epithelial calcification or papillary apocrine changes (Dupont and Page 1985). From the biopsies, 1,835 (90 %) women were eligible for the study and consisted of 1,412 women with non-complex fibroadenomas and 422 women with complex fibroadenomas. In addition to assessing the presence of complex features in the fibroadenomas, the authors also assessed the type of epithelial proliferation in the parenchyma surrounding the fibroadenoma. Other factors assessed included race, family history of breast cancer, parity, age at first delivery, age at menarche and age at menopause. Eighty-seven women with fibroadenomas developed breast cancer on follow-up, 58/1,413 (4.1 %) women with simple fibroadenomas and 29/422 (6.9 %) complex fibroadenomas. The controls were divided into two groups of women listed in the Connecticut Tumor Registry who were at risk of developing breast cancer and the patients' sisters-in-law nearest in age to the patient as population-based control. The overall RR for breast cancer was 1.61 in women with fibroadenomas when compared to 2.17 of the control group (relatives

to the sisters-in-law). The RR elevated to 3.10 in the later women with complex fibroadenomas and remained elevated for decades after diagnosis. The presence of proliferative disease in surrounding parenchyma of simple fibroadenomas elevated the RR to 3.88, which reduced to 3.47 in proliferations without atypia and elevated to 7.29 when atypical hyperplasia was present. Women with complex fibroadenomas and a family history of breast cancer had an RR of 3.72. The message from this paper is that a complex fibroadenoma is a risk factor for subsequent cancer and that the proliferations in the parenchyma surrounding the fibroadenoma should be assessed as this increases the risk in both simple and complex fibroadenoma. The authors also advised mammographic surveillance of women with complex fibroadenoma and a family history of breast cancer from the age of 35–40. Although the study had two control groups, only the results from the patients' sisters-in-law were included in the abstract and discussed in this paper. The value of RR for the Connecticut Tumor Registry women is much lower than the patients' sisters-in-law.

Seven years after Dupont and colleagues (1994) had documented the potential malignant risk associated with fibroadenomas, Carter et al. (2001) followed up women in the same cohort with fibroadenomas containing epithelial proliferations classified as ALH, ADH and epithelial proliferation with minimal atypia and no atypia. The overall prevalence of ALH and ADH in fibroadenomas was 0.81 %. Minimal or no atypia within a fibroadenoma appeared to be correlated with proliferative disease in the adjacent parenchyma but was not predictive of well-established atypia. Only 7 % of the women with well-developed atypia developed invasive carcinoma on follow-up. Three women with minimal atypia developed invasive carcinoma. The authors reported that atypia within a fibroadenoma did not predict for the presence of atypia in the adjacent parenchyma. They also reported that atypia confined to the fibroadenoma did not increase a clinically significant risk for subsequent breast carcinoma, greater than that of fibroadenoma alone. This statement is contradictory to RR of atypical hyperplasia in a fibroadenoma previously documented to be 7.29 by authors from the same institute (Dupont et al. 1994). In a separate study, McDivitt et al. (1992) reported a fibroadenoma as an independent risk factor with an RR of 1.7 for fibroadenoma without hyperplasia and 3.7 for fibroadenoma with hyperplasia but no atypia. The presence of atypical epithelial hyperplasia and fibroadenoma substantially increased the RR to 6.9.

8.1.9 Should a Pathologically Proven Fibroadenoma Be Excised?

With the use of stereotactic and vacuum-assisted needle core biopsies, it is possible to confirm the benignity of screen-detected fibroadenomas and spare these women unnecessary surgery. The age limit at which fibroadenomas should be excised varies from 30 to 40 years. This partly depends on the past experience of the institute. If a carcinoma was previously overlooked as a fibroadenoma, this creates anxiety among the clinicians, who would wish to avoid a similar occurrence. Shabtai et al. (2001) examined specimens from 147 patients with the diagnosis of fibroadenoma, 30 of which were mammographically detected. They reported the presence of epithelial proliferation in fibroadenomas in 48 % of the patients. The proliferations included sclerosing adenosis (23 %), duct ectasia (17.7 %), apocrine metaplasia (15.6 %), florid fibrocystic disease (12.9 %), duct papillomatosis (11.6 %), infiltrating ductal carcinoma (5.4 %), ductal carcinoma in situ (3.4 %) and a single case of lobular carcinoma in situ (0.6 %). Seven of the patients with breast cancer were older than 40 years. Based on these findings, they recommended surgical excision of fibroadenomas in women over 40 years of age. Other authorities recommend excision of fibroadenomas in patients over 35 years of age (Sainsbury et al. 1988; Kuijper et al. 2001) on the assumption that this will remove potentially malignant epithelium. The mean age of the 105 patients reported by Diaz et al. (1991) who had carcinoma (mostly in situ) associated with fibroadenoma was 44. From the patients' view, psychologically,

palpable fibroadenomas in younger women are more likely to be excised than a screen-detected impalpable lesion. Greenberg et al. (1998) provide an algorithm in the management of patients with fibroadenomas. The authors advocate follow-up of patients below the age of 35 years and to excise the fibroadenoma if it increases in size or if the fibroadenoma had not completely regressed by the age of 35 years. In women over 35 years of age, the authors advise follow-up for 6 and 12 months and excise if the lesion enlarges or if there is incomplete regression. The UK NHS Breast Screening Programme does not advise excision of biopsy-proven screen-detected fibroadenomas unless on patients' request. As with most breast lesions, multidisciplinary team discussion of the patient is essential. Besides surgery, cryoablation of the fibroadenomas has been considered a safe mode of treatment in women who desire definitive therapy without surgical intervention (Nurko et al. 2005).

8.2 Phyllodes Tumour

8.2.1 Clinical Features of Phyllodes Tumour

Phyllodes tumour, also termed cystosarcoma phyllodes (*Gk* sarcoma = fleshy tumour; phyllo = leaf-like) and was described by Johannes Muller in 1838 (Fiks et al. 1981). 'Cystosarcoma phyllodes' is a rarely used term in publications because not all phyllodes tumours are sarcomas, i.e. malignant based on the on the histological features. Phyllodes tumour is the terminology also used by the World Health Organization (1981) and depending on the histological features requires qualification as to whether it is benign, borderline or malignant. Phyllodes tumour is a rare lesion which accounts for 0.3–0.9 % of all breast tumours (Kessinger et al. 1972) with an incidence of 2.1 per million, which peaks between the ages of 45 and 49 years (Bernstein et al. 1993; Salvadori et al. 1989). The patients present with a rapidly growing mass. The mass is firm, nontender, mobile and well-circumscribed. The veins over the mass may be prominent. Ulceration and bilateral presentation are rare (Bernstein et al. 1993; Reinfuss et al. 1996). Some patients have past history of a fibroadenoma. Patients may also present with symptoms of metastatic disease in bone, lungs and liver (Abe et al. 2011). The differential diagnosis includes angiosarcoma, giant fibroadenoma, inflammatory cancer, breast abscess and lipoma.

8.2.2 Radiological Features of Phyllodes Tumour

Based on the radiological–pathological conferences of the University of Texas MD Anderson Cancer Center (Lifshitz et al. 2003), on mammography, phyllodes tumours appear lobulated, round or oval masses. They are usually well-circumscribed and not calcified (Fig. 8.15a). On sonography, phyllodes tumours are well-defined, solid masses with heterogenous internal echoes without posterior acoustic attenuation (Fig. 8.15b). A diagnosis of phyllodes should be considered if sonography reveals fluid-filled elongated spaces or clefts in the solid mass. It is difficult to differentiate phyllodes tumours from fibroadenomas on sonography or mammography. On T2-weighted MR images, phyllodes tumours are usually identified as oval, round or lobulated masses with circumscribed margins and homogenous high signal intensity. On dynamic contrast-enhanced MR images, phyllodes tumours show rapid enhancement (Lifshitz et al. 2003). MR imaging may be used to delineate the full tumour extent and potential satellite lesions before surgical excision. It is not possible to distinguish between a benign and malignant phyllodes tumour on the basis of sonographic and mammographic findings (Liberman et al. 1996). Figure 8.15a, b illustrates the mammographic and sonographic features of histologically proven benign phyllodes tumour. The initial needle core biopsy was reported as a fibroepithelial tumour of undetermined malignant potential, B3 (Fig. 8.15c), which required surgical excision.

8.2.3 Pathological Features of Phyllodes Tumour

Phyllodes tumours are classified into benign, borderline and malignant based on the characteristics

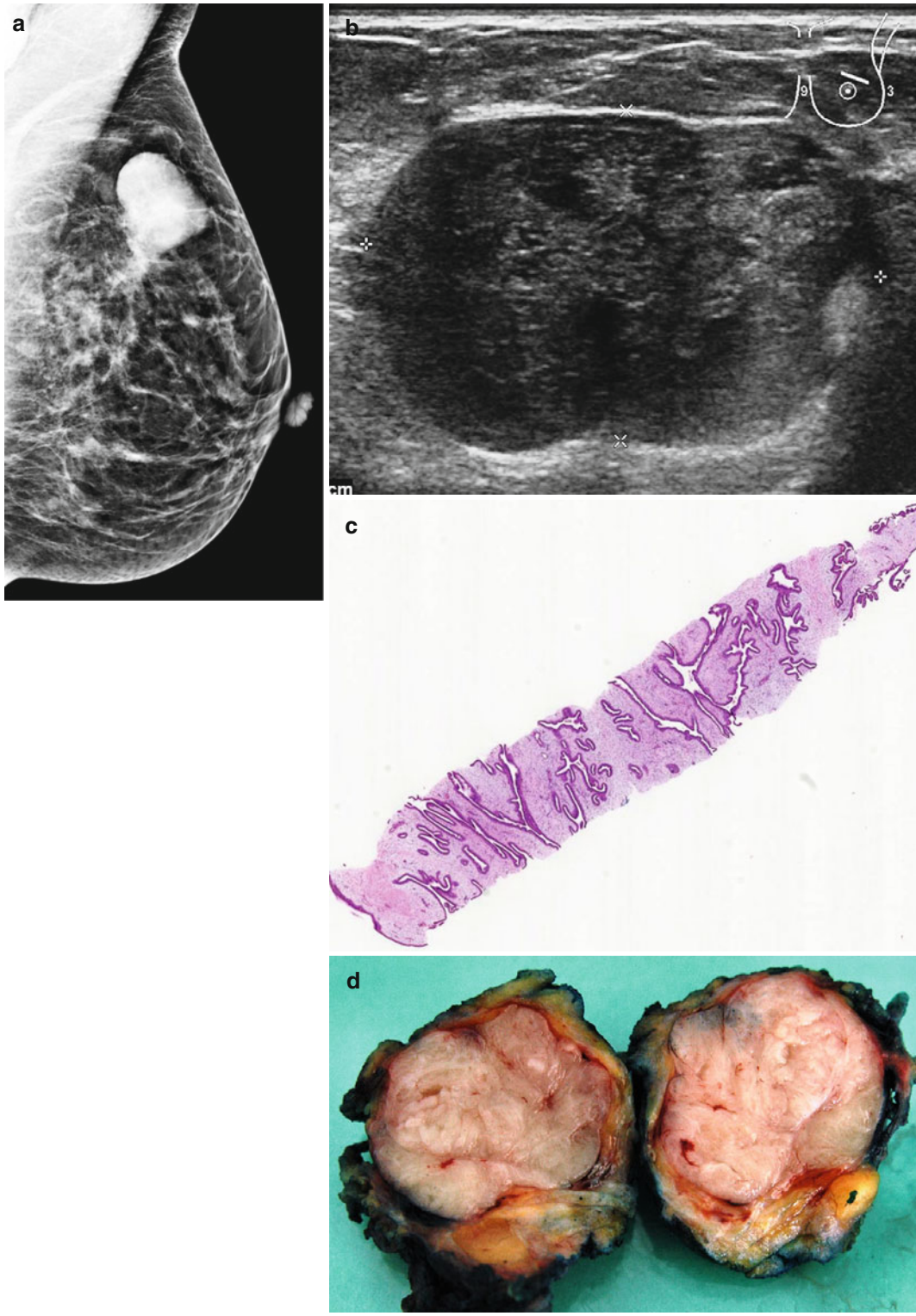
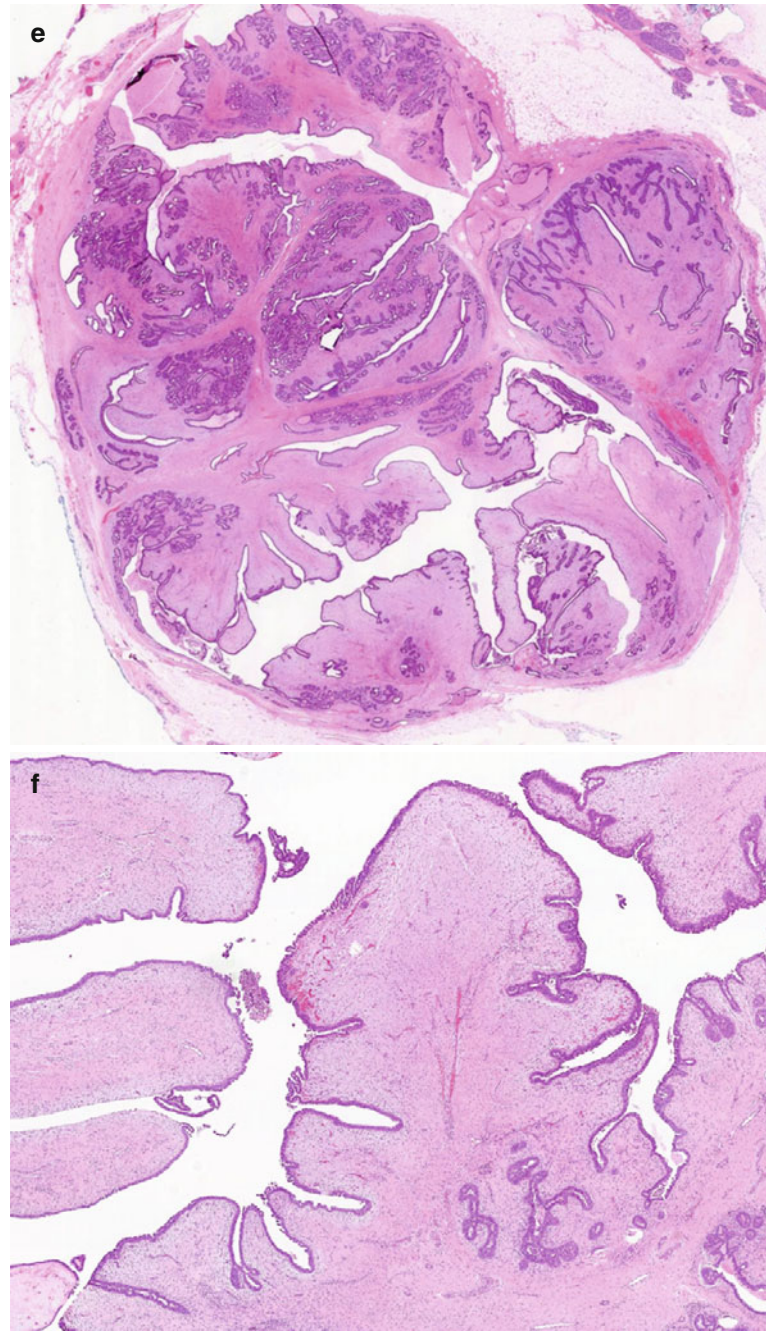


Fig. 8.15 (**a**) Mammographic appearance of a benign phyllodes tumour as a well-circumscribed soft tissue mass. (**b**) The ultrasound showed a well-defined mass with low echoes and small cystic areas; overall grade R4. (**c**) The needle core biopsy has reported a fibroepithelial tumour, B3. (**d**) The excised tumour shows a well-circumscribed mass with a white lobulated white cut surface. (**e**) The histology of the tumour show typical clefting growth pattern with variable cellularity. (**f**) Benign phyllodes tumour with no mitotic activity or cytological atypia at high magnification

Fig. 8.15 (continued)



of the stroma (Salvadori et al. 1989). Based on mitotic activity, Rosen (2009) classifies benign tumours to have 0–2/10HPF (high-power field), borderline/low grade malignant tumours, 2–5/10HPF and malignant tumour ≥6/10HPF.

Tan et al. (2005) carried out a review of 335 women diagnosed with phyllodes tumour in the Department of Pathology, Singapore General Hospital, to relate the pathological features to prognosis. At the time of writing, it was probably

the largest series of phyllodes tumours and provides comprehensive pathological features of phyllodes tumours. The women's ages ranged from 15 to 69 years (mean, 41.4 years; median, 42.0 years). The women were further subdivided in three age groups: younger than 25, N = 38 (11.3 %); 26–39 years, N-104 (31.0 %) and 40 years or older, N = 193 (57.6 %). The tumours affected the right and left breasts equally and two women had bilateral tumours. The tumours ranged in size from 0.9 to 25 cm (mean, 5.4 cm; median, 4 cm). The size ranges for the three categories were benign, 0.9–20 cm (mean, 4.3 cm); borderline, 1.2–22 cm (mean, 8.1 cm); and malignant, 2–25 cm (mean, 9.2 cm). Macroscopically 278 (83 %) tumours were described as circumscribed, 20 (6 %), as poorly circumscribed and the nature of the remaining 37 (11 %) tumours was not documented in the reports. Additional features noted macroscopically included cystic degeneration in 48 (14.3 %) tumours, necrosis in 13 (3.9 %) tumours, haemorrhage in 38 (11.3 %) tumours and ulceration of the skin in three patients (2 with malignant phyllodes tumours, 17 and 16.5 cm in diameter and one borderline tumour, 19 cm in diameter). Figure 8.15d illustrates the macroscopic appearances of a phyllodes tumour with a solid lobulated appearance.

Histological classification Std revealed 250 (74.6 %) benign tumours, 54 (16.1 %) borderline tumours and 31 (9.3 %) malignant tumours. The tumour is characterised by proliferation of stromal elements separated by epithelium to give rise to the frond or leaf-like structures which differentiates a phyllodes tumour from a fibroadenoma (Fig. 8.15e, f). The degree of stromal hypercellularity, cytological atypia, and stromal overgrowth increases from benign to the malignant tumours and the border can be circumscribed or infiltrative (Tan et al. 2005). Mitotic activity ranged from nil to 80 mitoses per 10HPF; mean, 4.45/10HPF; median, 2/10HPF, with mean mitotic rates for benign tumours, 1.99/10HPF; borderline tumours, 7.59/10HPF; and malignant tumours, 19.52/10HPF. Microscopic infiltrative margins and necrosis were more apparent in malignant tumours than benign or borderline tumours. Pseudoangiomatous stromal hyperplasia (PASH) was present in 245 (73.1 %) tumours and absent in 90 (26.9 %). Forty-three (12.8 %) women had recurrent disease and consisted of 25/225 (10 %) with benign tumours, 11/43 (20 %) with borderline tumours and 7/24 (23 %) malignant tumours. Recurrence was correlated with grade, stromal atypia, stromal hypercellularity and infiltrative borders. The presence of PASH on the margin was an independent predictor of recurrence. Negative margins and presence of PASH reduced the recurrence hazards by 51.3 % and 51.7 %, respectively. Seven women died from metastatic malignant phyllodes tumour.

8.2.4 Fibroepithelial Tumour in a Needle Core Biopsy

Fibroadenoma and phyllodes tumour are both classified as fibroepithelial tumours and can arise simultaneously in the same breast. Tan et al. (2005) reported that 4.2 % of fibroadenomas occurred synchronously with phyllodes tumours. Phyllodes tumours and fibroadenomas are not readily distinguishable radiologically. This is further compounded by the fact that some fibroadenomas can have a hypercellular stroma which on needle core biopsy closely resembles a phyllodes tumour. Wherever possible it is important to make a diagnosis of fibroadenoma or phyllodes tumour on needle core biopsies because conservative management or enucleation will suffice for fibroadenoma, whereas phyllodes tumour requires excision with adequate margin. The UK NHS Breast Screening Programme Guidelines (2001) classify fibroepithelial lesions with cellular stroma on biopsy as B3, i.e. lesion of uncertain malignant potential and therefore requires excision biopsy. In an attempt to refine the diagnostic accuracy, Jacobs et al. (2005) assessed the histological features of fibroepithelial lesions with cellular stroma in needle core biopsy in conjunction with immunocytochemistry stains. The stromal features of fibroepithelial lesions have been described above in Para 8.2.3. Twenty-nine needle core biopsies were analysed, and on excision, 12 were fibroadenomas and eight phyllodes tumours, one patient was excluded as the excision specimen contained benign fibromatous-like

features. Twenty-four needle core biopsies with sufficient material were stained with antibody to Ki67 (proliferation marker) and topoisomerase IIα (topo II, another marker for cell proliferation). Topo II is an enzyme that breaks and rejoins DNA strands (Roca 1995) and p53. Fifteen of the cases were fibroadenomas and nine were phyllodes tumours on excision specimens. There was an increase in proliferation activity in phyllodes tumours when compared to fibroadenomas. The median Ki67 and topo II indices were 1.6 (range 0.4–4.4) and 2.8 (range 0–10.2) for fibroadenomas, respectively, and 6.0 (0–18.0) and 7.0 (1.2–290) for phyllodes tumour, respectively. P53 did not distinguish fibroadenomas from phyllodes tumours. The authors concluded that assessing cellularity and mitotic activity in conjunction with proliferation indices may help determine the probability of phyllodes tumour in a needle core biopsy and may guide management of these cases (NHSBSP 2001).

8.2.5 Genetic Alterations in Fibroepithelial Tumours

There is molecular evidence that the stromal component in fibroadenomas is polyclonal and that in phyllodes tumours is clonal (Noguchi et al. 1993; Kuijper et al. 2002). In a study of the fibroadenoma, Noguchi et al. (1995) demonstrated clonal progression in three fibroadenomas which progressed to phyllodes tumours and hypothesised that the fibroadenoma was a possible precursor or progenitor lesion of the phyllodes tumour. In a patient with synchronous fibroadenoma and phyllodes tumour, Separately Hodges et al. (2009) demonstrated loss of heterozygosity in both the fibroadenoma and phyllodes tumour. The phyllodes tumour showed allelic loss at TP53 which was not present in the fibroadenoma. The authors concluded that the fibroadenoma and phyllodes tumour were clonally related and allelic loss at TP53 implied progression of fibroadenoma to phyllodes tumour. This view has also been supported by clinico-pathological follow-up studies. Abe et al. (2011) reported a favourable prognosis in patients with phyllodes tumour which transformed from fibroadenomas than from phyllodes tumours which arose de novo. In a separate study, Laé et al. (2007) demonstrated a progressive increase in the number of genetic imbalances from benign, borderline and malignant phyllodes tumours with the latter exhibiting the most genetic imbalances. They suggested that the genetic information could be used as an addition to the histological features to classify tumours into benign or malignant.

As with the fibroadenoma there are several case reports of DCIS, LCIS and invasive carcinoma arising within a phyllodes tumour (Kodama et al. 2003; Nomura et al. 2006; Padmanabham et al. 1997), but there is no consensus as to whether the epithelial component in phyllodes tumours is an independent risk factor for progression cancer. This is pertinent in phyllodes tumours which arise in older women than with fibroadenomas; older women have a high risk of developing epithelial cancer independent of other factors. On a molecular level Noguchi et al. (1993) reported that the epithelial component of the phyllodes tumour was polyclonal. In a review article on the relationship of the stroma and epithelium in the phyllodes tumour, Jara-Lazaro and Tan (2009) challenged the notion of the phyllodes tumour epithelium being an 'innocent bystander'. A study by Sawyer et al. (2000) on 47 phyllodes tumours reported allelic imbalances on 3p and 1q in 24 % and 30 % of cases, respectively. Five tumours had changes in both the epithelium and the stroma; eight tumours had detectable changes only in the stroma and another eight only in the epithelium. These results indicated that the genetic changes in individual phyllodes tumour are sometimes discordant. Thus, either both parts of the tumour have independent clonal origin or the stroma and the epithelium originate from the same clone and acquire different mutations during tumour progression. In support of this epithelial–stromal interaction, Jara-Lazaro and Tan (2009) pointed

out that morphologically there is epithelial participation in the stromal expansion of phyllodes tumours and mitoses are frequently found in the periductal stroma, suggesting that the stromal growth may be dependent on the epithelium. Based on these findings the carcinoma in phyllodes tumour may arise independently due to clonal proliferation of the epithelium or may be part of the stromal–epithelial interaction, giving rise to concurrent stromal and epithelial neoplasia. To date none of the studies have reported phyllodes tumour as a risk factor of breast cancer.

8.3 Fibroadenomatoid Hyperplasia

Fibroadenomatoid hyperplasia is also termed sclerosing lobular hyperplasia or fibroadenomatoid mastopathy. Histologically, fibroadenomatoid hyperplasia resembles a fibroadenoma but consists of small multiple lobules separated by fibrous stroma without the typical circumscription of a fibroadenoma. Because of the rather indistinct nature of the lesion, it is most likely to be classified by pathologists as fibroadenoma or fibrocystic change, as the latter is usually present in most breast biopsies. Indeed, the UK NHS Breast Screening Programme guidelines for pathology reporting in breast cancer classify fibroadenomatoid hyperplasia under fibroadenoma (NHSBSP 1997). Fibroadenomatoid hyperplasia is usually present as an incidental finding in other benign lesions or in random tissue sampled in cancerous breasts either symptomatic or screen-detected (Fig. 8.16). Well-defined fibroadenomas can also be associated with fibroadenomatoid change.

Kovi et al. (1984) reported the presence of fibroadenomatoid hyperplasia in association with a fibroadenoma in 50 % of the patients. However, this study was confined to young black women, which is not representative of the general population. In 1987, Hanson and co-workers examined 200 consecutive biopsies to determine the frequency of fibroadenomatoid mastopathy, which had been coded as fibroadenoma or fibrocystic disease. The authors identified 23 (11.5 %) lesions, which met the criteria of fibroadenomatoid mastopathy. The lesions were admixed with dilated ducts, ‘epitheliosis’ and adenosis. The natural history of fibroadenomatoid hyperplasia is unknown. However, it has been suggested that this condition may be a harbinger of, or is responsible for, recurrent multiple fibroadenomas (Hanson et al. 1987; Rosen 2001). The risk factor, if any, of subsequent invasive cancer associated with fibroadenomatoid hyperplasia is unknown.

Fibroadenomatoid hyperplasia can be detected mammographically by the presence of ill-defined soft tissue density with or without calcification

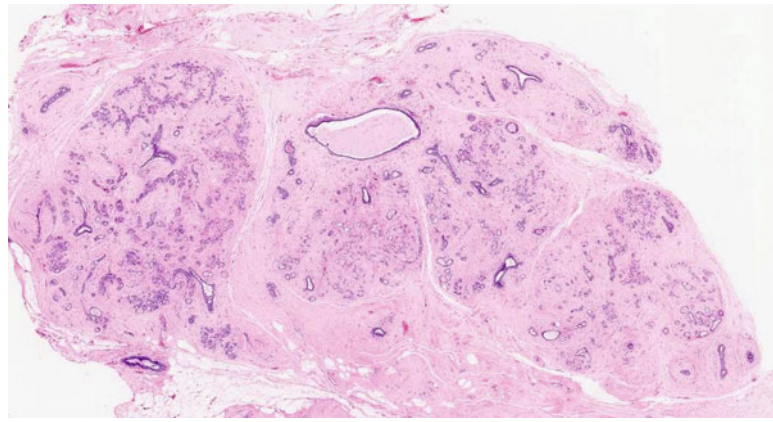


Fig. 8.16 Incidental fibroadenomatoid hyperplasia in a specimen excised for breast cancer. There are ill-defined hyalinised lobules resembling a fibroadenoma

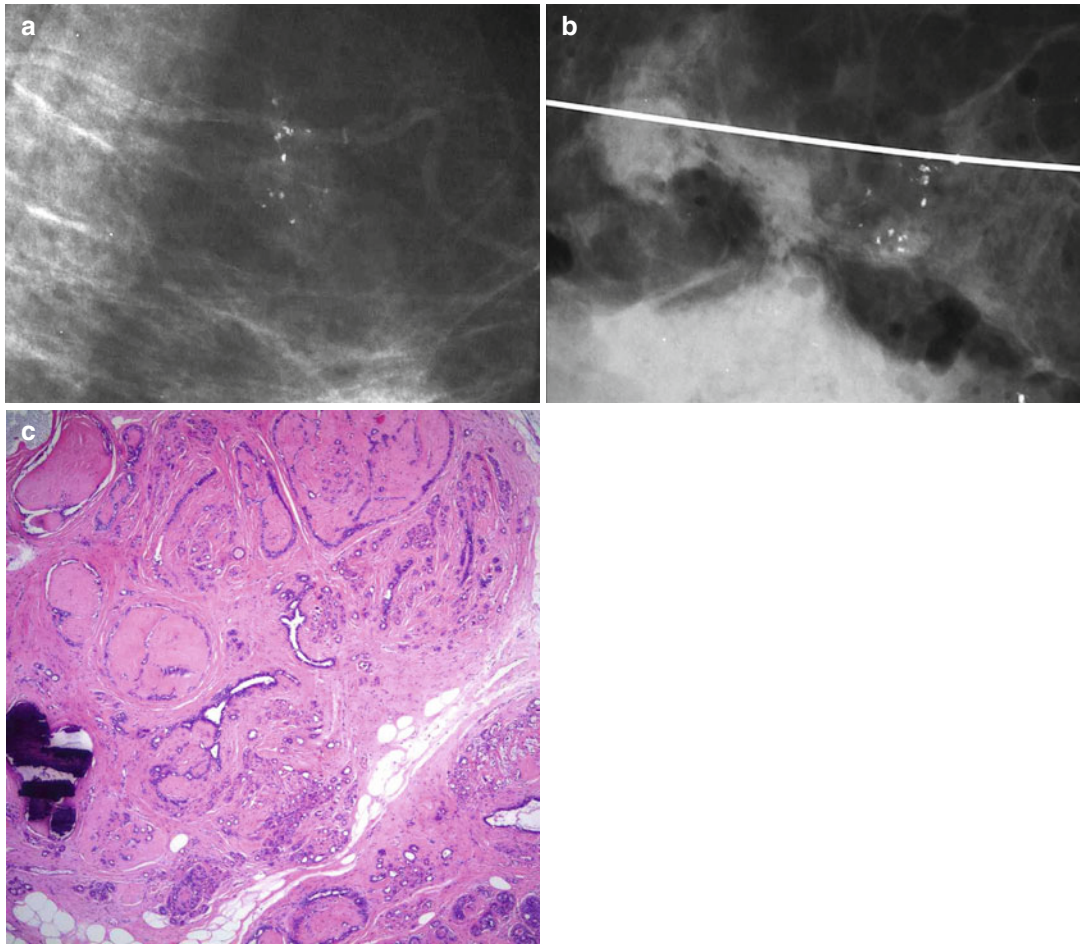


Fig. 8.17 (**a**) Indeterminate screen-detected calcification graded as R3 in a 71-year-old woman. (**b**) Localisation mammography of the microcalcification. (**c**) The histology showed calcified fibroadenomatoid hyperplasia with ill-defined lobulation of the fibroepithelial tissue resembling a fibroadenoma

(Fig. 8.17). Kamal et al. (1998) reviewed 54 mammographically detected lesions, which were compatible with the diagnosis of fibroadenomatoid hyperplasia. Eleven cases were confirmed on biopsy (nine core biopsies, two excision biopsies). In all 11 patients, there was granular microcalcification, which varied in shape, size and density, with no associated mass. They concluded that the diagnosis of fibroadenomatoid hyperplasia could be confirmed in needle core biopsies.

Previously, Poulton et al. (1995) reviewed the mammographic and sonographic features of 15 patients who had biopsy-proven sclerosing lobular hyperplasia (age range 21–46 years). Seven of the women were black and eight were white. Eight had symptomatic breast lumps, one had tenderness, one had nipple discharge and the remainder had screen-detected lesions. The mammographic features included well-defined masses in eight patients (size range 1.0–8.0 cm). Microcalcification was reported in a 46-year-old woman; asymmetric density was present in two patients, and the mammographs were reported as normal in five patients. The sonographic

features included solid well-defined masses with either homogeneous or mixed echoes in ten out of 14 patients. Acoustic shadowing was present in only one of the patients. The sonograms were normal in four women. The authors concluded that the imaging features were not diagnostic and in most cases the features suggested a fibroadenoma. Both Kovi et al. (1984) and Poulton et al. (1995) reported palpable fibroadenomatoid hyperplasia with diameters up to 5.0 and 8.0 cm, respectively, which is more in keeping with a fibroadenoma than fibroadenomatoid hyperplasia.

8.4 Hamartoma

Hamartomas were first described by Prym in 1928, who referred to them as mastomas. The term hamartoma was introduced by Arrigoni and co-workers in 1971. If palpable, hamartomas are clinically indistinguishable from fibroadenomas and they can occur in women of all ages. Breast hamartomas are rare, but their existence is now frequently reported in the literature because of the routine use of mammographic examination (Daya et al. 1995). The rarity of hamartomas may also be due to under-reporting by pathologists, as the lesion may be reported as normal breast tissue or breast tissue with no diagnostic features.

A hamartoma is a localised tumour-like lesion caused by malformation of the tissue indigenous to that part of the body or organ, resulting in an imperfect disorderly differentiation. Hamartomas can occur in any part of the body, and in the breast, they are composed of breast lobules, ducts and associated mesenchymal tissue (including fat) arranged in an abnormal fashion (also termed adenofibrolipoma). The diagnosis of hamartoma is based on clinical, radiological and pathological correlation. In one of the largest series studied by Charpin et al. (1994), 41 hamartomas were identified in 5,834 breast biopsies over a period of 7 years. This constituted 1.2 % of benign lesions and 4.8 % of benign breast tumours.

8.4.1 Mammographic Features of Hamartoma

There is disagreement among radiologists as to whether a positive diagnosis of a breast hamartoma can be achieved using either mammography or ultrasonography alone or a combination of the two. For those who believe that the diagnosis of a hamartoma can be made on mammography, the diagnostic features include a smoothly defined mass that contains fat admixed with fibroglandular tissue in variable amounts, a thin full or partial rim of pseudocapsule to give a characteristic pattern of 'cut sausage' (Heywang-Köbrunner et al. 2001). If these diagnostic features are present, needle core or excision biopsy can be avoided. Calcification may or may not be present (Muller 2002), and the presence of calcification should always be evaluated.

Hessler et al. (1978) reviewed the mammographic features of 16 cases of histologically confirmed hamartomas and concluded that mammography was accurate in detecting hamartomas with the possibility of avoiding surgery. The following year Andersson and colleagues (1979) reached a similar conclusion when they reviewed five cases of mammary hamartomas. They concluded that the radiological features of hamartomas were 'characteristic' and allowed a tentative diagnosis in most cases. This view was challenged 10 years later by Helvie and co-workers (1989), who reviewed mammograms of 17 women with pathologically proven breast hamartomas. Only two cases were considered to have 'classical' mammographic features of hamartomas. In three patients the appearances were suggestive of a carcinoma. These findings suggested that classic mammographic appearances of breast hamartomas are less common than previously reported. Aggelatou et al. (1998) reached the same conclusion when they reviewed mammograms from patients with histologically proven hamartomas. These investigators felt that, although mammography was helpful in the diagnosis of mammary hamartomas, the final diagnosis should be confirmed by histological analysis.

8.4.2 Sonographic Features of Hamartoma

If the mammographic features are not pathognomonic, ultrasound can be used as an ancillary diagnostic modality. On ultrasound imaging, hamartomas exhibit a smooth margin of a nodular lesion with or without delicate shadows. The fat is usually hypoechoic with the nodule (Heywang-Köbrunner et al. 2001). Adler et al. (1990) assessed the sonographic features of ten breast hamartomas to determine the diagnostic accuracy of this investigative modality. Mammographic appearances were 'characteristic' in five patients. However, the sonographic features were variable. The most frequent feature was that of a moderate to well-circumscribed, solid, hypoechoic mass with posterior acoustic shadowing. Two isoechoic hamartomas were difficult to visualise on ultrasonography. Adler and colleagues concluded that ultrasound had a minimal role in the diagnosis of breast hamartomas in view of the variable sonographic features. Because of this diagnostic variability, other investigators (Berna et al. 2001) used combinations of ultrasonography and computed tomography (CT) scanning to increase the diagnostic accuracy in mammographically detected hamartoma. CT scanning in combination with needle core biopsies was used in those patients with inconclusive mammographic and sonographic features. The authors found that the combination of the three imaging modalities plus needle core biopsy was essential in the diagnosis of breast hamartomas. Although the authors used CT scanning in this study, this facility is not readily available in routine breast screening units and is not therefore cost-effective. Ultrasonic or stereotactic-guided needle core biopsy may provide the diagnosis without subjecting the patient to a third imaging session and increased anxiety, especially if pursuing a potentially benign lesion.

8.4.3 Histological Features of a Hamartoma

Wahner-Roedler et al. (2001) reviewed hamartomas from 35 patients (age range 21–86 years) treated at the Mayo Clinic over a period of 10 years. Eighteen hamartomas were clinically palpable and the remainder were detected mammographically. Where the radiological images were available for review, 17 lesions were felt to be indeterminate, two were indeterminate, probably benign, and one was indeterminate, suspicious of malignancy. Only two lesions had typical radiological features of a hamartoma. Four lesions had foci of calcification. Pathologically hamartomas ranged in size from 1.0 to 7.5 cm. The margins were well-defined except in one lesion, but this was not a consistent feature. The mean percentage of fibrous tissue was 78 % (range 3–95 %), fat 13 % (range 0–95 %) and epithelium 9 % (range 1.0–60 %). Ductal hyperplasia was present in 27 % and adenosis in 70 %. Twelve per cent of patients had concomitant fibroadenomas. Four lesions had calcification. The authors could not confirm the pathological features that were reflected in the clinical or radiological features. The typical mammographic features in the early studies may have been attributed to larger and 'mature' lesions, which are now uncommon due to widespread use of mammographic screening. In addition to the heterogeneous features reported by Wahner-Roedler and colleagues, Tse et al. (2002) reported the presence of pseudoangiomatous hyperplasia and stromal giant cells. The features of a hamartoma are illustrated in Fig. 8.18. Presence of fat in the mammogram and on histology is considered diagnostic of a hamartoma. Risk of a subsequent carcinoma, if any, should be assessed according to the associated epithelial proliferations. Carcinoma arising in a hamartoma has been described (Coyne et al. 1992). This is most likely to be coincidental.

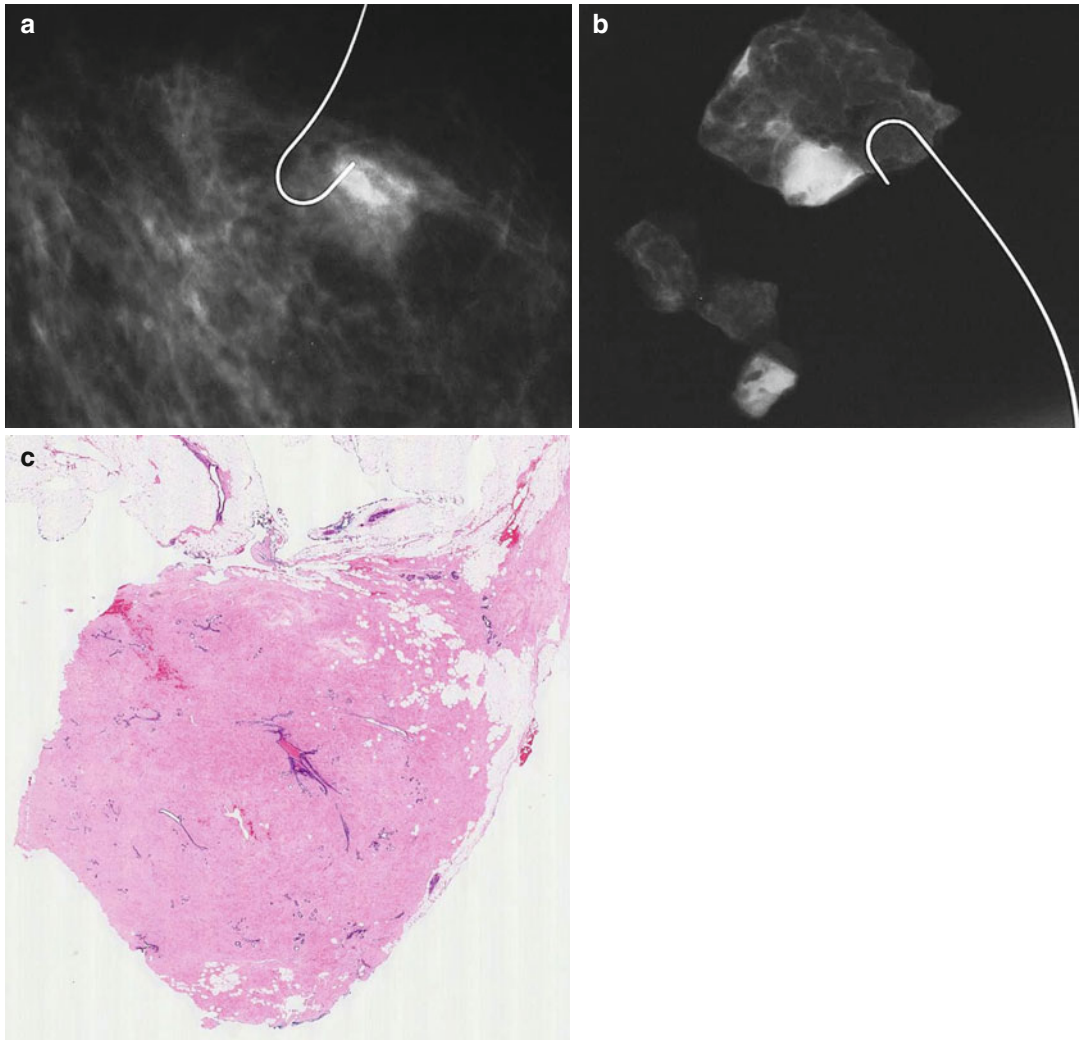


Fig. 8.18 (**a**) A screen-detected hamartoma in a 50-year-old woman shows a rather ill-defined margin and focal fat infiltration (*dark area near the tip of the hook wire*). (**b**) The foci of the fat are more prominent in the specimen X-ray, where the lesion is better defined than in the mammogram. (**c**) Whole mount section of the hamartoma shows a well-circumscribed lesion with hyalinised stroma with focal fat infiltration; the hyalinised stroma lacks lobulation, contains sparsely dispersed atrophic duct–lobular units and foci of mature adipocytes

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Infiltrative Pseudo-Malignant Lesions

9

Learning Points

- A radial scar mimics stellate cancer radiologically and pathologically.
- There is no consensus as to whether a radial scar is a marker for risk of cancer or a precursor of breast cancer.
- Needle core biopsies underestimate the presence of cancer in radial scars.
- The diagnosis of radial scar on radiology and needle core biopsy should prompt an excisional biopsy.
- Sclerosing adenosis can mimic cancer clinically, radiologically and pathologically.
- Sclerosing adenosis is frequently identified as an incidental finding in specimens excised for benign or malignant conditions.
- Immunocytochemistry markers are useful in sclerosing adenosis to demonstrate myoepithelial cells to confirm benignity.
- Diagnosis of sclerosing adenosis in a needle core biopsy is usually accurate if there is no radiological–pathological discordance.
- Apocrine adenosis is rare and its role as a precursor of malignancy has yet to be established.
- Micrograndular adenosis is unusual as a benign lesion because the glands lack myoepithelial cells.
- Microglandular adenosis histologically mimics invasive carcinoma.
- There is molecular evidence that microglandular adenosis may be linked to triple-negative breast cancer.

9.1 Radial Scar

The term radial scar (*strahlige Narbe*) was introduced by Hamperl in 1975 to describe a lesion with a stellate configuration, which mammographically and pathologically mimics invasive carcinoma. This term is simple and avoids the use of other multiple synonyms, which do not always reflect the intrinsic pathological features. Some of the terms applied to the radial scar include the following: sclerosing papillary proliferation (Fenoglio and Lattes 1974), but papillary proliferation is not always present in these lesions; infiltrating epitheliosis (Azzopardi 1979), which has a malignant connotation; and indurative mastopathy (Rickert et al. 1981) and yet in the majority of cases the lesion is not always palpable. Fisher et al. (1979) applied the term nonencapsulated sclerosing lesion.

Stellate lesions up to 9 or 10 mm can be classified as radial scars and, if larger, as complex sclerosing lesions (Anderson and Battersby 1985; Page and Anderson 1987). For simplicity, the term radial scar will be used in this book for

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_9, © Springer-Verlag Berlin Heidelberg 2014

benign stellate lesions. The incidence of radial scars in women undergoing screening mammography ranges from 0.04 % to 0.9 % (Wallis et al. 1993; Tabár and Dean 1985). The prevalence of radial scars in autopsy breast tissue is between 14 % and 28 % (Wellings and Alpers 1984; Nielsen et al. 1985). Incidental microscopic radial scars are commonly identified in breast tissue excised for benign or malignant disease. Although frequently screen-detected, palpable radial scars have also been reported (Wallis et al. 1993).

9.1.1 Pathogenesis of the Radial Scar

The evolution of the radial scar is ill understood, which may reflect the array of names applied to this lesion. Because of the frequent association of radial scars with fibrocystic change, some authorities believe they are a manifestation of fibrocystic change (Nielsen et al. 1985). Hamperl (1975) assumed that radial scars develop from obliterative processes involving the ducts. Fisher et al. (1983) postulated that radial scars arose from obliterative vascular processes. In an attempt to understand the pathogenesis of these lesions, Anderson and Battersby (1985) meticulously tabulated the histological features of 103 radial scars to assess common pathological features. They concluded that in the early stages, there was a secondary response to a central chronic inflammation with many spindle cells and minimal fibro-elastotic distortion of the parenchyma. In the late stage of the radial scar, there was considerable fibro-elastotic deposition associated with parenchymal distortion in a characteristic stellate configuration. As a follow-on to this study, in same periodical, in the same year, the same authors (Battersby and Anderson 1985) published results of an ultrastructural study on 38 radial scars. Twelve of these scars had associated carcinoma and the remaining 26 were benign. A third of the radial scars, which were regarded to be in the early stage of development, had abundant spindle cells. These cells had features of a myofibroblast on electron microscopy, which included endoplasmic reticulum and prominent myofilaments. The myofibroblasts had close association with collagen and elastic fibres. The 'mature' radial scars had few myofibroblasts remaining in the stroma. The stromal cells in the immature lesions were related to degenerating duct–lobular units, which frequently showed loss of basal lamina. The authors concluded that the obliteration of the central duct–lobular units appeared to be a prominent feature in the genesis of the radial scar. The presence of fibro-elastotic core is a common feature in radial scars which Wellings and Alpers (1984) used as the inclusion criterion when they carried out subgross analysis of radial scars. However, elastosis per se should not be applied to determine benignity, as elastosis occurs in both benign and malignant lesions (Azzopardi 1979).

Kulka et al. (1996) demonstrated morphological differences between benign and malignant stellate lesions when they examined 500–1,000 micron sections with infrared microscopy. The stellate extensions of complex sclerosing lesions (radial scar) consisted mostly of epithelial structures, whereas those of stellate cancers had a predominance of fibrous tissue.

9.1.2 Radiological Features of the Radial Scar

Radial scars are small and usually impalpable stellate (spiculate) lesions, which are often identified in breast tissue excised for cancer or other benign proliferations (Andersen and Gram 1984; Nielsen et al. 1985, 1987). Spiculated lesions can be a result of benign or malignant processes and these include sclerosing adenosis, postsurgical scar, radial scar, post-traumatic oil cysts and infiltrating ductal carcinoma (Franquet et al. 1993). The radial scar is a prototype stellate lesion, which mammographically can be indistinguishable from a carcinoma (Fig. 9.1). Mammographic features that have been found to be common to radial scars include radiolucent central core, elongated radiating spicules and infrequent calcification (Fig. 9.2). Fenoglio and Lattes (1974) attributed the central radiolucency to the

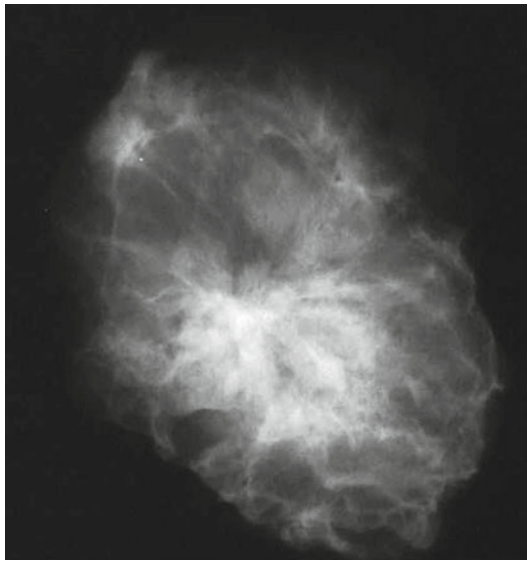


Fig. 9.1 The specimen X-ray shows an ill-defined stellate lesion, which was present as an architectural distortion in the left breast during mammographic screening. The lesion is better defined in the specimen X-ray than in vivo

presence of a hypertrophic fibroelastic core, which is surrounded by radiating (stellate) proliferations of the duct system.

In the early days of screening mammography, the absence of calcification in stellate lesions was thought to discriminate radial scars from carcinomas. However, in a retrospective review of 225 consecutive stellate lesions, Mitnick et al. (1989) found that the radiological features used to distinguish benign from malignant stellate lesions were unreliable but indicated that the presence of calcification could be useful. They reported 14 out of 73 (19 %) carcinomas with radiological features of a radial scar. The presence of microcalcification in the 11 patients with carcinoma assisted the authors to distinguish carcinoma from radial scar. Four of the nine biopsy-proven radial scars had a dense central region simulating the appearance of a scirrhous carcinoma. From these findings the authors concluded that stellate

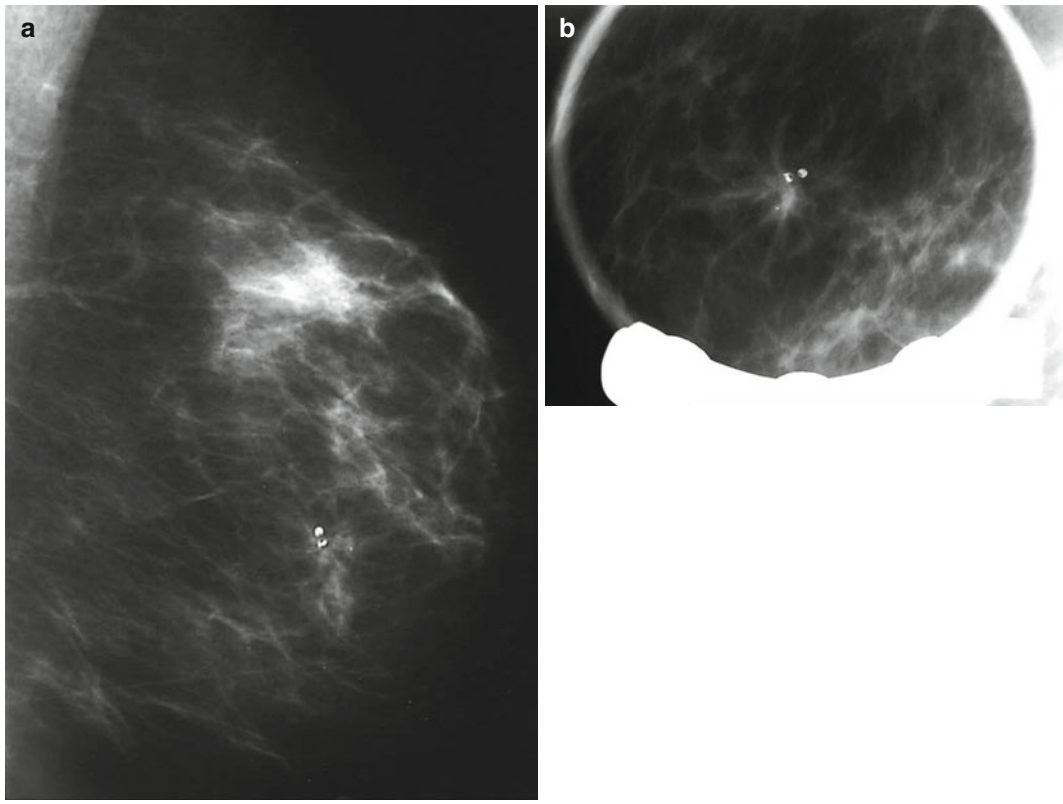


Fig. 9.2 (**a**) Screen-detected area of architectural distortion with focal calcification. (**b**) **T**he magnification view shows enhanced stellate configuration

lesions with radiolucent cores associated with calcification were suggestive of carcinoma. However, in a separate study, Adler et al. (1990) reported that the presence of calcification or radiolucent core was not a useful criterion in differentiating carcinomas from radial scars. The presence of calcification in radial scars has also been reported in several publications (Nielsen et al. 1987; Orel et al. 1992; Franquet et al. 1993). Although the calcification is not always apparent in the in vivo mammogram, it may be highlighted in the specimen radiographs (Adler et al. 1990). King et al. (2000) reviewed the mammographic and pathological features of 45 patients who had undergone localisation excision for radial scar. Only ten patients had mammographic and histological evidence of radial scar. Twenty-nine patients had only mammographic and six had only histological features of a radial scar. Carcinoma was identified in 18 patients with mammographic features of radial scars.

The sonographic features of radial scars are not diagnostic either. The lesions produce ill-defined images with poor echogenicity and shadowing. The radiating spicules make it difficult to differentiate a radial scar from carcinoma (Cosgrove and Svensson 2001). However, Cohen and Sferlazza (2000) suggested that sonography may be useful in assessing subtle mammographically detected radial scars, especially when they are present in only one view and cannot be specifically localised. Because of the lack of pathognomonic features on radiological analysis, stellate lesions should be biopsied and managed appropriately. MRI did not differentiate benign radial scars from those harbouring malignancy (Cha et al. 2007), but was found useful in a separate study by Perfetto et al. (2009).

9.1.3 Pathological Features of Radial Scar

A microscopic or evolving radial scars can be identified in tissue excided for other benign of malignant lesion (Fig. 9.3). The hallmark of the radial scar is the presence of central fibroelastotic core which may contain blood vessels. However, not all radial scars have the elastotic component and central fibrous tissue may contain tubular structures to mimic tubular carcinoma (Fig. 9.4). Calcification may be present in the

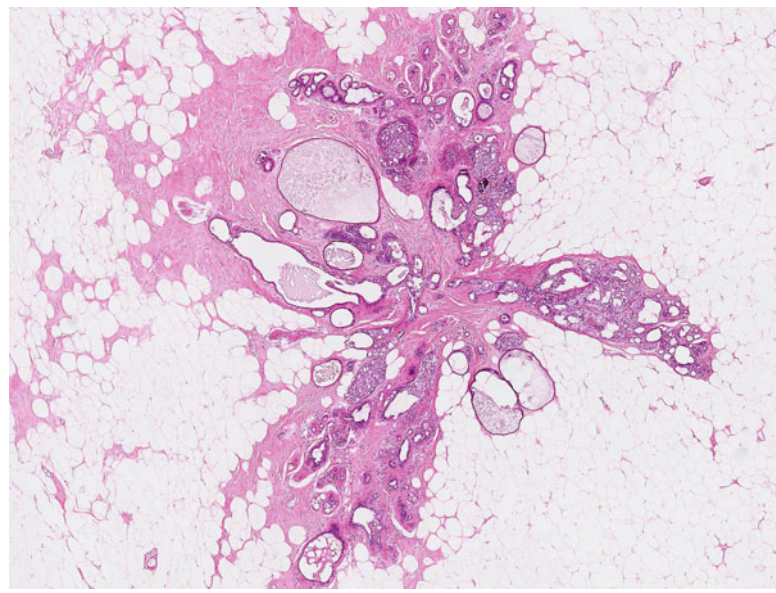


Fig. 9.3 Microscopic evolving radial scar as an incidental finding in a mastectomy specimen for breast cancer. Even at this stage, the typical radiating morphology is apparent

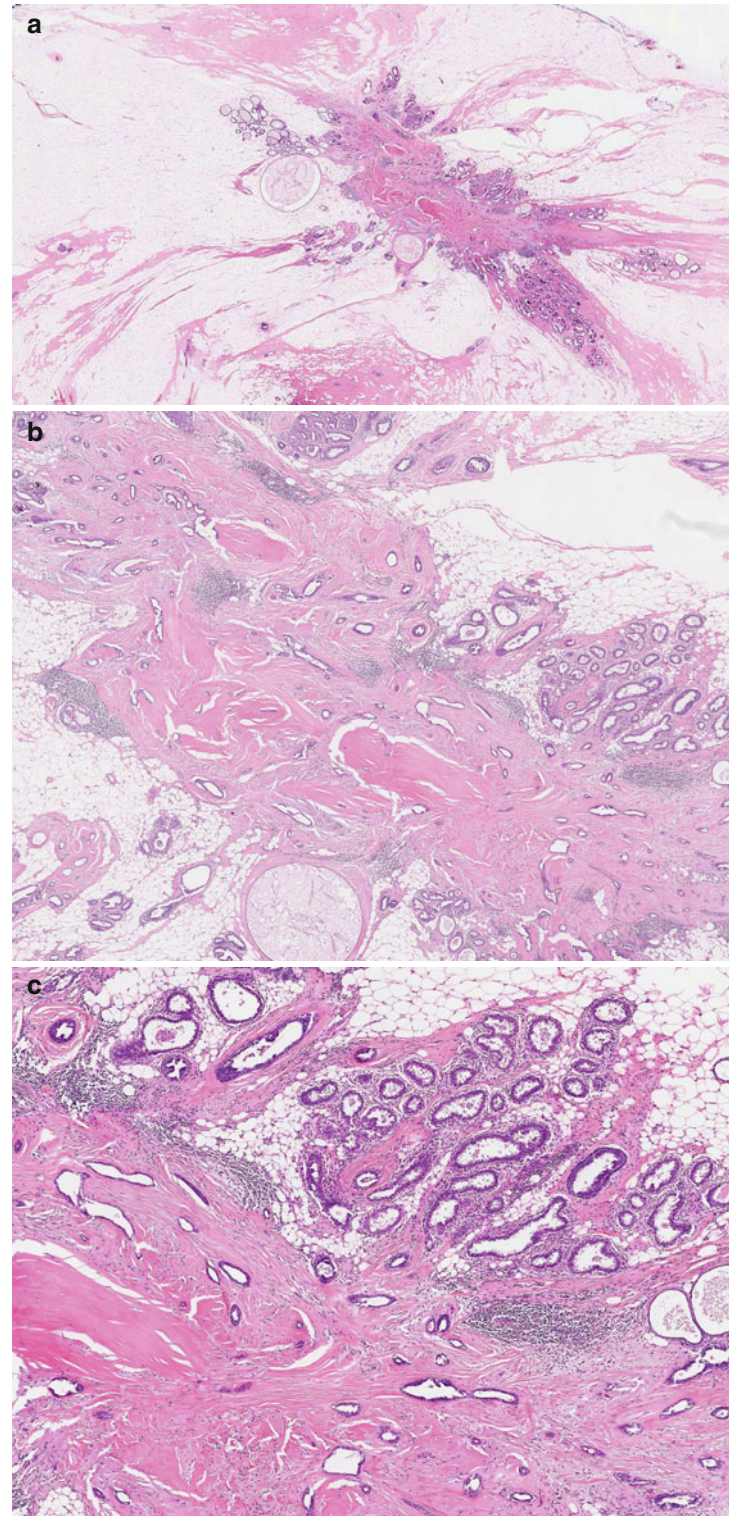


Fig. 9.4 (**a**) Whole mount section of a radial scar with central fibrosis, but no elastotic features. (**b**) High power of the central core to illustrate the lack of elastosis; tubular structures mimicking tubular carcinoma are evident in the central fibrotic stroma and (**c**) Columnar cell change at the periphery of the fibrotic core (same lesion in Fig. 9.1)

central fibrous core (Fig. 9.5). The fibrous tissue radiates outward to give rise to the characteristic star-like appearance (Fig. 9.5). The proliferation at the periphery of the radial scar is variable and can include cysts, florid UDH, ADH, papillomas, fibrocystic with apocrine metaplasia, columnar cell lesions and early invasive carcinoma (Kennedy et al. 2003). The radial scar in Fig. 9.5 shows cysts with associated florid UDH at the periphery. The main differential diagnosis of a radial scar is a stellate cancer. Some of the stellate cancers contain a fibro-elastotic core which makes some authorities believe that these cancers develop in a radial scar (Fig. 9.6). The fibro-elastotic core in Fig. 9.6 is better developed than that in the radial scars above, which provides compelling evidence for advocates of the radial scar as a precancerous lesion.

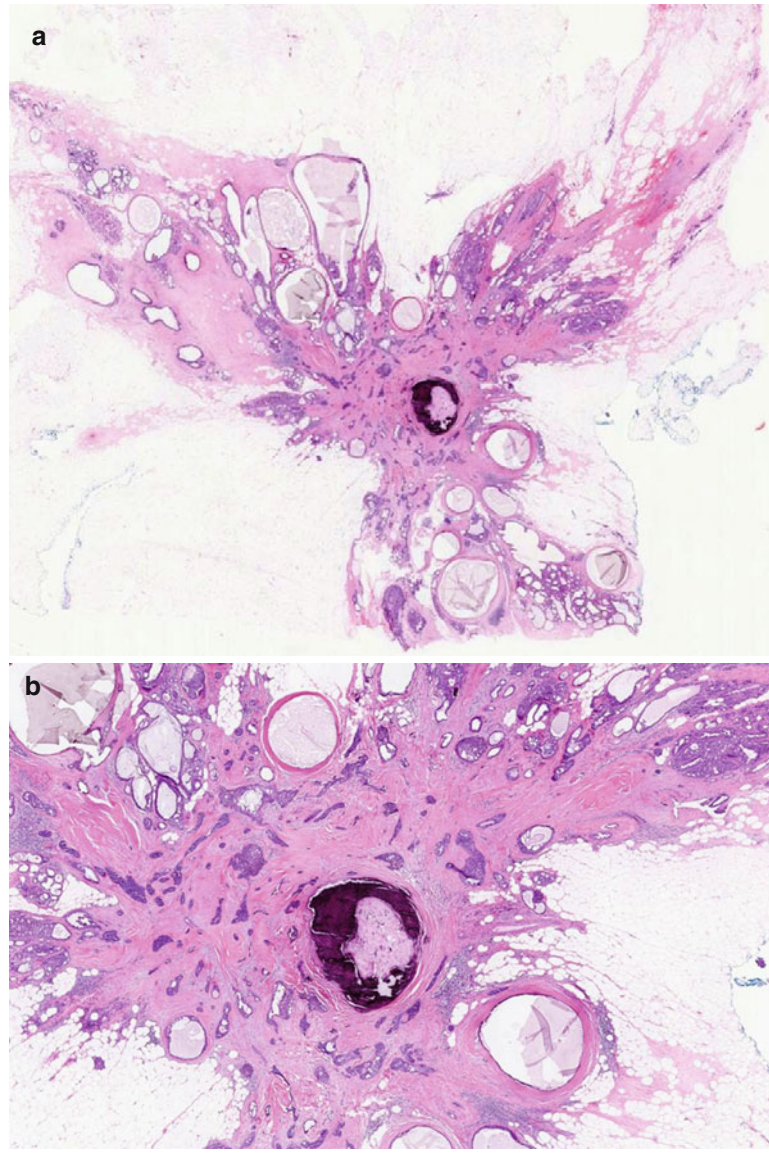
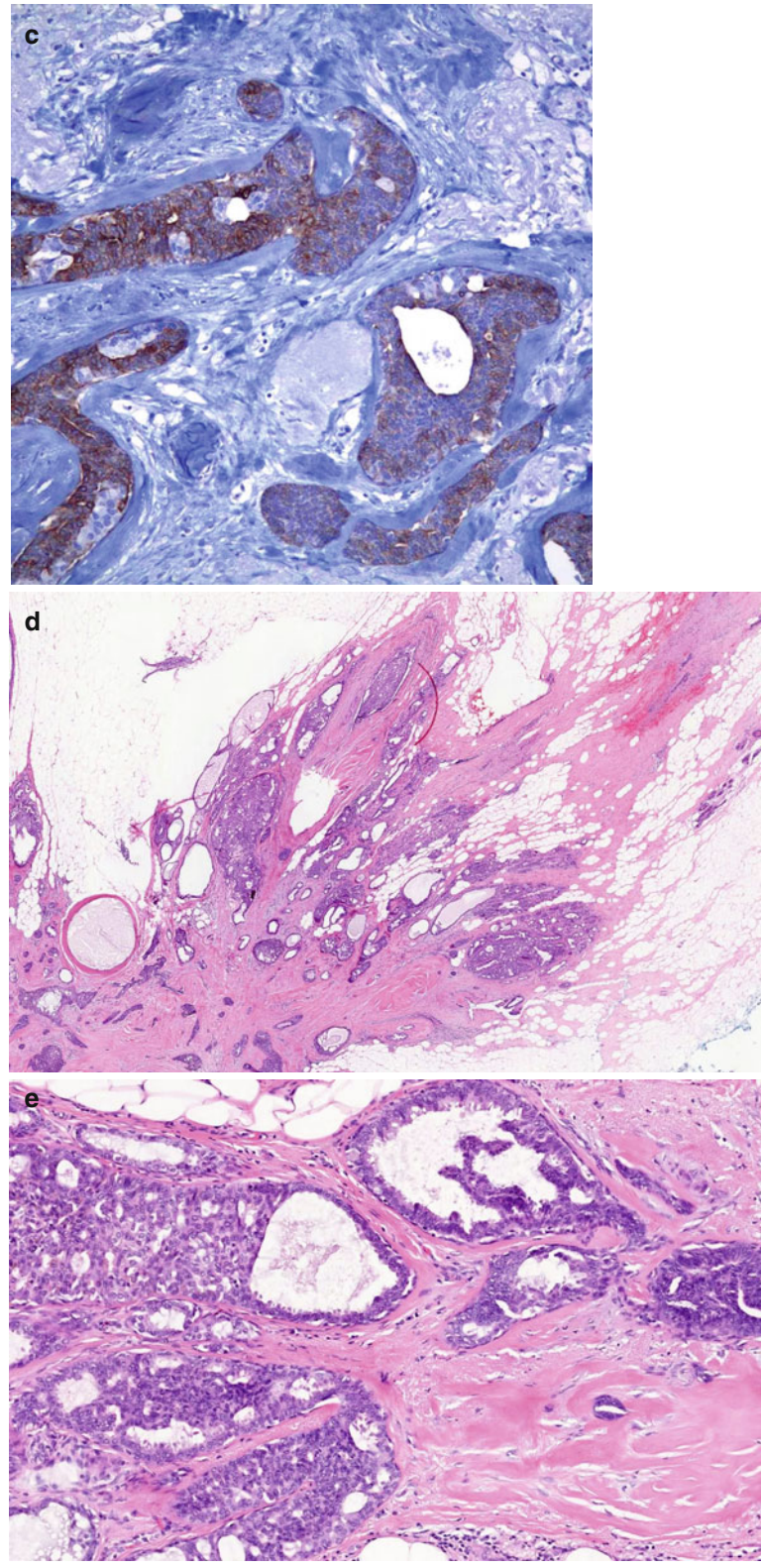


Fig. 9.5 (**a**) Whole mount section of large radial scar, 25 mm in diameter, with central fibro-elastotic core and focal calcification. (**b**) In the core there are islands of entrapped epithelial cells. (**c**) Entrapped epithelial cells are positive with CK5/6 which confirms benignity. (**d**) The fibrous radiations contain cysts and prominent usual ductal hyperplasia (UDH). (**e**) High magnification highlights UDH in a fibro-elastotic stroma (same lesion in Fig. 9.2)

Fig. 9.5 (continued)



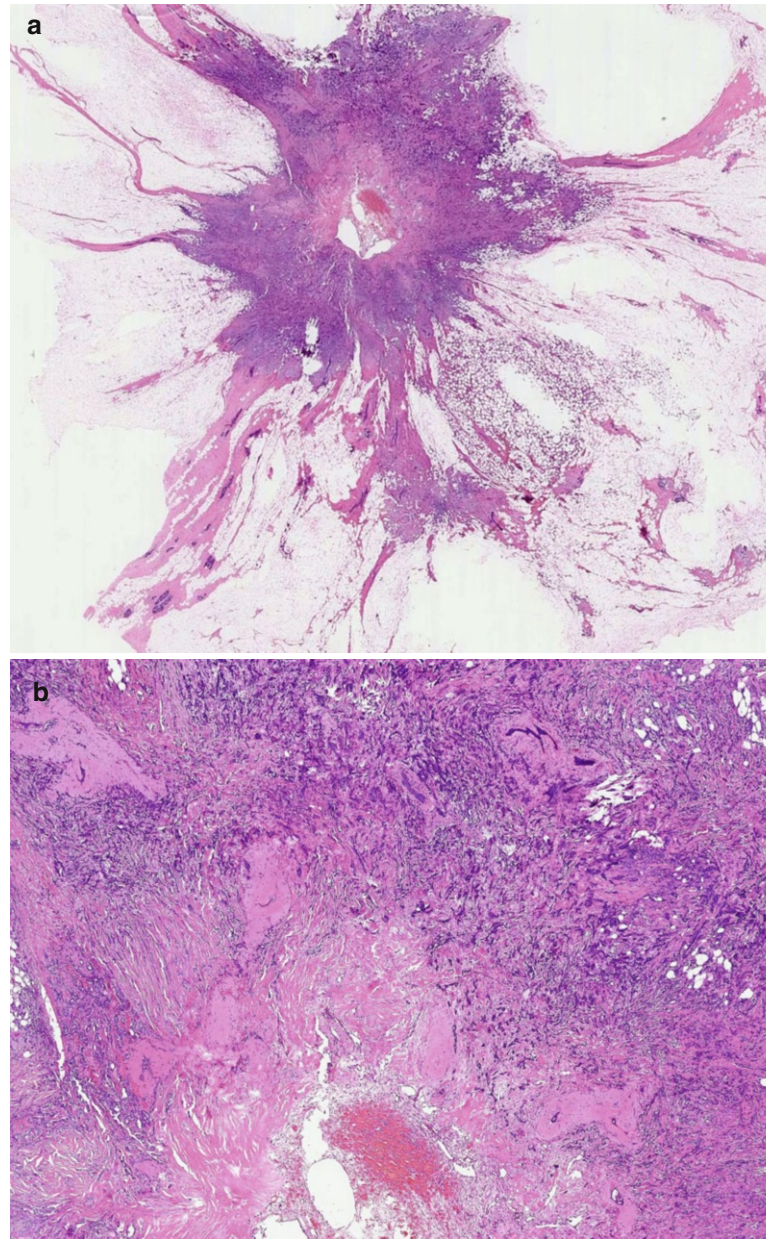


Fig. 9.6 (**a**) Stellate cancer which can mimic a radial scar radiologically. (**b**) High magnification illustrates the fibro-elastotic core, which is better developed here than that in the radial scars above

9.1.4 Management of Patients with Radial on a Needle Core Biopsy

If a radial scar is detected mammographically, the general recommendation is to excise it as cancer cannot be excluded. The UK NHS Breast Screening Programme classifies a radial scar in a needle core biopsy as a B3 category lesion (NHSBSP Publication No 50 2001), but how frequent is the upgrade of benign radial scar on biopsy to a high-grade lesion such as DCIS or invasive cancer in the excision biopsy? In a retrospective review of 4,458 consecutive image-guided needle core biopsies performed at the University of Udine in Italy, between 2000 and 2008, Linda et al. (2010) identified 79 lesions diagnosed as radial scars (1.8 %); these 62 radial scars in 62 women were analysed in the study as

they had pathology of the excision specimen. Of the 62 lesions, five (8 %) were reported as malignant at surgical excision (3 DCIS; 1 IDC; 1 ILC; none were tubular); 40 (65 %) were graded as high-risk lesions (33 radial scars; 6 ADH; 1 FEA) and 17 (27 %) benign lesions (18 fibrocystic change; 7 sclerosing adenosis; 2 UDH). In this study, percutaneous biopsies underestimated malignancy in 5/62 (8 %). Neither mammographic nor ultrasonographic features could predict the lesions which would yield cancer in the excision specimens. The authors pointed out that underestimation of malignancy in radial scars occurs due to sampling error but also from the diagnostic error in the difficulty in differentiating a radial scar from tubular carcinoma. In this study Linda and co-authors (2010) reviewed 11 publications from 1996 to 2008 and the underestimation of cancer in biopsies reported as radial scars was 0–40 %. In a separate study, López-Medina et al. (2006) and co-authors identified eight cancers (18 %) in 43 excision specimens of patients with a diagnosis of radial scar on needle core biopsy. Morgan and colleagues (2012) reported a similar prevalence to Linda et al. (2010) of six cancers (9 %) identified in 67 patients with a diagnosis of radial scar on needle core biopsy. Based on these findings the overall consensus is that all patients with percutaneous diagnosis of radial scar should undergo surgical excision regardless of mammographic or sonographic features.

9.1.5 Molecular Features of the Radial Scar

Jacobs and colleagues (2002) performed in situ hybridisation on several stromal elements in nine radial scars, 15 cases of normal tissue and four invasive carcinomas. Compared with normal tissue, the radial scars showed focal increased blood vessels using immunocytochemistry to factor VIII-related antigen. The in situ hybridisation showed focally increased expression of mRNA for collagen type 1, total fibronectin and other stromal and vascular elements. The pattern of mRNA expression in the radial scars was similar to that seen in the four invasive carcinomas. The authors concluded that the similarities between radial scars and invasive breast cancers with regard to mRNA expression for several stromal and vascular factors suggest similar disturbances in stromal–epithelial interactions in both lesions. In a separate study, Iqbal and colleagues (2002) demonstrated allelic imbalance and LOH, on p16 and 8p which are genetic alterations usually present in breast cancer. These results suggest clonal proliferation and possibly a precursor of breast cancer. In the same study, Iqbal and co-authors also demonstrated LOH and allelic imbalances in different types of proliferation associated with radial scar which included hyperplasia of usual type, sclerosing adenosis and apocrine metaplasia suggesting that the radial scar consists of a mixture of multiple proliferations, potentially clonal which were independent from lesions outside the radial scar. The authors surmised the radial scar was an independent risk factor for breast cancer but also provided a cumulative risk in association with other benign breast disease. They also postulated that this would explain the increased risk of malignancy associated with larger radial scars (Sloane and Mayers 1993; Jacobs et al. 1999). Iqbal and colleagues could not confirm whether the radial scar was a marker for risk of malignancy or a premalignant lesion and recommended further studies with a wider range of genetic markers.

9.1.6 Is the Radial Scar a Premalignant Lesion?

The frequent presence of tubular structures within the fibro-elastotic core of the radial scar, which closely resembles tubular carcinoma, has led to the belief that radial scars represent an early stage of tubular carcinoma (Fisher et al. 1983; Linell and Rank 1989). Carcinoma arising in association with radial scars is well documented, but there is no consensus as to whether or not these lesions are premalignant or just markers of subsequent risk of malignancy. Linell and Rank (1989) believed that the corona of the radial scar consists of contracted lobules and ducts around a sclerotic/elastotic centre. These

contracted lobules and ductules were demonstrated to be part and parcel of the terminal duct–lobular units, which are the origin of cancer (Wellings et al. 1975). From their well-illustrated monogram, Linell and Rank (1989) demonstrated that some tubular carcinomas arose in radial scars. In addition to the elastotic centre, they emphasised the fact that both tubular carcinomas and radial scars are stellate shaped and are rarely more than 10 mm in diameter. This view that radial scars are precursors of tubular carcinoma is not widely accepted. In a subgross analysis of radial scars, Wellings and Alpers (1984) identified only a single case of ductal carcinoma in situ when they examined 83 radial scars. These authors concluded that a radial scar is at least a 'marker' for risk of cancer development.

In a separate study, Nielsen and colleagues (1987) examined breast tissue from 84 consecutive autopsies of women with clinical diagnoses of invasive breast cancer. Radial scars were found in contralateral breasts in 35 patients (42 %). Four women had radial scars in the ipsilateral breast with cancer. One woman had invasive cancer with morphological features compatible with, but not diagnostic of transition from a radial scar. Six radial scars had associated ductal or lobular carcinoma in situ and two had atypical hyperplasia. The frequency of radial scar was significantly higher in women with fibrocystic disease (55 %) compared to women without (24 %). Although this study did not imply that radial scars were potentially premalignant, the authors noted that radial scars containing high-risk epithelial proliferations such as atypical hyperplasia and carcinoma in situ which were associated with an increased risk of subsequent breast cancer.

Sloane and Mayers (1993) reviewed 126 radial scars and complex sclerosing lesions to determine factors associated with malignancy and atypical hyperplasia. They reported a clear relationship between the size of the lesion and the presence of atypical hyperplasia. Atypical hyperplasia and carcinoma were uncommon in lesions less than 6–7 mm but more frequent in larger lesions. Complex sclerosing lesions with carcinoma and atypical hyperplasia were also common in women older than 50 years and infrequent below the age of 40. The types of carcinomas associated with the radial scars included small and large cell DCIS, LCIS, tubular and ductal carcinoma. As most radial scars or other stellate lesions are screen-detected, this study emphasises the significance of excising these lesions to exclude malignancy, especially in older women.

9.1.7 The Radial Scar as a Risk Factor of Subsequent Cancer

In an attempt to ascertain the cancer risk associated with a radial scar, Jacobs et al. (1999) carried out a case–control study on 1,396 women who had had biopsies for benign breast disease. The women were followed up for 12 years and 99 (7.1 %) had a diagnosis of radial scar. Most of the radial scars were incidental microscopic findings with an overall median size of 4.0 mm. Single radial scars were present in 60.6 % of the women. Thirty-two per cent (32/99) of the women with radial scars developed breast cancer compared to 17 % (223/1,297) of the control group without radial scars. Women with radial scars tended to be older (>45 years) and most likely to be postmenopausal than those without radial scars. These findings partly concurred with the results of Sloane and Mayers (1993). There was no relationship between the presence of radial scar, age at menarche, parity, age at birth of first child or body mass index.

Jacobs et al. (1999) also assessed the benign disease associated with the radial scars and classified this into nonproliferative and proliferative disease without atypia and atypical hyperplasia. The RR of developing subsequent breast cancer in women with proliferative disease without radial scar was 1.5 and this doubled to 3.0 in women with radical scar. Women with atypical hyperplasia but no radical scar had an RR of 3.8; this increased to 5.8 when the women had a radial scar. These relative risks were adjusted for age, year of biopsy of benign breast lesion and follow-up interval. Adjustment for other breast cancer risk factors such as age at menarche, family history of breast cancer, body mass index, menopausal status, parity and age at birth of first child did not significantly alter the RR. Women with nonproliferative benign breast disease with a single radial scar had an RR of 2.5 compared with

similar women with multiple radial scars with an RR of 4.3. The presence of atypical hyperplasia increased the RR from 3.5 in women with single radial scars to 8.4 when multiple radial scars were present. When the size of the radial scars was taken into account, lesions larger than 4 mm had a higher RR than smaller lesions. Women with proliferative disease without atypia associated with radial scars of 4.0 mm had an RR of 3.5, and this increased to 8.8 when atypical hyperplasia was present. There was not much difference between proliferative disease without atypia (RR = 2.4) and atypical hyperplasia RR = 2.0 when radial scars less than 4.0 mm were present. From this study, Jacobs and colleagues postulated that the increased risk associated with radial scars could be related to disturbances between the interaction of the epithelial and stromal elements. In addition to highlighting the risk associated with radial scars, this study is also important to remind pathologists assessing benign breast disease to include the size and the number of radial scars. Jacob's study was on symptomatic patients with incidental radial scars. As radial scars tend to affect older women (>50 years) who are in the screening age group, separate studies are required to assess the risk of screen-detected radial scars.

Sanders et al. (2006) recorded lower RR than Jacobs et al. (1999). The authors followed up 880 women with a diagnosis of radial scar enrolled in the Nashville Breast Cohort for 20.4 years. Sixty-two (7 %) women developed invasive breast cancer compared to 5.5 % controls. The RR of developing invasive breast cancer was 1.82 (95 % CI, 1.2–2.7) at 10 years. When the analysis was restricted to women over 49 years of age, the RR increased to 2.14 (95 % CI, 0.6–2.8). The RR declined with increasing years of follow-up. Approximately 92 % of the women with radial scars had proliferative disease, the RR of radial scar with associated atypical hyperplasia was 6.72 (95 % CI, 2.5–18). These authors attributed the increased risk of subsequent cancer to the presence of proliferative disease rather than the radial scar per se. Similarly, Andersen and Gram (1984) had previously followed up 32 women with radial scars without atypical epithelial proliferation for a mean of 19.5 years (range 15–24 years) and only one patient developed cancer.

9.2 Sclerosing Adenosis

9.2.1 Pathogenesis and Clinical Features

Foote and Stewart (1945) initially described sclerosing adenosis as a lesion that presented as a palpable symptomatic tumour or as a microscopic incidental finding. Sclerosing adenosis arises as a result of proliferation of the terminal duct–lobular units in a disordered manner caused by an increase in acinar and myoepithelial cells and stromal elements (Jensen et al. 1989). In 1970, Tanaka and Oota (1970) carried out a detailed stereomicroscopic study of thick sections to ascertain the pathogenesis of mastopathic breast disease. From the stereomicroscopic images, the authors described sclerosing adenosis as proliferating parallel arrays of ductules, which sprouted abruptly from large flattened ducts to create 'bundles of noodles' forming knots or whorls. They noted that lobular formation was rarely seen in these lesions, which is in contradiction to the widely held view that sclerosing adenosis is a lobulo-centric process (Wellings et al. 1975). Sclerosing adenosis can be identified as a component of other proliferative lesions such as radial scars or fibroadenomas. Sclerosing adenosis has the ability to mimic cancer clinically and radiologically. Patients can present clinically with a palpable mass or detected radiologically through the screening process.

9.2.2 Radiological Features of Sclerosing Adenosis

In the screening age group, sclerosing adenosis can be detected as the main pathological lesion or identified incidentally in the background of other lesions, benign or malignant. In Lanyi's series (1986) of 52 patients who underwent biopsies for mammographically detected clustered microcalcification, sclerosing adenosis was detected in 15 patients (28.8 %). Nineteen out of 38 patients with diffuse milk of calcification cysts had a diagnosis of sclerosing adenosis on biopsy which he termed microcystic adenosis (Fig. 9.9c).

Microcalcification, radial structures or a combination of the two are the main mammographic features of sclerosing adenosis. The calcification

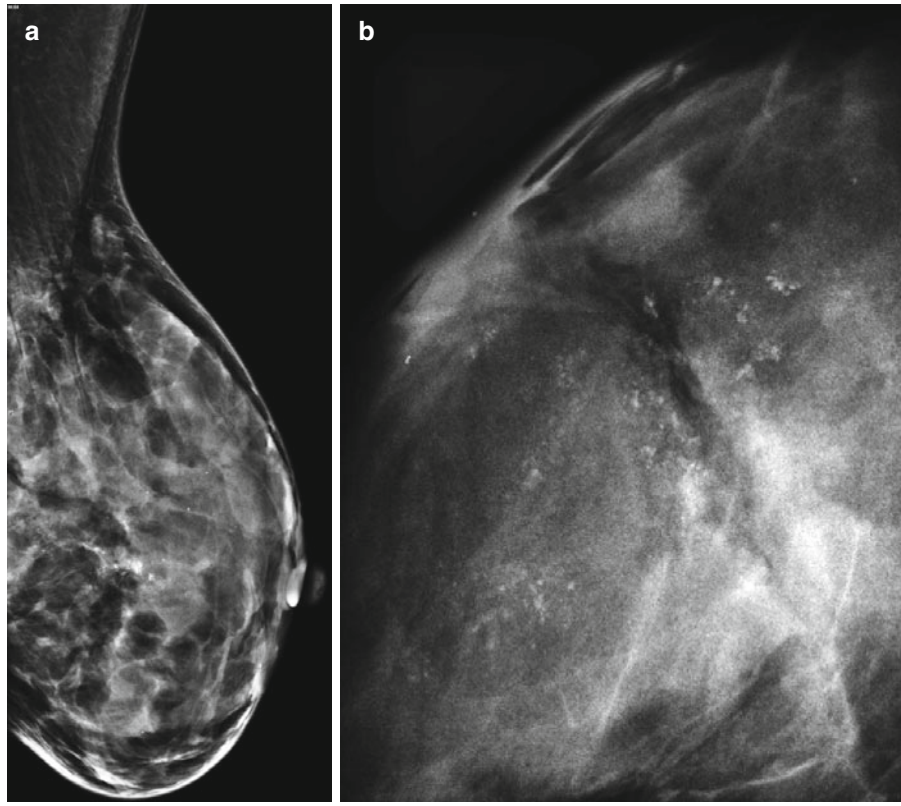


Fig. 9.7 (**a**) A large area of coarse calcification due to sclerosing adenosis which was graded as R4. (**b**) High magnification at the time of stereotactic biopsy. The biopsy was reported as calcified sclerosing adenosis (B2) but the abnormality was excised due to radiological–pathological discordance

in sclerosing adenosis is polymorphous (Fig. 9.7), and Lanyi believes this develops as the lobular cysts containing milk of calcium and psammoma bodies become 'distorted' by the proliferating myoepithelial cells and fibrous tissue (Fig. 9.9). However, the calcification in sclerosing adenosis is not always apparent radiologically but can be detected on histology. In some cases of sclerosing adenosis excised on the basis of clustered microcalcification, the calcification was present in the adjacent cysts, not in the compressed acini of sclerosing adenosis (Lanyi 1986). Although mammographically the pattern of calcification in sclerosing adenosis is variable, round- or rosette-shaped clusters are suggestive of sclerosing adenosis. Extensive diffuse microcalcification is rare (Lanyi 1986). Sometimes the calcification can be quite atypical and simulates malignant calcification (MacErlean and Nathan 1972; Lanyi 1986). When a mass lesion is present, sclerosing adenosis may appear multilobulated, focal, diffuse, nodular or spiculated (Cyrlak et al. 1999).

DiPiro and colleagues (2000) reviewed the mammographic and sonographic features of 12 patients (age range 26–61) with histologically proven nodular adenosis. Four patients presented symptomatically and in eight women the lesions were detected radiologically. Mammography was performed in ten patients; the lesions had a lobular circumscribed pattern in seven women and indistinct partly obscured or completely obscured masses in three women. One lesion contained mammographically heterogeneous calcifications. Ultrasonography was performed in seven patients and five revealed oval masses, one was lobular and another was irregular. All lesions were hypoechoic and six were circumscribed. No lesion revealed posterior acoustic shadowing of sound and five masses had posterior acoustic enhancement. Because the mammographic and

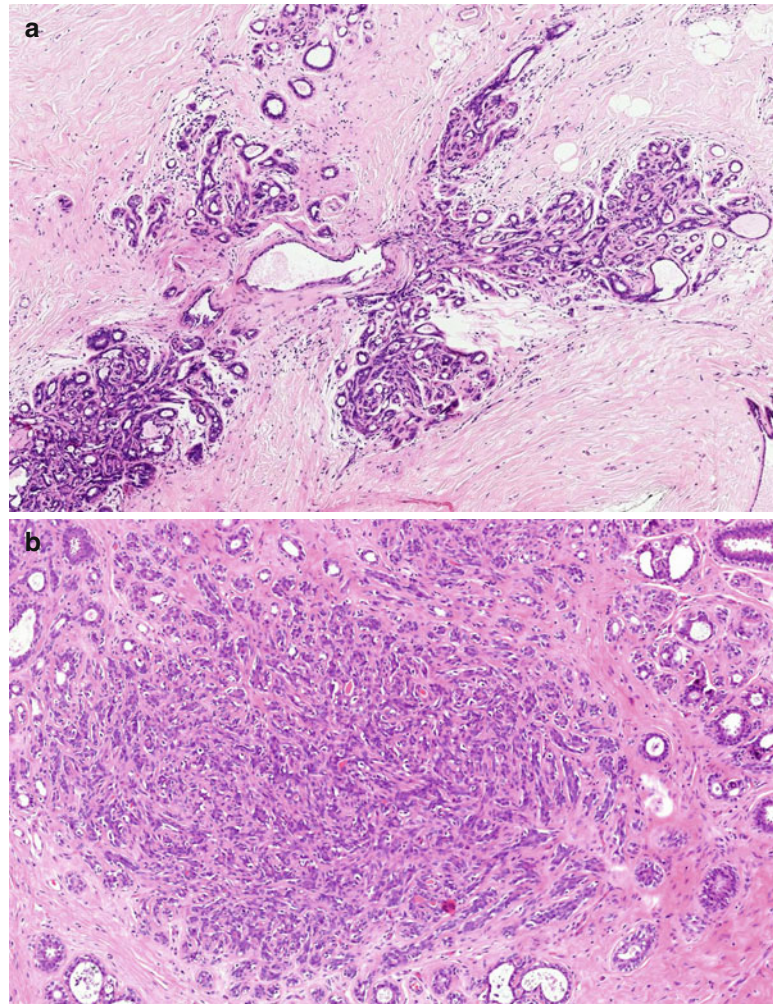


Fig. 9.8 (**a**) Incidental microscopic sclerosing adenosis in a specimen excised for other abnormality. Note the expansion of the TDLUs with a hyalinised stroma. (**b**) Is another microscopic sclerosing adenosis with a fibroblastic stroma

sonographic features of nodular adenosis were not specific, the authors recommended needle core or excisional biopsy. Nielsen and Nielsen (1986) did not find any radiological pathognomonic features when they reviewed 18 cases of histologically verified adenosis tumours.

9.2.3 Pathological Features of Sclerosing Adenosis

Sclerosing adenosis is a common finding in breast specimens excised for other lesions. When sclerosing adenosis presents with a tumour-forming lesion, the cut surface has a white fibrous appearance with ill-defined margins, but generally there are no specific macroscopic features.

Histologically there is proliferation of the TDLUs characterised by an increase in the number of acini that may produce a mass (florid adenosis) or in the extreme (adenosis tumour) or become surrounded by stromal sclerosis (sclerosis adenosis) (Nielsen 1987). Sclerosing adenosis represents a spectrum of benign alterations of breast tissue; the minimal form of which is an incidental microscopic finding (Fig. 9.8) considered to be a variation of normal (Hughes et al. 1987). The fibrous component (sclerosing) which depends on the age of the lesion can be either fibroblastic (Fig. 9.8b) or hyalinised (Fig. 9.8a). In most cases the fibrosis is hyalinised indicating a long-standing lesion. The epithelial component (adenosis) denotes an increase in acini with distortion of the TDLU resulting in an infiltrative

pattern within the fibrous component to mimic invasive cancer. In screen detected sclerosing adenosis, calcification is a common pathological finding. It is unusual for sclerosing adenosis to present as an extensive disease process (Fig. 9.9a). The lesion in Fig. 9.7 was excised due to

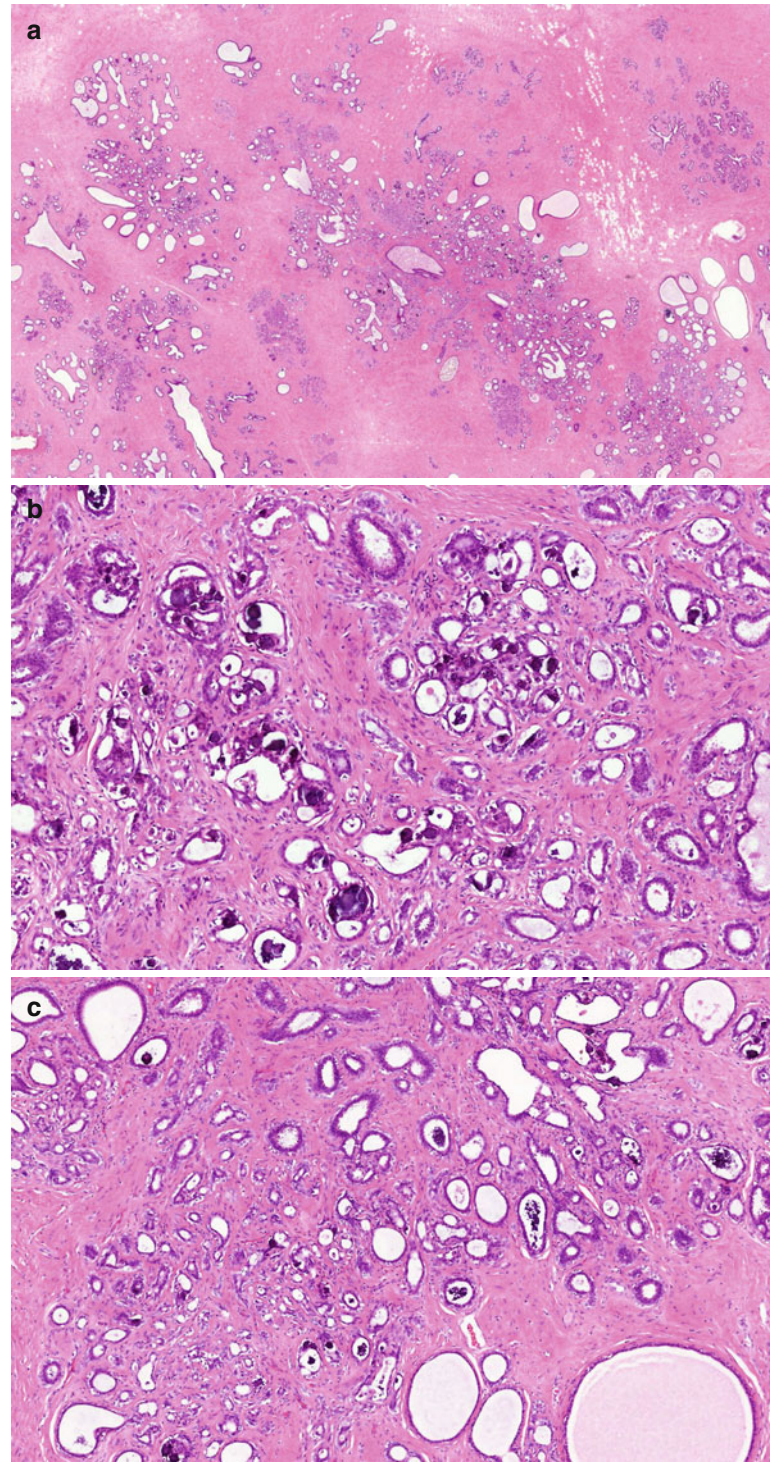
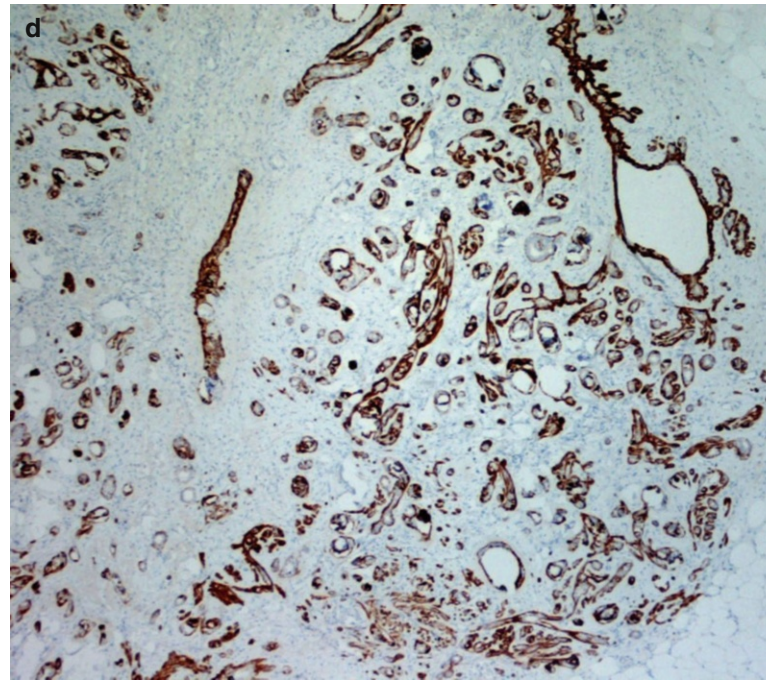


Fig. 9.9 (**a**) Unusually sclerosing adenosis can be quite extensive as illustrated in this case with multiple distorted lobular units with associated calcification and cysts; excision specimen of Fig. 9.7 above. (**b**) On high magnification, the calcification is coarse and pleomorphic despite being psammomatous in nature. (**c**) Sometimes the calcification is present in cysts, which Lanyi termed microcystic adenosis. (**d**) The myoepithelial cells in sclerosing adenosis are highlighted by immunocytochemistry staining with CK 5/6 which confirms benignity, which is useful in needle core biopsies

Fig. 9.9 (continued)



radiological–pathological discordance (R4, B2). The calcification which distorts the lobules is typically psammomatous, but with a coarse features, hence the radiological appearance (Fig. 9.9b). Sometime the calcification is present in cysts, which Lanyi termed microcystic adenosis (Fig. 9.9c).

Because of the infiltrative pattern, sclerosing adenosis can be difficult to distinguish from invasive carcinoma; and immunocytochemistry is useful to highlight myoepithelial cells which are preserved in sclerosing adenosis and absent in invasive carcinoma. Antibodies to myoepithelial cells include high molecular weight cytokeratins CK5 and CK14, smooth muscle actin (SMA), calponin and p63. CK5/6 also highlights basal cells (Fig. 9.9d), which is useful in needle core biopsies. Besides the pseudo-malignant pattern, sclerosing adenosis is frequently associated with lobular or ductal carcinoma, either in situ or invasive. In these circumstances, it can be difficult to assess the extent of the truly neoplastic proliferation when admixed with sclerosing adenosis (Fechner 1981). Cancerisation of sclerosing adenosis with DCIS (Fig. 9.10) also makes assessment for invasive disease difficult (Chan and Ng 1987). In difficult cases, immunocytochemistry markers may assist in delineating benign from malignant epithelium (Rasbridge and Millis 1995). Myoepithelial cells can be highlighted by use of alpha-smooth muscle actin, S100 protein and cytokeratin 5/6. Useful basement membrane markers include collagen IV and laminin.

9.2.4 Genetic Alterations in Sclerosing Adenosis

As with any other benign breast lesions, there is constant search for a molecular marker which may assist in determining whether a lesion is premalignant or not. Using the polymerase chain reaction (PCR), Washington et al. (2000) analysed LOH at 14 loci in seven chromosomes in different benign breast lesions including sclerosing adenosis. In four out of 23 cases of sclerosing adenosis, the authors demonstrated LOH at 13q (2 cases), 17p and 17q (2 cases) which suggested presence genetically altered cells which may be a precursor to malignancy. In another study, LOH was assessed in normal and benign lesions including sclerosing adenosis in breast cancer specimens from five patients who were BRCA1/2 carriers (Cavalli et al. 2004). The

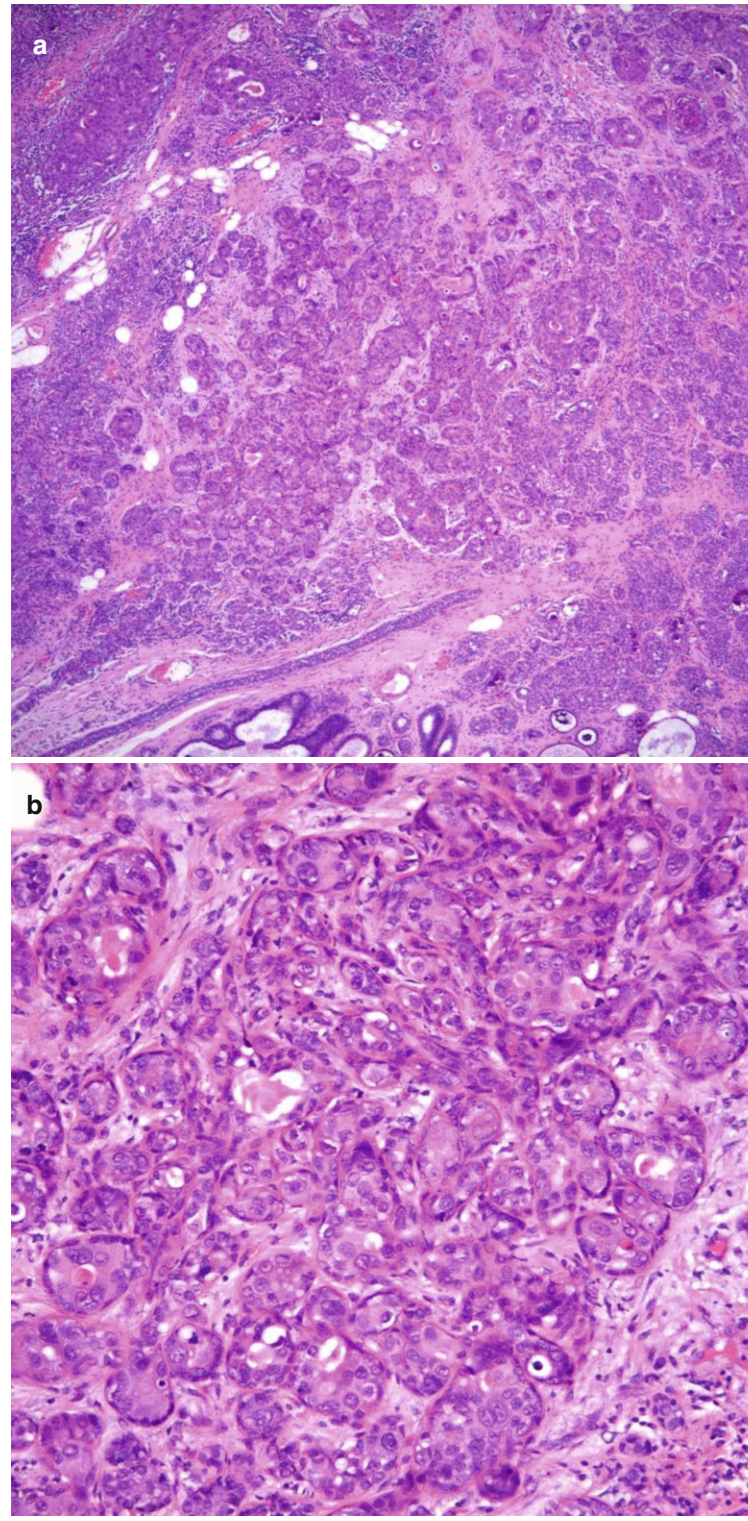


Fig. 9.10 (**a**) Cancerisation of sclerosing adenosis with DCIS, which closely mimics invasive cancer. (**b**) Higher magnification clearly highlights the DCIS and sclerosing adenosis

authors analysed 105 samples for LOH on chromosome 17q with the locus for BRCA1 gene, chromosome 13q with the locus for BRCA2 gene and FHIT gene at 3p14.2. LOH of FHIT (fragile histidine triad) is a putative tumour-suppressor gene which is frequent in breast cancers of patients who are BRCA2 carriers (Ingvarsson et al. 2001). Cavalli and co-authors demonstrated LOH in 44 out of 75 (59 %) samples with sclerosing adenosis and 15 out of 30 (50 %) normal TDLUs. The authors suggested a field change effect of early genetic events preceding morphological changes in the mammary glands of BRCA mutation carriers.

9.2.5 Management of Sclerosing Adenosis in a Needle Core Biopsy

Sclerosing adenosis is usually an easy diagnosis to make on needle core biopsy which should not require any further action unless there is a clinico-pathological discordance. In a retrospective radiological–pathological review, 88 cases (7.8) out of 1,116 needle core biopsies were reported as sclerosing adenosis, Gill et al. (2003) noted that sclerosing adenosis was a minor component in the core biopsies of 44 lesions which included: one invasive carcinoma, one DCIS, one ADH and one ALH. In the other half (44 lesions; 50 %), sclerosing adenosis was a major component which included four DCIS with clustered calcification and seven ADH with amorphous calcification. In 30 patients with 33 lesions without atypia or malignancy, sclerosing adenosis was the major finding at core biopsy and these patients formed the study population. One speculated mass was considered discordant and excised and showed radial sclerosing lesion with 2–5 mm foci of invasive lobular carcinoma. Seventeen (53 %) of the remaining 32 lesions manifested as masses; 10 (5 %) were circumscribed; five (29 %) were indistinctly marginated (one with punctate calcifications); and two (12 %) were partially circumscribed and partially obscured (one with amorphous calcification). Fifteen (47 %) lesions manifested as clustered calcifications, nine (60 %) were amorphous and indistinct, four (27 %) were pleomorphic and two (13 %) were punctate. Of the 27 lesions with at least a 20-month follow-up, 26 (96 %) were believed to have been accurately sampled at core biopsy. Of the six radial sclerosing lesions associated with the original 88 lesions, only three were prospectively sampled. The authors concluded that sclerosing adenosis is an acceptable result in the core biopsies of circumscribed masses and non-palpable indistinctly marginated masses and for clustered amorphous, pleomorphic and punctate calcification. However, reporting of coexisting radial sclerosing lesion should prompt excision. When malignancy was present with sclerosing adenosis, the core biopsy was accurate in six (86 %) of the seven coexistent malignancies in this study. The message from this paper is that a confident diagnosis of sclerosing adenosis on needle core biopsy is possible, and if there is no radiological–pathological discordance, there is no need for surgical excision. In a separate review of 41 patients who had the primary diagnosis of sclerosing adenosis on needle core biopsy, Taskin et al. (2011) also noted that the diagnosis of sclerosing adenosis was possible in a needle core biopsy, and the final decision not to excise should be made at a multidisciplinary team meeting.

9.2.6 Sclerosing Adenosis as a Risk Factor for Breast Cancer

When Foote and Stewart (1945) examined 200 breasts without cancer and 300 breasts with cancer, they identified 12.5 % and 7 % of sclerosing adenosis in benign and malignant breasts, respectively. They did not feel there was morphological evidence to indicate that sclerosing adenosis was precancerous. Likewise, Lanyi (1986) felt that

sclerosing adenosis had no clinical significance as long as the fibromyoepithelial proliferation did not create a nodular tumour with pseudo-infiltration, which could be mistaken for cancer. The main clinical significance of sclerosing adenosis is the infiltrative histological appearance with a risk of false-positive diagnosis of malignancy leading to overtreatment, which may include mastectomy (Nielsen 1987). Histological perineural invasion, when present, can also be mistaken for malignancy. Because of the risk of a false-positive diagnosis, frozen section diagnosis should be avoided.

As with most benign lesions, there is disagreement among breast clinicians as to whether or not sclerosing adenosis is a risk factor for subsequent malignancy. Several papers have reported the occurrence of carcinoma in association with sclerosing adenosis without indicating whether this was a symbiotic existence or whether sclerosing adenosis was a marker for increased risk of malignancy or premalignant lesions. Oberman and Markey (1991) reported the presence of LCIS in association with sclerosing adenosis in seven patients; one patient had DCIS and another had mixed DCIS and LCIS. The authors felt that the occurrence of sclerosing adenosis and LCIS was coincidental because both lesions arise from the same breast lobules.

Jensen and colleagues (1989) attempted to clarify whether sclerosing adenosis was a risk factor of malignancy or not. They reviewed 10,366 excised benign biopsies and from these they identified 547 lesions that met the criteria of sclerosing adenosis. Of the 3,303 women they followed up, 349 had sclerosing adenosis. Eighty-four of the women were followed up for 17 years. The majority (237) of the patients were in the 41–50 age group, with a few (26) in the 51–60 age group, indicating that sclerosing adenosis was a premenopausal lesion. The overall RR for developing invasive cancer was 2.1 in women with sclerosing adenosis regardless of the presence of atypical hyperplasia; this declined to 1.7 when patients with atypical hyperplasia were excluded. Based on these findings, sclerosing adenosis was classified into the category of proliferative disease without atypia, with an average risk of 1.5–2.0 above that of the general population. When women with sclerosing adenosis and atypical hyperplasia only were assessed, the RR elevated to 6.7. However, the family history of breast cancer did not elevate the risk when sclerosing adenosis was assessed independently without associated atypical hyperplasia. In addition, the authors noted a positive association of sclerosing adenosis with ALH which was 2.7 times more frequent than other lesions. In a separate study, Bodian et al. (1993) reported a relative risk of 2.9 in patients with adenosis (not specified) and this was elevated to 3.7 in patients with combined adenosis and intraductal papilloma.

9.3 Apocrine Adenosis

9.3.1 Morphological Features of Apocrine Adenosis

Simpson, Page and Dupont (1990) defined apocrine adenosis as the presence of apocrine cytology in a recognisable lobular unit, which may or may not be deformed with some loss of the lobulo-centric pattern. Apocrine adenosis is usually associated with sclerosing adenosis or radial scars (Fig. 9.11). The cells of apocrine adenosis show abundant eosinophilic cytoplasm. The nuclei are large and pleomorphic with prominent nucleoli. The combination of a pseudo-infiltrative morphology and large pleomorphic cells makes apocrine adenosis appear malignant, more so than conventional sclerosing adenosis. There is confusion in the literature as to what breast lesion qualifies for the term apocrine adenosis (Page and Simpson 2001; Endoh et al. 2001). For the purpose of this book, apocrine adenosis is restricted to lesions such as radial scars, complex sclerosing lesions or sclerosing adenosis with associated apocrine cytology (Fig. 9.11).

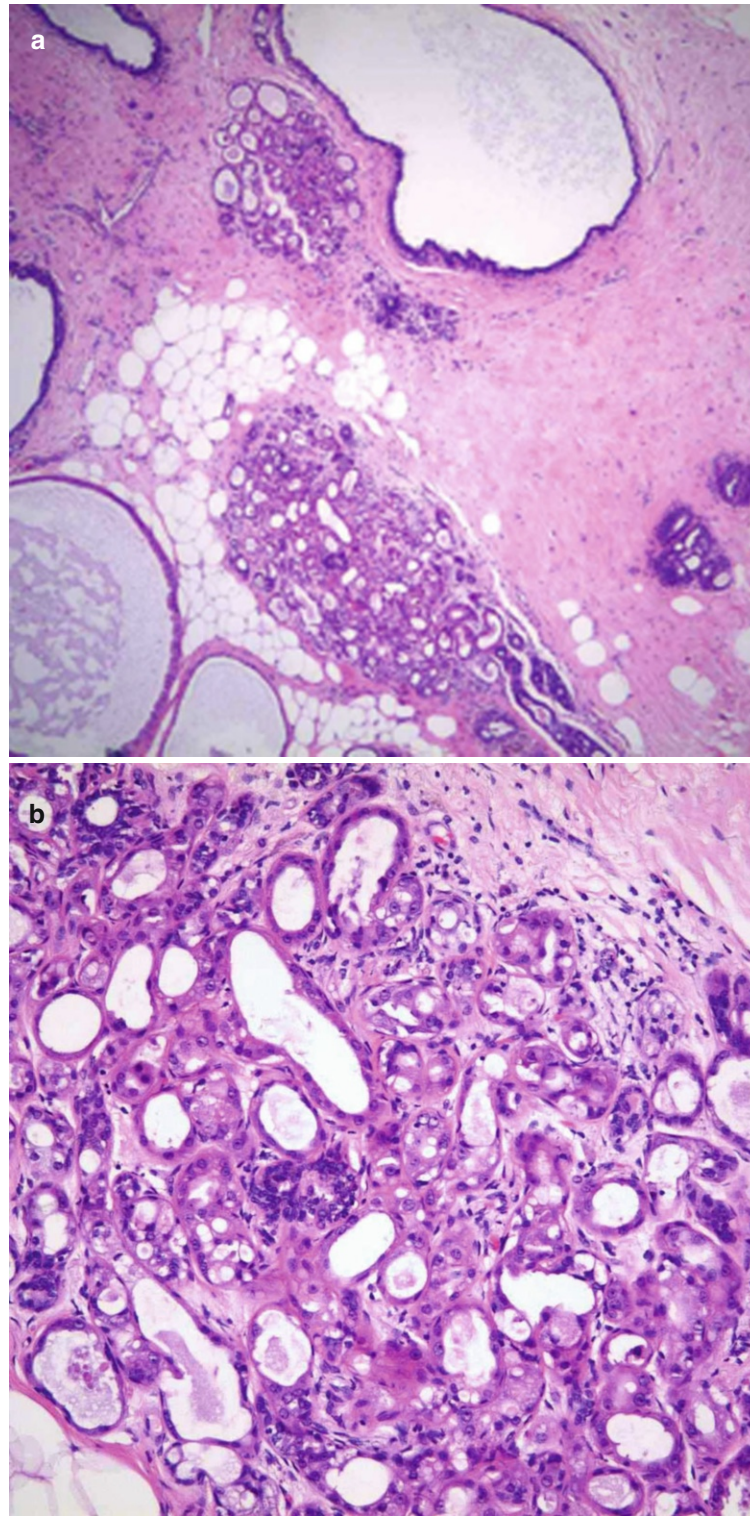
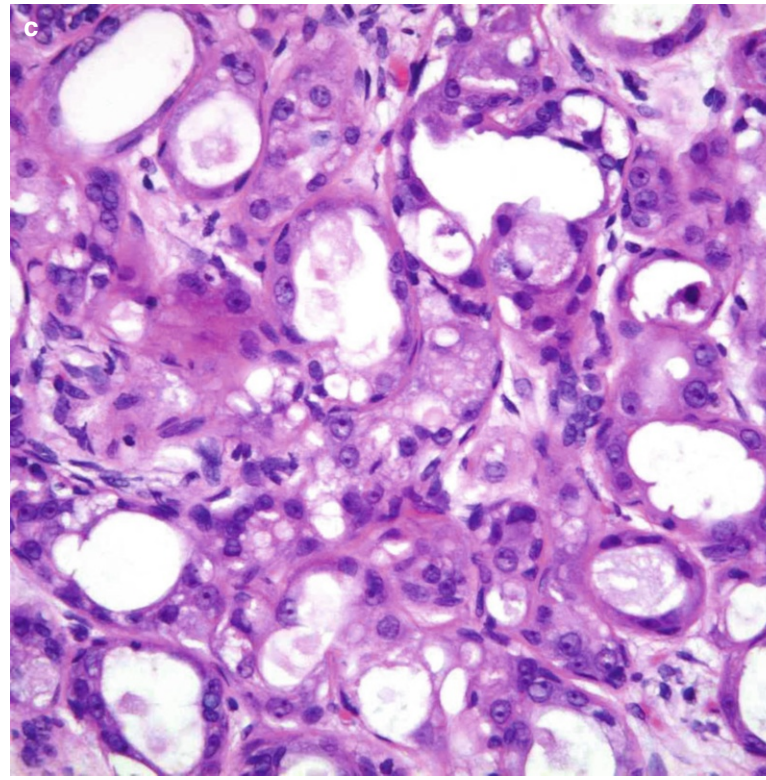


Fig. 9.11 (**a**) Two foci of apocrine adenosis were present in the radial scar in Fig. 9.5. Similar to sclerosing adenosis, apocrine adenosis typically consists of enlarged distorted lobules. (**b**) At high magnification, apocrine adenosis closely mimics invasive carcinoma with distorted lobules and related fibrous stroma (**c**). The cells show large amounts of eosinophilic cytoplasm with indistinct cell borders. The nuclei are large and pleomorphic with prominent eosinophilic nucleoli

Fig. 9.11 (continued)



9.3.2 Clinical Significance of Apocrine Adenosis

In a follow-up study by Simpson and colleagues (1990), apocrine adenosis was classified as such when apocrine cytology was present in enlarged lobular units (>2 mm) of sclerosing adenosis, complex sclerosing lesions and ductal adenoma. The unifying concept in these lesions was the adenotic pattern in association with apocrine cytology. The authors identified features of apocrine adenosis in 3 % (123) of the patients from a cohort of 3,490 patients from their local hospital who had undergone excision biopsies for symptomatic benign lesions and 55 referred cases from other hospitals. Despite the bizarre appearance of the nuclei associated with prominent nucleoli and abundant cytoplasm, Simpson and colleagues refrained from applying the term atypical apocrine adenosis, a term Carter and Rosen (1991) readily embraced. The average age of the 55 referred patients in Simpson's study was 58 years, and in 59 % of the patients, the slides had been referred on suspicion of malignancy or felt to be malignant. The majority of cases of apocrine adenosis were mammographically detected and histological calcification was present in 46 cases (82 %). Atypical hyperplasia was present in 12 cases (21 %). The average age of the 123 locally treated patients with biopsies containing apocrine adenosis was 43 years. Although these biopsies were performed in the pre-mammographic period, 31.6 % of the apocrine adenosis showed histological calcification, and 10.2 % of the cases had associated atypical hyperplasia. Unlike the referred cases, the apocrine adenosis patients treated at the local hospital group were incidental findings. The study reported a positive association between apocrine adenosis and atypical hyperplasia, which was 2.5 times that seen in other large cohorts without apocrine adenosis. Although the association of apocrine adenosis and atypical hyperplasia increased the risk of malignancy, because of the atypical hyperplasia is an independent risk factor, the study did not prove that apocrine adenosis was an independent risk factor for malignancy.

Carter and Rosen (1991) studied 51 patients with lesions they termed atypical apocrine metaplasia in sclerosing adenosis. These lesions were morphologically similar to those described by

Simpson et al. (1990). The average age of the women was 58 years and the lesions tended to be small (less than 10 mm) and 78 % were detected mammographically. This study also highlights the pseudo-malignant nature of these lesions, which led to a false-positive diagnosis and subsequent mastectomy in four patients. None of the 47 patients with intact breasts developed malignancy on follow-up and the potential premalignant nature of this lesion was not proven. Similarly, Makunura et al. (1994) reported a case of apocrine adenosis arising in a radial scar, which was diagnosed as malignant on cytology and resulted in local excision and axillary dissection. Because apocrine epithelium is negative for oestrogen and progesterone receptors, this may reinforce a false-positive diagnosis of high-grade DCIS or poorly differentiated carcinoma in a needle core biopsy. The presence of apocrine cells in cytology or needle core biopsy should be interpreted with caution.

Seidman et al. (1996) applied the term atypical apocrine adenosis to lesions that displayed pleomorphic nuclei, three times the size of normal ductal epithelium. Using these criteria they followed up 37 women with atypical apocrine adenosis for an average of 8.7 years. Four patients developed invasive carcinoma after a mean of 5.6 years (three ipsilateral, one contralateral). The RR for developing carcinoma was calculated to be 5.5. All the patients who developed carcinoma were over 60 years of age with a mean age of 70 years. In women over 60 years, the calculated RR of developing carcinoma was 14. This study showed that atypical apocrine adenosis conferred an increased risk of subsequent breast cancer in older women. The authors postulated that apocrine adenosis might represent in situ apocrine carcinoma, which is difficult to diagnose because of the unusual architectural and cytological features. Although the calculated RR in this study is compelling, the number of patients in this study was very small. Fuehrer et al. (2012) also followed up 37 women with atypical apocrine adenosis diagnosed between 1967 and 1991, and only three of them developed cancer at four, 12 and 18 years of follow-up. The authors concluded that apocrine adenosis was rare and should not be regarded as a direct histological precursor to breast cancer.

The premalignant nature of apocrine adenosis may be elucidated by the use of molecular markers. Wells et al. (1995) reported expression of C-erbB2 in 12 out of 21 cases of apocrine adenosis and six cases were positive for p53. In a separate study, C-erbB2 expression was reported in apocrine adenosis without gene amplification (Selim et al. 2000) suggesting possible late gene amplification in the pathogenesis of apocrine-derived cancers. C-erbB2 protein expression is usually associated with gene amplification and the lack of this in Selim's study questions the quality of their immunocytochemistry results. Loss of heterozygosity and allelic imbalance has also been identified in apocrine adenosis, suggesting an early event in the pathogenesis of breast cancer (Selim et al. 2001). C-myc overexpression in apocrine adenosis is thought to be an early change in carcinogenesis (Selim et al. 2002). There are still a lot of unanswered questions regarding the biological behaviour of apocrine adenosis.

9.4 Microglandular Adenosis

9.4.1 Pathological Features of Microglandular Adenosis

Microglandular adenosis (MGA) is an uncommon lesion initially described by McDivitt and colleagues in 1968. Clement and Azzopardi (1983) further reported and characterised this lesion in detail in six cases when they described lesions with 'naked' glands lying in adipose tissue. MGA is characterised by proliferation of small glandular structures, separated by a stroma which histologically mimics invasive tubular carcinoma. This mimicry is exaggerated by the apparent lack of a myoepithelial cell layer with immunocytochemistry markers (Eusebi et al. 1993). Eusebi and colleagues investigated four cases of MGA and ten tubular carcinomas and reported lack of myoepithelial cells on immunocytochemistry staining. The lack of myoepithelial cells in one of the cases was confirmed by electron microscopy. This lack of myoepithelial cells was felt to be unique in MGA as a benign lesion, a feature also confirmed by Tavassoli and Bratthauer (1993). Collagen IV and laminin, which should be present in MGA and absent in tubular carcinoma, can also be applied to confirm the diagnosis (Kay 1985).

Because of the infiltrative nature, the accurate assessment of the gross appearance of MGA is

difficult to determine. Lesions have been estimated to be 3–4 cm in most cases and sometimes as large as 20 cm. Histologically MGA consists of small glands or acini which appear to infiltrate the stroma in a diffuse pattern or as isolated structures in to the related fat (Fig. 9.12) There are no

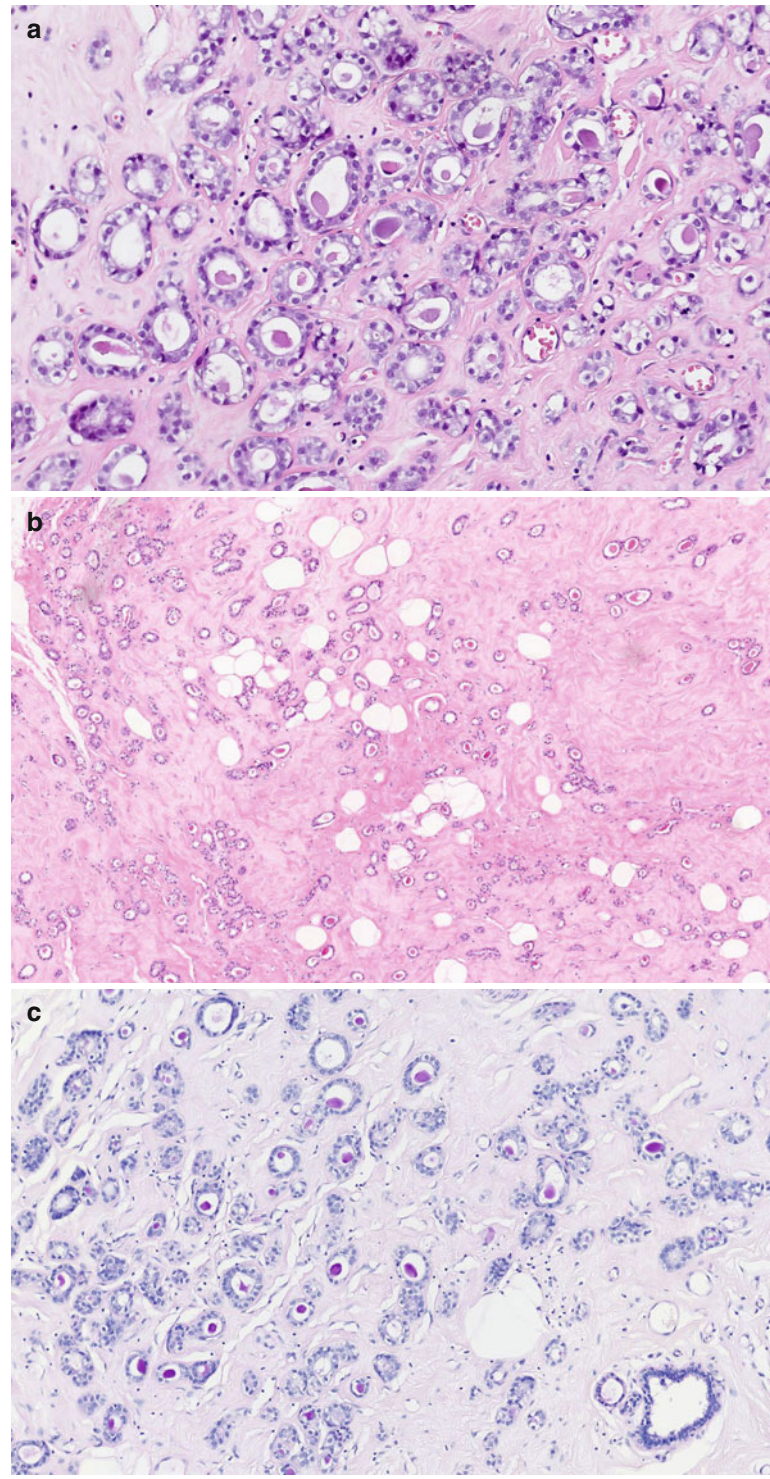


Fig. 9.12 (**a**) Microglandular adenosis consist of crowded glands apparently infiltrating the fibrous stroma; the glands are lined by a single layer of epithelium devoid of a myoepithelial layer 'naked' glands. The glands contain eosinophilic luminal secretions. (**b**) In another field, the glands are sparsely distributed in the stroma and associated fat. (**c**) The luminal secretions are PAS-positive and resistant to diastase digestion. (**d**) Lack of the basal myoepithelial layer is demonstrated by the negative staining with the CK5/6 antibody. The duct acts a positive control. (**e**) This micrograph illustrates tubular carcinoma as a comparison to microglandular adenosis. The infiltrative structures are tubular and the cells exhibit luminal snouts, which are typically absent in microglandular adenosis whose glandular structures tend to be round (By courtesy of Dr W. Mohamid, cellular pathologist at Chase Farm Hospital, UK)

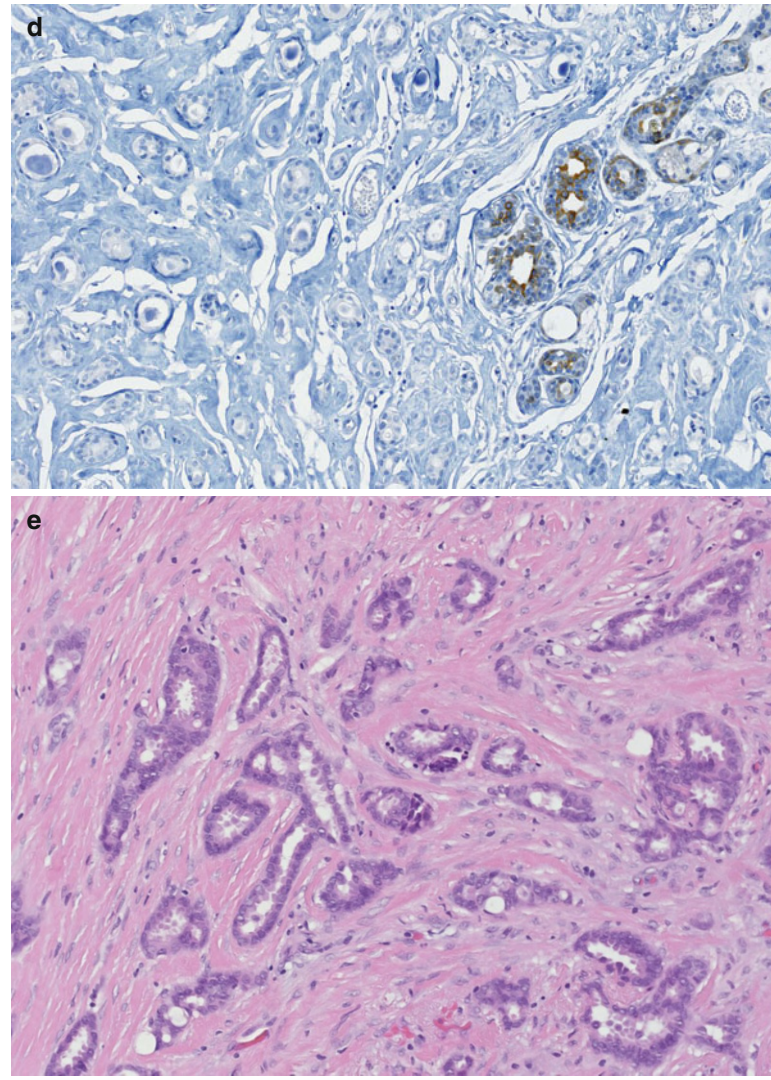


Fig. 9.12 (continued)

myoepithelial cells ('naked' glands). Some glands contain luminal secretions which are periodic acid-Schiff (PAS) positive and resistant to diastase digestion and may calcify (Rosen 2009). The main differential diagnosis of MGA is tubular carcinoma, which exhibits a teardrop glandular morphology instead of round acini of MGA. Tubular carcinoma cells also exhibit luminal snouts which are not apparent in MGA (Fig. 9.12a, e).

MGA exhibits a heterogenous immunocytochemistry staining pattern as demonstrated by Khalifeh et al. (2008). The cells are positive for S100 protein and epidermal growth factor (EGFR) but lack cytokeratin CK5/6 which stains the myoepithelial cells in benign lesions; but the cells are positive for CK8/18 which stain the luminal cells. MGA is negative for Her2 oestrogen and progesterone receptors. Epithelial membrane antigen (EMA) is also absent in MGA which differentiates this lesion from tubular carcinoma; the latter expresses EMA (Rosen 2009).

9.4.2 Radiological Features of Microglandular Adenosis

The radiological features of pure MGA are not properly documented in the literature because the lesion is rare and usually presents

symptomatically or as an incidental finding in specimens excised for another pathological process. However, Sabaté and colleagues (2002) reported the radiological features of MGA in a 22-year-old woman who was a carrier of the BRCA1 gene mutation and was referred for screening. The protocol for follow-up in genetically predisposed women in this institute included clinical examination, mammography, high-resolution sonography and magnetic resonance imaging. The clinical examination was negative. Mammography revealed dense breasts without any abnormality. Sonographic examination identified a 10 mm hypoechoic lesion with irregular but well-defined margins. The width of the lesion was greater than its height, with discrete micro-lobulations. Magnetic resonance showed a small, ill-defined lesion with moderate early and delayed enhancement. There was no rim enhancement, washout or internal septations, but on T2-weighted images, the lesion was hyperintense. The sonographic features were suspicious of malignancy. A core biopsy and subsequent excisional biopsies were performed. The histological features were those of microglandular adenosis. The radiological features of the MGA correlated well with the pathological findings. The irregular borders of the sonographic images corresponded with infiltrative pattern pathologically. However, the benign nature of the lesion on the magnetic resonance images suggested a possible fibroadenoma. In this case, the presence of BRAC1 gene mutations prompted a biopsy. If the radiological features reported in this single case of pure MGA are typical, mammography may not be the ideal modality to identify MGA, especially in dense breasts.

9.4.3 Clinical Significance of Microglandular Adenosis

Because MGA exhibits a pseudo-infiltrative growth pattern, the main risk is to misdiagnose carcinoma in a needle core biopsy, which may result in unnecessary aggressive surgery. There are several reports of carcinoma arising in association with MGA, making it potentially a precursor of invasive cancer. Rosenblum et al. (1986) reported carcinoma arising in MGA in seven patients aged between 39 and 72 years. The women had presented with symptomatic masses, clinically suspicious of malignancy. Pathological assessment identified proliferations, which qualified to be classified as atypical MGA, suggesting a progressive disease process from benign → atypia → malignancy. The carcinoma arising in MGA maintained the alveolar pattern of adenosis. From these observations, the authors concluded that MGA may be a precursor of carcinoma and recommended clinical follow-up of affected patients; and if atypia is present, wide excision and follow-up similar to other forms of atypical hyperplasia is recommended. The same group at later stage (James et al. 1993) from the Memorial Sloan–Kettering Cancer Center, New York, reviewed 60 patients with microglandular adenosis. Fourteen women (23 %) had carcinoma arising in conjunction with MGA. The authors described the clinico-pathological, immunohistochemical and prognosis of the carcinomas. The median age was 47 years (range 26–68 years). All patients presented with a mass. Six patients (45 %) had a family history of breast cancer. The carcinomas had a solid growth pattern resembling MGA. Lymph node metastases were present in three out of the 11 patients who had axillary dissection. Ten patients who were treated with mastectomy were recurrence-free with a median follow-up of 57 months (range 3–108 months). Two of three patients who had excisional biopsies were recurrence-free 12 and 105 months later. The third patient had bone metastases at 51 months. Invasive carcinoma arose in MGA in 13 patients and this was associated with an in situ component. One patient had benign MGA and carcinoma developed in the contralateral breast. On immunocytochemistry staining, the basement membrane was preserved in MGA and carcinoma in situ but was disrupted or absent in invasive carcinoma. The carcinomas were positive for cytokeratin, S100 protein and Cathepsin D. Two cancers were positive for progesterone receptors and one of these for oestrogen receptors. One carcinoma was positive for Her2 and four were immunoreactive for p53. The authors concluded that carcinoma

arising in MGA had distinct histopathological and immunocytochemical features. The cancers had a relatively good prognosis despite the histological and immunohistochemical features usually associated with poor prognosis. This may be significant as genetic alterations associated with family history of breast cancer have been detected in patients with AGA-associated proliferations (Para. 9.4.4). This also adds weight to the isolated case report by Sabaté et al. (2002) which raises the possibility of MGA being associated with BRAC1-associated cancer.

A separate study by Koenig et al. (2000) reported 19 carcinomas (in situ and invasive) arising in MGA. The majority of the patients presented symptomatically, but in four patients the carcinomas were detected mammographically. In 18 out of 19 cases, there was transition from MGA to carcinoma through an intermediate lesion, atypical MGA to invasive cancer. The study included a case of atypical MGA without overt malignancy. The glands of atypical AGA were irregularly shaped, closely packed and cytologically atypical with no luminal secretions. Solid proliferations in atypical AGA were also noted. The DCIS was either Grade 2 or 3. The invasive cancers were morphologically diverse and included two with basaloid morphology and two with metaplastic features. More importantly, except for one case, oestrogen and progesterone receptors were negative in all lesions. The authors concluded that this study clearly defined the features of atypical MGA and its role in the evolution of carcinoma from AGA. Khalifeh et al. (2008) reviewed 11 patients with MGA, three of whom had uncomplicated MGA, two had atypical MGA and six had MGA-associated carcinoma which showed heterogenous features. All the invasive carcinomas had a ductal component, two had basal-like features, two had acini-like structures, four produced basement membrane material and one had sarcomatoid features and one had adenoid cystic features. Based on the morphological features highlighted in the above publications, the presence of an intermediate lesion such as atypical MGA implicates MGA as a potential precursor of invasive cancer. The cancers in Khalifeh's series were ER, PR and Her2 negative (triple receptor negative). All the cancers were CK8/18 and EGFR (basal-like features) positive. Based on this immunophenotype, the authors concluded that all the cases showed luminal type differentiation by CK8/18 expression indicating that MGA-associated carcinoma may not fit well into the current proposed molecular classification of breast cancer.

9.4.4 Molecular Features of MGA

Several reports have documented carcinoma arising from MGA and the presence of borderline lesion atypical microglandular adenosis (AMGA). Geyer and colleagues (2009) carried out immunohistochemical investigations and molecular studies in a lesion which contained MGA, AMGA and high-grade invasive ductal carcinoma of no special type (IDC-NST). MGA, AMGA and IDC-NST were negative for ER, PR and Her2 (triple receptor negative), but all were positive for S100 protein and CK8/18. CK5/6 was equivocal, but p63 was completely negative. The latter two markers highlight myoepithelial cells; p53 was negative in all three proliferation. Ki67 was reported as 5 %, 25 % and 65 % in MGA, AMGA and IDC-NST, respectively, demonstrating progression of increasing proliferation activity. This immunoprofile is similar to that reported by Khalifeh et al. (2008) in three cases of MGA, two cases of AMGA and five cases of carcinoma associated with MGA. By using comparative genomic hybridization, Geyer et al. (2009) demonstrated similarities in all three lesions at genetic level. The profiles were characterised by low copy number changes with increasing complexity as the lesions evolved from MGA to IDC-NST. Gains of 1p12, 5q13 and 15q11, aneusomy/polysomy of chromosome 7 and losses of 2p11, 4p16, 8q21, 17q12 and 1p13 were identified across the spectrum. IDC-NST displayed additional gains and losses of several regions such as gain of 3q23–q29 and loss of 14q32.13–q32.31. Pearson's corrections between the different components of the case revealed remarkable similarities at genetic level (MGA versus AMGA: 0.8525, $p<0.0001$;

AMGA versus IDC-NST: 0.8822, $p<0.0001$; MGA versus IDC-NST: 0.8833, $p<0.001$) providing strong molecular evidence that the three lesions are clonally related.

Because the MGA-related lesions lacked gains of 1q and 16p and loss of 16q, chromosomal aberrations usually found in lesions pertaining to the low-grade breast neoplasia, the authors suggested that MGA may be one of the earliest morphologically identifiable precursors of high-grade tumours. The authors concluded that based on the immunoprofile and chromosomal aberrations, MGA was at least a clonal lesion and a possible non-obligate precursor of subgroup of high-grade triple-negative and basal cell-like breast carcinoma. The authors also suggested that MGA renamed microglandular adenoma as adenosis reflects a hyperplastic lesion. In a separate study of carcinoma arising in MGA, Shin et al. (2009) also demonstrated concordant molecular alterations in MGA, AMGA and MGA-associated carcinoma, indicating probable clonal evolution with MGA as a non-obligate precursor for breast cancer. The authors also noted that the molecular features of MGA and AMGA were similar to those found in basal-like carcinomas of the breast, suggesting they may be related to these tumours. Furthermore, MGA is usually negative for ER, PR and Her2, positive for S100 protein, EGFR and p53, characteristics shared by 'triple-negative' and basal-like carcinomas. These features were also associated with ER-negative, basal-like and BRCA1-associated breast cancer. The role of MGA in familial breast cancer requires further investigation.

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Epithelial Proliferative Lesions 10

Learning Points

- UDH is a common finding in specimens excised for benign disease or breast cancer.
- ADH is difficult to differentiate from low-grade DCIS resulting in high intra-and interobserver variation on reporting.
- Diagnosis of ADH in the needle core should lead to excision biopsy to exclude high-grade lesions.
- There is no consensus on how to manage ADH on the margin in a lumpectomy specimen; therefore, MDT discussion is important.
- Lobular neoplasia (LN) should be excised if present on needle core to exclude high-grade lesions.
- There is no consensus regarding risk of bilateral cancer in patients with LN.
- LN should be managed conservatively if it is an incidental finding in a specimen excised for another lesion.
- Molecular studies indicate that LN is both a risk marker and non-obligate precursor of invasive carcinoma.
- Intraductal papillomas can arise centrally or at the periphery of the breast.
- Diagnosis of a papillary lesion on biopsy should prompt an excisional biopsy as a high-grade papillary neoplasm cannot be excluded.
- Intraductal papillomas behave as both a marker and precursor of malignancy.
- The diagnosis of pregnancy-like changes should not be made in a lactating breast.

10.1 Usual Ductal Hyperplasia (UDH)

The normal breast tissue consists of branching ducts, which terminate into the secretory lobular units. The ducts and lobules are lined by two layers of epithelium consisting of the inner secretory epithelial layer and the outer myoepithelial layer. An increase in the number of epithelial cells, three to four cells above the basement membrane, without bridging or distension of the lumina, indicates mild epithelial hyperplasia (Fitzgibbons et al. 1998). Mild epithelial hyperplasia is not associated with increased risk of malignancy (Rogers 1987). This pattern of mild epithelial proliferation is present in most specimens excised for benign and malignant breast tissue.

Usual ductal hyperplasia (UDH) denotes a step further in the proliferation of breast epithelium and is diagnosed by the presence of four or more cell layers above the basement membrane. This proliferation is also termed hyperplasia of usual type (HUT) moderate epithelial hyperplasia without atypia, proliferative disease without atypia (PDWA), regular epithelial hyperplasia or ordinary epithelial hyperplasia. The term 'usual' is intended to emphasise the fact that the epithelial

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_10, © Springer-Verlag Berlin Heidelberg 2014

proliferation is the type commonly present when the number of cells is increased within a basement membrane-bound space (Page 1992). Use of terms such as epitheliosis and papillomatosis should be avoided when describing epithelial hyperplasia, as they are confusing and non-specific.

UDH is usually present in specimens excised for malignant or benign breast lesions. The latter include fibrocystic change, radial scars, atypical hyperplasia, fibroadenomas or intraductal papillomas. Any of these lesions can be symptomatic or screen detected. It is unusual for mild or moderate epithelial hyperplasia without atypia to be the main mammographic abnormality to prompt an excisional biopsy, but occasionally calcification can lead to mammographic detection. UDH is architecturally heterogeneous, which could make histological classification difficult.

10.1.1 Pathological Features of UDH

The intraductal proliferation can exhibit interconnecting arcades with false glandular lumina, solid proliferation or micropapillary structures (Fig. 10.1). Apocrine cells may also

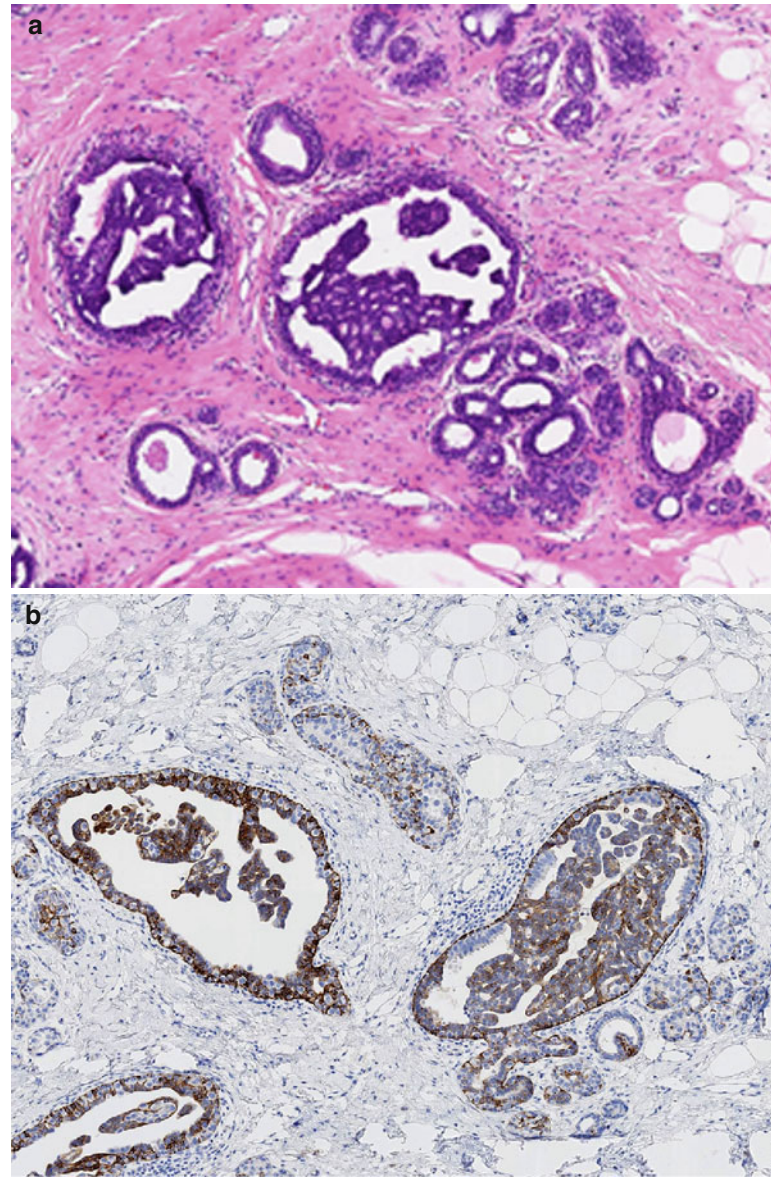
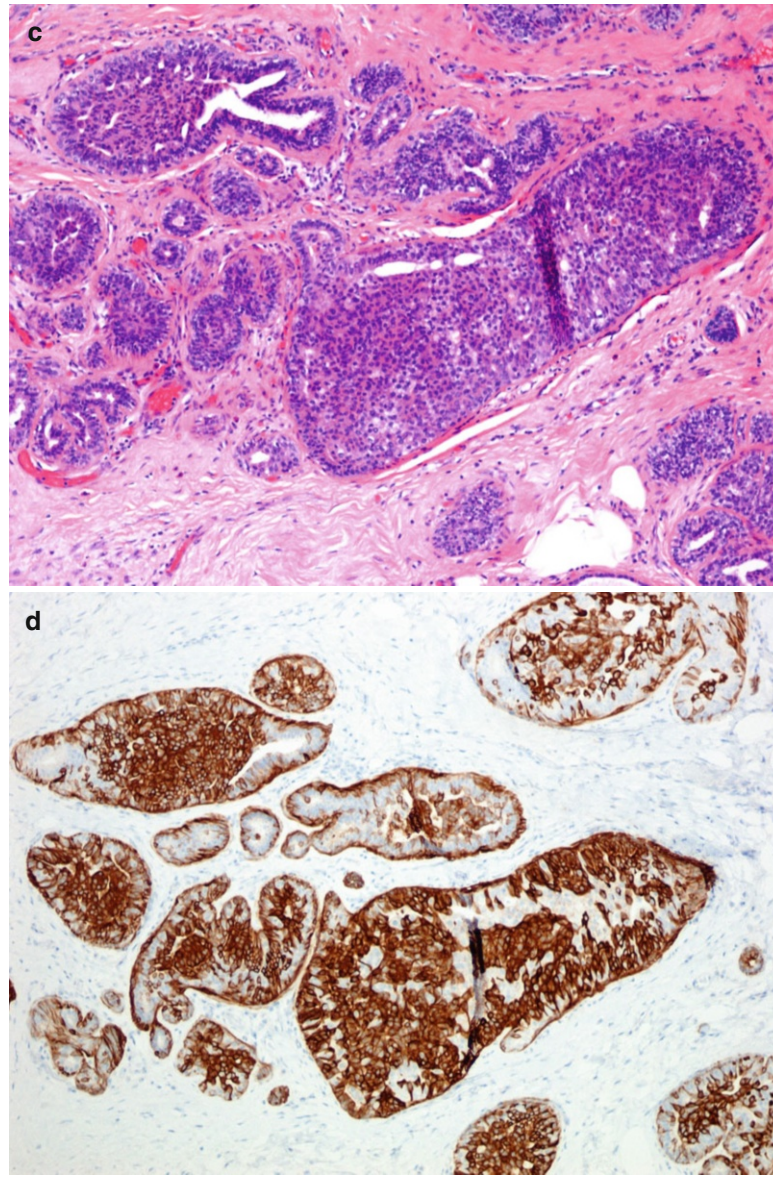


Fig. 10.1 (**a**) Usual ductal hyperplasia (UDH) consisting of epithelial proliferation with false lumina. (**b**) Staining with CK5/6 confirms a benign proliferation. (**c**) UDH with solid proliferation. (**d**) Staining with CK5/6 confirms a benign proliferation

Fig. 10.1 (continued)



be present. Despite the architectural heterogeneity, the hallmark of UDH is the lack of cytological atypia. The proliferation invariably shows a mixture of epithelial and myoepithelial cells. Frequently, immunocytochemistry markers are applied as an adjunct to conventional haematoxylin and eosin staining in the differential diagnosis of hyperplastic or neoplastic proliferation. Cytokeratins 5 and 6 (CK5/6) have been found to be useful in differentiating hyperplastic from neoplastic proliferations of the breast by highlighting myoepithelial (basal) cells which are present in benign but not neoplastic proliferations (Otterbach et al. 2000; Boecker et al. 2001).

It has been generally assumed that in the pathogenesis of breast cancer, there is a progressive intraductal epithelial proliferation from UDH through ADH to DCIS and subsequent invasive cancer. This concept has been challenged. Using double immunofluorescence analysis and Western blotting, Boecker et al. (2002) identified a third cell type within the normal breast tissue, which expresses cytokeratin 5 (CK5) only. The authors claim that this CK5-positive cell represents the adult stem cell,

which gives rise to glandular and myoepithelial cell lineage. Double staining revealed UDH and ADH and DCIS were phenotypically different. UDH expressed CK5, whereas ADH and DCIS were positive for CK8/18/19 but negative for CK5. This study considered the CK5-positive cell in epithelial hyperplasia of usual type as the progenitor or committed stem cell, which proliferates into glandular cells via intermediate stages. The results of this double-labelling technique suggest that UDH is unlikely to be an 'obligate' precursor of DCIS. Shaaban et al. (2003) reported progressive decline in the expression of oestrogen receptor-β (ER-β) from normal epithelium, UDH, DCIS and invasive carcinoma. ER-β expression was significantly lower in UDH than normal lobules. The authors postulated that ER-β protein downregulates promotion of neoplastic progression in benign lesions of the breast. In a separate study, Mao et al. (2010) reported 100 % expression of ER-α in 77 cases of UDH and none of the cases expressed p53 protein.

10.1.2 Genetic Alterations in UDH

O'Connell and colleagues (1998) investigated loss of heterozygosity (LOH) at 15 genetic loci including 16p, 17p and 17q in 399 putative precursors of invasive breast cancer, which consisted of 211 UDH, 51 ADH, 81 non-comedo DCIS and 56 comedo DCIS. Although the prevalence of LOH was low in epithelial hyperplasias from non-cancerous breasts, they reported high LOH in tissue harvested from cancerous breasts in 37 % of UDH, 45 % of ADH, 77 % of non-comedo DCIS and 80 % of comedo DCIS. These lesions shared LOH with synchronous cancers at one or more loci, supporting the theory that the putative precursors and the cancers were genetically related. Lakhani et al. (1996) also detected allelic imbalance in UDH, suggesting that the proliferations were clonal and possibly neoplastic. Clonality in some cases of UDH was also reported using comparative genomic hybridisation (CGH) (Jones et al. 2003). This study reported, among others, loss of material on chromosomes 1p, 16p, 17q and 22p, which are the common loci for genetic alteration in invasive breast cancer. In a previous study also applying CGH, Gong et al. (2001) reported chromosome copy number alterations on 16q (five cases) and 17p (two cases) in UDH and ADH in cases where these lesions occurred concurrently. However, only one out of nine cases of pure UDH showed CGH abnormalities.

Further molecular studies to clarify the role of UDH in the pathogenesis of breast cancer were carried out by Xu and colleagues (2008) when they investigated chromosomal imbalances and clonality by using CGH. The mean value of chromosomal alteration was 1.95 (39/20) in UDH, 9.5 (19/2) in ADH, 11.0 (33/3) in DCIS and 18.2 (89/5) in invasive ductal carcinoma. Some common deletions were in chromosomes 1p, 13q and 16q with high frequency of amplification in 1q, 3p, 6p, 11q, 12q, 13q, 16p, 17q and 20q. The results revealed that the deletion of DNA copy was lowest in UDH with a linear increase in ADH, DCIS and IDC (invasive ductal carcinoma). In this study, a significant number of UDH shared common genetic alterations with ADH, DCIS and IDC suggesting that UDH was a putative precursor of ductal carcinoma. These results are in conflict with Boecker and colleagues' (2001) findings using immunocytochemistry staining.

10.1.3 UDH as Risk Factor of Subsequent Malignancy

When Dupont and Page (1985) followed up women aged between 20 and 55 years with PDWA, they reported a RR of subsequent cancer of 1.9 times that of the general population. The presence of family history of breast cancer elevated the risk to 3.2. Women over 55 years of age with PDWA had a RR of 2.2 times that of women without proliferative disease. The presence of calcification plus PDWA in women over 55 years of age was associated with an RR of 5.6 compared to women of the

same age group without proliferative disease. In an autopsy study, Kramer and Rush (1973) examined breast tissue from 70 women who were over the age of 70 and found intraductal epithelial hyperplasia in 69 % of cases and 43 % of the lesions were considered severe. These two studies suggest that significant epithelial hyperplasia is more prevalent in older women than younger women.

Tavassoli and Norris (1990) followed up 117 women (age range 15–75) with ordinary or regular intraductal epithelial hyperplasia for 4.5–25.7 years (median, 14 years). They recorded regular or ordinary epithelial hyperplasia if two ducts, ductules or transformed lobules were involved. The proliferation exhibited tufts, bridges, arcades, layers and irregular and peripheral fenestrations with or without streaming of cells. The cell population consisted of myoepithelial, epithelial and apocrine metaplastic cells. Apocrine cells were present in 102 of the 117 biopsies and 83 biopsies had apocrine hyperplasia. Sclerosing adenosis was present in 80 biopsies and calcification in 20 biopsies. During follow-up, invasive carcinoma developed in three women in the ipsilateral breast, ductal carcinoma in situ (DCIS) developed in the ipsilateral breast in one woman and in the contralateral breasts in two women. One of the women with combined regular intraductal hyperplasia, sclerosing adenosis and calcification also developed carcinoma. Atypical intraductal hyperplasia developed in the ipsilateral breasts in five patients and in the contralateral breast in one patient. The prevalence of cancer associated with regular intraductal epithelial hyperplasia was only 2.6 % at 14 years compared to 9.8 % at 8 years in women with atypical ductal hyperplasia (ADH) in the same study. This study also highlighted the importance of age when considering the risk of subsequent malignancy. Carcinoma did not develop in women below the age of 30 who had regular epithelial hyperplasia in their biopsies, whereas carcinoma subsequently developed in 1.9 % of the women between 31and 45 years of age and in 3.8 % of the women over 45 years of age. In contrast, an average of 10 % of women with ADH in the same study developed carcinoma in the three age groups (< 30, 31–45, > 45). The average interval for developing subsequent carcinoma was similar, 8.3 years in women with regular intraductal hyperplasia and 8.8 years in women with ADH.

Table 10.1 Different RR values of developing breast cancer in patients with UDH

Publication	Relative risk
Dupont and Page (1985)	1.9
Carter et al. (1988)	1.9
London et al. (1992)	1.6
McDivitt et al. (1992)	1.8
Bodian et al. (1993)	2.2

The report by Tavassoli and Norris (1990) highlights the difficulties in assessing mixed epithelial proliferations and in determining which of these is clinically significant. However, assessing UDH is less controversial than assessing ADH. In several studies that assessed the risk of UDH with regard to progression to invasive malignancy, there was overall concordance in the results obtained (Table 10.1). Unlike ADH, a diagnosis of UDH does not warrant intensive follow-up. Based on these reports, if UDH is the only abnormality in a needle core biopsy, this does not require surgical excision, unless there is clinical, radiological discordance. These patients do not require chemoprevention or regular screening (Kiluk et al. 2007). However, as the above studies have demonstrated, epithelial hyperplasia is more prevalent in older women with a higher risk of cancer when compared with younger women.

10.2 Atypical Ductal Hyperplasia (ADH)

10.2.1 The Concept of Atypical Ductal Hyperplasia

Although pathologists recognised a borderline lesion for a long time, the concept of atypical hyperplasia (ADH) implying a possible risk of subsequent malignancy or a premalignant lesion

was not universally acceptable (Gallagher and Martin 1969; Black et al. 1972; Ashikari et al. 1974). Azzopardi (1979) felt strongly that the term atypical hyperplasia was inappropriate and believed this would 'frighten surgeons into performing unnecessary mastectomies'. With the current multidisciplinary team approach to patient care, the risk of the surgeon making single-handled decisions should be rare.

The histological diagnosis of ADH is fraught with inconsistencies because of marked intraobserver and interobserver variation among pathologists when classifying this lesion (Rosai 1991; Sloane et al. 1994; Jain et al. 2011). Black and Chabon (1969) classified intraductal epithelial proliferations into five grades as follows: 1, normal; 2, hyperplasia; 3, distinct but minimal atypia; 4, atypia suggestive of carcinoma in situ; and 5, atypia consistent with carcinoma in situ. Although this five-tier grading was replaced by the three grades of Page and Rogers (1992), it would have been useful to maintain the minimal atypia grade of Black and Chabon, as most pathologists have discovered that there are epithelial proliferations that show cytological atypia without sufficient architectural changes for the lesion to be accommodated into the ADH or DCIS categories.

Tavassoli and Norris (1990) defined atypical hyperplasia as a lesion having 'cytological and architectural features of non-necrotic intraductal carcinoma and the changes may involve two or more ductules, but the involved ducts or ductules should measure less than 2 mm in diameter'. The criterion of ADH proposed by Fechner and Mills (1990) was 'when there is partial involvement of a duct by alterations architecturally and cytologically indistinguishable from cribriform carcinoma'. Rogers (1987) deemed a lesion to exhibit features of ADH 'when either cytological or pattern criteria of DCIS are met, but both are not present in full flower'. It is this lack of a concrete definition that made and still makes the accurate diagnosis of ADH difficult and results in the variation of the level of risk of subsequent breast cancer attributed to ADH. One typical example is the so-called clinging carcinoma of Azzopardi (1979), which was classified as a variant of DCIS, whereas the UK National Health Service Breast Screening Programme classified this lesion as ADH (NHSBSP 1997). This lesion is now classified as flat epithelial atypia (FEA); see Chap. 11.

10.2.2 Radiological Features of ADH

ADH is rare as a sole symptomatic breast lesion but is reported frequently in mammographically detected lesions with variable prevalence of between 7 % and 10 % (Sneige et al. 2003; Rubin et al. 1988). In one of the largest series to be reported, ADH was identified in only 3.6 % of more than 10,000 biopsies excised for symptomatic breast disease (Dupont and Page 1985). Although ADH can be detected mammographically as the dominant lesion due to the presence of microcalcification (Sneige et al. 2003), in the majority of cases, there are other associated lesions such as DCIS, fibrocystic change, radial scars or intraductal papillomas.

Rubin et al. (1993) reviewed the mammographic and histological features of 21 patients with atypical hyperplasia (ductal, lobular or mixed), 40 patients with DCIS and 14 patients with DCIS plus micro-invasion. The mean age of patients with atypical hyperplasia was 54.7 years (range 41–79 years), compared with 57.4 years (range 29–85 years) for patients with DCIS and 60.6 years (range 37–88 years) for patients with DCIS plus micro-invasion. These findings suggest that atypical hyperplasia was more frequent in younger women than older women, implying an age-related progression of epithelial proliferation to overt malignancy. Calcification was detected mammographically in 59 % of cases of atypical hyperplasia, 68 % DCIS and 79 % DCIS and micro-invasion. Other mammographic abnormalities associated with atypical hyperplasia included: parenchymal distortion (23 %), mass lesion (9 %) and no abnormality (9 %). On histological examination, calcification was present in 95 % of cases of atypical hyperplasia. The calcification was

present in atypical hyperplasia or DCIS and the surrounding benign breast tissue in 20 %, benign tissue only in 75 % and other calcification in 5 % of the cases. This highlights the fact that calcification noted at histological examination does not necessarily represent the mammographic abnormality and radio-pathological correlation is essential to achieve appropriate patient management. Rubin and colleagues (1993) confirmed previous reports that there are no radiological pathognomonic features of atypical hyperplasia. The authors reported parenchymal distortion and calcification noted mammographically, which led to the diagnosis of atypical hyperplasia, was associated with other benign proliferative diseases rather than specific to atypical hyperplasia. Furthermore in 82 % of cases of atypical hyperplasia, the foci were less than 5 mm in size and this was unlikely to produce a mammographic abnormality. However, 71 % of the women with atypical hyperplasia had dense breasts (Wolfe Category P2 or DY, see Chap. 16; Wolfe 1976), compared with 60 % with DCIS and 50 % with DCIS plus micro-invasion. The mammographically dense breasts may reflect the young age of the women.

In a separate study, Helvie and colleagues (1991) reviewed mammograms and histological slides of 58 patients with a diagnosis of atypical hyperplasia. The authors reported 41 % (24/58) concordance between mammographic and histological features of ADH, mostly due to the presence of clustered microcalcification. However, the features were not pathognomonic.

10.2.3 Pathological Features of ADH

ADH is a borderline intraductal proliferation, with a potential to progress to DCIS. ADH is particularly difficult to distinguish from low-grade DCIS with a cribriform or micropapillary pattern. Page and Rogers (1992) set out criteria to assist in the diagnosis of ADH, which are based on the architectural and cytological features and the size of the lesion. By applying these criteria, a diagnosis of ADH should be made when there is partial involvement of two-membrane-bound spaces by a population of atypical cells similar to those seen in non-comedo DCIS. Although ADH can be detected as the dominant lesion mammographically, usually this is associated with DCIS or another high-grade lesion (Fig. 10.2). The atypical cells are usually polarised and are present above the basement membrane. Previously, Tavassoli and Norris (1990) assessed the anatomic extent of atypical hyperplasia and applied a size limit of less than 3 mm for an intraductal proliferation to qualify for the diagnosis of ADH. The rationale for this was that there are some ducts larger than 10 mm, which may contain highly atypical neoplastic cells, and one should not hesitate to render a diagnosis of intraductal carcinoma in these circumstances. The UK National Health Service Breast Screening Programme (NHSBSP 1997) advocates that the diagnosis of ADH should be made if the diagnosis of DCIS is seriously being considered and the lesion measures between 2 and 3 mm in diameter. The criteria that differentiate UDH, ADH and low-grade DCIS are set out in Table 10.2.

10.2.4 Genetic Alterations in ADH

Breast cancer is thought to develop from normal epithelium through the following sequence: UDH → ADH → DCIS → IDC. Unlike in Vogelstein's model of colorectal cancer (1988), genetic abnormalities are not mirrored by corresponding phenotypic changes. Aubele et al. (2000) carried out a study of lumpectomy specimens from five patients using laser microdissection of areas of ductal hyperplasia without atypia, ADH, DCIS and IDC for correlation of genotypic and phenotypic changes. The results revealed an increasing mean number of chromosomal abnormalities (gains and losses), with an increase in the histological severity of the disease process. Chromosomal changes found in each of the four histological proliferation included gains on 10q, 12q, 16p and 20q and loss on 13q. In ductal

hyperplasia without atypia, gain on 20q as well as loss on 13q was detected in high frequency (four out of five samples). Alteration identified in more than 50 % of ADH samples included gains on 3p, 8q, 15q and 22q and loss on 16q. In DCIS, gains of DNA on 1q and 17q and loss on 4q were additionally found, and in IDC, further gains on 6p, 10q, 11q and 17p were identified. These chromosomal alterations suggest that the regions harbour tumour suppressor genes or oncogenes significant for the development of ductal carcinoma of the breast. In a separate study using

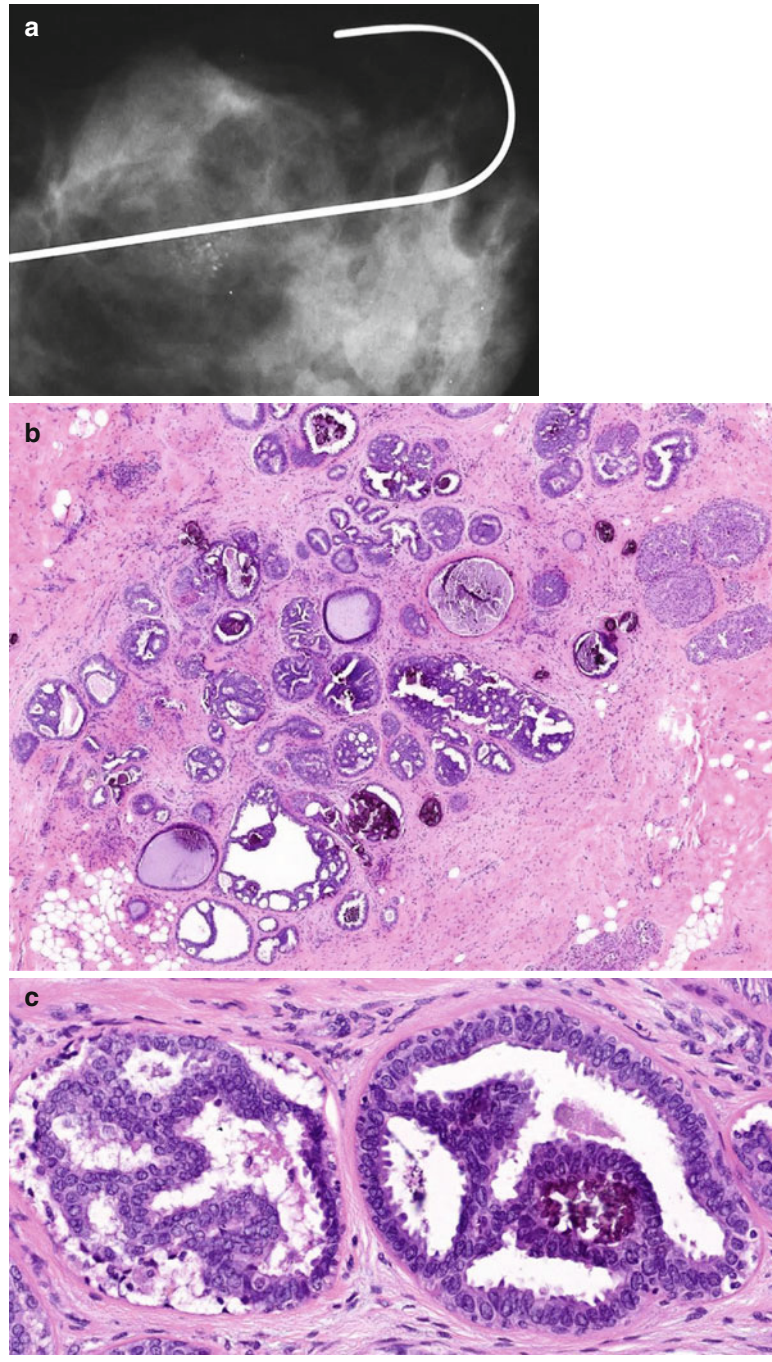
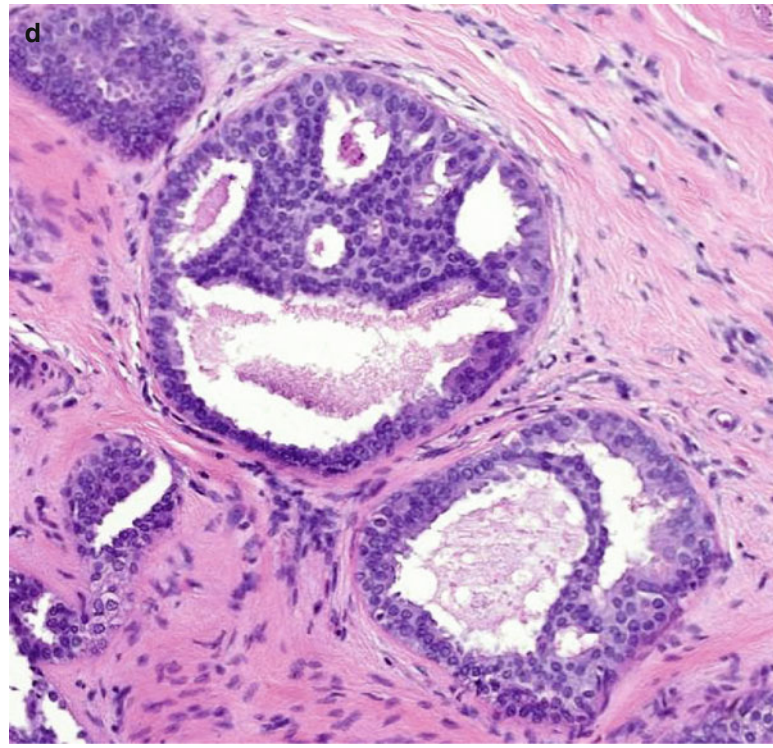


Fig. 10.2 (**a**) This specimen X-ray shows a focus of mammographically detected indeterminate microcalcification (R3). The needle core biopsy was not diagnostic. (**b**) The main lesion in the excision biopsy was low-grade DCIS with a predominantly cribriform pattern, which measured 5 mm in diameter. (**c**) There are also ducts showing features of ADH and this demonstrates how difficult it is to differentiate ADH from low-grade DCIS. In this field, the calcification is present ADH. (**d**) This field shows non-calcifying ADH with central monomorphic cells creating cribriform and bridging patterns

Fig. 10.2 (continued)



tissue from nine patients with ADH and adjacent UDH and nine patients with pure UDH, Gong et al. (2001) reported loss of 16q in five cases of ADH and loss of 17p in two cases of ADH. These chromosomal abnormalities were also demonstrated in the adjacent UDH. Only one of the cases of pure UDH showed chromosomal abnormalities. This data suggest that UDH may represent a precursor lesion of ADH. In a different study, loss of heterozygosity (LOH) in invasive cancer on chromosome 2p, 11p and 17q was shown in 37 % cases of UDH, 45 % of ADH, 77 % non-comedo DCIS and 80 % of comedo DCIS supporting the notion that the putative precursors associated with the invasive cancer were genetically related (O'Connell et al. 1998) (Table 10.3).

Although it is generally accepted that ADH and DCIS share the same genetic abnormalities and hence may represent a continuum of the same disease process (Lakhani et al. 1995; Chuaqui et al. 1997), the role of usual hyperplasia as a putative precursor of breast cancer is not universally accepted (Boecker et al. 2002).

10.2.5 Management of Patients with ADH in a Needle Core Biopsy

The prevalence of ADH in needle core biopsies varies in different institutions and has been reported as 9 % (Liberman et al. 1994), 4.5 % (Moore et al. 1994), 3.4 % (Menes et al. 2009) and 1.2 % (Deslauriers et al. 2012). Despite the lack of specific mammographic abnormality, the diagnosis of ADH in a needle core biopsy should lead to an excisional biopsy because associated DCIS or invasive carcinoma cannot be excluded. Several studies have documented the presence of high-grade lesions in the excision specimens of patients with the diagnosis of ADH on needle core biopsy, usually termed underestimation of a high-grade lesion. When Ely and colleagues (2001) correlated the results of 47 needle core biopsies reported as showing ADH with the excision specimens, they reported the following lesions: benign lesions without atypia, 14; ADH, 13; ALH, 3; DCIS, 15; and invasive carcinoma, 2. The higher the number of cores with multiple foci of ADH, the more advanced the lesion in the

Table 10.2 A comparison of histological features of ductal hyperplasia and DCIS

Histological features	Usual type ductal hyperplasia	Atypical ductal hyperplasia	Low nuclear grade DCIS
Size	Variable size but rarely extensive unless associated with other benign processes such as papilloma or radial scar	Usually small (less than 2–3 mm) unless associated with other benign processes such as papilloma or radial scar	Rarely less than 2–3 mm and may be very extensive
Cellular composition	**Mixed. Epithelial cell and spindle-shaped cells[a] present. Lymphocytes and macrophages may also be present. Myoepithelial hyperplasia may occur around the periphery**	May be uniform cell population but merges with areas of usual type hyperplasia within the same duct space. Spindle-shaped cells may be intermingled with the proliferating cells	**Single-cell population.** Spindle-shaped cells not seen. Myoepithelial cells usually in normal location around duct periphery but may be attenuated
Architecture	Variable	Micropapillary, cribriform or solid patterns but may be rudimentary	**Well-developed micropapillary, cribriform or solid patterns**
Lumina	**Irregular, often ill-defined peripheral slit-like spaces are common and a useful distinguishing feature**	May be distinct, well-formed rounded spaces in cribriform type. Irregular, ill-defined lumina may also be present	**Well-delineated, regular punched-out lumina in cribriform type**
Cell orientation	**Often streaming pattern with long axes of nuclei arranged parallel to direction of cellular bridges, which often have a 'tapering' appearance**	Cell nuclei may be at right angles to bridges in cribriform types, forming 'rigid' structures	**Micropapillary structures with indiscernible fibrovascular cores or smooth, well-delineated geometric spaces. Cell bridges 'rigid' in cribriform type with nuclei orientated towards the luminal space**
Nuclear spacing	**Uneven**	May be even or uneven	**Even**
Epithelial/ tumour cell character	Small ovoid but showing variation in shape	Small uniform or medium-sized monotonous cell population present at least focally	**Small uniform monotonous cell population**
Nucleoli	Indistinct	Single small	Single small
Mitoses	Infrequent with no abnormal forms	Infrequent, abnormal forms rare	Infrequent, abnormal forms rare
Necrosis	Rare	Rare	If present, confined to small particulate debris in cribriform and/or luminal spaces

Major diagnostic features are shown in bold type

[a]These cells are usually called myoepithelial cells but immunohistological studies have shown that they have characteristics of basal keratin-type epithelial cells (Bocker et al. 1992) (Reproduced with permission from the NHS National Breast Screening Programme, Pathology reporting in breast cancer screening 1997)

excision biopsy (Kohr et al. 2010). In some studies, cases previously reported as showing ADH in needle core biopsies yielded in situ or invasive carcinoma in up to 50 % of the cases (Liberman et al. 1994; Gadzala et al. 1997).

In a separate study, Renshaw et al. (2001) reviewed 95 cases that met the authors' criteria of ADH. The subsequent resection specimens showed DCIS in 13 patients, ADH in 31, LCIS in six and benign proliferative lesions in 45. These authors claim that the low prevalence of carcinoma in the excision biopsies was due to stringent criteria applied to the diagnosis of ADH. These figures are not significantly different from those of Ely and colleagues (2001). Lack of ADH in the excision specimen has also been attributed to complete removal of the small foci of ADH in the needle core biopsies. Complete removal of

Table 10.3 A comparison of ALH and ADH with emphasis on RR value

Criterion	ALH	ADH
Radiological features	None	+/− calcification
Breast at risk of cancer	Both, but mostly ipsilateral	Both, but mostly ipsilateral
Type of carcinoma	Ductal or lobular	Mostly ductal
RR value of subsequent cancer		
All women	4.2	4.3
No family history	3.5	3.2
Positive family history	8.4	9.7
Age 20–30	0.0	7.0
Age 31–45	2.7	4.5
Age 46–55	6.4	3.5
Age 56–65	0.0	6.5
Age >65	0.0	5.0
Absolute risk	13 % over 16 years	12 % over 16 years

The numerical data in the table were reproduced from Page DL, Dupont WD, Rogers LW, Rados MS (1985) Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer 55: 2698–2708 (Reproduced with permission from the authors and publishers, Wiley-Liss Inc., a subsidiary of John Wiley & Sons, Inc)

small foci of DCIS or ADH is frequently reported with the use of a mammotome (Adrales et al. 2000). Sneige et al. (2003) reported complete removal of ADH using directional vacuum-assisted biopsies in 24 out of 42 cases when they compared the needle core biopsies with the excision specimens; DCIS was identified in three cases and the remaining 15 showed residual ADH. Assessing the number of units (ducts and lobules) involved by ADH can assist in predicting which patients would have residual or high-grade disease in excision specimens; the higher the number of TDLUs involved, the more the likelihood of yielding a higher-grade lesion in the excision specimen (Ely et al. 2001; Sneige et al. 2003). Because some foci of calcified ADH are completely removed during vacuum-assisted biopsies, some authors advocate avoiding excisional biopsies in these patients if the follow-up mammograms lack microcalcification and there is appropriate radiological–pathological correlation (Adrales et al. 2000; Sneige et al. 2003).

In a separate study, Eby and colleagues (2009) compared the yield of ADH when using a 9-gauge vacuum-assisted breast biopsy device and an 11-gauge device. The authors also compared the frequency of upgrade of ADH to higher-grade lesion in the excision specimen. ADH was diagnosed in 141 out of 991 biopsies (14.2 %). The frequency of ADH was 83/600 (13.8 %) for the 9-gauge device and 59/391 (14.8 %) for the 11-gauge device. The yield of carcinoma (in situ and invasive) was 16/74 (21.6 %) for the 9-gauge device and 10/49 (20.4 %) for the 11-gauge device. The results show that there was no difference between 9-gauge and 11-gauge device.

10.2.6 Management of ADH on the Margin in a Lumpectomy Specimen

The decision to excise a mammographic detected abnormality following the diagnosis of ADH in a needle core biopsy is universally accepted. However, there is no consensus among pathologists or surgeons on how to manage ADH at the margin of a lumpectomy performed for early-stage cancer. This is compounded by the intra- and interobserver variation which makes the diagnosis of ADH unreliable. Nizri et al. (2012) sent a survey to the members of the American Society of Breast Surgeons (ASBS) and received 477 responses; 377 of the respondents dedicated more than 50 % of their practice to breast surgery and 50 % were from academic cancer centres or dedicated breast centres. When asked how to manage the diagnosis of ADH within 1 mm of breast conserving surgical specimens, 61 % favoured no further surgery while 30 % recommended selective re-excision. Eighty percent of surgeons practising at cancer centres would recommend no further surgery while 30 % recommended selective re-excision and 0 % recommended routine re-excision when ADH involved the margin. In contrast, 54 % of surgeons in private practice would recommend no further excision, 40 % would selectively re-excise and 5 % would routinely excise. In a separate study in the UK, a questionnaire was sent to 200

breast surgeons requesting responses related to various aspects of margin in breast conserving surgery. Ninety one percent of the respondents indicated they would not alter their treatment management if ADH was present on the margin but both invasive and in situ carcinoma were 10 mm clear of the margin. The remaining 9 % of the surgeons would reconsider re-excision or perform mastectomy (Young et al. 2007). Ghofrani et al. (2006) also demonstrated that there was no consensus among pathologists when faced with the diagnosis of ADH on the margin. The authors distributed five problem scenarios to 300 pathologists for them to decide whether the images were DCIS or ADH and if the lesion was on the margin, would the pathologist recommend re-excision. One of the images consisted of unequivocal DCIS adjacent to duct partially filled with cribriform proliferation. Of 230 respondents, 56.5 % considered the partial cribriform proliferation within a duct adjacent to unequivocal DCIS as ADH and 37.7 % would recommend re-excision if this was on the margin. Of the 43.5 % who diagnosed the partially involved duct as DCIS, 28.0 % would recommend re-excision if it were on the margin.

When Baker et al. (2012) reviewed the literature on the subject of evaluating ADH in breast-conserving surgery, they only found very few studies on this subject. One study was from the Mount Sinai Medical Centre (Arora et al. 2008) and the authors' objective was to determine the rate of residual pathology in patients who had re-excision for ADH involving the margin. The study was a retrospective review of 44 lumpectomy specimens with ADH involving the margins reported between 2000 and 2006. Twenty-four patients (55 %) had re-excision. Slides were reviewed to verify the diagnosis of ADH near the margin and the presence of residual disease on the re-excision specimen. Fifteen patients (63 %) had pure ADH, 7 (29 %) had ADH and DCIS and two (8 %) had invasive carcinoma. Of the 15 patients who had ADH, 6 (40 %) had residual pathology, thus: ADH (2), DCIS (2) and invasive carcinoma (2). This was a very small study but the authors concluded that further re-excision was recommended if ADH was present on the margin of a lumpectomy specimen. An earlier study by Goldstein et al. (1998) reported ipsilateral recurrent disease in 6 out of 94 patients treated with local excision followed by radiotherapy when DCIS and ADH were 2 mm from the margin. The follow-up for this study was only 26 months. Greene and colleagues (2006) reviewed 747 patients with biopsy proven ADH and 155 of these had pure ADH without associated premalignant or malignant breast disease. The excision biopsies of 68/155 (44 %) patients with pure ADH had negative margins and 7 (5 %) had positive margins and 80 (52 %) had no comment on the margin status. There was no re-excision of the patients with positive or close margins who were followed up for 0–119 months (mean 26 months). Seven patients presented with new findings at the site of their original excisional biopsy, six with benign lesions and one with invasive carcinoma. The authors concluded that clear margins at surgical excision for ADH did not affect the risk of developing subsequent malignancy. Based on the above publications, it is clear that there is no consensus on the management of ADH on the margin and further studies are required with long follow-up periods to establish the significance of ADH on the margin in a lumpectomy specimen.

Patients with ADH also benefit from tamoxifen as a chemopreventative strategy. In the Breast Cancer Prevention Trial (NSABP-P1), tamoxifen reduced the risk of breast cancer in 86 % of women with atypical hyperplasia (Fisher et al. 1998).

10.2.7 ADH as Risk Factor of Subsequent Malignancy

Because women with ADH can develop cancer in either breast, the proliferation used to be considered a marker for malignancy. However as previously alluded to ADH shares some genetic abnormalities with DCIS and invasive carcinoma

which indicates a precursor lesion. Most of the information available on the risk of subsequent cancer associated with ADH is based largely on the work by Page and colleagues (1985). The authors identified 377 biopsies (3.6 %) with atypical epithelial hyperplasia from a total of 10,542 biopsies. The atypical proliferations consisted of 2.1 % ADH and 1.6 % atypical lobular hyperplasia (ALH). The women with the diagnosis of ADH and other benign breast disease were followed up for an average of 17 years (range 1.4–24.3 years). Eighteen women out of 150 with ADH subsequently developed invasive cancer, with ten of the cancers arising in the ipsilateral breast. Fourteen of the women developed cancer within 10 years of follow-up. The average age of women with ADH was 46 years (range 20–84 years), and for those who developed cancer the average age was 48 years (range 28–73 years). From these findings, the calculated RR of developing breast cancer in women with ADH was 4.4 times that of women without proliferative disease. The calculated absolute risk of women with ADH developing invasive cancer within 10–15 years of biopsy in the ipsilateral or contralateral breast was approximately 10 %. The presence of family history (mother, sister or daughter) increased the RR to 8.9 times that of the general population with an absolute risk of about 20 % at 15 years. In essence, the combination of ADH and family history doubles the risk for breast cancer to that in line with DCIS. DCIS is associated with 10–11 times the risk of subsequent invasive carcinoma (Rogers 1987). The combination of atypical hyperplasia and calcification increases the RR from 4.4 to 6.5.

Tavassoli and Norris (1990) reported similar observations when they followed up 82 patients with atypical intraductal hyperplasia from 1.4 to 27.8 years (median 12.4 years). Seven out of eight patients who developed invasive carcinoma did so within 17 years of follow-up. They calculated the RR of ADH for developing subsequent carcinoma to be 4.7. Six of the patients had ipsilateral cancer. Palli et al. (1991) reported an RR of 13 in women with ADH, but this was a relatively small study with a short follow-up period.

10.2.8 Follow-Up of Patients with ADH

If a higher risk lesion was excluded by excisional biopsy in patients with the diagnosis of ADH, Page (1992) advocated annual mammography of both breasts with the aim of detecting cancer at an early curable stage. Women with ADH who develop cancer during follow-up do so within 10–15 years (Dupont and Page 1985; Page and Dupont 1992; Tavassoli and Norris 1990). The risk of cancer declines after 10 years. In Institutions which utilise the Gail Model for risk assessment, Kiluk et al. (2007) divide the patients into low risk if Gail Model score is less than 1.67 and high risk if the score is more than 1.67. Patients with a Gail Model score of less than1.67 require routine screening of yearly clinical examination and yearly mammography. Women with a Gail Model score of more than 1.67 are followed by 6-monthly clinical examinations and yearly mammography with or without MRI. Genetic testing should be considered if there is a family history of breast cancer. The women should also be offered the opportunity to discuss the risk and benefits of chemoprevention using selective oestrogen receptor modulators (SERM) such as tamoxifen. Tamoxifen inhibits binding oestrogen to the oestrogen receptor. In the Breast Cancer Prevention Trial, the National Surgical Adjuvant Breast and Bowel Project (NSABP1) P-1 compared tamoxifen and placebo in over 1,300 women with a Gail Model score of ≥1.66 %. The study was halted due to a 49 % reduction in invasive breast cancer. More specifically, tamoxifen reduced the risk of breast cancer in 86 % of patients with atypical hyperplasia. The RR of adverse effects of tamoxifen such as endometrial cancer and thromboembolism were reported as recorded as 2.53 and 3.01, respectively. Prophylactic mastectomy should be considered only in patients with genetically proven susceptibility when regular mammographic follow-up is unacceptable (Simmons and Osborne 1999); the rationale being that mastectomy would remove more breasts than would necessarily develop cancer.

10.3 Lobular Neoplasia

10.3.1 The Concept of Lobular Neoplasia

Haagensen et al. (1978) introduced the term lobular neoplasia (LN) to avoid the use of the term carcinoma in an era when conservative management of breast cancer was uncommon. In this detailed clinico-pathological discussion, it is clear that lobular neoplasia was used for both ALH and LCIS, as the authors describe the early lesion with proliferation of neoplastic cells, which 'eventually fill up the acini and obliterate their lumens'. There is evidence from follow-up studies that when properly classified, the risk associated with ALH is lower than that of LCIS (Dupont and Page 1985). Rosen (2001) believes that the term LN should be used to indicate a spectrum of lobular proliferations, which include mild atypia, atypical hyperplasia (ALH) and fully developed LCIS. Despite combining ALH and LCIS in the same category, the RRs for ALH and LCIS are four and 10–11 times that of the general population, respectively (Dupont and Page 1985; Page et al. 1991). The term lobular neoplasia is now included in the WHO classification of breast tumours (Tavassoli and Devilee 2003) and UK NHS Breast Screening Programme guidelines on report Breast Cancer (2005).

Mastracci et al. (2007) took a broader view on the classification of LN which the authors base on the extent of the disease within the terminal duct and lobular unit and within the breast in general. The authors classified lobular neoplasia in six categories:

(a) Minimal atypical lobular hyperplasia when the lobular units are expanded by four to five cells across an acinus diameter
(b) Atypical lobular hyperplasia when the TDLU is populated by lobular cells with a minimum number of eight cells across based on the study by Page and colleagues (1985)
(c) ALH with ductal involvement by cells of ALH (DALH), usually termed pagetoid spread when of ALH undermine the normal ductal epithelium
(d) LCIS when there is marked distortion and distension of more than 50 % of acini within a lobular unit
(e) Invasive lobular carcinoma

The authors claim that it is important to distinguish minimal ALH from conventional ALH because the latter confers a higher risk of subsequent malignancy. Because of this confusion in terminology, Galimberti and co-authors (2013) suggest abandoning the terms DCIS and LCIS and replace them with ductal intraepithelial neoplasia (DIN) and lobular intraepithelial neoplasia (LIN) terms originally introduced by Tavassolli (1998, 2005). The authors claim the terms are confusing; DIN will eliminate the word carcinoma in lesions which do not metastasise, reduce risk of overtreatment and will be in line with other intraepithelial neoplasias of the cervix, vagina, vulva and prostate.

The cell type in ALH and LCIS is identical and the major difference between the two is that in ALH, 50 % of the lobules are partially filled by lobular neoplastic cells whereas in LCIS the lobules are completely filled (Page et al. 1991). In both symptomatic patients and the screening population, lobular neoplasia is usually an incidental finding in biopsies excised for another abnormality such as fibrocystic change, radial scar, fibroadenoma or invasive carcinoma.

10.3.2 Genetic Alterations in Lobular Neoplasia

Using the technique of comparative genomic hybridisation, Lu et al. (1998) investigated 31 cases of LCIS and 14 of ALH. Comparative genomic hybridisation (CGH) analysis is a technique where 'test' DNA is compared with normal DNA on metaphase chromosome spreads to assess copy number changes. Computer-aided analysis can identify chromosome loci that differ from normal. These loci are potential sites of amplification of oncogenes or losses of tumour suppressor genes. This method can be applied to paraffin-embedded tissue, and with use of microdissection allows for precise analysis of even

small lesions as ALH/LCIS. Loss of heterozygosity (LOH) studies refers to identification of loci in the 'test' DNA that have 'lost' one copy of a gene, presumably through DNA deletion. This event is often associated loss of a tumour suppressor gene (Lakhani et al. on behalf of Eusoma 2006). Lu et al. (1998) demonstrated loss of material from chromosomes 16p, 16q, 17p and 22q and gain of material at 6q in equal frequency in 14 ALH and 28 LCIS. These results indicated that ALH and LCIS are both neoplastic and share identical genetic abnormalities. Based on these morphologic and molecular features, Lishman and Lakhani (1999) advocated abandoning the separation of ALH and LCIS and use the collective term lobular neoplasia, as both lesions are neoplastic and share the same genetic abnormalities.

In a more in depth study on ALH, Mastracci and co-workers (2006) reported gains at 2p and losses at 7p and 22q. Alterations common to LCIS included a gain at 20q and loss at 19q. Losses at 16q were common to both ALH and LCIS. Loss at 16q and gain at 1q are the most frequent events found in invasive lobular carcinoma (ILC) both by chromosomal CGH and array CGH (Mastracci et al. 2006). The E-cadherin gene (CDH1) is located on chromosome 16 and is a candidate tumour suppressor gene that is involved in cell–cell adhesion and its loss in ALH and LCIS might point towards progression to ILC. E-cadherin is absent in lobular neoplasia on immunocytochemistry staining but present in ductal carcinoma (Gamallo et al. 1993). These molecular studies indicate that ALH and LCIS are not just markers but non-obligate precursor lesions, i.e. the progression to malignancy requires additional genetic events (Mastracci et al. 2007). Mastracci and colleagues (2007) suggest that the additional chromosomal alterations which include loss at 1p, 11p and 17p and gain at 1q identified in synchronous ALH, LCIS and ILC may contribute to progression. This concept that ALH and LCIS are both neoplastic is partially supported by follow-up studies. Although the RRs for ALH and LCIS are different, there is minimal difference in absolute risks. The absolute risk of subsequent cancer for LCIS is 17 % at 15 years compared with 13 % at 16 years for ALH (Dupont and Page 1985; Page et al. 1991). When he introduced the term LN, Haagensen recommended systemic follow-up rather than mastectomy, which is now the current recommended protocol in most breast disease units.

10.3.3 Radiological Features of Lobular Neoplasia

Lobular neoplasia has no clinical or specific mammographic features. ALH or LCIS are usually identified incidentally in biopsies targeted for other lesions. However, there are some cases of LN which have been identified due to the presence of microcalcification (Liberman et al. 1999; Georgian-Smith and Lawton 2002; Shin and Rosen 2002). ALH was the lesion responsible for the radiological abnormality in 1 out of 11 patients compared to 20 out of 42 patients with ADH in the same series (Helvie et al. 1991). Two forms of calcification are recognised with LCIS. The calcification in pleomorphic LCIS with central necrosis has an amorphous appearance and resembles that of high-graded DCIS (Liebens et al. 2008). In contrast, the calcification in classical LCIS with no necrosis is similar to that found in benign proliferative change; the calcification is clustered, punctate, variably dense and small or equal to or less than 0.5 mm (Liebens et al. 2008). The authors emphasised that the majority of the LN does not present with a mass or contain microcalcification; therefore mammography and ultrasound have no role prospectively diagnosing LCIS.

MRI is used to assess multifocality and bilateral disease once diagnosis of ILC is made but not as diagnostic utility in LN. However, MRI was used as an additional surveillance imaging modality in 378 patients at risk of developing breast cancer, and 252 had LCIS on previous surgical biopsy (Port et al. 2007). All patients underwent yearly mammography and twice yearly clinical breast examination. Additional screening MRI was performed at the discretion of the physician and patient. Cancer was

detected in 6/46 (13 %) MRI-generated biopsies. All six cancers were detected in five patients (one with bilateral breast cancer) with LCIS. The patients in this group were young and had a strong family history of breast cancer. MRI detected these cancers most likely because young women tend to have dense breasts and MRI is superior to mammography in detecting lesions in dense breasts.

10.3.4 Pathology of Lobular Neoplasia

Although the term LN should be restricted to ALH and LCIS, some authorities include ILC in this classification (Mastracci et al. 2007). For this reason ILC will be included in the illustration to demonstrate a continuum of the same disease process. ALH is characterised by partial distension of the TDLU with neoplastic (Fig. 10.3a–c) cells. The cells are uniform with little or no cytological atypia. There is no mitotic activity. The cells show partial loss of E-cadherin on immunocytochemistry staining. In contrast, LCIS shows full expansion of the TDLU with uniform neoplastic cells similar to ALH (Fig. 10.3d). When lobular neoplastic cells undermine duct epithelium, usually termed pagetoid spread of ALH, Mastracci and colleagues termed this ductal ALH (DALH) as illustrated in Fig. 10.3e. The presence of invasive lobular carcinoma (ILC), DALH,

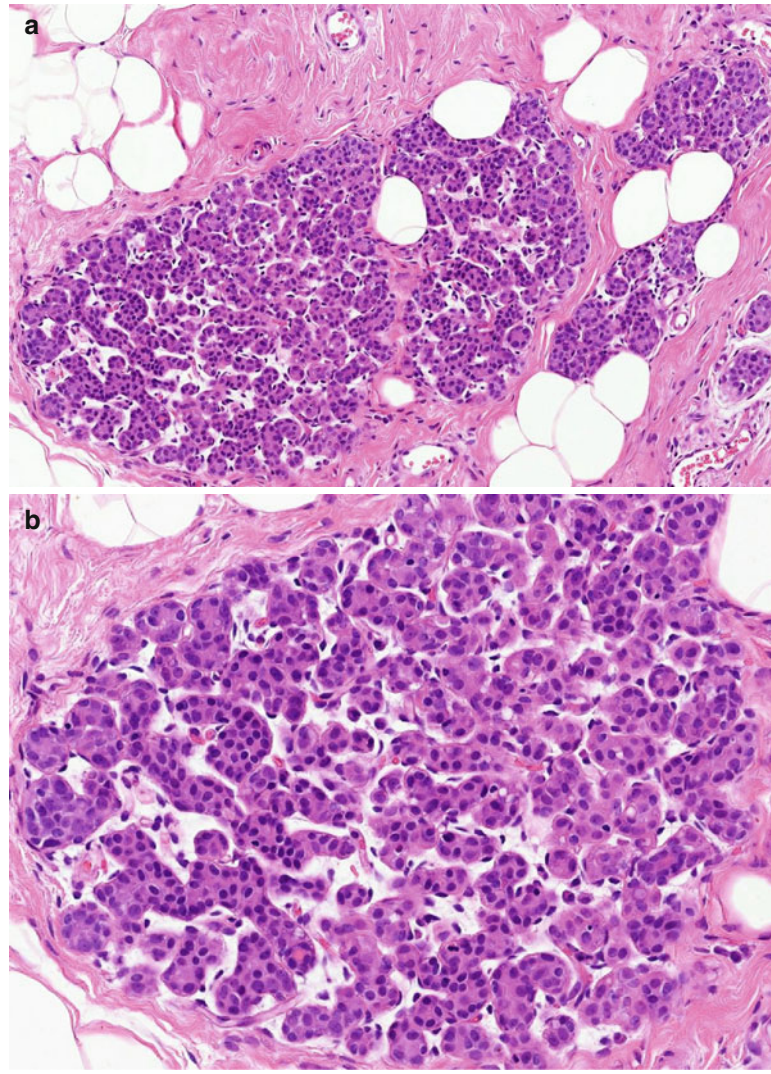
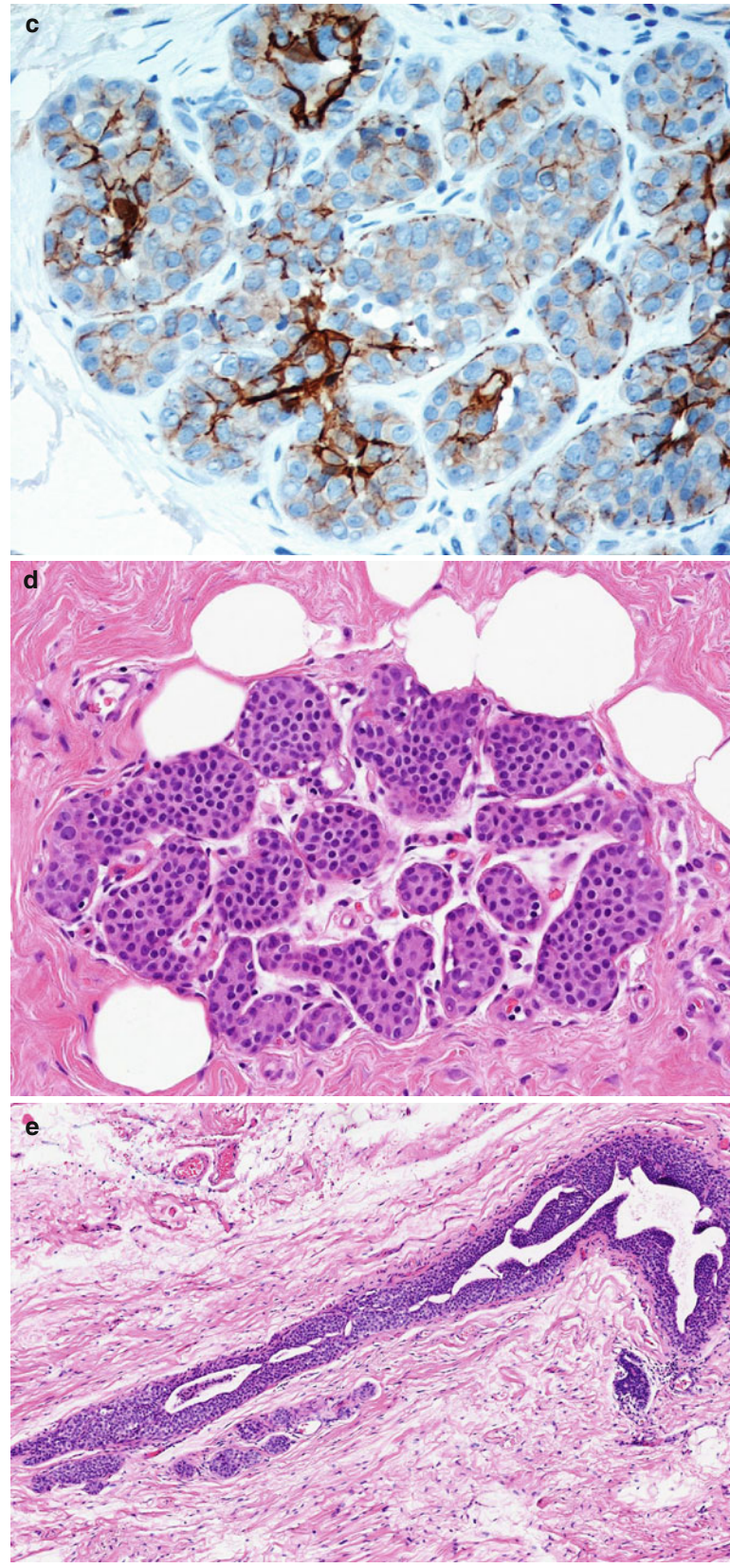


Fig. 10.3 (**a**) ALH characterised by partial distension of the lobular unit. (**b**) At high magnification, the ALH consists of lobular units partially distended by small monomorphic neoplastic cells (**c**) ALH showing partial staining with E-cadherin. (**d**) This figure illustrates LCIS lobules fully distended with neoplastic cells. (**e**) When lobular neoplastic cell involve the duct this is termed pagetoid spread or ductal ALH (DALH). (**f**) This field illustrate invasive lobular carcinoma (ILC), DALH, ALH and LCIS demonstrating a continuum of the same disease process. (**g**) At high magnification, ILC is exhibits linear proliferation with some cells showing intracytoplasmic mucin (private acini). (**h**) Calcification in lobular neoplasia can be detected mammographically, but usually this is at microscopic examination

Fig. 10.3 (continued)



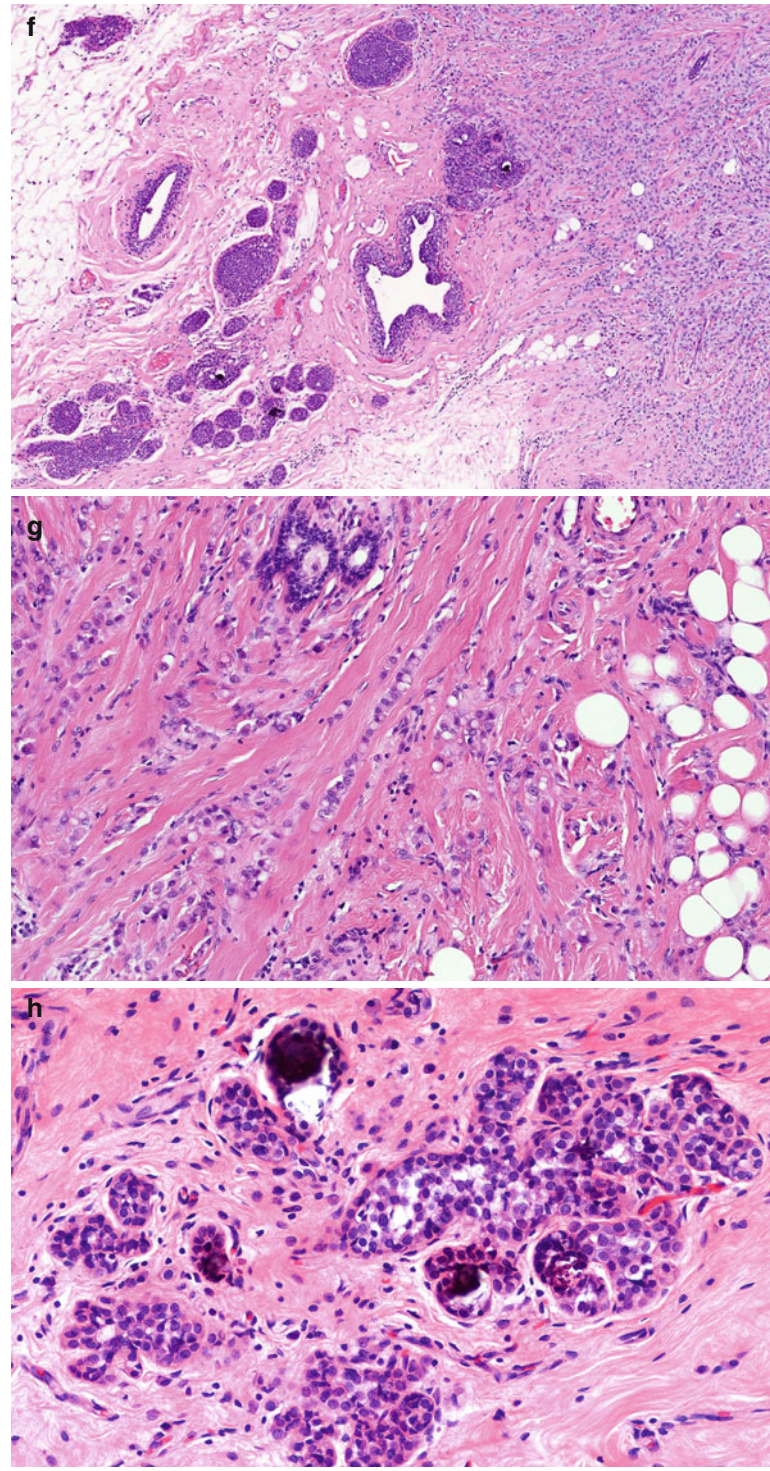


Fig. 10.3 (continued)

ALH and LCIS in the same field demonstrates a continuum of the same disease process (Fig. 10.3f). In a separate field ILC exhibits linear proliferation with cells showing intracytoplasmic mucin termed private acini (Fig. 10.3g). Linear proliferation of neoplastic cells is not unique to lobular carcinoma as this also occurs in ductal carcinoma. Calcification is rare as a mammographic abnormality in LN but this is often detected at microscopic examination (Fig. 10.3h).

10.3.5 Management of Lobular Neoplasia (LN) in a Needle Core Biopsy

Several retrospective studies have reported the detection of a high-grade lesion in the excision specimen when LN was present in the needle core biopsy. Arpino et al. (2004) reviewed 2,053 needle core biopsies and 106 (5.2 %) biopsies had atypical proliferation consisting of 49 (46 %) ADH and 45 (42 %) LN and 12 (12 %) had both ADH and LN. Malignancy in the excision specimen was identified in 3 out of 21 (14 %) of the LN group (2 LCIS, 1 ALH) and 4 out of 12 (33 %) of patients with both ADH and LN. The LN group consisted of 2 LCIS and 1 ALH. In a separate study, Cangiarella and colleagues (2008) reviewed 38 cases of LN consisting of 18 ALH and 20 LCIS diagnosed on needle core biopsy with subsequent excision biopsies. Carcinoma (DCIS or invasive carcinoma) was present in one case of ALH (6 %) and two cases of LCIS (10 %); overall upgrade of 8 % (3/38). Of note in this report is that two cases of ALH and nine of LCIS had radiological calcification as the main pathological abnormality (11/38; 21 %). The authors also reviewed 24 published reports (1999–2007) on ALH and LCIS diagnosed at needle core biopsy with subsequent excisional biopsies. Carcinoma was found in the excision biopsies in 0–67 % (mean 13 %). Seven reports representing 9 % of the publications did not find carcinoma at surgery. For biopsies with LCIS, carcinoma was found in 0–50 % (mean 20 %) in the excision biopsies. Five reports, representing 9 % LCIS of the cases did not find carcinoma at surgery. Overall carcinoma was reported in 13 % of ALH (51/393) and 20 % of LCIS (61/307) including the authors' publication of three cases. In probably the largest series, Brem and colleagues (2008) retrospectively reviewed 278 needle core biopsies reported as LN to determine whether there was a difference between ALH and LCIS in underestimation of malignancy in the needle core biopsies. Of the 164 patients who subsequently underwent excision biopsies, 67 patients had LCIS and 97 had ALH. Cancer was detected in 17/67 (25 %) of patients with LCIS and in 21/97 (22 %) ALH indicating that there was no difference in underestimation of cancer with diagnosis of LCIS or ALH on needle core biopsy. The message in all of the above publications is that detection of LN in needle core biopsy should prompt surgical excision depending on the radiological abnormality and multidisciplinary team discussion. However, O'Malley (2010) is more prescriptive and advises excision of LN when present in the needle core biopsy when the following conditions apply:

(i) When another lesion that would in itself lead to excision, such as atypical ductal hyperplasia, is also present in the core biopsy
(ii) When there is discordance between the radiological and pathological findings
(iii) When there is associated mass lesion or area of architectural distortion
(iv) If the lesion shows indeterminate features between ductal and lobular proliferation
(v) If the morphology is consistent with pleomorphic LCIS or other variants of LCIS

The NHSBSP (2001) classifies LN as a B3 lesion, i.e. lesion of undetermined malignant potential and therefore requires excision. No further surgical excision is required if LN is present on the excision margin.

10.3.6 ALH as Risk Factor for Malignancy

ALH is most prevalent in perimenopausal women (Page et al. 1985; Haagensen et al. 1978). Most of the data on the clinical significance of ALH comes from two follow-up studies by Page and colleagues published in 1978 and 1985. In 1978 (Page et al. 1978) the authors followed up 925 patients; 33 (3.6 %) women had ALH and four of

these subsequently developed carcinoma. When ALH was present in young women aged between 31 and 45 years, the RR was 6.06 and this reduced to 3.17 in women over 45 years. In the 1985 follow-up study, Page and colleagues (1985) identified ALH in 126 out of 10,542 women (1.6 %). Sixteen women (12.6 %) subsequently developed carcinoma. Only 2 of the 16 carcinomas were classical invasive lobular carcinoma and the remainder were ductal of no special type or mixed. One woman had bilateral disease, four had contralateral disease and the remainder had ipsilateral cancer. The interval between biopsy and developing carcinoma was 4.6–21.9 years. The RR of developing carcinoma in this study was 4.2 and this doubled to 8.4 in patients with a family history of cancer in a first-degree relative (sister, mother, daughter). Unlike the 1978 study, the RR in the 1985 study was higher (6.4) in women aged between 46 and 55 years with a diagnosis of ALH when compared with the younger age group (31–45 years) who had an RR of 2.7. Overall 13 % of the women with ALH developed invasive carcinoma with an average of 16 years follow-up. In a different study, Marshall et al. (1997) reported a higher risk of subsequent cancer in premenopausal women with ALH (odds ratio = 9.6; 95 % CI, 3.3–27.8) when compared with postmenopausal women (odds ratio = 3.7; 95 % CI, 1.3–10.2). In a follow-on study, Page and colleagues (1988) assessed lobular neoplasia with ductal involvement which Mastracci et al. (2007) classify as ductal ALH (DALH) (pagetoid spread) and this had a higher RR of subsequent malignancy of 6.8 times that of the general population when compared with women with LN alone. Although ALH was considered a marker for subsequent cancer because of the bilateral nature of the disease process and the fact that both lobular and ductal carcinoma developed on diagnosis of the lesion, molecular analysis results are more in keeping with a precursor lesion.

10.3.7 LCIS as Risk Factor for Malignancy

Although LCIS is lumped together with ALH under the collective term of LN, Page et al. (1985) demonstrated that LCIS has an RR of 8–10 when compared to ALH with an RR of 4.2. Similar to ALH, LCIS can be multifocal in the ipsilateral breast and bilateral and for this reason was classified as a risk marker. However, molecular analysis revealed shared genetic alterations with ILC, and LCIS is considered a non-obligate precursor of invasive cancer. The NSABP-P1 trial reported an equal incidence of invasive carcinoma in patients with a history of LCIS with 12.99 events per 1,000 patients, compared to 10.11 events per 1,000 patients without atypical hyperplasia (Fisher et al. 1998). It is not possible to compare the LCIS and ALH in this study because ALH and ADH were combined in the assessment. The majority of the cancers were ductal (49 %), but invasive lobular carcinoma occurred in higher frequency (23 %) than the general population (6.5 %). As with ALH, excision biopsy is recommended on diagnosis of LCIS on needle core biopsy. On excision biopsy, DCIS and invasive ductal carcinoma were identified in 10–35 % of patients with the diagnosis of LCIS on needle core biopsy (Lechner et al. 1999; Shin and Rosen 2002; Arpino et al. 2004; Chuba et al. 2005). Once a high-grade lesion has been excluded, patients with LCIS are closely followed with or without chemoprevention (Kiluk et al. 2007). The UK NHS Breast Screening Programme classifies lobular neoplasia as a B3 lesion and therefore required excision if identified on needle core biopsy.

Classical LCIS should be distinguished from pleomorphic LCIS (Eusebi et al. 1992) which morphologically resembles high-grade DCIS. Pleomorphic LCIS lacks E-cadherin on immunocytochemistry staining. There is minimal data on this lesion.

10.3.8 What Is the Risk of Bilateral Cancer in Patients with Lobular Neoplasia?

There is a general belief that the presence of LN in one breast confers the risk of subsequent malignancy in both breasts and this was a justification for bilateral mastectomy and classified LN as risk marker rather than a precursor. When Page and colleagues (1985) followed up patients with ALH,

11 of the 16 women (69 %) who developed cancer did so in the ipsilateral breast. As a follow-on study, Page et al. (2003) studied the laterality in women with a diagnosis of ALH on biopsy. They carried out a retrospective cohort study on 252 women who had a diagnosis of ALH on surgical biopsy. The overall RR of developing carcinoma in this study was 3.1 (95 % CI 2.3–4.3, $P<0.0001$). Fifty of the 252 women (20 %) developed invasive carcinoma. In 34 women (68 %), the breast cancer developed in the ipsilateral breast with ALH and 24 % in the contralateral breast. Two women had bilateral cancer and laterality was unknown in two women. The overall ratio of ipsilateral to contralateral cancers without other atypical lesions was 17:5. This was in keeping with previously published data, which had shown that invasive carcinoma arising in the background of ALH was predominantly ipsilateral (Page et al. 1985; London et al. 1992). In Page's latest series (2003), 36 % of the women were aged 31–45 years and 43 % were aged 46–55 years at the time of biopsy. The mean age at diagnosis of invasive carcinoma was 63.2 years. Carcinoma developed within an average of 14.8 years from the time of biopsy. The authors concluded that ILC is three times more likely to arise in the breast diagnosed with ALH than the opposite breast; and suggested that ALH was a premalignant lesion which was intermediate between a local precursor and generalised risk for both breasts.

In a separate study, Chuba et al. (2005) investigated the incidence rates of invasive breast cancer after the diagnosis of LCIS by using the Surveillance, Epidemiology and End Results (SEER) data. The study investigated 4,853 women with a diagnosis of LCIS, 350 of whom developed invasive breast cancer. The authors compared 350 patients with LCIS with 255, 114 women with primary breast cancer. The incidence of invasive breast cancer in women with LCIS was 7.1 % ± 0.5 % over a period of 10 years. Invasive breast cancer detected after partial mastectomy occurred in either breast (46 % ipsilateral and 54 % contralateral); however, after mastectomy, most cancers were contralateral (94.7 %). Invasive cancer occurring after LCIS was invasive lobular carcinoma in 23.1 % compared to 6.5 % of patients with primary breast cancer. Based on these findings the authors concluded that LCIS was a marker of risk of malignancy and close follow-up was considered adequate.

In another study of 37,692 patients with DCIS and 4,490 patients with LCIS from the SEER database, Li et al. (2006) compared the risk of the subsequent invasive cancer. Incidence rates for DCIS were 5.4/1,000 person-years and 4.5/1,000 person-years for ipsilateral and contralateral breasts, respectively; whereas the incidence for LCIS were 7.3/1,000 person-years and 5.2/1,000 person-years, respectively. LCIS patients were 5.3-fold more likely than DCIS patients to develop invasive lobular carcinoma. These authors concluded that LCIS may be a precursor rather than just an ambiguous risk factor for invasive breast cancer, and therefore, localised treatment for LCIS may be warranted.

Based on the above studies, it appears that the debate regarding whether LN causes bilateral invasive carcinoma is unresolved, but the consensus is that LN should be managed conservatively and not by bilateral mastectomy.

10.4 Intraductal Papillomas

Intraductal papillomas (IDPs) of the breast can be solitary or multiple. Papillomas are intraductal proliferations characterised by formation of villous-like or arborescent structures consisting of fibrous cores covered by myoepithelial and epithelial cells. The papillary projections proliferate within dilated ducts or dilated TDLU. The proliferation does not always produce papillary luminal projections but the papillary proliferations may interlace to produce a solid pattern. Muir (1941) postulated that the stimulus, which initiates the process, acts primarily on the epithelium, leading to an increase on the surface; this in turn leads to a coordinated growth of the connective tissue, resulting in the typical branching cores covered by epithelial cells. As the epithelial growth accelerates, this leads to loss of stroma and creation of acinus-like structures. The prevalence of IDPs is reported in up to 5 % in a series of benign lesions (Lewis et al. 2006). Because there are

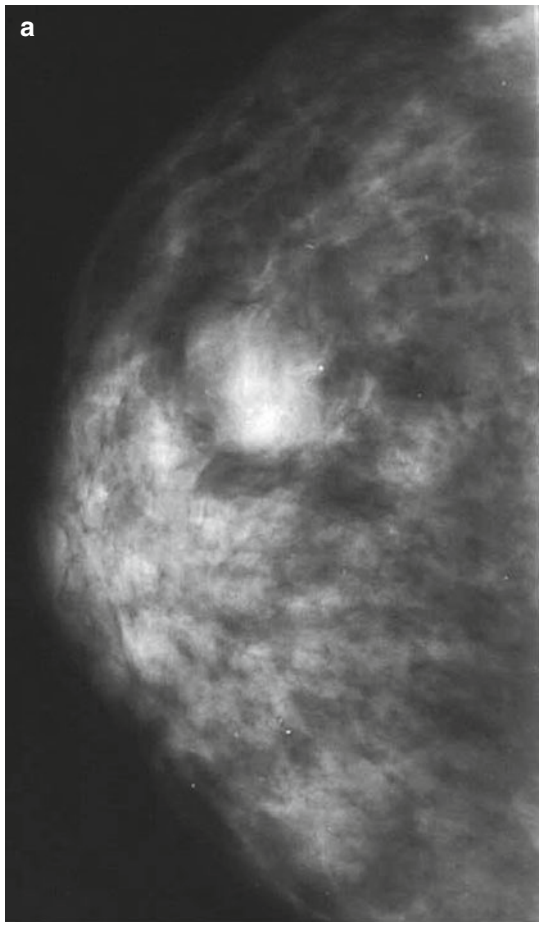
some differences in the biological behaviour between solitary and multiple IDPs, the lesions will be discussed separately.

10.4.1 Solitary Intraductal Papilloma

Solitary IDPs occur in middle-aged women with an average age of 48 years and the prevalence decreases with age (Haagensen et al. 1951; Haagensen 1986a). Because solitary IDPs arise centrally in the subareola region, they are also referred to as central IDPs. Solitary IDP presents with unilateral serous or bloody nipple discharge (Cardenosa and Eklund 1991; Woods et al. 1992).

In patients with solitary IDPs who present with nipple discharge, the mammography is usually normal. When abnormal, the mammographic features include a smooth-walled, well-defined mass or increased retro-areolar opacity (Woods et al. 1992; Yang et al. 1997). If they are large, IDPs cannot easily be differentiated from carcinomas. Papillomas with cystic dilatation may create a halo on mammography (Fig. 10.4a).

Galactography is the radiological examination of the lactiferous ducts using contrast



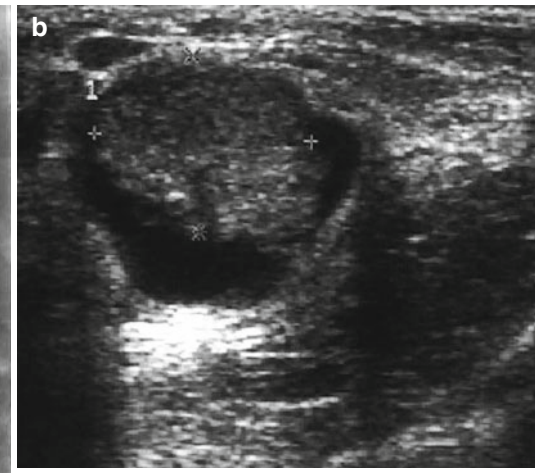
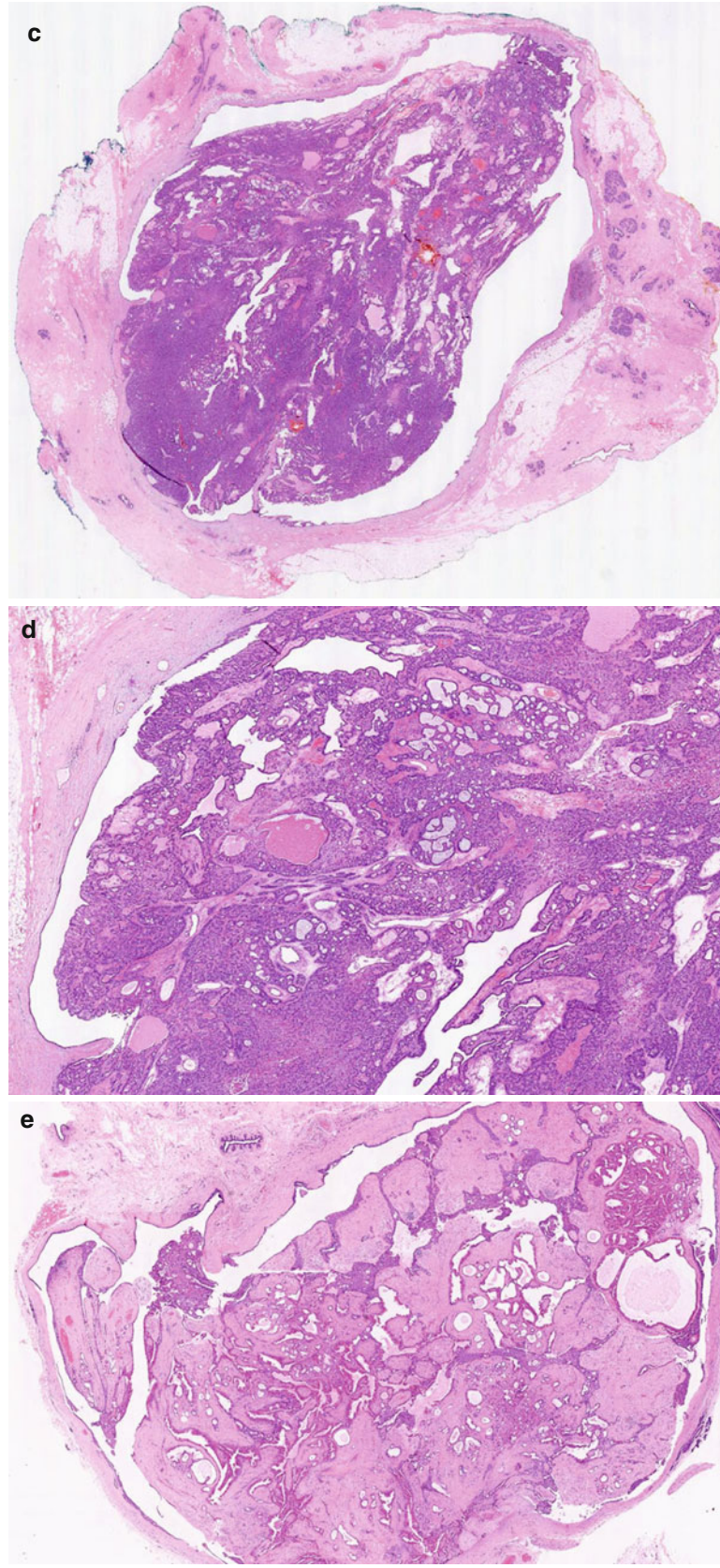


Fig. 10.4 (**a**) The mammogram shows a lobulated soft tissue density in the right breast suggestive of solid tumour (R4) in a 56-year-old woman. (**b**) The ultrasound shows a solid mass within a cystic cavity. (**c**) The whole mount section shows a solitary benign intraductal papilloma, surrounded by a cystic cavity. This corresponds to the sonographic features. (**d**) The papilloma shows a predominantly solid growth pattern with no proper luminal papillary projections. (**e**) Apocrine differentiation is not an uncommon feature in papillomas, and this usually implies benignity. (**f**) Higher magnification of the apocrine metaplasia

Fig. 10.4 (continued)



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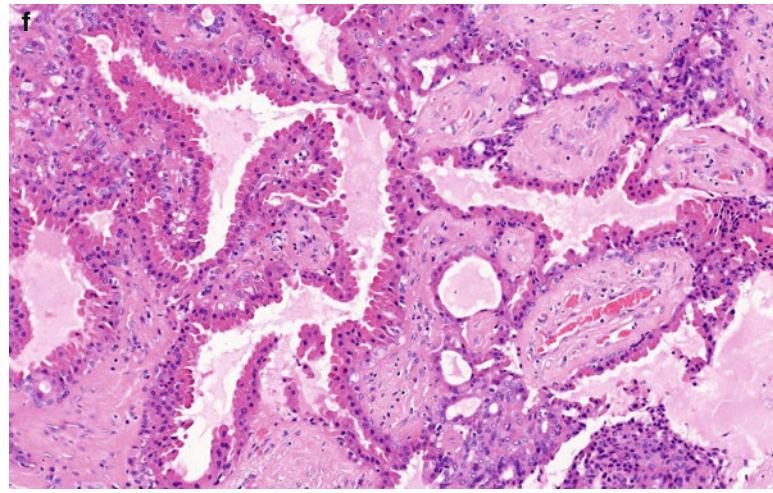


medium, which assists in the assessment of pathological nipple discharge. The imaging can identify normal ducts, duct ectasia or a filling defect. The latter could be due to a papilloma or carcinoma. In the presence of filling defect, an excision biopsy is mandatory for a definitive diagnosis. In experienced breast disease units, galactography has been reported as an accurate method of detecting IDPs (Cardenosa et al. 1994; Woods et al. 1992). Use of aspiration cytology through a catheter followed by galactography yielded a diagnostic accuracy of 97.1 and 94.6 % for carcinomas and papillomas, respectively, in women presenting with nipple discharge (Hou et al. 2002). The authors utilised aspiration cytology through the ductogram catheter and they found this to be more accurate than conventional squeezing cytology. This is because the amount of cytological material yielded through the catheter is substantial for diagnosis when compared to squeezing the nipple, which can be traumatic to the patient with minimal yield of cells.

Unlike mammography, ultrasonography is usually abnormal in women with solitary IDP (Fig. 10.4b). The sonographic features of papillomas include a well-defined, solid, hypoechoic nodule or lobulated lesion or a smooth-walled cystic lesion with solid components (Yang et al. 1997). Dilated ducts are also common with associated intraluminal echoes. However, ultrasound cannot distinguish intracystic carcinoma from papilloma. Other lesions, which can mimic IDPs on ultrasound, include fibroadenomas and phyllodes tumours. Patients with nipple discharge and a negative mammogram usually have a positive ductogram (Cardenosa and Ekuland 1991; Woods et al. 1992).

MR can be a useful additional imaging modality in papillomas. Francis et al. (2002) compared the mammographic, sonographic and magnetic resonance (MR) appearances of symptomatic IDPs. The authors retrospectively reviewed histologically confirmed IDPs from 35 women, age range 28–82 years (only one patient below the age of 40). All but one patient had presented symptomatically, with 23 women reporting nipple discharge. Mammography was reported as normal in 15 women and identified only one papilloma. Ultrasound was reported as normal in one patient and as papilloma in six patients. The remaining lesions were reported as duct ectasia, cysts, fibroadenoma or other benign breast lesions. Only two patients had MR imaging and both were reported as having papilloma. It is difficult to draw any conclusion from this study with minimal data. Rovno et al. (1999) reported solitary IDPs showing dilated ducts and well-circumscribed mass with enhancement on MR imaging. However in a separate study, the enhancing features of the papillomas were difficult to distinguish from malignancy (Daniel et al. 2003).

Orel et al. (2000) investigated 23 patients with nipple discharge, 22 of whom had negative mammography and one had failed galactography. Fifteen patients had excisional biopsies; eleven of these (73 %) MRI findings correlated with histological findings. MRI demonstrated four of the six benign papillomas and one of the two fibroadenomas as circumscribed enhancing subareola masses. One of the MRIs was negative and benign tissue was reported on excisional biopsy. MRI findings were suspicious in six out of the seven patients. The authors concluded that MRI can identify both benign and malignant lesions and is a non-invasive alternative to ductography.

Histologically a solitary IDP consists of a cystically dilated duct containing intraluminal fibroepithelial proliferation with a papillary or solid growth pattern (Fig. 10.4c). Positive staining with CK5/6, p63 and alpha smooth muscle actin also highlight myoepithelial cells. Apocrine metaplasia and fibrosis are sometimes present in solitary IDP (Fig. 10.4e–f). The differential diagnosis of solitary IDP includes multiple intraductal papilloma, DCIS involving papilloma, encysted non-invasive papillary carcinoma, papillary DCIS and invasive breast cancer (Warrick and Allred 2012).

10.4.2 Multiple Intraductal Papillomas

Multiple IDPs are smaller than solitary IDPs and they tend to arise at the periphery of the breast. By using three-dimensional reconstruction, Ohuchi et al. (1984) were able to demonstrate that multiple IDPs originate from the TDLU whereas the solitary IDPs originate from the larger ducts. In their atlas of subgross pathology, Wellings et al. (1975) distinguished between papillomas involving the TDLU which they called hyperplastic terminal duct with papilloma and those involving larger ducts, which they called ductal papillomas. The latter are classified as solitary IDPs (see above).

Multiple IDPs arise in middle-aged women with a mean age of 41.2 years at the time of diagnosis and prevalence significantly decreases after the age of 55 (Haagensen et al. 1951; Haagensen 1986b). The prevalence of multiple IDPs ranges from 0.6 % to 4.6 % (Lewis et al. 2006; Sohn et al. 2007; Schnitt et al. 1993).

Multiple IDPs are usually asymptomatic and are discovered incidentally on breast biopsies excised for other lesions. However, multiple papillomas can be mammographically detected due to calcification (Fig. 10.5). Mammographic calcification may be polymorphous, punctate or flaky (Lanyi 1986). In older women with fatty breasts, peripheral papillomas stand out mammographically as nodular, round or oval masses with variable sizes (Heywang-Köbrunner et al. 2001). In non-calcifying IDPs, the patient may present with non-specific symptoms (Fig. 10.6). Gross examination is generally not informative as the lesions are usually too small to identify. On histology, lesions are characterised by multiple intraductal proliferations of fibrovascular cores lined by epithelium supported by basal myoepithelial layer. The cells show some variation in size and shape but mitotic activity is rare. The luminal proliferation exhibits a branching papillary morphology.

The main differential diagnosis IDPs includes UDH, papillary DCIS, intracystic papillary carcinoma and papillary apocrine metaplasia. As with solitary IDPs, immunocytochemistry staining with CK5/6 and p63 will assist in differentiating benign IDPs from papillary DCIS (Tan et al. 2005). A central intracystic papilloma which had eroded through the nipple is illustrated in Fig. 10.7 and this lacks myoepithelial staining with CK5/6.

10.4.3 Management of Papillary Lesions on Needle Core Biopsy

The UK NHS Breast Screening Programme (2005) classifies papillary lesions on a needle core biopsy into the B3 category and therefore requires excisional biopsy. However, on review of the literature, there are advocates for conservative management if a confident

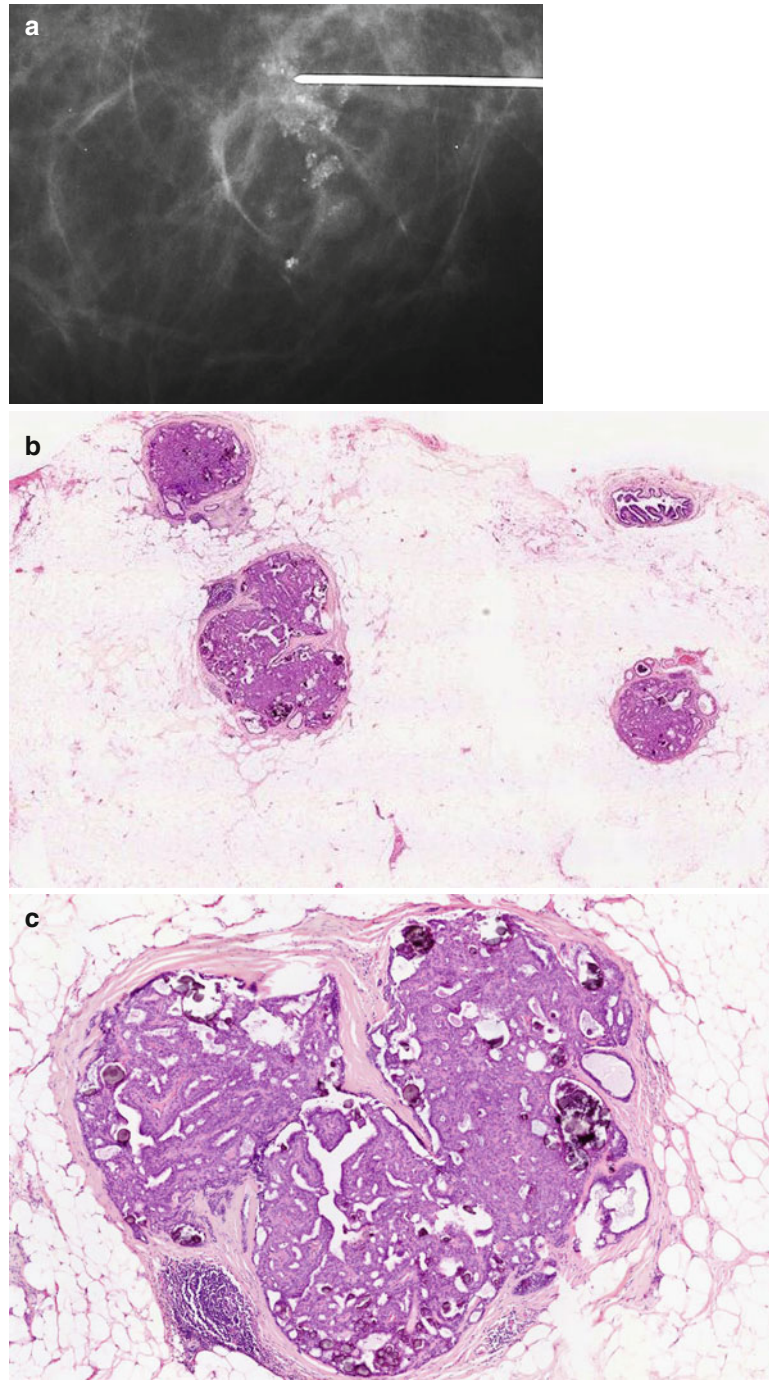


Fig. 10.5 (**a**) A focus of mammographic microcalcification associated with soft tissue density in a 67-year-old woman. The radiologist reported the lesion as probably calcified papillomatosis. (**b**) The excision biopsy shows multiple peripheral intraductal papillomas with psammomatous microcalcification. This low-power field illustrates only three of the papillomas. (**c**) Similar to the previous case, these multiple papillomas showed a predominantly solid growth pattern with psammomatous microcalcification

diagnosis of benign IDP is made on needle core biopsy and others who recommend excisional biopsy. Wiratkapun et al. (2013) retrospectively reviewed 130 non-malignant papillary lesions in 127 patients diagnosed on needle core biopsy followed by excision biopsy; 76 (58 %) of the lesions were located centrally and 54 (42 %) lesions were located at the periphery. The mammographic and ultrasound BIRADS classification was as follows: 4A, 68 lesions (52 %); 4B, 38 lesions (29 %); and 4C, 13 lesions (10 %). Four lesions (3 %) were classified as BIRADS 5 and seven lesions (5 %) as BIRADS 3. The needle core biopsies were classified as papillary lesions without atypia in 91 (70 %) cases and with atypia in 39 (30 %) of the cases. Subsequent excisional biopsy was performed for 84 (65 %) lesions. The excision biopsies yielded benign papillary lesions without atypia in 41/84 (49 %), papillary lesions with atypia in 31/84 (37 %) and malignancy with 10 DCIS and IDC in 12/84 (14 %). The overall upgrade was 17/91 (19 %) to atypical papillary lesions in the benign category and 12/39 (31 %) to malignancy in the atypical category. There was no upgrade to malignancy in the benign papillary lesions at needle core biopsy. There was no malignancy on follow-up of 46 patients who did not undergo surgery. The patients who were followed up for 24 months or more had the following BIRADS categories: 1 in 4 (9 %) patients, 2 in 37 (80 %) patients and 3 in 5 (11 %) patients. If only the cases which had

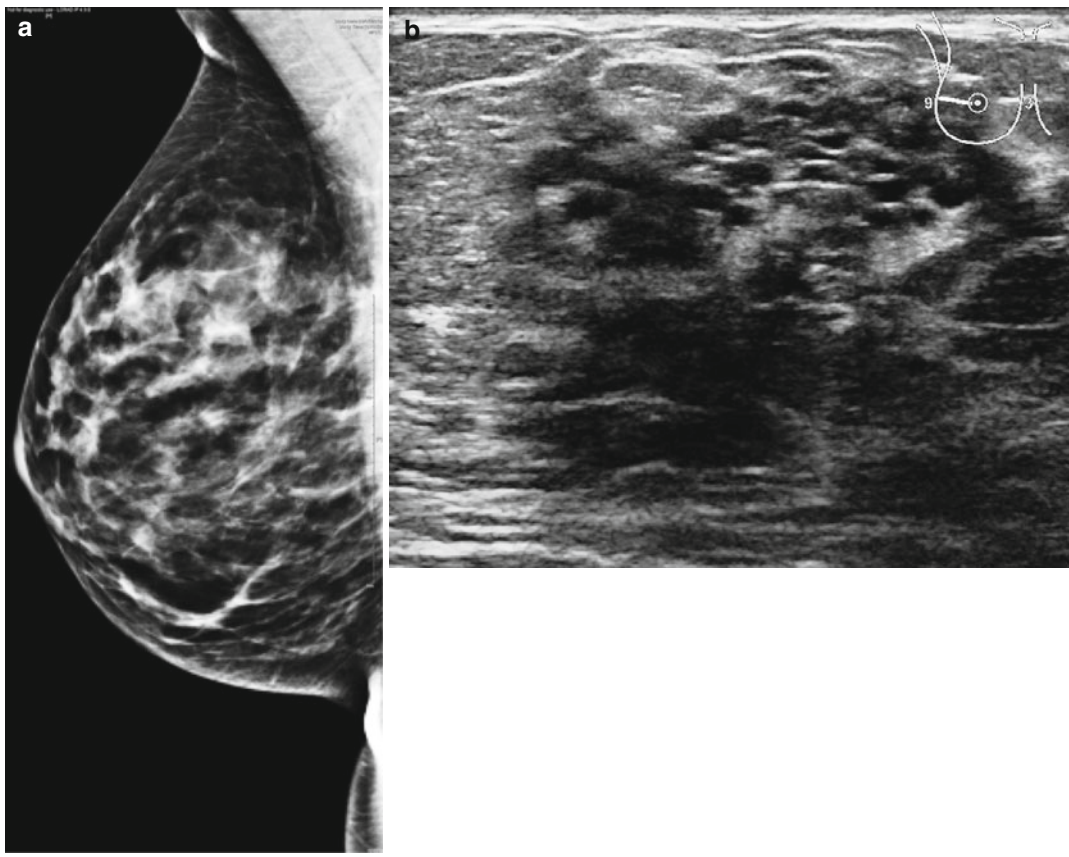
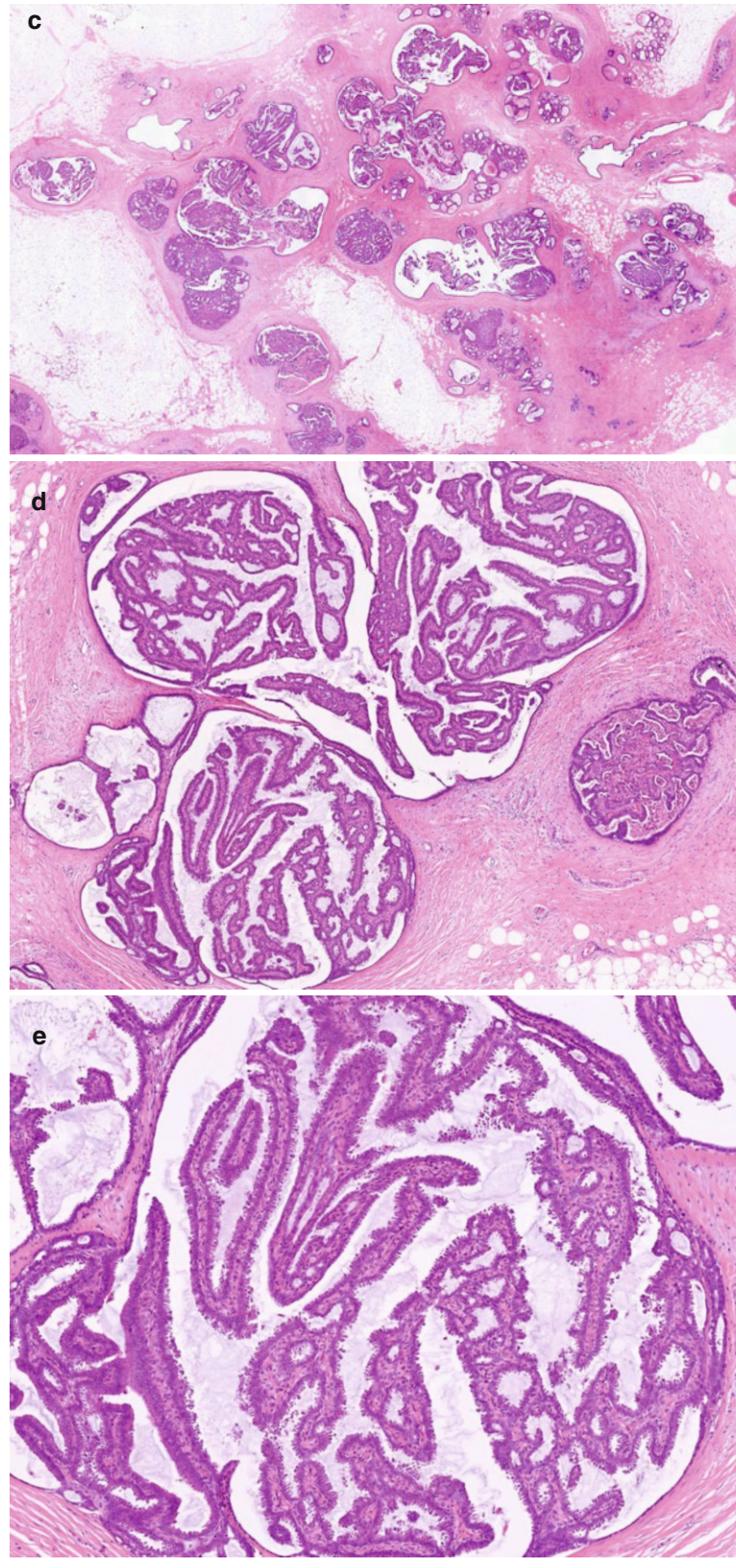


Fig. 10.6 (**a**) Mammogram of non-calcifying papilloma the woman presented with a history of trauma with no specific features. (**b**) The ultrasound suggested fibrocystic disease. (**c**) The needle core biopsy showed a papillary lesion (Fig. 5.4) leading to excision of multiple intraductal papillomas. (**d**) Medium magnification of intraductal papillomas with typical fibrovascular cores lined by benign epithelial cells. (**e**) At higher magnification, the cells show columnar cell change. (**f**) Myoepithelial cells in the intraductal papilloma are highlighted by positive staining with CK5/6

Fig. 10.6 (continued)



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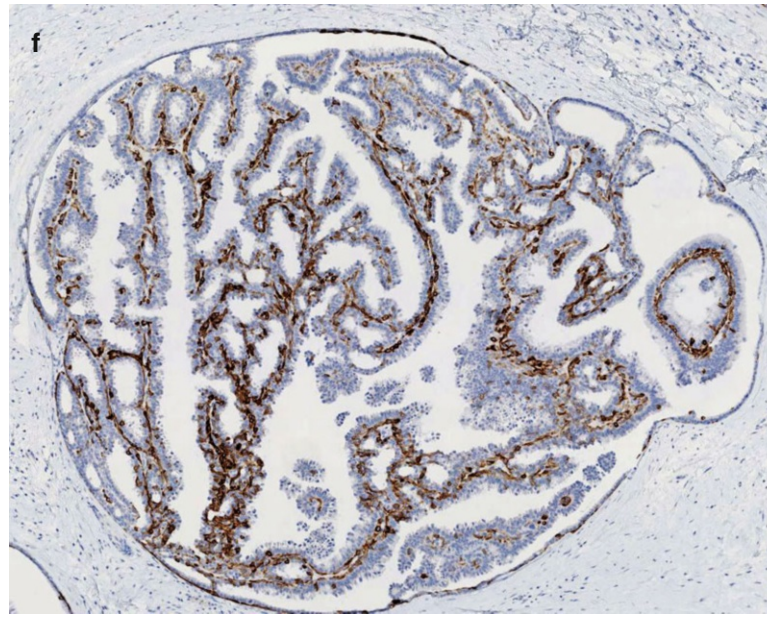

excision biopsies were analysed (84/130 (65 %) lesions), the upgrade would be 0 % for upgrade for benign to malignancy, 33 % for upgrade of benign to atypical papillary lesion and 38 % for upgrade from atypical papillary lesion to malignancy. The authors concluded that needle core biopsy was accurate in diagnosis of benign papillary lesions, but all the papillary lesions with high BIRADS category or atypia on needle core biopsy should be excised. They also recommend that of all papillary lesions diagnosed at needle core biopsy should be excised. In the same report, Wiratkapun and colleagues (2013) reviewed studies on papillary lesions diagnosed at needle core biopsy with subsequent excision biopsies published between 1999 and 2012 including their current report with the number of cases ranging from 26 to 215. There was an upgrade from benign papillary lesions to malignancy only in six publications. In the remaining publications, the upgrade from benign papillary lesion to ranged from 4 % to 29 %. When there was atypia in the needle core biopsies, the upgrade to malignancy ranged from 6 % to 71 %. From this review, there were no determinant features which could predict an upgrade to malignancy.

10.4.4 Are Intraductal Papillomas Premalignant?

In the early years of the twentieth century, women who presented with bloodstained nipple discharge were subjected to radical mastectomy. This was a result of either unclear histological criteria to differentiate intracystic papillary carcinoma from IDPs, resulting in most papillomas being treated as carcinomas, or the belief that papillomas are premalignant. Moore et al. (1961) invited three expert pathologists to review papillary tumours, which were followed by cancer, and three of the lesions were considered to be cancer from the beginning, but four were benign. Because of this early pathological confusion, there was no agreement as to whether or not papillomas were precancerous. Several prominent clinicians in breast disease did not believe that papillomas were precancerous because of the low prevalence of carcinomas detected when they investigated this lesion (Hart 1927; Hendrick 1957; Kraus and Neubecker 1962; Azzopardi 1979). The low rate of subsequent malignancy in these studies may be explained by the fact that most patients with papillomas were treated with mastectomies. None of

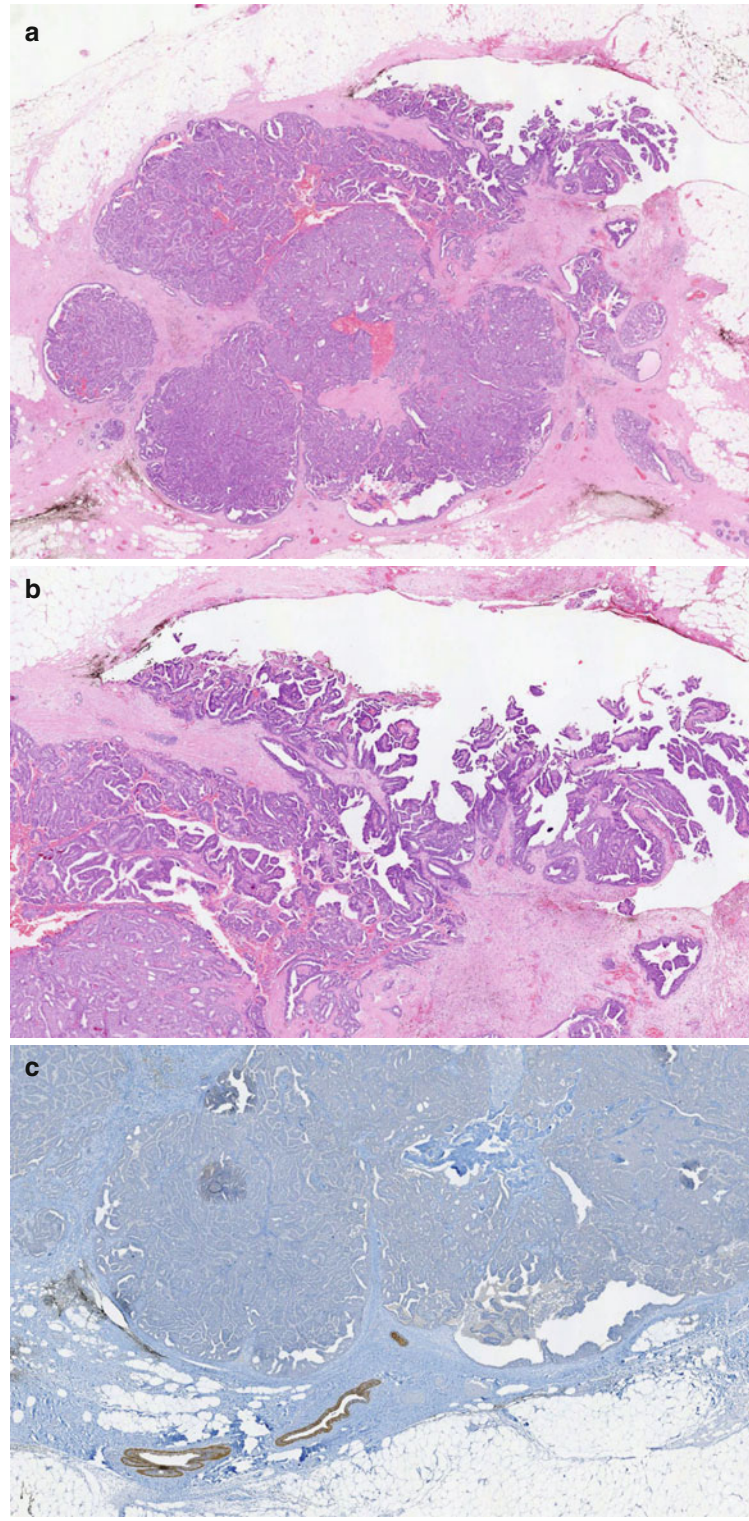

Fig. 10.7 (**a**) This is an example of an intracystic papillary carcinoma for comparison with benign papillomas. The lesion presented symptomatically in elderly woman eroding through the nipple. (**b**) In contrast to the papilloma, the carcinoma cells are monomorphic. There is nuclear stratification and moderate variation in size and shape. (**c**) The carcinoma shows complete loss of CK5/6-positive cells with immunocytochemistry staining. Note internal control of a benign duct expressing CK5/6

the 66 out of 95 patients with IDPs followed-up by Hart (1927) developed carcinoma. Seventy-nine of the patients in this series were treated with either simple or radical mastectomy for the presence of papillary tumours. Azzopardi (1979) did not regard papillomas as premalignant due to the rarity of a borderline lesion in continuity with an overtly malignant papillary tumour. He believed papillary carcinoma arose de novo and that the apparent premalignant transformation of papillomas was due to under-diagnosis of papillary carcinoma and rarely over-diagnosis of pseudo-infiltration in benign papillomas. However, an equally prominent pathologist, Robert Muir (1941), had earlier illustrated in his paper 'The evolution of carcinoma of the mama', the transition between benign papilloma and invasive malignancy, especially in relation to multiple papillomas. Muir believed that increased hyperplastic growth of the epithelium in a papilloma with associated reduced stroma would culminate in malignancy. There is now some supporting evidence that some papillomas, in particular those located in the periphery of the breast, are associated with an increased risk of breast cancer (Haagensen et al. 1951; Carter 1977).

With the increase in pathological knowledge and use of ancillary tests such as immunocytochemistry, it should be possible to differentiate IDPs from intracystic carcinoma. Cytokeratin 5/6 highlights the basal epithelial cells in papillomas, which should mostly be absent in papillary carcinoma (Figs. 10.6f and 10.7b, c). Cyclin D1 has been reported to be differentially expressed in papillary carcinoma when compared with papillomas (Saddik et al. 1999).

10.4.5 Supportive Evidence for Intraductal Papillomas as Premalignant Lesions

Carter (1977) followed up 64 patients with confirmed IDPs for up to 17 years and six of them developed cancer (two in situ, four invasive). However, the papillomas had associated fibrocystic disease, fibroadenoma, epithelial hyperplasia and/or 'papillomatosis'. Only two of the patients who developed carcinoma had multiple papillomas without associated significant epithelial hyperplasia. Carter pointed out that in the presence of other epithelial proliferations, it is difficult to determine whether IDPs per se were responsible for the progression to malignancy.

In an attempt to prove that IDPs are capable of malignant transformation, Papotti et al. (1984) utilised immunohistochemical staining to differentiate benign from malignant proliferations. The authors studied 18 patients with combined IDPs and DCIS. Benign IDPs retained a myoepithelial cell layer with the smooth muscle actin stain, whereas carcinomatous cells showed luminal positivity with carcinoembryonic antigen (CEA). In some cases there was a combination of features of benign papilloma and carcinoma in situ in the same duct. These combined features were present morphologically and with immunocytochemistry staining, which showed a mixture of smooth muscle actin and CEA-positive cells. The investigators interpreted these findings as evidence of malignant transformation of IDPs rather than cancerisation of the papillomas by ductal carcinoma.

In a further attempt to elucidate the possible precancerous nature of IDPs, Ohuchi et al. (1984) investigated 25 specimens containing IDPs by applying three-dimensional reconstruction. Fifteen patients had multiple IDPs and ten had solitary lesions. The multiple papillomas arose in TDLUs, the part of the breast where cancers arise. In six patients, the papillomas (five multiple, one solitary) were associated with previously undiagnosed DCIS. The DCIS associated with peripheral multiple papillomas showed a mixture of papillary and cribriform features, whereas the DCIS from the solitary papilloma showed mixed cribriform and comedo patterns. One of the cases also showed invasive carcinoma with a predominant intraductal component. The reconstruction revealed anatomic continuity between papilloma and carcinoma in situ with interposing borderline changes. The carcinoma in situ and the IDPs arose in the same terminal duct–lobular units.

The precancerous nature of IDPs was further highlighted by Raju and Vertes (1996). The authors compared 20 women with IDPs with associated ADH (age range 27–78) and 77 women with IDPs without atypia (age range 22–80). All patients had presented symptomatically. Of the 12 patients with IDPs and ADH who were followed up, three developed in situ or invasive carcinoma. One patient developed high-grade DCIS in the ipsilateral breast at 8 years and invasive carcinoma in the contralateral breast at 18 years. Another patient developed high-grade DCIS in the ipsilateral breast at 2 years and another had contralateral invasive carcinoma at 15 years. Of the control group, one ipsilateral and two contralateral carcinomas were reported. Compared with other studies (Carter 1977; Murad et al. 1981), which followed up patients with IDPs who subsequently developed carcinoma, the study by Raju and Vertes had fewer patients developing carcinoma despite the presence of ADH, which on its own confers a fourfold risk of malignancy when compared with the general population. The study may have over-diagnosed the presence of ADH.

Ali-Fehmi et al. (2003) compared the epithelial proliferations associated with multiple papillomas (28 patients), DCIS (20 patients) and invasive carcinoma (13 patients). Papillomas were classified as multiple when at least five lesions were present. The patients with papillomas had presented symptomatically with a breast lump. There were associated multiple papillomas in the cases with DCIS and invasive carcinoma. Fibrocystic change and florid adenosis were present in the background of multiple papillomas. Twelve out of 28 papillomas (43 %) had associated ADH and in seven patients the papillomas were also atypical. Four of the patients with multiple papillomas developed contralateral lesions (three multiple papillomas, one invasive carcinoma). Only one patient developed ipsilateral carcinoma on follow-up (mean 47 months). In the patients with papillomas and DCIS, the latter was predominantly (85 %) low grade. The DCIS arose from within or immediately adjacent to the pre-existing papillomas. Of the patients with invasive carcinoma in the background of multiple papillomas, the carcinomas were mostly small (less than 2.0 cm), node negative and oestrogen-receptor positive. Five of the patients with carcinoma developed contralateral lesions, which included one with multiple papillomas, one with multiple papillomas and DCIS, one with DCIS, one with LCIS and one with an invasive carcinoma. From these observations, the authors concluded that the associations of multiple papillomas with the premalignant and malignant proliferations and bilateral disease implied that multiple papillomas represented a marker of constitutionally increased breast cancer risk.

10.4.6 Intraductal Papillomas as a Risk Factor of Malignancy

Although several of the above-mentioned studies and others arrived at the conclusion that papillomas are possibly precancerous based on morphological features such as architectural and cytological atypia or carcinoma associated with IDPs, none of the studies assessed the risk of subsequent malignancy. This is important if IDPs are an incidental finding in excision biopsies for other benign lesions, whether symptomatic or screen detected. Page and colleagues (1996) assessed the IDPs in a nested case-controlled study of 368 women with a histological diagnosis of benign IDP in excision biopsies. The study consisted of 31 women with papillomas who subsequently developed cancer and 91 women with papillomas as controls. The papillomas were divided into small (3 mm diameter) and large lesions (more than 3 mm diameter). The site of the papillomas was noted, which was important in women who subsequently developed cancer. The biopsies were assessed for the presence of epithelial hyperplasia of usual type and atypical hyperplasia within the papilloma and the surrounding breast tissue. Papillomas were considered to have epithelial hyperplasia if the fibrovascular core was covered by piled-up epithelial cells four layers thick or more, excluding the myoepithelial cells. Papillomas with epithelial proliferations consisting of three or more cells thick with irregular slit-like spaces were classified as showing ordinary (usual) hyperplasia. Atypical hyperplasia was deemed to be present when epithelial proliferation with architectural and cytological features

that fall short of the diagnosis of DCIS according to previously defined criteria (Page and Rogers 1992). Epithelial proliferation within the papillomas was identified in 47 patients (39 usual hyperplasia; eight ADH). In the majority of papillomas, foci of ADH consisted of less than 25 % of the whole papilloma. The ADH exhibited cribriform or micropapillary patterns. Epithelial proliferations outside the papillomas were present in 65 out of 122 biopsies (31 women with papillomas who developed cancer and 91 women with papillomas but no cancer). Ten patients had ADH and four had ALH. Of the 31 patients who subsequently developed invasive carcinoma, six had papillomas associated with atypical hyperplasia (follow-up range 2–13 years). Five of the cancers developed in the ipsilateral breast (two at the site of previous papillomas) and one patient had contralateral carcinoma. Four carcinomas were invasive of no special type, one invasive cribriform and the other invasive papillary carcinoma. The latter was at the site of previous papilloma with atypical hyperplasia. The papillomas of the other 25 patients who developed invasive carcinoma had no associated atypia (six ipsilateral, six contralateral, two bilateral, 11 locations unknown). The follow-up period was from 1 to 24 years (median 8 years). Only two patients in the control group had atypical hyperplasia in the papillomas and they did not develop carcinoma during the follow-up period.

From this study, Page and colleagues (1996) reported that the risk of developing subsequent invasive carcinoma in women with papillomas approached 3.5 times that of the general population. The risk was high in women with micropapillomas (3 mm) irrespective of the presence of family history or atypical hyperplasia or other proliferative disease outside the papilloma. On the other hand, the larger papillomas (>3 mm) without atypia had a much lower risk of 1.8 times that of the general population. Micropapillomas tend to be multiple and larger papillomas are usually solitary (Haagensen et al. 1951). Page's paper did not evaluate multiplicity. From calculations based on six patients with papillomas containing atypical hyperplasia who subsequently developed cancer compared with two patients of the control group who did not, the relative risk for subsequent cancer was 7.5. This doubled to 15.8 when atypical hyperplasia was also present in the surrounding breast tissue. However, the authors accepted the fact that they were comparing only six patients with atypia who developed carcinoma with two controls who did not. Patients with papillomas without associated atypia had an overall risk of 1.8, which is similar to the general population with proliferative disease without atypia. Another important factor highlighted by this study is that carcinoma related to papillomas tends to arise in the ipsilateral rather than the contralateral breast. Although the number of patients with papillomas associated with ADH was small (six) compared with 20 patients studied by Raju and Vertes (1996), both studies emphasise the significance of atypia as an additive risk factor of malignancy in patients with papillomas. In a separate study, Lewis et al. (2006) analysed the risk of malignancy in 480 women with papillomas. The authors divided the papillomas into four groups, thus: single papillomas = 372, single papilloma with ADH or ALH = 13, multiple papillomas (>5) = 41 and multiple papillomas with ADH or ALH = 13. The RR of developing breast cancer for the different groups was reported as follows: single papilloma RR, 2.04 (95 % CI 1.66–2.16); single papilloma with ADH or ALH RR, 5.11 (95 % CI 2.64–8.92); multiple papillomas RR, 3.01 (95 % CI 1.10–6.55); and multiple papillomas with ADH or ALH RR, 7.01 (95 % CI 1.91–17.97). In this study there was no difference between the occurrences of the cancer in the ipsilateral or contralateral breast. The values of the RR in this study are similar to those published by Page and colleagues (1996) above.

Most of the studies that reported in situ or invasive carcinoma arising in the background of papillomas document invasive carcinoma of no special type. Only Ohuchi et al. (1984) reported a papillary carcinoma admixed with cribriform carcinoma in situ in five out of the six patients with incidental carcinomas identified during three-dimensional reconstruction. The paucity of papillary carcinoma arising in a background of intraductal papillomas appears to confirm Azzopardi's (1979) belief that intracystic carcinomas may arise de novo, not from intraductal papillomas. Local excision of papillomas with

Table 10.4 A comparison of clinical, radiological and pathological features of central and peripheral papillomas and intracystic carcinoma

Lesion	Clinical features	Radiological features	Histological features
Central papilloma	Nipple discharge usually present; tend to be large (> 3 mm) and single	Mammography: usually normal +/−opacity; ultrasound: dilated duct + soft tissue density; ductogram: filling defect; calcification rare	Coarse fibrovascular cores; myoepithelial and epithelial layer; apocrine metaplasia may be present, mitosis +/−; old haemorrhage may be present
Peripheral papilloma	No nipple discharge; discrete or ill-defined mass or nodularity; small and multiple (3 mm)	Mammography: multiple soft tissue opacity; calcification may be present	As for central papilloma above
Intracystic carcinoma	Nipple discharge present in 30 % of patients[a]; mass usually present up to 5 cm in diameter	Mammography: round circumscribed soft tissue lesion[b]; ultrasound: hypoechoic cystic lesion with posterior enhancement; calcification may be present	Fine fibrovascular core; myoepithelial layer usually absent; cells uniform and monomorphic; mitoses present

[a]Carter (1977)
[b]Estabrook et al. (1990)

mammographic follow-up is now the recommended management of these patients (Carter 1977; Page et al. 1996). Table 10.4 highlights the differences between intraductal papillomas and intracystic carcinoma.

10.4.7 Genetic Alterations in Intraductal Papillomas

Molecular studies have demonstrated LOH at loci 16p13 and 16q21 in both benign and malignant papillary lesions, whereas LOH at locus 16q23 was limited to malignant lesions (Di Cristofano et al. 2005). Lininger and co-workers (1998) produced similar results when they demonstrated LOH at 16p13 in papillary carcinoma, intraductal papilloma and florid epithelial hyperplasia. These studies demonstrate sharing of genetic abnormalities between papillary carcinoma and IDPs suggesting that papillomas may be precursor lesions of papillary carcinoma. The studies did not differentiate between solitary and multiple IDPs. As the cancer arising in patients with IDP can affect either breast and the cancers are predominantly of no special type, this would classify IDP as a marker for risk of malignancy. The work by Ohuchi et al. (1984) which demonstrated papillomas in continuity with cancer is in favour of a precursor lesion. The molecular studies also favour a precursor lesion.

10.5 Pregnancy-Like Change

The state of pregnancy-like changes, also termed pseudo-lactational changes, should, by definition, occur in women who are not pregnant or lactating. The changes can also occur in nulliparous women and this is usually detected as an incidental finding in breast tissue excised for benign or malignant disease. Pregnancy-like changes have been reported with equal frequency in both surgical and autopsy material at 3.1 % and 3 % by Kiaer and Andersen (1977) and Frantz et al. (1951), respectively. The cause of these lactational changes is unclear. Hyperprolactinaemia or ingestion of phenothiazines, antihypertensives or oestrogenic medication can induce pregnancy-like changes (Tavassoli and Yeh 1987; Shin and Rosen 2000).

When the luminal secretions calcify, this can lead to mammographic detection (Fig. 10.8). On histology, there is expansion of the TDLUs containing luminal secretions. The TDLUs are lined by cells with pale vacuolated cytoplasm. The nuclei protrude into the lumen to create a hobnail pattern with decapitation of secretions. The calcification is of psammomatous type.

In a report on this lesion, Shin and Rosen (2000) documented 12 lesions with pregnancy-like changes in non-lactating women. The women were aged between 38 and 52 years (median 45 years, mean 44 years). All women

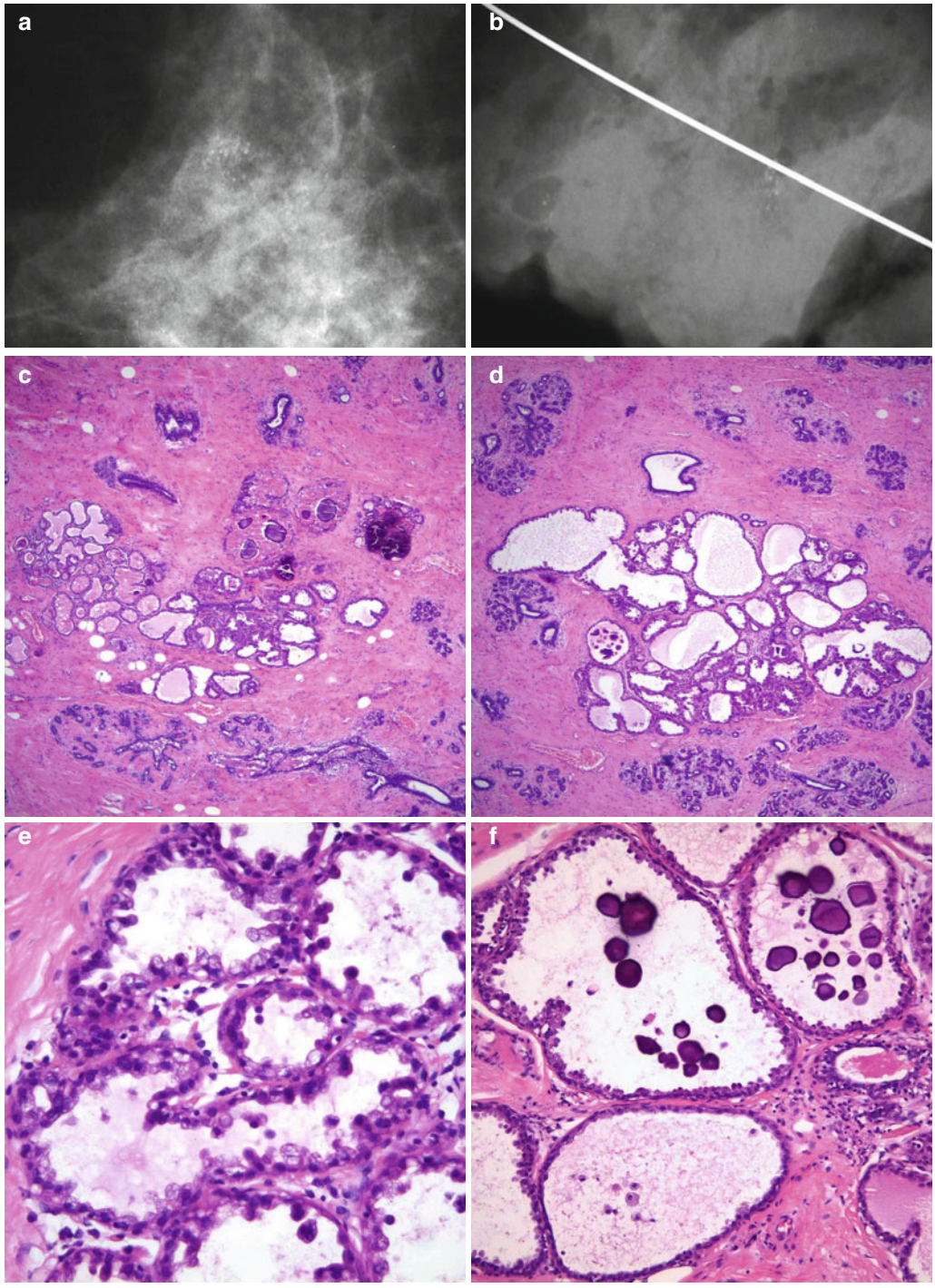

Fig. 10.8 (**a**) Localised area of punctuate microcalcification due to pregnancy-like features in a 54-year-old woman on hormone replacement therapy, radiologically graded as R3. The needle core biopsy suggested epithelial hyperplasia of uncertain malignant potential (B3). (**b**) The specimen X-ray shows the targeted focus of microcalcification in the path of the guide wire. (**c**) Histologically calcification is present in lobules showing pregnancy-like changes. (**d**) Some lobules are distended with secretions. Nascent calcification is noted in some units. (**e**) The lobules are lined by cells with vacuolated cytoplasm and nuclei protrude in the lumen, to give rise to a hobnail pattern. (**f**) Some lobules are lined by flat epithelium and contain luminal eosinophilic secretions. The calcification noted mammographically has a laminated morphology

were pre- or perimenopausal. In six patients, the lesions were mammographically detected due to the presence of microcalcification; one patient had an abnormal mammogram, four had mammographically detected masses, and one presented with galactorrhoea. In addition to the pregnancy-like changes, cystic hypersecretory hyperplasia was also identified in five specimens. In four specimens pregnancy-like changes merged imperceptibly with cystic secretory hyperplasia. The latter is differentiated from pregnancy-like changes by the presence of luminal secretions, which resemble thyroid colloid. This study highlighted another benign lesion, which causes indeterminate mammographic microcalcification. The lesions can be multifocal, with normal lobules almost masking the pregnancy-like changes.

This risk of carcinoma associated with pregnancy-like changes is unknown. However, Rosen illustrated atypical pregnancy-like hyperplasia mostly associated with cystic hypersecretory lesions (Rosen 2001). Shin and Rosen (2000) advise 3- to 6-monthly mammographic follow-up if calcification is identified in needle core biopsies, provided the mammographic lesion was adequately sampled.

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Columnar Cell Lesions

11

Learning Points

- CCLs invariably present as microcalcification on screening mammography.
- Previous different terminologies make the assessment of the biological significance of CCLs difficult.
- CCLs are currently classified as columnar cell change with or without atypia and columnar cell hyperplasia with or without atypia.
- The WHO classified columnar cell change with atypia and columnar cell hyperplasia with atypia as flat epithelial atypia also termed flat DIN.
- Flat epithelial atypia is a B3 lesion, and when present in a core biopsy, requires excision.
- Excision of flat epithelial atypia may yield high-risk lesions such as ADH, DCIS and invasive carcinoma
- Morphological features and genetic alterations implicate CCLs as a non-obligate precursor of breast cancer.

11.1 Previous Terminology

When the first edition of the book was written, there was a lot of confusion in the published literature regarding the nomenclature and the biological significance of columnar cell lesions. This is illustrated in Table 11.1 which highlights the different names applied to this lesion.

The earliest description of the columnar cell lesion was by Foote and Stewart in 1945 when they termed the lesion blunt duct adenosis. In Foote and Stewart's series, blunt duct adenosis affected small or large areas of the breast tissue with formation of cysts in some cases. They postulated that blunt duct adenosis originated from terminal ducts with obliteration of the lobules as the process expands to dilated lobules. Blunt adenosis was identified with equal prevalence (26 %) in both cancerous and non-cancerous breasts, but with fewer lesions in the 50–60 age group compared with the younger women. Other epithelial proliferations associated with blunt duct adenosis in both cancerous and non-cancerous breast included 'ductal papillomatosis', intraductal papillomas, apocrine epithelium, sclerosis adenosis, fibroadenoma and periductal mastitis. This study could not associate blunt duct adenosis with the genesis of breast cancer.

Shaaban and colleagues (2002) performed one of the largest studies on blunt duct adenosis. They reviewed 674 benign biopsies from 120 patients (age range 18.3–82.65 years) who subsequently developed breast cancer and 382 patients (age range 18.12–77.82 years) who did not. The latter group of patients acted as a control group. The patients were followed up for 6.30–235.57 months, with an average of 66.95 months. The overall RR of developing subsequent breast cancer was 1.18 (CI = 0.93–1.50) which the authors based on the following six categories of blunt duct adenosis:

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_11, © Springer-Verlag Berlin Heidelberg 2014

Table 11.1 Various terminology applied to columnar cell lesions

Terminology	Reference
1. Blunt duct adenosis	Foote and Stewart (1945)
2. Columnar metaplasia	Bonser et al. (1961)
3. Atypical lobule	Wellings et al. (1975)
4. Clinging carcinoma	Azzopardi (1979)
5. Columnar alteration of lobules	Page and Anderson (1987)
6. Hypersecretory hyperplasia with atypia	Page et al. (1996)
7. Cancerisation of small ectatic ducts lined by atypical ductal cells with apocrine snouts	Goldstein and O'Malley (1997)
8. [a]Columnar alteration with prominent apical snouts and secretions (CAPSS)	Fraser et al. (1998)
9. Atypical cystic lobule	Oyama et al. (1999)
10. Columnar cell hyperplasia	Rosen (1999)
11. Columnar cell lesions	Jacobs et al. (2002)

[a]Prior to the unifying concept by Schnitt and Vincent-Salomon (2003)

1. Blunt duct adenosis without calcification – dilated acini within the TDLUs with 'blind-ended' morphology and lined by a single layer of columnar epithelium. This lesion was present in 12.5 % of study cases and 6.02 % of controls (RR = 2.08; CI = 1.12–2.85).
2. Blunt duct adenosis with calcification – psammomatous calcification was present in 14.16 % of study cases and 8.11 % of controls (RR = 1.75; CI = 1.00–3.04).
3. Blunt duct adenosis with columnar cell metaplasia – columnar epithelium with no atypia exhibiting apical snouts was present in equal proportions in 30 % of study cases and 29.84 % of controls (RR = 1.01; CI = 0.73–1.38).
4. Blunt duct adenosis with atypical columnar cell metaplasia – this lesion was noted in 6.66 % of study cases and 2.87 % of controls (RR = 2.32; CI = 0.95–5.62).
5. Blunt duct adenosis with ductal epithelial hyperplasia of usual type – this lesion was present in 6.66 % of study cases and 8.11 % of controls (RR = 0.82; CI = 0.34–1.74).
6. Blunt duct adenosis with atypical ductal hyperplasia (ADH) – this lesion was noted in 1.66 % of study cases and 1.04 % of controls (RR = 1.59; CI = 0.30–8.58).

Although the RR of subsequent breast cancer associated with pure blunt duct adenosis was significant (2.08), the risk associated with blunt duct adenosis and epithelial hyperplasia of usual type and ADH was insignificant. The authors acknowledged that this could be due to the low numbers of patients with biopsies containing epithelial hyperplasia of usual type and ADH. This study by Shaaban and colleagues was important in linking an epithelial proliferation now termed CCL with risk of subsequent malignancy.

The term columnar alteration with prominent apical snouts and secretions (CAPSS) was introduced in 1998 by Fraser and colleagues. The authors reviewed mammographic and pathological features of excision biopsies from 100 patients. The biopsies had been excised because of the presence of mammographic calcification. The mammographic features of these lesions were reviewed to assess the pattern of calcification, whether round or pleomorphic, the presence or absence of branching and the size of the calcification. The calcifications identified in CAPSS with no associated neoplastic lesion were more likely to be round and non-branching, and this was similar to that of benign breast biopsies without CAPSS. The features were in contrast to the branching and pleomorphic calcification usually associated with DCIS or invasive carcinoma.

In this series, 42 % of biopsies had lesions with features of CAPSS and 74 % of these had associated calcification. Histologically, the calcification was of psammomatous type, which is usually but not exclusively seen in low-grade DCIS. The epithelial changes in CAPSS varied from cells with simple columnar alterations to lobules with nuclear stratification and more pronounced cytoplasmic snouts. Other lesions exhibited epithelial tufting, bridges, micropapillary structures and prominent nuclear atypia. In 38 % of the biopsies, CAPSS was associated with low-grade DCIS, mostly of micropapillary cribriform type. In these cases, DCIS and CAPSS frequently coexisted in the same duct–lobular units. The authors concluded that CAPSS represented a spectrum of lesions, which ranged from simple columnar alterations to changes of low-grade DCIS.

11.2 Current Terminology

Schnitt and Vincent-Salomon (2003) proposed a simplified nomenclature for columnar cell lesions based on four patterns. This classification covers most of the different patterns of columnar cell lesions previously described in the literature. In all four categories, the TDLUs are invariably dilated:

1. Columnar cell change – the TDLUs are lined by one or two cell layers. The columnar cells show uniform ovoid to elongated nuclei with inconspicuous or absent nucleoli. The apical snouts are usually exaggerated; luminal secretions and calcification may or may not be present. Examples of this include blunt duct adenosis.
2. Columnar cell hyperplasia – the TDLUs show epithelial stratification of more than two cell layers without complex architectural patterns. The columnar cells show ovoid to elongated nuclei, with or without hobnail features. The nucleoli are absent or inconspicuous. The apical snouts are often exaggerated. Luminal secretions and calcifications are often present and the latter are usually of psammomatous type. Examples in this category will include some forms of CAPSS.
3. Columnar cell change with atypia – the TDLUs are lined by one or two cell layers. There is a subtle low-grade cytological atypia and the cells may resemble those of tubular carcinoma. Apical snouts may be prominent. Luminal secretions and psammomatous calcification may be present. The so-called clinging carcinoma and some forms of CAPSS would be classified into this category.
4. Columnar cell hyperplasia with atypia – the TDLUs show cellular stratification consisting of more than two cell layers, but complex architectural patterns are not present. Cytological atypia is present but may be subtle. The cells may resemble those of tubular carcinoma. Apical snouts may be exaggerated; luminal secretions and psammomatous calcifications may be present.

Schnitt and Vincent-Salomon pointed out that lesions with high cytological atypia or complex architectural patterns such as micropapillae; rigid cellular bridges, bars and arcades; or sieve-like fenestrations with evidence of cellular polarisation should be classified as DCIS or ADH according to the well-established criteria (Page et al. 1985). They discouraged grading atypia in columnar cell lesions as mild, moderate or severe.

The World Health Organization Working Group on the Pathology and Genetics of Tumours of the Breast (Tavassoli et al. 2003) combined columnar cell change with atypia and columnar cell hyperplasia with atypia into 'flat epithelial atypia'. Flat epithelial atypia (FEA) is defined as 'a presumably neoplastic intraductal alteration characterised by replacement of the native epithelial cells by a single or 3–5 layers of mildly atypical cells'. This lesion is also classified as ductal intraepithelial neoplasia grade 1a (DIN1a). In 1979, Azzopardi described a lesion he termed 'clinging carcinoma' which consisted of ducts lined by a single layer of atypical cells. These atypical cells could be easily missed on examination under low power or be dismissed as fibrocystic change. Although Azzopardi acknowledged that 'blebbing of the luminal margin is characteristic of benignity…', he concluded that in clinging carcinoma this might represent an early feature of malignancy. This term was largely ignored in the literature by the WHO (Tavassoli et al. 2003). Moinfar refers to this lesion as flat DIN (2009). In this review of the diagnostic criteria, differential diagnosis, molecular genetic findings and clinical relevance, Moinfar concluded that flat DIN represents one of the earliest morphological recognisable neoplastic alterations of the breast that is commonly associated with mammographically suspicious microcalcification.

Walker et al. (2012) applied the above classification of CCLs to the NHS Breast Screening Programme reporting criteria in the management of these lesions when present in a needle core biopsy as follows:

- Columnar cell change – B1
- Columnar cell hyperplasia – B2
- Atypical ductal hyperplasia/FEA – B3
- DCIS – B5a

11.3 Radiological Features of CCLs

The publication by Fraser and Colleagues in 1998 on CAPSS highlighted CCLs as important mammographic detected lesion. In this study, microcalcification was present in 74 % of the cases with round and pleomorphic appearances. Branching microcalcification was present in only 11 % of the cases. A later study by Kim et al. (2006) retrospectively reviewed the mammographic and sonographic features of twelve lesions in nine patients who had undergone excisional biopsies and had confirmed diagnosis of CCLs. Microcalcifications were present in nine out of twelve lesions (75 %) with clustered pattern of distribution in all lesions. In five lesions, the microcalcification was amorphous or indistinct, pleomorphic in three lesions and round shaped in one lesion. The microcalcification ranged in size from 3 mm to 10 mm (mean, 6 mm). All nine patients had ultrasound examination. Two patients had no sonographic abnormality. Of the seven lesions which showed up on ultrasound, three were masses only, three were masses with calcification and one lesion had calcification only. The lesions were indistinct and ranged in size from 4 mm to 11 mm (mean, 7.7 mm). Eleven of the lesions were classified as BI-RADS 4 (92 %) and one as category 3 based on sonographic appearances. Of the three lesions with histological atypia, two were classified as category 4a and the other 4c. On histology, four lesions were classified as columnar cell change, five columnar cell hyperplasia and three columnar cell hyperplasia with atypia. The authors concluded that the mammographic microcalcification in columnar cell lesions was indistinguishable from that of other lesions such as atypical ductal hyperplasia or DCIS.

In a separate study, Solorzano and colleagues (2011) retrospectively reviewed the radiological features of 33 lesions which had been reported as flat epithelial atypia (FEA). Twenty-two of the 33 (67 %) cases of FEA were sampled under stereotactic guidance and eleven (33 %) lesions under ultrasound guidance. Twenty-seven lesions were apparent mammographically and six lesions were occult. FEA was detected mammographically due to the presence of microcalcification in 26/33 cases (61 %), as a mass associated with calcification in a single lesion, masses without calcification in four lesions and parenchymal distortion in two lesions. The calcification had an amorphous, coarse and fine pleomorphic appearance, ranging in size from 3 mm to 40 mm (median, 10 mm). There was clustered distribution in 14/20 (70 %) and the remainder were linear or segmented. In the same study, 21 patients had ultrasound assessment and 11 of these had no abnormality. The ultrasound abnormalities included mass lesions or architectural distortion with an irregular shape, microlobulated margins or hypoechoic. This study again demonstrates that CCLs or FEA have no specific radiological features.

The diagnosis of calcifying CCLs in needle core biopsies is prompted by the radiological abnormality usually BI-RADS 3 or BI-RADS4 lesion. In probably one of the largest reviews to date, of 3,437 needle core biopsies from three hospitals in the Netherlands, Verschuur-Maes and colleagues (2011a) assessed the prevalence of CCLs detected using digital mammography and ordinary screening mammography. They documented that the needle core biopsies of lesions noted on digital mammography reported more CCLs (10.8 %) compared to 4.9 % reported using conventional screening mammography (95 % CI 1.48–2.51). Most of the lesions were CCLs without atypia, 8.2 % and 2.8 % for the digital mammography and conventional screening mammography, respectively; whilst the prevalence of CCLs with atypia remained constant (2.0 % vs. 2.6 %).

A cluster of microcalcification magnified from conventional screening mammography (Fig. 11.1a) showed columnar cell hyperplasia on histology. Another patient with magnified screen-detected pleomorphic microcalcification was taken using digital mammography (Fig. 11.2a). The histology showed CCH

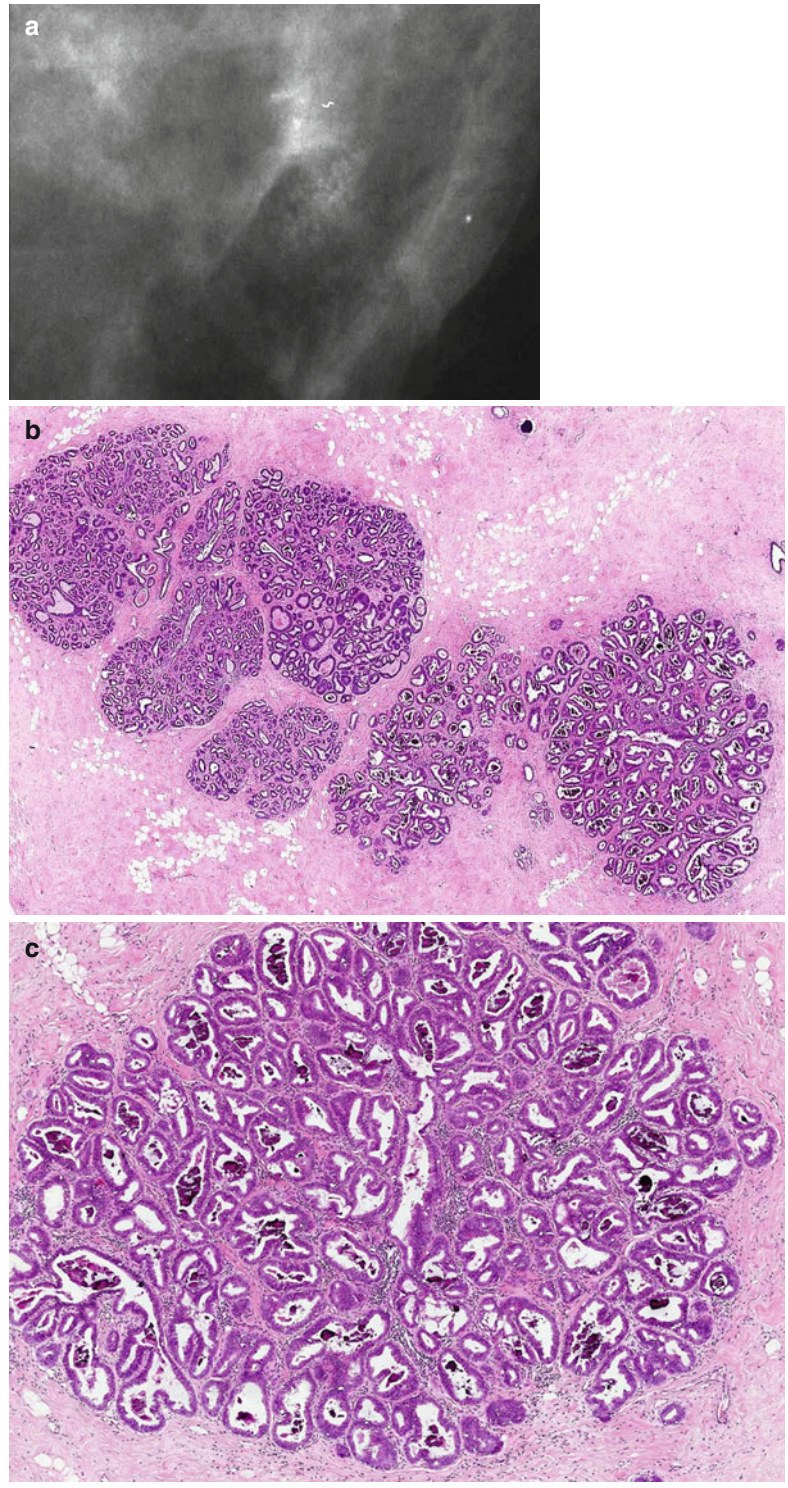


Fig. 11.1 (**a**) Magnified focus of screen-detected microcalcification with image taken using conventional mammography (R3). (**b**) The histology shows enlarged and expanded TDLs. (**c**) The calcification is partly psammomatous and has 'fractured' appearance in a TDLU with columnar cell hyperplasia. (**d**) In columnar cell hyperplasia, the TDLU is lined by two or more layers of epithelial cells with occasional luminal papillae. The cells show prominent luminal snouts (Erratum: This case was misclassified as UDH in the first edition as Fig. 6.1)

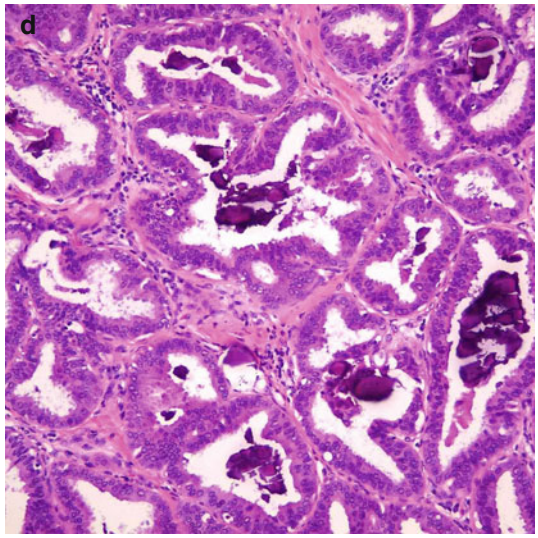


Fig. 11.1 (continued)

with atypia (FEA). The image taken using digital mammography is clearly sharper than that of conventional mammography. Another focus of indeterminate microcalcification (Fig. 11.3a) in a conventional mammogram is better defined in specimen X-ray. Microscopically there was a mixture of CCH with and without atypia as well as CCL with ADH.

11.4 Pathological Features of CCLs

Columnar cell lesions represent a spectrum of architectural and cytological alteration in the TDLU. The most common method of detection is mammography during screening for breast cancer (Figs. 11.1, 11.2, 11.3, and 11.4). The cases demonstrate the heterogeneity of CCLs in the distortion of the TDLU and the pattern of microcalcification, and the only unifying feature is the presence of cellular luminal snouts. The morphology of the TDLU in Fig. 11.1 due to CCH is relatively maintained. In a needle core biopsy, it is rather difficult to assess the full architecture of TDLU in this case of screen-detected FEA (Fig. 11.2). In the lesion showing a mixture of CCH with and without atypia as well as CCL-ADH (Fig. 11.3), there is prominent architectural distortion of the TDLU in an expansive manner. The architectural distortion is taken a step further in the lesion excised from a 63-year-old woman following mammographic detection (Fig. 11.4). The TDLU is cystically dilated. This lesion would be consistent with lesions described by Marton Lanyi (1986) as microcystic adenosis with acini so enlarged to a point of cystic dilatation but remains with the lobular boundaries. At higher power, the cystically dilated units are lined by single layer of cells with luminal snouts which qualifies for the classification as CCH without atypia.

CCLs can be identified as incidental findings in specimens excised for malignant or benign breast lesions such as fibroadenoma (Fig. 8.14) or radial scars (Fig. 11.5) and can exhibit unusual morphology as the clear cell change in the myoepithelial cells in this columnar cell hyperplasia present in fibroadenomatous change in a 71-year-old woman (Fig. 11.6). Different lesions can be present in the same excision biopsy. Table 11.2 summarises the salient morphological features of

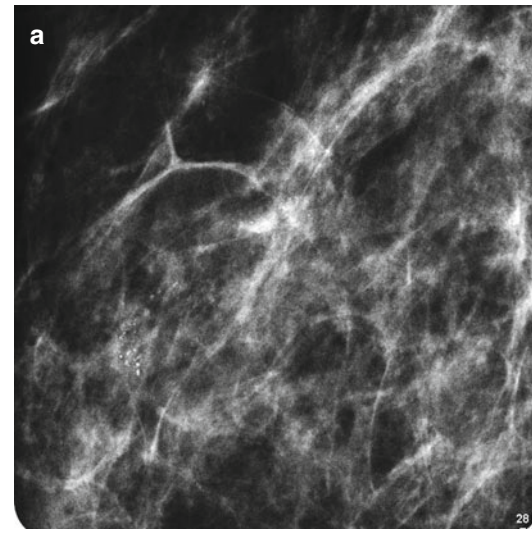
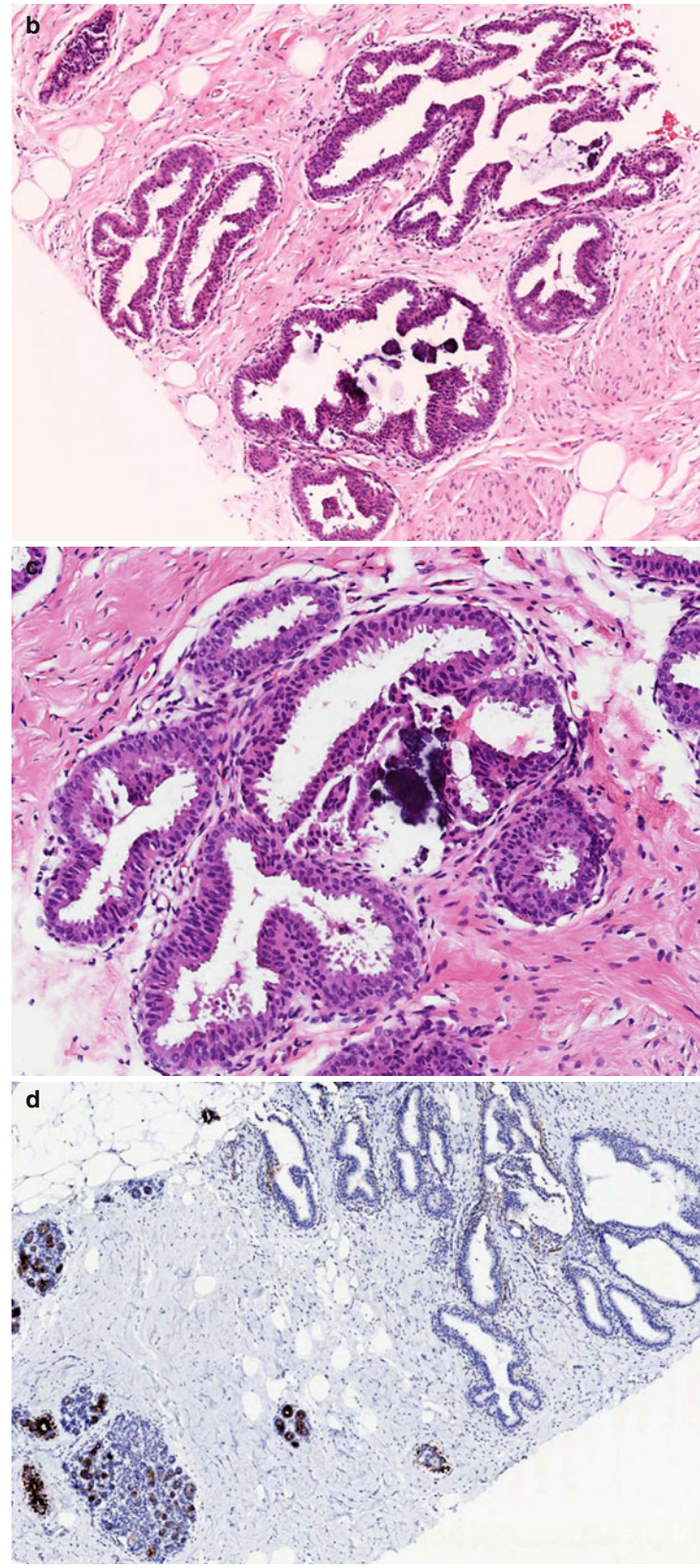


Fig. 11.2 (**a**) Magnified area of screen-detected pleomorphic microcalcification taken using digital mammography (R4). (**b**) The needle core biopsy showed columnar cell hyperplasia with atypia/flat epithelial atypia (FEA). (**c**) High magnification of FEA showing variation in nuclear size and shape and luminal snouts. (**d**) CCL lesions lack basal epithelial cells on staining with CK5/6 antibody. Normal lobules cat as positive controls

Fig. 11.2 (continued)



columnar cell change, columnar cell hyperplasia and flat epithelial atypia through to ADH/DCIS.

Columnar cell lesions should not be confused with unrelated lesions such as cystic hypersecretory hyperplasia and cystic hypersecretory ductal carcinoma in situ of the breast (Guerry et al. 1988). These lesions typically consist of dilated TDLUs containing homogeneous eosinophilic secretions simulating thyroid colloid. Pseudo lactational changes, which occur in the absence of breastfeeding or hormone replacement therapy, can mimic columnar cell lesions and appropriate clinical information may assist in classifying these lesions (see Fig. 10.8). Cells with pseudo lactational change exhibit vacuolated cytoplasm. The apocrine metaplastic cell is the prototype bearer of cytoplasmic snouts and shows abundant eosinophilic cytoplasm. Apocrine cells are negative

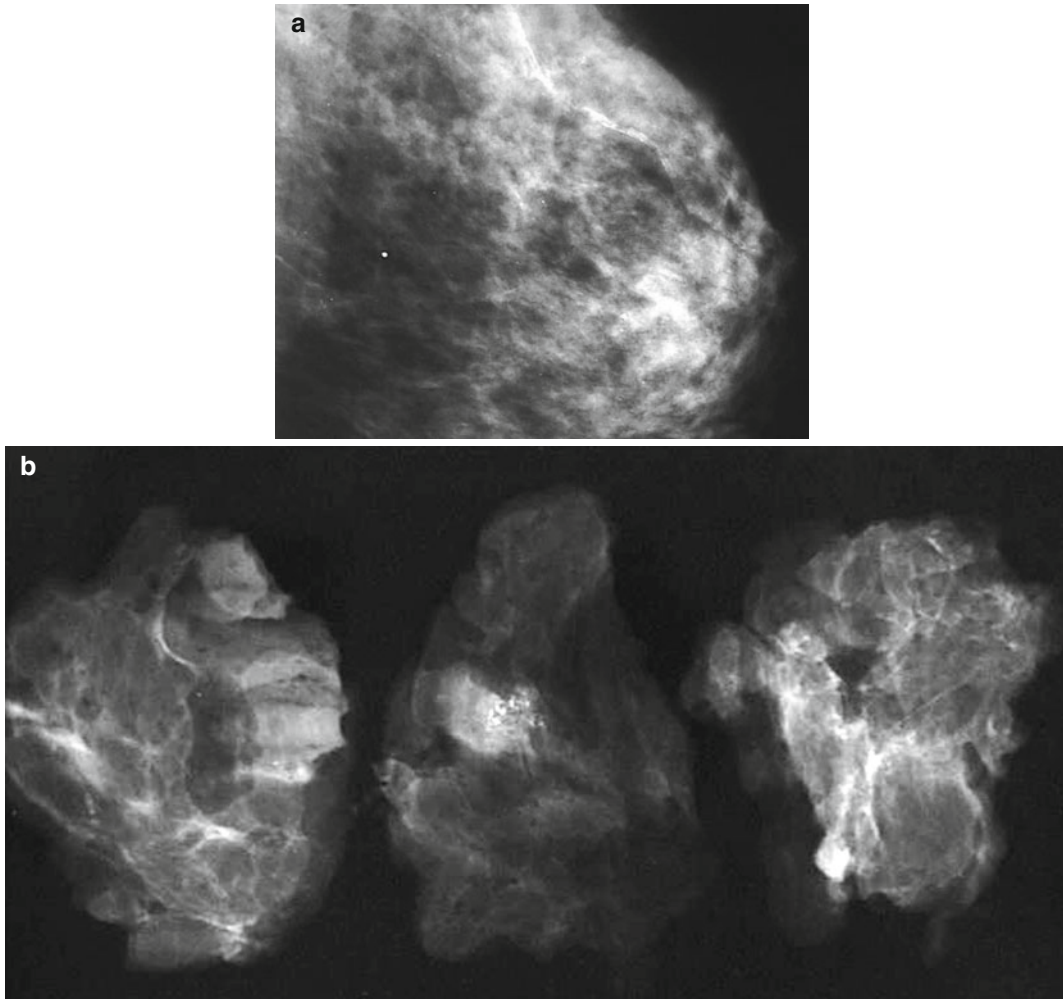


Fig. 11.3 (**a**) Screen-detected cluster of indeterminate microcalcification (R3) in the postero-medial aspect of the breast in a 73-year-old woman not on hormone replacement therapy. Vascular calcification is also present. (**b**) The lesion was unsuitable for stereotactic biopsy. Localisation excision biopsy was performed. The sliced specimen X-ray highlights the microcalcification. This helps to target the area with abnormality when selecting tissue block, without processing large amounts of tissue. (**c**) Low-power image of a 10 mm lesion which showed a mixture of columnar cell hyperplasia with and without atypia as well as columnar cell lesions with ADH with calcification. (**d**) High magnification of a distorted TDLU showing some architectural atypia. (**e**) CCL-ADH showing both architectural and cytological atypia with luminal snouts and psammomatous microcalcification (**f**) Another field to highlight the cytological atypia

Fig. 11.3 (continued)

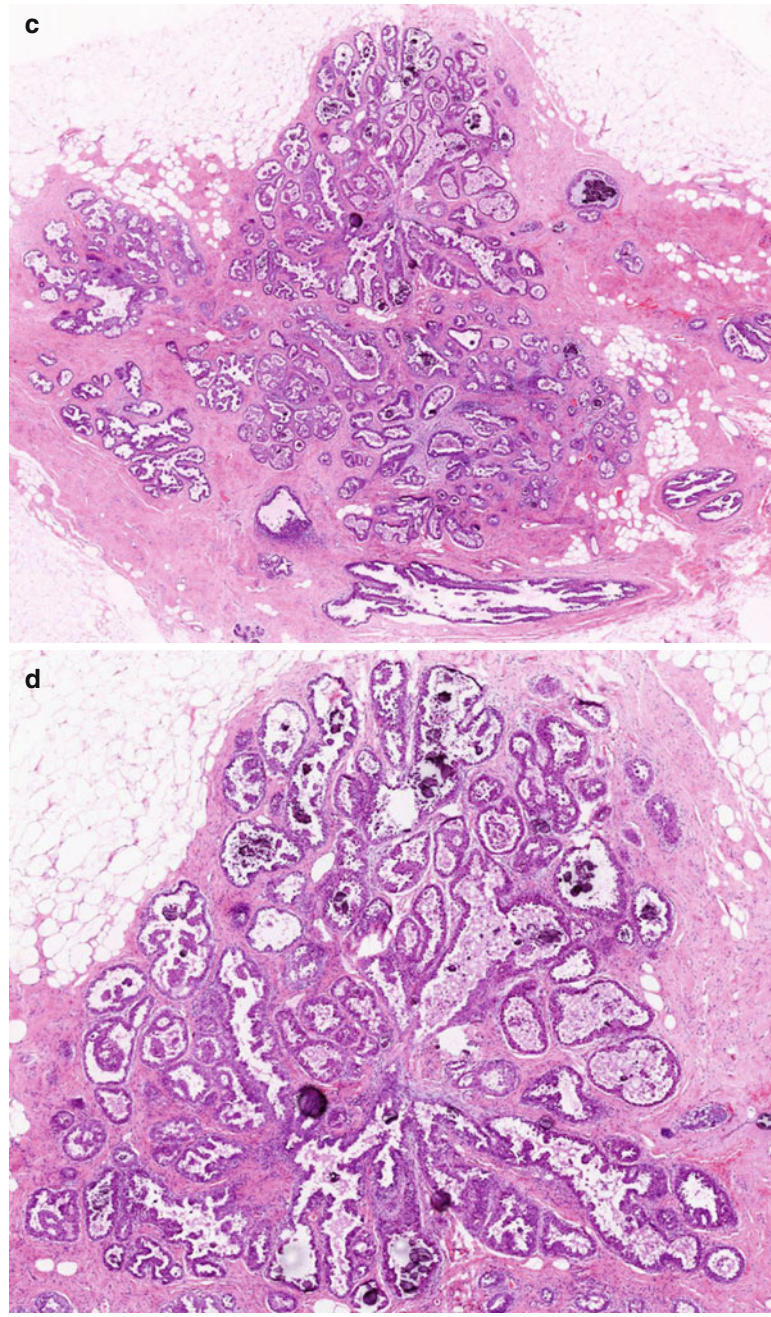
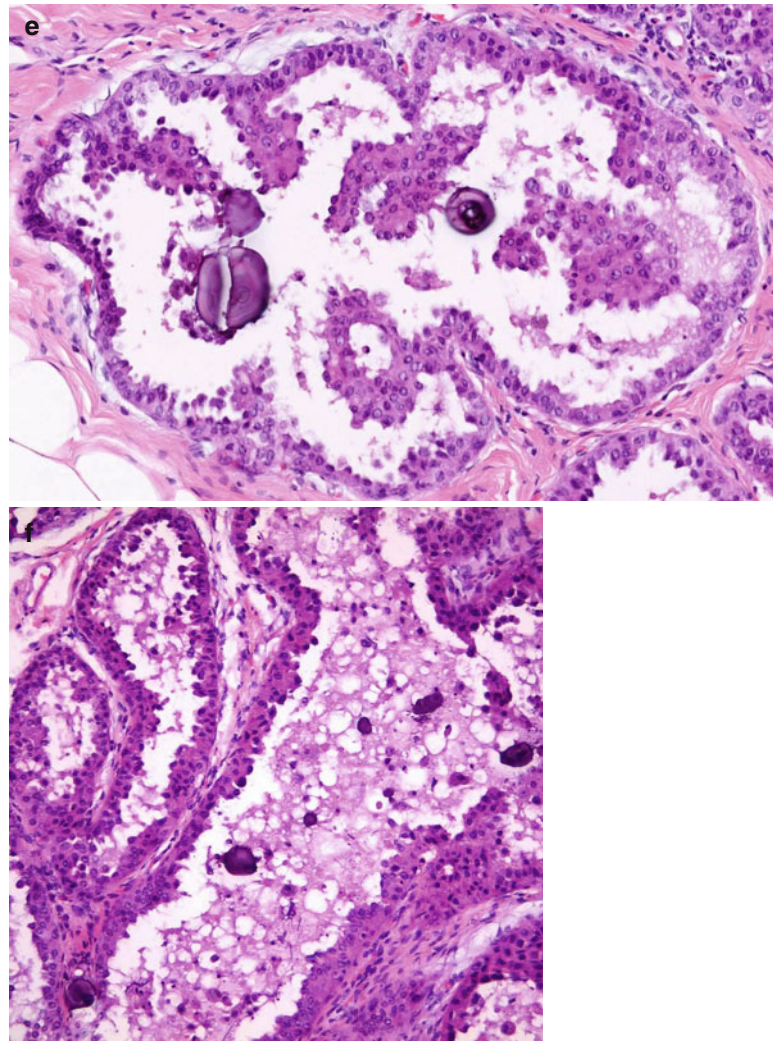


Fig. 11.3 (continued)



for oestrogen and progesterone receptors, and this should distinguish them from columnar cell lesions, which express these hormone receptors (Oyama et al. 1999; Fraser et al. 2000).

Verschuur-Maes and Van Wiest (2011) described a mucinous variant of CCL. The authors identified mucin-producing CCL in 17 out of 291 (5.8 %) cases, and in three out of 21 cases, the lesions had features amounting to ADH-CCL. Columnar cell change without atypia was the most common type of mucinous CCL which was detected mammographically due to the presence of microcalcification. Muc 2 was expressed in intraluminal mucin in 12 out of 15 (80 %) and showed cytoplasmic expression in five out of 15 (33 %) mucinous CCLs. In the same series, mucinous CCLs were more identified in association with 46 mucinous carcinomas than in 46 ductal carcinomas (28 % vs. 9 %). The authors reported an overall incidence of mucinous CCL to be 0.5 % in needle core biopsies and therefore rare.

Columnar cell lesions typically express oestrogen and progesterone receptors, which assist in differentiating them from apocrine

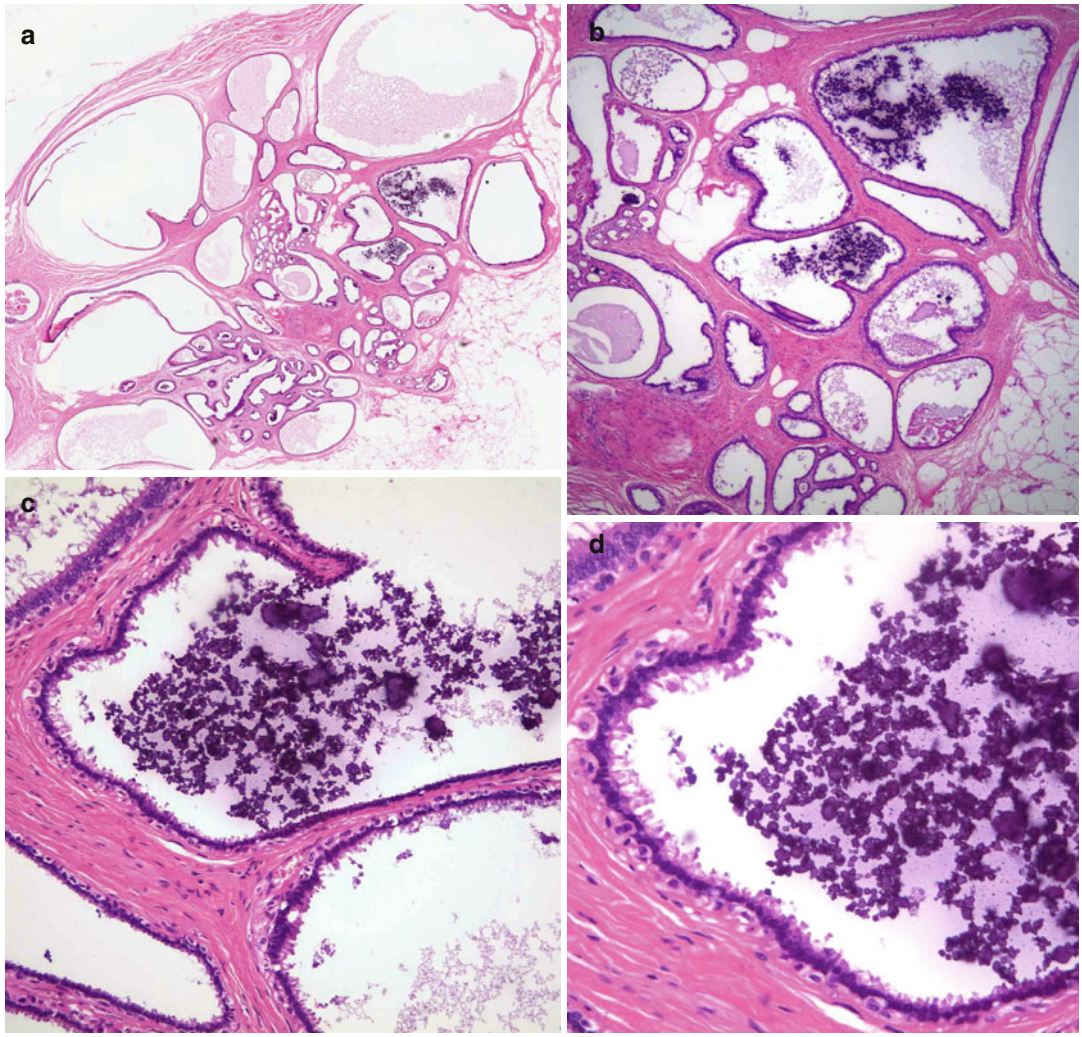


Fig. 11.4 (**a**) Another screen-detected calcified lesion with columnar cell change in a 63-year-old woman with cystically dilated TDLU resembling fibrocystic change. (**b**) The calcification is not present in all cysts which suggests progressive deposition. The calcification shows an amorphous dispersed pattern. (**c**) The cysts are lined by a simple layer of epithelium with apical snouts. There is no eosinophilic cytoplasm usually seen in apocrine metaplasia of fibrocystic change. (**d**) High magnification of the cystic columnar cell lesion, which shows prominent apical snouts, but no cytological atypia

metaplasia, which lacks these receptors (Oyama et al. 1999; Fraser et al. 2000; Tremblay et al. 2005). Apocrine metaplasia expresses androgen receptors. CCLs lack basal epithelial cells on staining with CK5/6 cytokeratin (Otterback et al. 2000). This assists in differentiating CCLs from lesions such as usual ductal hyperplasia. CCLs have been found to be consistently positive for Cytokeratin 19 but negative for Cytokeratin 14 (Oyama et al. 1999; Simpson et al. 2005). Increased proliferation activity with the MIB-1 antibody has also been reported with increased cytological atypia (Fraser et al. 2000). Other immunophenotypic features include positive staining for cyclin D1 and BcL2 (Oyama et al. 1999; Fraser et al. 2000).

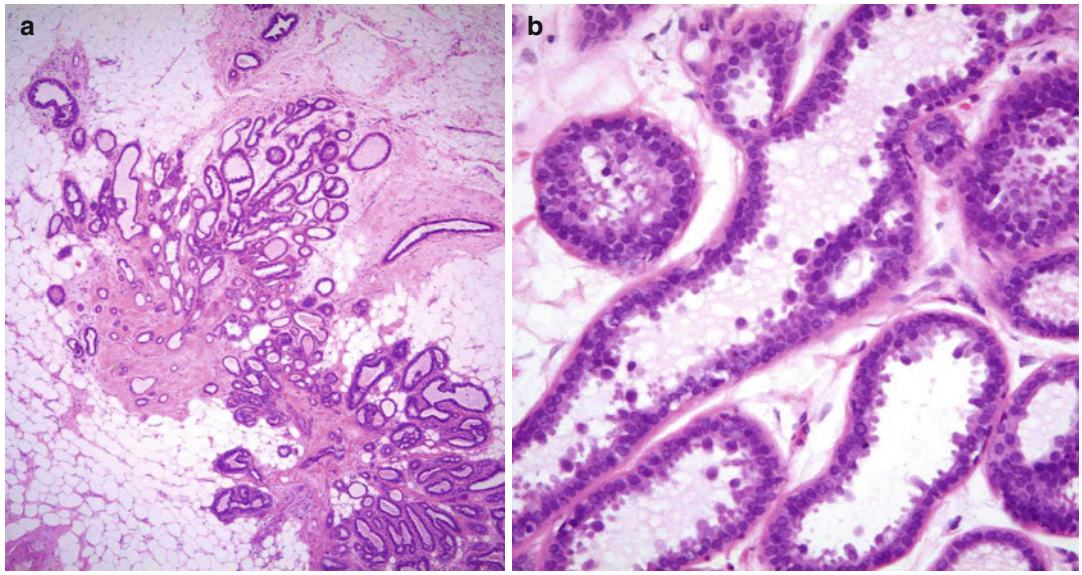


Fig. 11.5 (**a**) Columnar cell change is present in the radiations of a screen-detected radial scar. (**b**) At high magnification, the TDLU is lined by a single layer of epithelial cells with apical snouts. There is no atypia

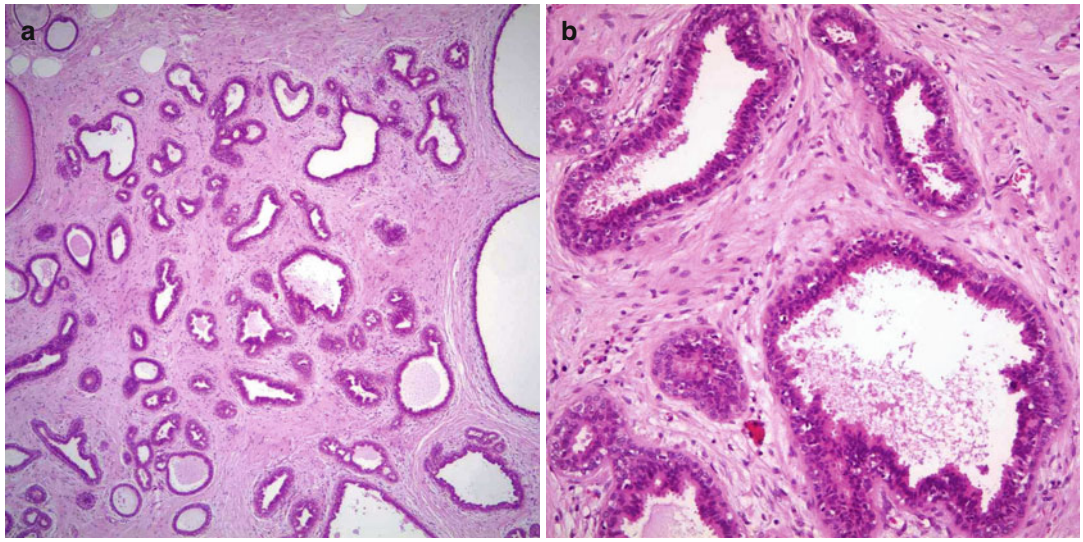


Fig. 11.6 (**a**) Widespread incidental columnar cell hyperplasia in a specimen excised for screen-detected microcalcification in fibroadenomatoid change in a 71-year-old patient (see Fig. 8.17). (**b**) At high magnification, there is epithelial hyperplasia and luminal snouts, but no cytological atypia. (**c**) In a different field, there is epithelial hyperplasia; myoepithelial cells are prominent and these unusually exhibit clear cytoplasm. (**d**) Higher magnification to highlight clear cytoplasm of the myoepithelial cells supporting the columnar cells (Erratum: Fig. 11.6a and d classified as columnar cell change in Fig. 9.2a, b)

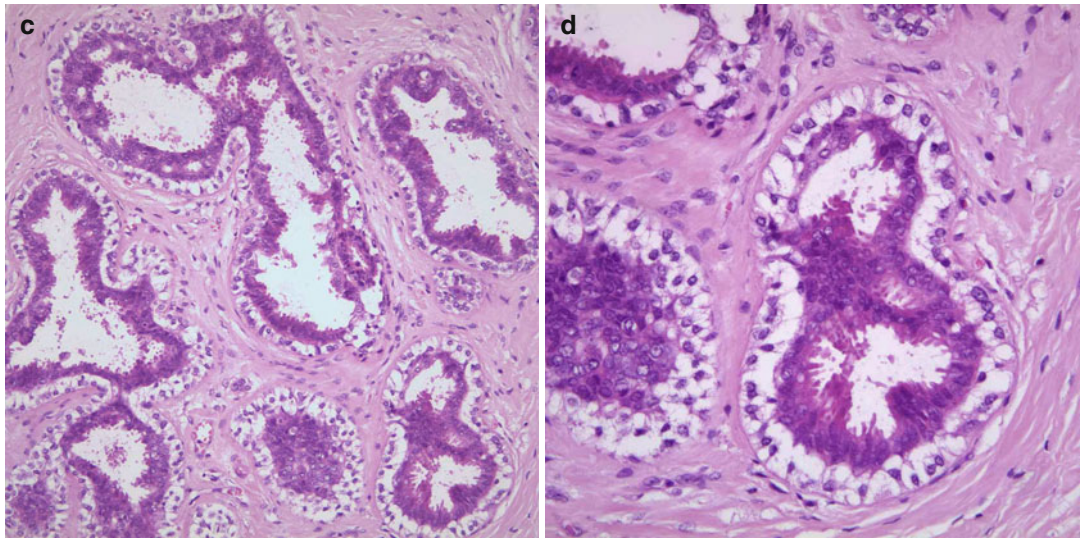


Fig. 11.6 (continued)

11.5 Genetic Alterations in CCLs

As CCLs are found in high frequency in association with lobular neoplasia, low-grade DCIS, invasive tubular carcinoma and invasive lobular carcinoma (Tarek et al. 2007), it is important to establish whether the CCL is the precursor for cancer at molecular level. A review of the morphological, immunophenotype and genetic alterations of the CCLs by Turashvilli and colleagues (2008) concluded that CCLs represented the earliest histological identifiable non-obligate precursor of low-grade breast carcinomas. This may be an oversimplification of the biological behaviour of CCLs because the lesions are quite prevalent in biopsies excised for benign lesions. However there is molecular evidence of genetic alteration in CCLs which appears to represent a continuum of in situ to invasive carcinoma. Several studies have shown loss of chromosome 16q in breast cancer and this chromosome and other genetic alterations have been investigated in CCLs. Moinfar and colleagues (2000) assessed loss of heterozygosity (LOH) in 22 cases of ductal intraepithelial neoplasia (DIN) flat type (clinging carcinoma), currently classified as flat epithelial atypia by the WHO. Thirteen cases were associated in infiltrating carcinoma and five cases with conventional DCIS. LOH was detected in 17/22 lesions (77 %) and monoclonality was established in two cases. The most common genetic alterations were at chromosomes 11 q, 16 q and 3p with LOH in 50 %, 45 % and 41 %, respectively, in informative cases. The DIN flat type showed the same genetic alterations (LOH) identified in adjacent in situ and infiltrating ductal carcinoma. Only one case of normal breast epithelium from reduction mammoplasty exhibited LOH. The authors concluded that DIN represented one of the earliest morphologically recognisable neoplastic alterations of the breast. The authors also noted that DIN flat type usually present at the periphery of tubular carcinoma, bears striking cytological features and genetic alterations to DIN flat type, further adding weight that CCLs are precursors of breast cancer. Moinfar and co-authors further postulated that flat DIN may be the explanation, at least in part for the over

Table 11.2 Comparison of pathological features of the spectrum of entities from columnar cell change through to ADH/DCIS

	Diagnosis			
Feature	Columnar cell change	Columnar cell hyperplasia	FEA	ADH/DCIS
Topography	TDLU, acini may be mildly dilated or of normal size	TDLU, acini may be mildly dilated or of normal size	TDLU, often microcystically dilated acini	TDLU ± adjacent ducts
Shape of acinar spaces	Irregularly shaped luminal margin	Irregularly shaped luminal margin	Often rounded acinar spaces, with smooth inner margin	Often rounded acini, but with complex structures extending into lumen (see architecture, below)
Architecture	Flat	Tufts and mounds	Flat or tufted, not complex	Complex with micropapillary or cribriform structures
Stratification/multilayering	Not present	Present	May be present	May be present
Luminal secretions often with microcalcification	Present	Present	Present	May be present
Nuclear size	Small to medium	Small to medium	Small to medium	Small to medium
Nuclear shape	Oval, elongated	Oval, elongated	Often, but not always, rounded	Rounded
Nuclear texture	Bland	Bland	Speckled chromatin pattern may be present	Speckled chromatin pattern common
Pleomorphism[a]	Uniform	Uniform	Uniform to moderately pleomorphic	Uniform
Position of nuclei within cell	Basally placed	Basally placed	Often central	Central
Nucleoli	Not conspicuous	Not conspicuous	Not conspicuous, but may be evident	Not conspicuous, but may be evident
Mitoses	Generally absent	Generally absent	Generally scarce	Generally scarce
Extent	May be focal or extensive	May be focal or extensive	May be a focal area within background of non-atypical CCL	May be focal area within background of non-atypical CCL. By definition ADH is small/microfocal

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[a]If marked pleomorphism, the lesion does not fall with the spectrum of CCLs but should be regarded as high-grade DCIS

ADH atypical ductal hyperplasia, *CCLs* columnar cell lesions, *DCIS* ductal carcinoma in situ, *FEA* flat epithelial atypia, *TDLU* terminal ductal lobular unit

20 % report incidence of breast cancer recurrence observed with 'negative' margins in biopsies. Recurrent loss of 16q in CCLs, a frequent genetic alteration seen in low-grade DCIS and invasive carcinoma, further advances the hypothesis that CCL represents both morphologic and molecular continuum with the advanced lesions and, therefore, a non-obligate, intermediary step in the development of some forms of low-grade in situ and invasive carcinoma (Simpson et al. 2005; Turashvilli et al. 2008).

11.6 Clinical Significance of CCLs

There is an emerging consensus that CCL represents a precursor or at least a marker for increased risk of cancer. Because CCLs were previously published under different names, it is difficult to reconcile the different conclusions of each study with current unified terminology by Schnitt and Vincent-Salomon (2003). When faced with the diagnosis of CCL in a needle core biopsy, the two main questions facing the multidisciplinary team looking after the patient are as follows:

(i) Does the lesion need excision?
(ii) If excised and there is no cancer, what is the risk of progression to malignancy?

11.6.1 Prevalence of Carcinoma Following Diagnosis of CCL

In a large literature review, Verschuur-Maes (2012) reported the underestimation and progression risk of CCLs diagnosed by needle core biopsy in the following lesions:

1. CCL without atypia followed by surgical excision biopsy (SEB)
2. CCL with atypia followed by SEB
3. ADH-CCL followed by SEB

11.6.2 CCL Without Atypia and SEB

The review identified 630 patients with CCL without atypia and 70 (11 %) had undergone SEB; five patients had DCIS and five had invasive carcinoma, giving a pooled underestimation risk of 15 % (95 % CI 7–30 %). The pooled underestimation risk for all with needle core biopsies with CCL without atypia was 1.5 % (95 % CI 0.6–4 %). The remainder of the patients who had SEB had benign lesions.

11.6.3 CCL with Atypia and SEB

The CCL with atypia category consisted of 668 patients and 389 (58 %) patients had SEB and 57 'events' were recorded with a pooled underestimation risk of 17 % (95 % CI 10–27 %). The patients included 37 (10 %) with DCIS and 20 (4 %) with invasive carcinoma. The overall pooled underestimation risk for all patients with CCL with atypia in needle core biopsies was 9 % (95 % CI 5–14 %). The remainder of the patients had benign lesions which included CCL with atypia, lobular intraepithelial neoplasia and ADH.

11.6.4 ADH-CCL and SEB

The ADH-CCL category consisted of 374 patients and 310 (83 %) of the patients had SEB with recorded 61 'events' consisting of 28 (12 %) patients with DCIS and 28 (12 %) patients with invasive carcinoma and four with uncategorised events with a pooled underestimation of risk of 26 % (95 % CI 16–40 %). The overall pooled underestimation risk for all patients with ADH-CCL on needle core biopsies was 20 % (95 % CI 13–28 %). The remaining patients in this category had CCL with atypia, lobular intraepithelial neoplasia, ADH and other benign lesions.

11.6.5 Management of Patients with CCL on Needle Core Biopsy

There are conflicting reports in the literature regarding the management of flat DIN/flat epithelial atypia when present in a needle core. Martel et al. (2007) identified 63 patients with flat DIN in 1,751 needle core biopsies over a period of 8 years, with follow-up available for 55 patients.

Of the 63 patients, 24 had excisional biopsies between 15 days and 10 years following the initial needle core biopsies. The authors reported infiltrating carcinoma in nine (14.3 %) patients, seven (11.1 %) in ipsilateral, and two (3.2 %) in contralateral breast. Five patients underwent an excision biopsy of the ipsilateral breast less than 3 months of the initial core biopsy and none had either invasive or in situ carcinoma. Martel and colleagues concluded that flat DIN1 was a marker of slightly increased risk for subsequent development of invasive carcinoma and if found in a needle core biopsy as the most advanced lesion, following mammographic correlation, excisional biopsy is not mandatory. The patients required close follow-up with repeat mammograms for early detection of any clinically occult carcinoma in the vicinity of flat DIN1 that may have been missed by the needle core biopsy. This report by Martel and colleagues is in variance with other publications which advocate excision biopsies if flat epithelial atypia is identified in needle core biopsies because of the high frequency of high-grade lesions in the excision specimens. In a study of 56 patients with 60 needle core biopsies containing FEA, Kunju and Kleer (2007) reported pure ADH, pure FEA and concomitant FEA and ADH in 13 %, 23 % and 64 % of the biopsies, respectively. Excisional biopsies in 48 of the 56 patients contained DCIS or invasive carcinoma in 10 patients (21 %), LCIS or ALH in five patients (11 %), residual ADH in 11 patients (23 %) and no atypia in 24 patients (50 %); three of 14 patients with pure FEA upgraded to DCIS or invasive carcinoma on excisional biopsy. The authors recommended excisional biopsies on diagnosis of FEA on needle core biopsy. Pandey and colleagues (2007) also advocate excision of FEA if present in needle core biopsies.

The above report by Verschuur-Maes (2012) clearly illustrates that conservative management of CCL identified on needle core potentially increases risk of missing high-grade lesions. As the terminology of CCL is better understood, there is now a growing consensus among multidisciplinary teams on how to manage patients with columnar cell lesions. However before the decision is made whether to excise the CCL or follow up the patient, the multidisciplinary team must decide whether the tissue in the needle core biopsy is representative of the radiological lesion; if not, vacuum-assisted needle core biopsies should be considered (Harigopal et al. 2002).

Table 11.3 Management of CCL when present in needle core biopsies

Lesion	Management
1. CCL without atypia on core biopsy	Examine at three levels Report as benign (B2)
2. CCL hyperplasia without atypia	Examine at three levels Report as benign (B2)
3. CCL with atypia/ FEA	Examine multiple levels Report as B3, excision required
4. ADH-CCL	Examine multiple levels Report as B3; excision required

The management of patients with CCL is based on the original paper by Schnitt and Vincent-Salomon (2003) and has been recently adopted by the NHS Breast Screening Programme in the UK and advocates excision of FEA when present in needle core biopsies (Walker et al. 2012). Table 11.3 summarises the management of patients with CCL in needle core biopsies.

11.6.6 Columnar Cell Lesions in Excisional Biopsies

There is very limited data on how to manage atypical columnar cell lesions in excision biopsies. Vincent-Salomon (2006) advises that if there is CCL with atypia in the excision biopsy, to assess further levels and submit extra tissue to search for ADH or DCIS. When the proliferation fulfils the criteria for ADH-CCL, the patients should be followed up as per conventional ADH which in some institutions is annual clinical and mammographic follow-up. If the CCL with atypia is associated with DCIS or invasive cancer, the patient should be managed as per the high-grade lesions. However, the following two questions arise:

(i) Is CCL included in the assessment of the size of the cancer or DCIS?
(ii) If atypical CCL is present on the margin, should this be considered as a positive margin?

Vincent-Salomon advises that the atypical CCL should not be included in measurement when assessing the size of DCIS or invasive carcinoma. Secondly the rate of progression of atypical CCL is slow and therefore should not be treated as a positive margin.

11.7 Long-Term Follow-Up of CCLs

Verschuur-Maes (2012) reported a review on three studies of patients with CCL with long-term follow-up. The review included two retrospective studies and one nested control study with a total of 408 patients (range 13–201 patients). The results could not be pooled because of the heterogenous nature of the studies. In the nested case control study, Boulos et al. (2008) followed up 47 patients with CCLs for a mean of 17 years and reported a relative risk (RR) of 1.5 (95 % CI 1.0–2.2) of developing invasive carcinoma following diagnosis of CCL in needle core biopsies compared to an RR of 3.5 (95 % CI 1.2–9 %) for patients with ADH-CCL. Verschuur-Maes et al. (2011b) followed up 201 patients with CCL for 5 months to 8 years (mean 3.5 years) and reported a progression risk of 0.5 % (95 % CI 0.04–2.3 %) for patients diagnosed with CCL without atypia and 23.1 % for patients with initial diagnosis of ADH-CCL (three patients developed invasive carcinomas). Fifty-eight patients in Martel and colleagues' study (2007) who had CCL with atypia on core biopsies were compared with 45 patients with similar lesions in Verschuur-Maes and colleagues' (2011b) study to give a total of 103 patients with 15 'events' (1 DCIS and 14 invasive carcinoma) which were recorded with pooled underestimation risk of 16 % (95 % CI 9.9–28 %). Patients in Martel et al. study were followed up for 5 months to 11 years (mean 3.5 years).

In summary, this study provided pooled underestimation risk for patients diagnosed with CCL without atypia, CCL with atypia and ADH-CCL of 1.9 %, 9 % and 20 %, respectively. However the authors concede that the results may not be representative because not all patients with CCL with atypia and ADH-CCL underwent excision biopsies. Other factors which may affect the results include the number of patients in the different studies and the fact that they were retrospective.

In one of the original follow-up studies on flat DIN under the name of clinging carcinoma was by Eusebi et al. (1989). Eusebi identified 21 cases of clinging carcinoma after reviewing 4,397 'benign' breast biopsies obtained from the files of departments of pathology in Northern Italy between 1965 and 1971. The study did not distinguish between clinging carcinoma of the monomorphic variant and more proliferative micropapillary DCIS (DIN) or high-grade DCIS. Two out of 21 patients died of breast cancer; one patient developed ipsilateral breast cancer and died 12 years after the biopsy; the second patient presented with infiltrating ductal carcinoma 6 years after the initial biopsy and died 4.9 years later. Two more patients were found to have persistent clinging carcinoma, one in the ipsilateral breast 11 months later. These results by Eusebi et al. indicated an absolute risk of 9.5 % with a mean follow-up of 16.7 years.

In another study, 59 patients with 'clinging carcinoma' were entered into the European Organisation for Research and Treatment of Cancer (EORTC) 10,853 randomised clinical trial which compared excision and radiation therapy and excision alone in women with DCIS (Bijker et al. 2001). There was no recurrence in the patients with a median follow-up of 5.4 years. This suggests that 'clinging carcinoma' has a low risk of progression to cancer.

11.8 Progression Risk of CCLs

As the biological behaviour of CCLs unveils through observational studies and use immunocytochemistry analysis and genetic analysis, there is accumulating evidence that CCL may be a putative precursor of lesion of low-grade invasive carcinoma. The association of CCL with tubular carcinoma and lobular carcinoma in situ has been reported in 100 % and 53 % of cases (Brandt et al. 2008). Brandt and colleagues termed this combination of tubular carcinoma, columnar cell

lesion and lobular carcinoma in situ as 'Rosen's triad' after Professor Rosen who first described the association (1999). CCL has been regarded as a 'missing link' between normal breast tissue and low-grade DCIS and low-grade invasive carcinoma (Simpson et al. 2005; Aulmann et al. 2009). Several studies have reported the presence of invasive carcinoma of 0–25 % in the subsequent surgical excision biopsies if a CCL is present in a needle core biopsy (Chivukula et al. 2009; David et al. 2006; Guerra-Wallace et al. 2004; Ingegnoli et al. 2010; Kunju and Kleer 2007; Martel et al. 2007).

In probably the largest study of columnar cell lesions using the unifying terminology by Schnitt and Vincent-Salomon (2003), Verschuur-Maes et al. (2011b) carried a retrospective study to the frequency of DCIS or invasive carcinoma in surgical specimens following the diagnosis of CCL in needle core biopsies. In the same study, the authors calculated risk of developing DCIS or invasive carcinoma in a 'wait and see' approach following the diagnosis of CCL in a needle core biopsy. Verschuur-Maes and colleagues (2011b) identified 311 women CCLs in 4,164 needle core biopsies in women aged between 25 and 85 years (mean age 51.7 years). The 311 CCLs consisted of 128 columnar cell change, 93 columnar cell hyperplasia (collectively CCLs without atypia), 69 CCL with atypia and 21 with ADH-CCL. In 52 out of 311 women with needle core biopsy diagnosis of CCL (N = 44) or ADH-CCL (N = 8), 51 women had ipsilateral excision biopsies; DCIS was identified in 9 (17 %) patients and invasive carcinoma in 7 (13 %) patients. On follow-up of these patients over a median period of 3.9 years, there was recurrent carcinoma after 2 years.

In the 'wait and see' group, there were 246 breasts with CCLs in 231 women and 13 breasts with ADH-CCL. The patients were followed up for 8 years. During the follow-up period, 19 surgical excision biopsies were performed between 5 and 51 months and nine invasive carcinomas were identified; six in the ipsilateral side and three in the contralateral breast. The chance of developing invasive carcinoma in the ipsilateral breast after diagnosis of CCL with atypia and ADH-CCL after 8 years follow-up was similar, approximately 16 %, whereas progression risk for CCL without atypia was very small at 2 %. On further analysis, the authors reported the RR of developing invasive carcinoma in the ipsilateral breast for CCL with atypia to be 19.9 (95 % CI 2.4–166.7; $p < 0.001$) and the RR for ADH-CCL, 25.3 (95 % CI 2.4–263.7; $p < 0.001$). The progression risk of CCL with atypia and ADH-CCL was similar at 2 % in the contralateral breast. When compared to CCL without atypia, RR for developing cancer in the contralateral breast with CCL with atypia was 4.4 (95 % CI 0.3–68.9; $p = 0.25$) and the RR for ADH-CCL was 13.5 (95 % CI 0.9–204.8; $p = 0.16$). When the invasive carcinomas of the ipsilateral and contralateral breasts were pooled together, the chance of developing carcinoma was 18 % for CCL with atypia and 22 % for ADH-CCL. The RR for developing cancer for CCL with atypia compared to CCL without atypia was 20.2 (95 % CI 2.4–169.1; $p < 0.001$) and the RR for ADH-CCL was 35.7 (95 % CI 39–324.9; $p < 0.001$). These RRs are quite high compared to those reported by Boulos et al. (2008) and Shaaban et al. (2002) who reported RR of 1.5 and 2.3, respectively. However the patients in these two studies had less than 8 years of follow-up; this may not be sufficiently long for the patients to develop malignancy.

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Mucocoele-Like Lesions

12

Learning Points

- MLLs are rare.
- MLLs have a wide age range of presentation from mid-20s to 70s.
- Most lesions are detected due to calcification on mammographic examination.
- The hallmark of MLL is the presence of cystic ducts with associated mucin extravasation into the stroma.
- MLLs can be associated with ADH, DCIS or mucinous carcinoma.
- There are no pathognomonic radiological features of MLL.
- All MLLs diagnosed on needle core biopsies require excision to exclude high-risk lesion.
- The risk of MLL of progressing to malignancy is unknown

12.1 Background

In 1986, Rosen described an entity he termed a mucocoele-like lesion (MLL) in six women aged between 26 and 61 years. Only one patient was postmenopausal. These lesions consisted of duct–lobular units that were dilated and distended with mucin, which extravasated into the surrounding stroma, reminiscent of salivary gland lesions. In five patients the MLL presented as a symptomatic mass, and in another patient it was an incidental finding in association with intraductal carcinoma. From his observations, Professor Rosen concluded that MLLs should be included in the differential diagnosis of mucinous carcinoma and the lesions in young patients should be treated with caution, as mucinous carcinoma is rare in this age group. The pathogenesis of MLLs is unclear. Breast epithelium secretes acid and neutral mucins, which are present in both benign and malignant lesions (Spicer et al. 1962). MLL most likely arises due to accumulation of mucin in the ducts and lobular units with resultant dilatations and subsequent leakage of the mucin into the surrounding stroma. Mucocoele-like lesion and mucocoele-like tumour are used interchangeably in the publications.

12.2 Clinical Features of MLLs

In the original description by Professor Rosen (1986), MLLs presented symptomatically due to the presence of a palpable mass in young women. In the subsequent published studies, it appears that when MLLs presented symptomatically, the lesions arise in young women. In the older women, MLLs are detected mammographically through the screening programmes and in most cases due to the presence of microcalcification (Davies et al. 1995). When MLLs occur in young women, the lesions tend to be benign.

Cheng and colleagues (2004) reviewed the cytological features of 20 aspirates of mucinous lesions. The aspirates revealed 12 mucinous

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_12, © Springer-Verlag Berlin Heidelberg 2014

carcinomas, two MLLs with atypical ductal hyperplasia, three MLLs with ductal hyperplasia and three simple MLLs. The average age of the eight women with MLL was 26.3 years (range 20–32), and the women with mucinous carcinoma had an average age of 51.5 years (range 34–75 year). Although the paper does not indicate the clinical presentation, it is most likely that the women aged 20–32 years with MLL presented symptomatically. In a separate Chinese publication, Ding and Yang (2008) also reported benign MLLs in nine women aged between 23 and 43 years of age with a mean age of 34 years. All nine women presented with clinically palpable lumps.

12.3 Radiological Features of MLLs

Since the first edition of this book, more data have been published on MLLs, albeit most of them are based on retrospective review of archival material on the clinical presentation, radiological and pathological features of MLLs. Most of the reported series are on mammographically detected MLLs. As MLLs are rare, most published series consist of relatively few patients. The rarity of the MLL is illustrated in the study by Glazebrook and Reynolds (2003) who set out to evaluate the mammographic and sonographic features of MLLs. They reviewed breast lesions in their department coded as mucocoele or mucocoele-like tumour between 1992 and 2001. This small number of patients may be attributed to the lack of recognition of the lesion by the pathologists. They identified only five patients in over 10,000 specimens. The patients were a 29-year-old woman who presented with a mass and 41-, 48-, 51- and 73-year-old women whose lesions were mammographically detected. In this small number of patients, the mammographic appearances of the mucocoele-like tumours included a well-defined nodule, irregular nodule, well-defined nodule with calcification, cluster of indeterminate calcification and pleomorphic calcification. The sonographic features included well-defined hypoechoic mass with central septation, cluster of complex cysts with calcification and tubular hypoechoic structures with low-level internal echoes. Three women had benign MLLs on histology of the excision biopsy, and two women had MLLs with ADH. Although the number of patients is small, this study illustrated the heterogenous radiological features of MLLs.

In a separate study of 12 patients from a New Zealand Breast Screening Programme (Ramsaroop et al. 2005), the authors also reported that mammographic features of MLLs were non-predictive. The mammographic features consisted of calcification (10 patients) mass only (two patients) and calcification and a mass (one patient). The pathology was reported as benign MLLs in five patients, MLL with ADH in a single patient, MLLs with DCIS or LCIS in three patients and MLL with invasive ductal carcinoma in a single patient.

The mammographic features of MLL were further analysed by Carkaci and colleagues (2011) when they reviewed the radiological and pathological features of 44 patients to determine whether excision is always warranted on the diagnosis of MLLs on needle core biopsies. In this study the most common mammographic appearance was calcification which was reported in 61 % (27/44) patients; 18 % (8/44) patients had a mass only; 16 % (7/44) had masses with associated calcification; and 2 (5 %) patients had mammographically occult MLLs which were detected on ultrasonography performed for other reasons. The author further analysed the pattern of the calcification and noted that the calcification of MLLs associated with DCIS was clustered/grouped coarse and heterogenous (two patients). Similarly, calcifications in MLLs without atypia were clustered/grouped and heterogenous (10 patients). In contrast, the calcification in MLLs with atypia was clustered/grouped, fine and pleomorphic (six patients). Although the authors applied the BI-RADS lexicon in assessing the lesions, they did not indicate which categories the MLLs fell into. However, as the patients had needle core

biopsies which prompted excision biopsies, therefore the mammographic abnormalities must have attained the threshold for biopsies, i.e. BI-RADS category 3 or above. In the same study by Carkaci and colleagues (2011), sonographic images were available in 17 patients and features included solid masses (seven patients), complex cysts (six patients) and negative ultrasound (four patients). Of the 13 patients with solid mass and complex cysts, four lesions had increased vascularity, another four lesions were avascular, eight lesions had posterior acoustic enhancement and four lesions had no posterior acoustic phenomenon. Although this study had more patients compared to other reported series, it just illustrates further that there are no radiological pathognomonic features of MLLs.

In an attempt to classify the MLLs according to BI-RAD5 criteria, Kim and colleagues (2011) retrospectively reviewed 72 MLLs in 68 women identified over a period of 10 years. They reported that calcification of indeterminate concern or higher probability of malignancy was more frequently present in MLLs with ADH or MLLs with malignancy than in pure MLLs (24/26 [92 %] vs. 17/27 [62.9 %]; $p=0.019$). The calcification was more frequently clustered or segmental. At ultrasound 69 of the MLLs (95.8 %) were present as cystic masses. Cysts with thick septations, clustered cysts and complex masses were more frequently seen in MLLs associated with ADH or malignancy than in pure MLLs (26/29 [89.7 %] vs. 13/40 [32.5 %]; $p=0.001$). Simple cysts, complicated cysts and cysts with thin septations were more frequently seen in pure MLLs than in MLL with ADH or malignancy (27/40 [67.5 %] vs. 3/29 [10.3 %]; $p<0.001$). When the lesions were analysed according to the BI-RADS category, one lesion was classified as category 2; seven, category 3; 60, category 4; and four, category 5. The positive predictive value for BI-RADS category 4 was 13.3 % (CI, 6.9–24.2 %) and for BI-RADS category 5 was 50 % (CI, 15–85 %). All MLLs with malignancy were classified as category 4 or 5. The authors concluded that BI-RADS assessment can be applied in the management of MLLs.

12.4 Pathological Features of MLLs

When the MLLs were first reported by Professor Rosen in 1986, the lesions were benign and presented symptomatically. As the pathologists become aware of the lesion, the spectrum of the disease is much broader and includes mucin-filled ducts, mucinous ADH and mucinous DCIS to frankly malignant lesions (Hemele-Bena et al. 1996). However, the concept of a malignant MLL is difficult to reconcile with the established morphology of mucinous carcinoma which consists of lakes mucin freely dissecting through the stroma. Is a malignant MLL mucinous carcinoma? If so, this is in conflict with the original definition MLL by Rosen which was a benign lesion.

Based on the images illustrated in Rosen's Breast Pathology (2009), a malignant MLL is classified as such if there is acellular extravasation of mucin into the stroma in association with DCIS and mucinous carcinoma.

Cystically dilated mucin-filled ducts are usually identified as an incidental lesions in a specimen excised for other breast condition as illustrated in the fibroadenoma containing mucin-filled ducts (Fig. 8.13). However, mucin-filled ducts are more often than not present in association with the classical benign MLL or in association with mucinous carcinoma. Figure 12.1 illustrates a spectrum of benign mucin-filled ducts, mucinous ADH, high-grade mucinous DCIS and malignant MLL, all of which were present in the background of mucinous carcinoma. Mucinous ADH has similar morphological features as conventional ADH, i.e. having features which fall short of the diagnosis of DCIS. The ADH can exhibit micropapillary or cribriform morphology. Morphologically mucinous DCIS exhibits a flat, papillary or cribriform pattern.

The classical MLL as described by Rosen is illustrated in Fig. 12.2 which was a screen-detected lesion due to the presence of calcification. There are multiple mucin-filled ducts lined by attenuated epithelium. The calcification exhibits a 'powdery' appearance, and extravasation of mucin is identified in the surrounding stroma.

12.5 Combined MLL and CLL

Increased awareness of MLLs and CCLs has led to reporting of these two lesions in the same specimen or in combination. A case report by Fadare and Mariappan (2008) in a 43-year-old women illustrates a typical MLL with cystically dilated units with associated mucin extravasation. Analysis of the lining of the ducts revealed features of CCL with atypia (flat epithelial atypia). In a separate study, Ohi et al. (2011) reported two lesions with combined CCL and MLL in 15 cases of MLL. In a larger study by Verschuur-Maes and Van Diest (2011) consisting of 4,164 needle core biopsies of the breast, the authors identified 291 CCLs and 21 ADH-CCL. Mucin was present in 17 of the 291 (5.8 %) of the CCL and in three of the

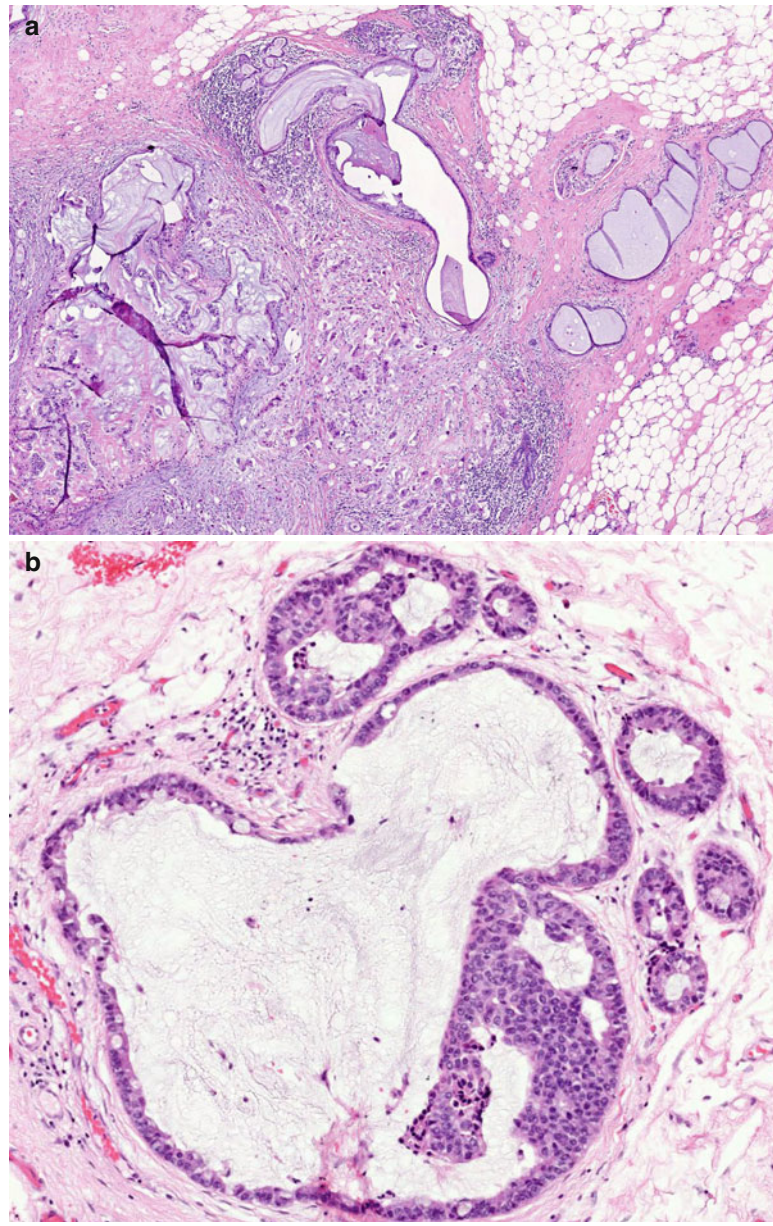


Fig. 12.1 (**a**–**d**) A spectrum of MLL-related lesions which were all present in the background of invasive mucinous carcinoma. (**a**) Benign mucin-filled ducts at the periphery of mucinous carcinoma. (**b**) Mucinous ADH has similar morphological features as conventional ADH, i.e. having features which fall short of the diagnosis of DCIS. (**c**) High-grade mucinous DCIS. (**d**) Malignant MLL showing acellular extravasation of mucin in association with invasive mucinous carcinoma. (**e**) Malignant MLL in association with DCIS. (**f**) Mucinous carcinoma consisting of lakes of mucin with floating mucinous carcinoma

Fig. 12.1 (continued)

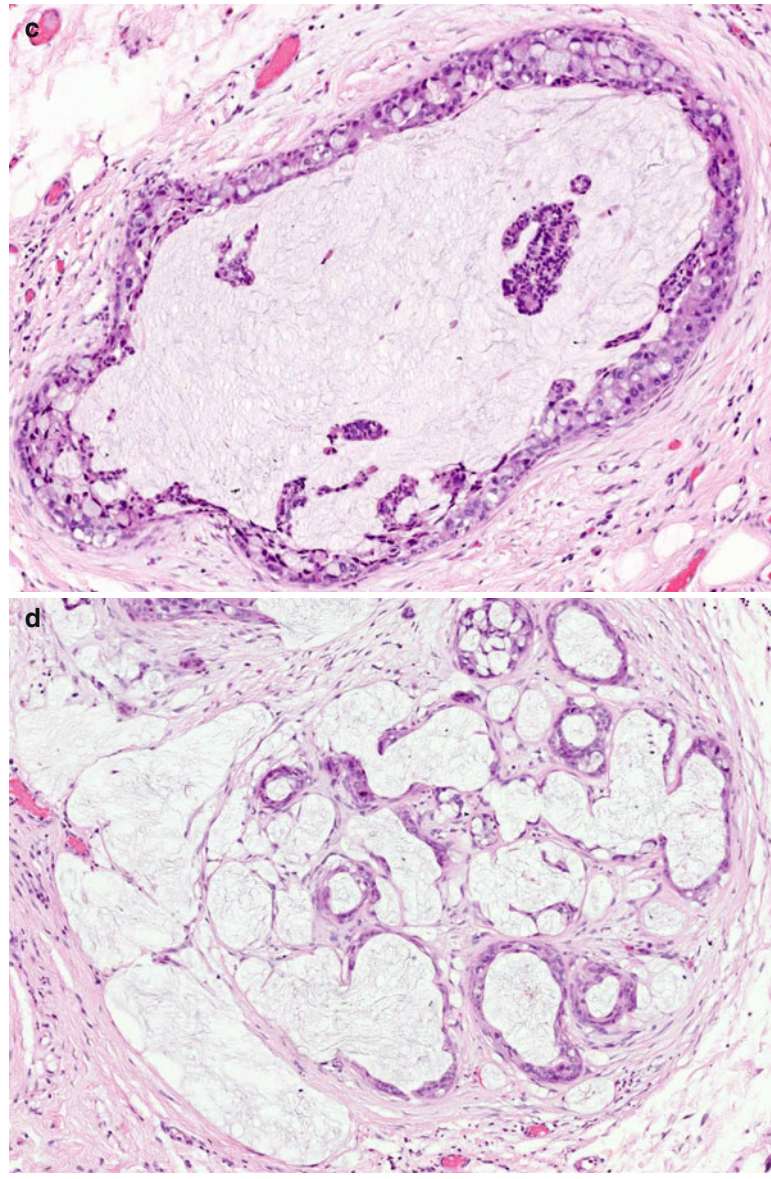
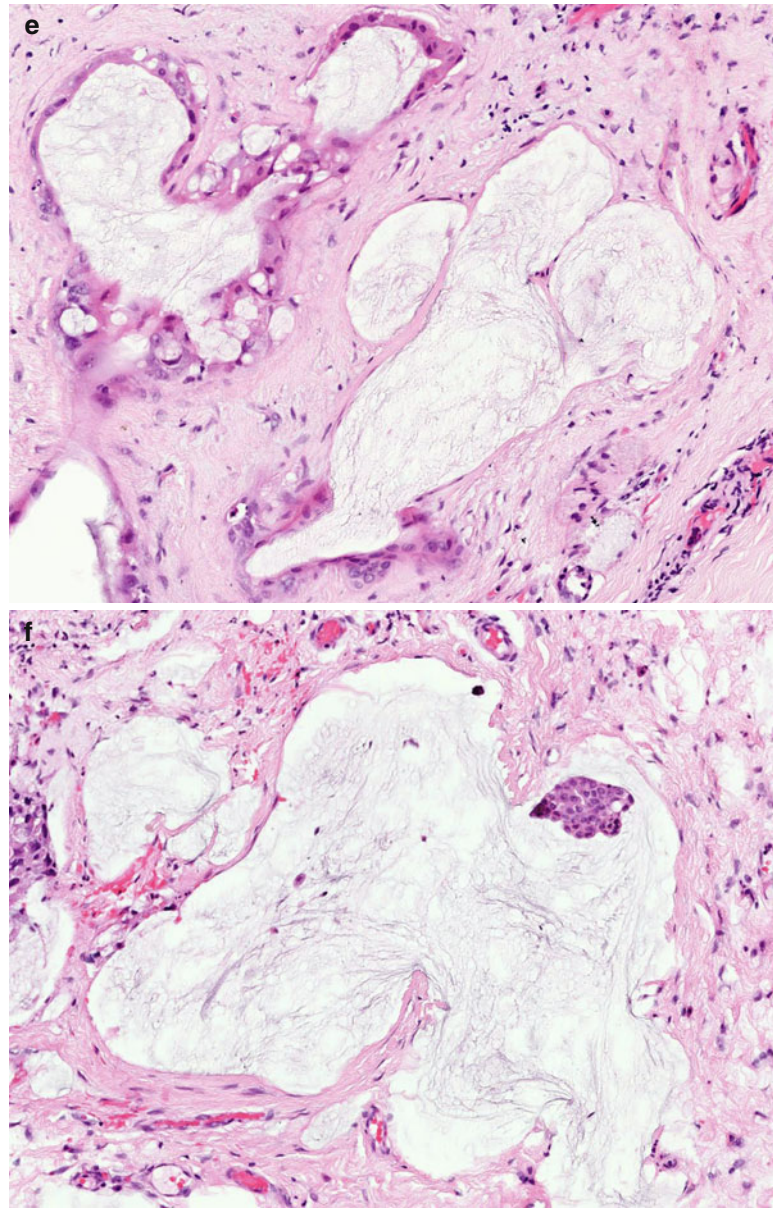


Fig. 12.1 (continued)



21 (14.3 %) of ADH-CCL collectively constituting 0.5 % of all the needle core biopsies. The most common pattern of mucinous CCL was columnar cell change without atypia which was detected mammographically due to the presence of microcalcification. During a median follow-up of 3.1 years, none of the patients developed DCIS or invasive carcinoma. The authors also noted that mucinous CCLs were significantly more common in association with 46 mucinous carcinomas than 46 ductal carcinomas (28 % vs. 9 %). The authors concluded that mucinous CCL are rare with a prevalence of 0.5 % in needle core biopsies of the breast and usually present with microcalcification. Although the lesions might play a role in the progression of mucinous lesions, the short-term progression to more advanced lesions was low.

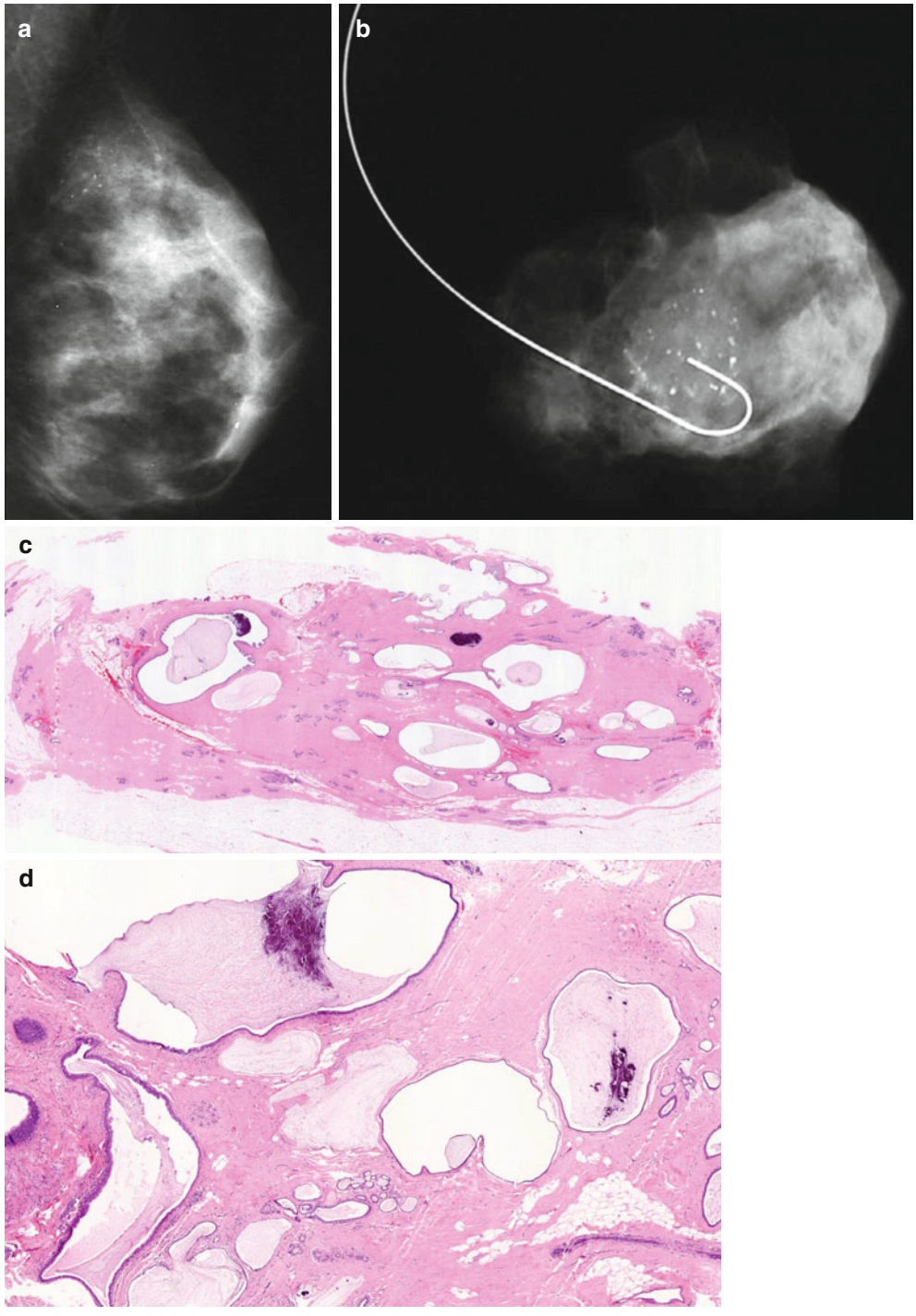


Fig. 12.2 (**a**) Screen-detected atypical microcalcification in a 55-year-old woman with features suspicious of DCIS (R4). (**b**) The specimen X-ray highlights the atypical nature of the calcification. The calcification is unusually ring shaped. (**c**) The whole-mount section of a mucocoele-like lesion shows multiple cystically dilated ducts, reminiscent of fibrocystic change. The radiological calcification is confirmed on histology. (**d**) Medium-power magnification to highlight the mucin-filled ducts. The calcification exhibits a rather powdery appearance. (**e**) The ducts are lined by attenuated epithelium, and a collection of 'naked' mucin in the stroma indicates extravasation diagnostic of benign MLL. (**f**) Periodic acid–Schiff stain and diastase (PAS-D) highlights the presence of neutral mucins within the mucin-filled ducts, including the focal extravasation

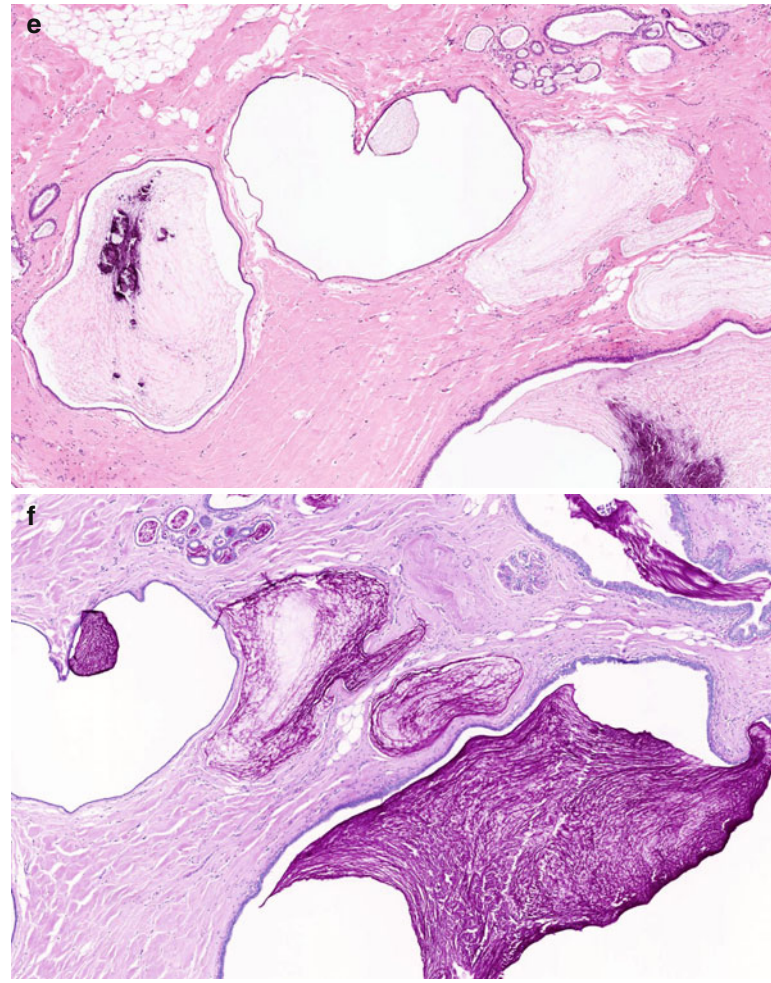


Fig. 12.2 (continued)

Concurrent CCH with atypia (FEA) and MLL is illustrated in Fig. 12.3. In a different field of the case illustrated in Fig. 11.1, there was a distorted and TDLU showing combined features of CCH with atypia and MLL. The mucin-filled ducts are lined by hyperplastic cells with luminal snouts.

12.6 Management of MLLs Diagnosed on Needle Core Biopsies

Carkaci and colleagues (2011) reviewed the radiological and pathological features of 44 patients to determine whether all MLLs diagnosed on needle cores require surgery. The mean age of the patients was 56 years (range 35–76 years). Sixteen patients had MLL diagnosed by needle core biopsy or fine needle aspiration cytology followed up by excision biopsy. Eighteen patients with a diagnosis of MLL on needle core biopsy had no surgical excision but were followed up clinically with imaging. Ten patients had MLL diagnosed on surgical excision without percutaneous biopsy or FNAC. When they analysed the pathology, 29 (66 %) of patients had MLL without atypia; 10 (23 %) of patients had MLLs associated with ADH and 5 (11 %) of patients had MLLs associated with DCIS. In three out of 16 (19 %) patients with MLL and ADH on needle core biopsy, the lesions were upgraded to DCIS. The authors concluded that surgery was warranted to exclude coexisting carcinoma in situ or carcinoma in specific situations

where needle core biopsies detect ADH or where a mass with indistinct or irregular margins is demonstrated on mammography or sonography.

As there are no specific radiological features of MLL, the above view is in variance with other studies which recommend surgical excision following diagnosis of MLL on needle core biopsy. In a study of 45 patients, Jaffer et al. (2011) evaluated the necessity to excise benign MLL diagnosed on needle core biopsies. All 45 patients had undergone excision biopsies. Most of the excisions had no residual mucocoele (37/45 = 82 %). In seven cases (15 %), atypical ductal hyperplasia was present, three with residual MLL. Radiological–pathological correlation was concordant in all cases except one

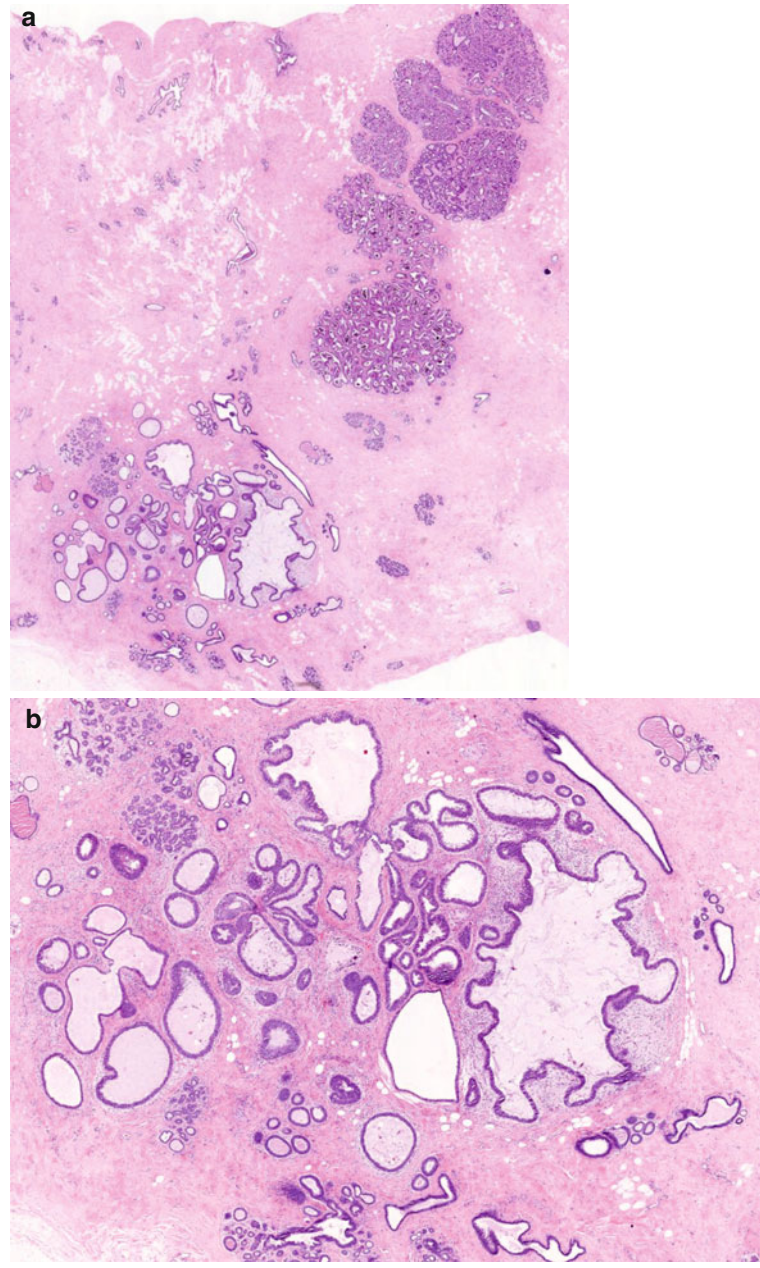
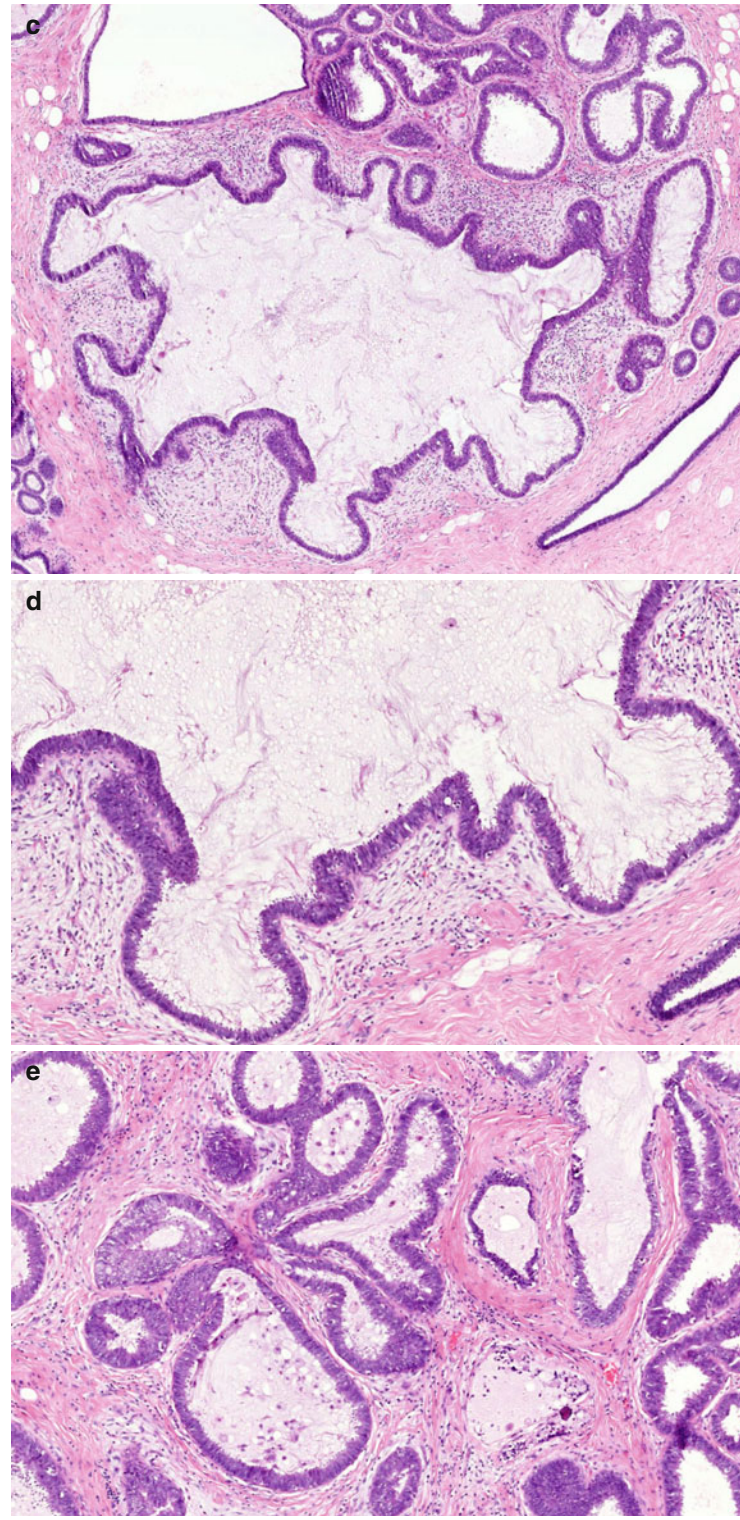


Fig. 12.3 (**a**) Low magnification of the CCL illustrated in Fig. 11.1 (*right* hand *corner*) and mucin-filled cystically dilated TDLU. (**b**) The enlarged TDLU consist of cystically dilated mucin-filled ducts with associated epithelial hyperplasia. (**c**) The mucin in the ducts at higher magnification. (**d**) The ducts are lined by atypical hyperplastic cells with apical snouts. (**e**) This field shows focal mucin extravasation diagnostic of MLL

Fig. 12.3 (continued)



case with suspicious calcification which showed ductal carcinoma in situ on excision. The overall upstage of benign MLL on needle core biopsy was 17.8 %. Because there are no radiological features which are predictive of atypia, and associated intra-lesional heterogenicity, Jaffer and colleagues recommended excision of benign MLL diagnosed on needle core biopsies. In the same study, Jaffer and colleagues reported that MLL affected older women as the lesions were detected due to microcalcification.

Carder and colleagues (2004) also recommend excision of MLL diagnosed on needle core biopsy following reporting of two cases of DCIS and one case of mucinous carcinoma of 10 patients who had undergone excision biopsy following diagnosis of MLL on needle core biopsy. However, in a review of 54 core biopsies of MLLs without atypia which were managed as B3 lesions, Rakha et al. (2013) identified only two low-grade cancers (4 %); and review of the literature in the same publication identified four cancers out of 106 MLLs without atypia. If there is atypia in the MLL, the yield of malignancy is up to 21 %. The authors concluded that the risk of malignancy is low after a core biopsy showing MLL without atypia, but much higher if there is atypia. They emphasise the importance to search for atypia by examination of multiple levels. The authors suggested that if no atypia is present, excision with a vacuum-assisted device after multidisciplinary team discussion may be a reasonable alternative to surgical excision.

12.7 Biological Significance of MLLs

Based on numerous case reports (Ro et al. 1991; Lee et al. 2001; Zhao et al. 2002) and routine pathological observations, there is a growing body of evidence that MLLs are possible precursors of mucinous carcinoma. Chinyama and Davies (1996) reviewed 962 breast cancers and 335 benign lesions and identified 38 (3 %) cases of mucin-filled ducts/MLLs. Twelve MLLs were screen detected, 11 of these on the basis of mammographic calcification. Histologically the calcification exhibited a predominantly amorphous pattern, but psammomatous and sandy-like features were also present. Mucin extravasation was noted in all screen-detected lesions, and calcification of the extravasated mucin was not uncommon. Mucinous atypical ductal hyperplasia (ADH) was present in eight of the 12 screen-detected MLLs without overt malignancy. Other epithelial proliferations associated with these lesions included radial scar, sclerosing adenosis, fibrocystic change, non-mucinous ADH and lobular carcinoma in situ. Incidental MLLs and other benign mucin-filled ducts were identified in 16 cases of ductal carcinoma (three ductal carcinoma in situ (DCIS), 13 invasive). In the same series, mucin-filled ducts with or without calcification, mucinous atypical hyperplasia and low-grade mucinous DCIS were identified in 12 patients with mucinous carcinoma, suggesting a continuum of the same disease process. In six mucinous carcinomas, amorphous calcification with a similar histological appearance to the MLLs was identified. Mucin-filled ducts and MLLs were more likely to be identified in screen-detected lesions than in symptomatic lesions. In addition, there was a high prevalence of mucinous ADH in screen-detected lesions. Based on previous studies, ADH is a known risk factor for subsequent malignancy (Page et al. 1985). The study by Chinyama and Davies highlighted a spectrum of mucin-filled ducts and MLLs in screen-detected lesions, ductal carcinoma of no special type and pure mucinous carcinoma, which may have a bearing on the incidence of mucinous carcinoma. Coincidentally, screen-detected MLLs constituted 3.9 % (25/646) of screen-detected lesions, which mirrored the prevalence of mucinous carcinoma of 4 % (24/599) in the symptomatic cancers.

In a separate study, Weaver et al. (1993) also demonstrated a spectrum of mucin-filled ducts in association with 23 mucinous carcinomas as follows: 15 cases with unremarkable epithelium, nine cases with typical ductal hyperplasia, five cases with ADH and 13 cases with mucinous intraductal carcinoma. In 18 mucinous carcinomas, five carcinomas had all four different types of mucin-filled ducts present. These observations

also support the notion of mucinous lesions representing a continuum of the same disease process. Ductal carcinoma associated with the mucin-filled duct and mucinous carcinoma tends to exhibit micropapillary or cribriform morphology (Chinyama and Davies 1996; Hamele-Bena et al. 1996; Weaver et al. 1993). Although the mucin-filled ducts are more prevalent in mucinous carcinomas, they can also be identified in ductal carcinoma of no special type and other benign lesions (Chinyama and Davies 1996; O'Connell et al. 1998; Weaver et al. 1993). This could explain the source of mixed carcinomas.

On a molecular level, O'Connell et al. (1998) demonstrated increased expression of MUC2 and MUC5 mRNA in mucinous carcinoma and associated mucin-filled ducts with epithelial hyperplasia without atypia, ADH and DCIS, indicating a field change in the mucinous lesions. Previously, Chinyama et al. (1996) had demonstrated the expression of MUC2 mRNA in mucinous carcinoma and mucinous atypical hyperplasia using isotopic in situ hybridisation. MUC6 and MUC7 mRNAs were also expressed in some mucinous carcinomas. MUC5 was reported in only 4 (6 %) of 66 non-mucinous ductal carcinoma indicating that it was specific for mucinous carcinoma (Schmitt et al. 1999).

Although it is generally believed that MLLs are possible precursors of mucinous carcinoma based on the presence of mucin-filled ducts, mucinous ADH, mucinous DCIS and mucinous carcinoma in the same lesion (Weaver et al. 1993; Chinyama and Davies 1996), there are no long-term studies which have assessed the risk of progression to malignancy on diagnosis of benign MLL or the presence of incidental mucin-filled ducts.

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Calcification in Benign Lesions 13

Learning Points

- Calcification in some benign lesions such as oil cysts and of vascular origin has pathognomonic features.
- Most calcifications reported in benign lesions are mammographically indeterminate.
- In some cases calcification can differentiate benign from malignant lesions.
- Breast calcifications consist of calcium phosphate or calcium oxalate.
- Calcium oxalate is usually present in benign lesions and is a cause of absent calcification on microscopy and requires polarising light.
- Calcium phosphate is more prevalent than calcium oxalate.
- Calcium phosphate is found in both benign and malignant lesions.

13.1 Overview of Mammographic Calcification

When Leborgne described the presence of calcification in breast cancer in 1951s (Leborgne 1951), he concluded that, with sufficient experience, it was easy to differentiate between benign and malignant calcification. This view was supported by Egan (1964), who stated that 'The typical calcifications are so pathognomonic of carcinoma. They are so specific that in their presence, a histologic diagnosis of benign disease usually indicates that either the surgeon has selected the wrong tissue for biopsy or the pathologist is in error'. However, Egan later conceded that although calcifications provide clues to estimate the risk of carcinoma, the signs are so 'nonspecific' that all radiologically demonstrable clusters of stippled calcification require histological examination (Egan et al. 1980). This latter statement is in keeping with the view of most radiologists, in that, although there are some pathognomonic features of benign or malignant calcification, there are a considerable number of indeterminate calcifications that require further investigation and subsequent biopsy to exclude malignancy.

Microcalcification occurs in luminal secretions, necrotic debris within the stroma in association with degenerative conditions, scar tissue, foreign bodies or lymph nodes. Because of the heterogeneous appearance of the calcification, it is not always possible to confidently confer a diagnosis of benignity, unless the calcification is overtly vascular or within an oil cyst. Features that indicate benign calcification include: isolated round calcification, scattered punctate calcification as seen in sclerosing adenosis or 'teacup' calcification of microcysts (Heywang-Köbrunner et al. 2001; Lanyi 1986). Calcification with a lobular pattern is also generally associated with benign breast disease. Solitary, diffuse distribution throughout the parenchyma or symmetrical distribution also suggests benign calcification. Lucent-centred calcifications also

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Table 13.1 Morphological features associated with benign calcification

Morphological features of calcification	Associated lesions
Shell-like calcification around a soft tissue density	Fibroadenoma, papilloma, oil cyst, foreign body reaction, e.g. silicone implant
Granular	Fibroadenomatoid hyperplasia, stromal calcification
Round calcifications with or without central radiolucency	Scars, fat necrosis, duct ectasia
Coarse, popcorn-like or bizarre	Fibroadenoma, papilloma
Coarse, needle-like +/− branching	Duct ectasia, scars, may be difficult to exclude ductal carcinoma in situ
Parallel/serpentine	Vascular
Teacup phenomenon	Fibrocystic change
Rosette-like/morula-like clusters, usually multiple and symmetrical	Microcystic/blunt duct adenosis
Widespread ill-defined/ punctate	Involuted breast

denote benignity. These are usually seen in fat necrosis, calcified debris in ducts and occasionally in fibroadenomas (American College of Radiology 1998). Table 13.1 summarises some of the different patterns of benign calcification and related lesions.

The nature of indeterminate calcifications can be confirmed only on histology, and this can exhibit either a psammomatous or an amorphous pattern. Both patterns of calcification are also associated with low- and high-grade ductal carcinoma in situ (DCIS), respectively, which could explain the indeterminate mammographic appearance.

The different patterns of calcifications are illustrated in the previous chapters in relation to specific conditions. However, it is important to reiterate that calcification in benign breast disease elevates the risk of malignancy to a higher level than if calcification was not present. In Dupont and Page's (1985) report on benign proliferative disease, women with atypical hyperplasia had a relative risk of 4.4, and this increased to 6.5 if calcification was present. Although this study was on symptomatic women with benign disease, most atypical hyperplasias are usually associated with mammographic calcification. In a separate study on post-mortem tissue, Bartow et al. (1990) reported a high prevalence of increased breast density, microcalcification and epithelial hyperplasia in women aged 35–49 compared with women over 50 years. However, the association was not statistically significant ($P \geq 0.07$).

13.2 Assessing Microcalcification

The presence of mammographic calcification is an important feature, which indicates underlying pathology within the breast tissue. Only 30–40 % of breast calcifications are malignant, the remainder being benign (Heywang-Köbrunner et al. 2001). The pattern of distribution and the size, shape and density of the calcification assist the radiologist in deciding whether a calcifying lesion is benign or malignant (Sickles 1986). Ultrasonography and magnetic resonance imaging have limited value in assessing calcifications.

Mammographic calcifications more than 2 mm in maximum dimensions are termed macrocalcifications and those smaller than 1 mm, microcalcifications (Bun 2002). Involutional calcification in lobules tends to be elusive and difficult to identify mammographically. These calcifications are small, round and multiple, with a powdery appearance, and tend to be spread over a large area. Secretory calcifications are also small and multiple. Although these patterns of calcification can be detected mammographically in isolation or as part of sclerosing adenosis, the calcification is frequently identified on histology the breast tissue excised for unrelated pathology. It is important to accurately compare the mammographic and histological features in screen-detected calcification to ensure that the features in the histological sections represent the mammographic lesion. The presence of histological calcification in a needle core does not necessarily indicate appropriate sampling (Fig. 13.1).

Grunert and colleagues (2001) investigated whether fourfold magnification mammography (direct magnification) was a superior technique

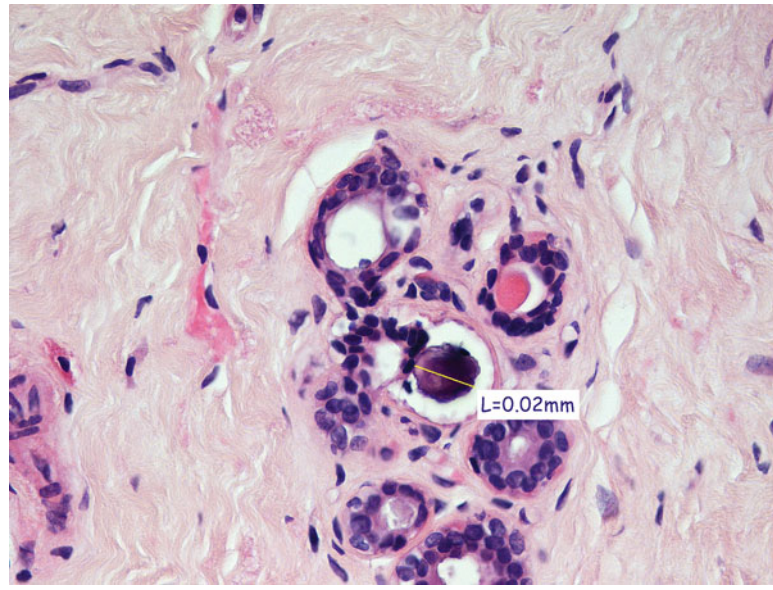


Fig. 13.1 Isolated microcalcification in TDLU was not the part of the targeted radiological lesion. The microcalcification was too small to be detected mammographically, and the biopsy was reported as B1

in differentiating benign from malignant calcification compared with conventional 1.5-fold magnification mammography. Five experienced radiologists assessed the pattern of mammographically detected calcification in 50 patients. The specificity and sensitivity of the two techniques were analysed using the receiver operating characteristics curve. Direct magnification was slightly but not significantly better than the conventional method in detecting malignancy ($P > 0.05$). Coarse, granular and pleomorphic microcalcifications were detected more frequently with direct magnification than with conventional magnification. Granular microcalcifications were more likely to be malignant, whereas a coarse pattern was associated with benign disease. Higher magnification did not significantly increase the yield of malignant disease based on the pattern of calcification.

13.3 The Nature of Breast Calcification

The two main types of breast calcification are composed of calcium oxalate or calcium phosphate. Calcium phosphate is the predominant component in both benign and malignant breast disease. To assess the chemical nature of microcalcification, Frappart and colleagues (1984) carried out a detailed analysis of calcification found in benign and malignant breast disease using light microscopy, transmission and scanning microscopy, microprobe analysis and X-ray diffraction. They extracted mammographically detected microcalcifications from 25 freshly excised specimens. Histologically, the specimens consisted of eight benign lesions, three in situ lobular carcinomas, four intraductal carcinomas and ten invasive carcinomas. The investigators identified two types of calcification. Calcium oxalate (type I) calcification was of crystalline nature, generally found within the breast parenchyma and difficult to extract. On microscopy, these microcalcifications were amber in colour and had a birefringent pattern under polarising light. On scanning microscopy, this form of calcium was pyramid shaped, and the calcium oxalate (weddellite) crystals were confirmed on X-ray diffraction. In contrast, calcium phosphate (type II) was noncrystalline and microscopically more voluminous than calcium oxalate. Calcium phosphate was non-birefringent, showed ovoid or fusiform shapes and was present in four benign lesions and 15 malignant lesions (ten invasive, five in situ). Calcium oxalate (weddellite) was present in four benign breast diseases and lobular carcinoma in situ, but not in DCIS or infiltrating

carcinoma. One case of mixed in situ lobular and ductal carcinoma contained both calcium oxalate and calcium phosphate. From this study the authors concluded that there was no typical 'benign or malignant' calcification in terms of chemical composition. However, calcium oxalate is more likely than calcium phosphate to be associated with benign breast disease such as apocrine cysts, dilated ducts and mastopathies. These observations were confirmed in a follow-up study by the same authors when they reported the presence of weddellite crystals in 11 out of 21 benign lesions (Frappart et al. 1986). Calcium oxalate crystal formation requires slow diffusion aided by the ability of the mammary epithelium to concentrate calcium ions from the milk. In contrast, calcium phosphate crystals tend to evolve more rapidly in areas of cellular necrosis in either benign or malignant lesions, and this is termed dystrophic calcification which exhibits an amorphous appearance (Figs. 13.2 and 13.3).

Although some patterns of benign calcifications can be diagnosed confidently on radiology, most of the lesions that are excised and turn out to be histologically benign are a result of indeterminate calcification. Granular or amorphous calcification is usually associated with high-grade DCIS, whereas laminated or psammomatous calcification is associated with low-grade DCIS (Foschini et al. 1996). Psammomatous calcification is related to luminal proteinaceous secretions in both low-grade DCIS and benign disease (Fig. 13.4).

Calcium oxalate is the most common cause of 'absent' mammographically detected calcification on histology (Fig. 13.5). The crystals do not stain with haematoxylin and eosin, von Kossa stain or alizarin red and require polarising microscopy for identification. Pretreatment of the sections with silver nitrate/rubeanic acid with 5 % acetic acid has been reported to highlight the calcium oxalate crystals (Tornos et al. 1990). Gonzalez et al. (1991) reported a predominance of calcium oxalate crystals in fibrocystic change with apocrine epithelium, supporting the concept that this is a form of secretory calcification. In this study, Gonzalez and colleagues identified 16 cases of apocrine metaplasia out of 119 breast biopsies. The cases with apocrine showed polarising calcium oxalate, which was absent in invasive carcinoma.

To determine whether an excisional biopsy could be avoided in patients with histologically proven calcium oxalate calcification, Winston and colleagues (1993) carried out a retrospective radiological and pathological study on 55 patients who had undergone excision biopsies for abnormal calcification. Forty-one of the

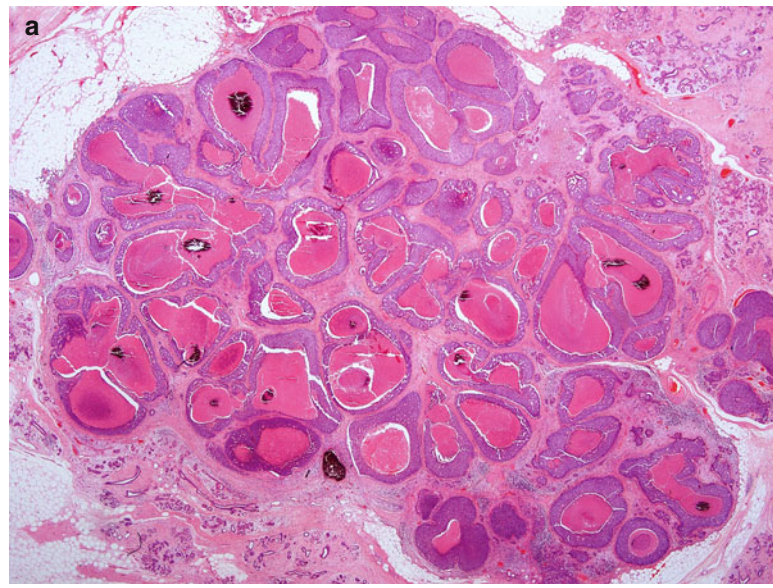
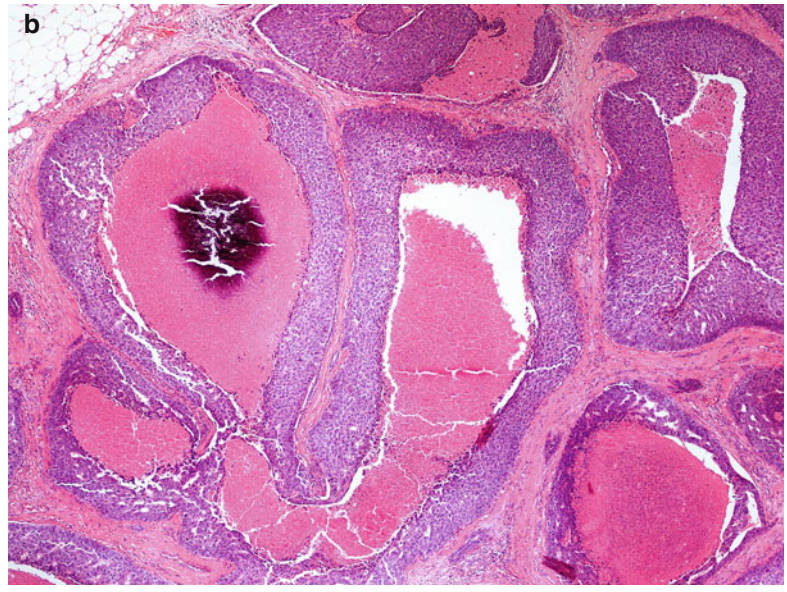


Fig. 13.2 (**a**) High-grade DCIS with widespread necrosis and amorphous dystrophic calcification. (**b**) High magnification to illustrate amorphous dystrophic calcification

Fig. 13.2 (continued)



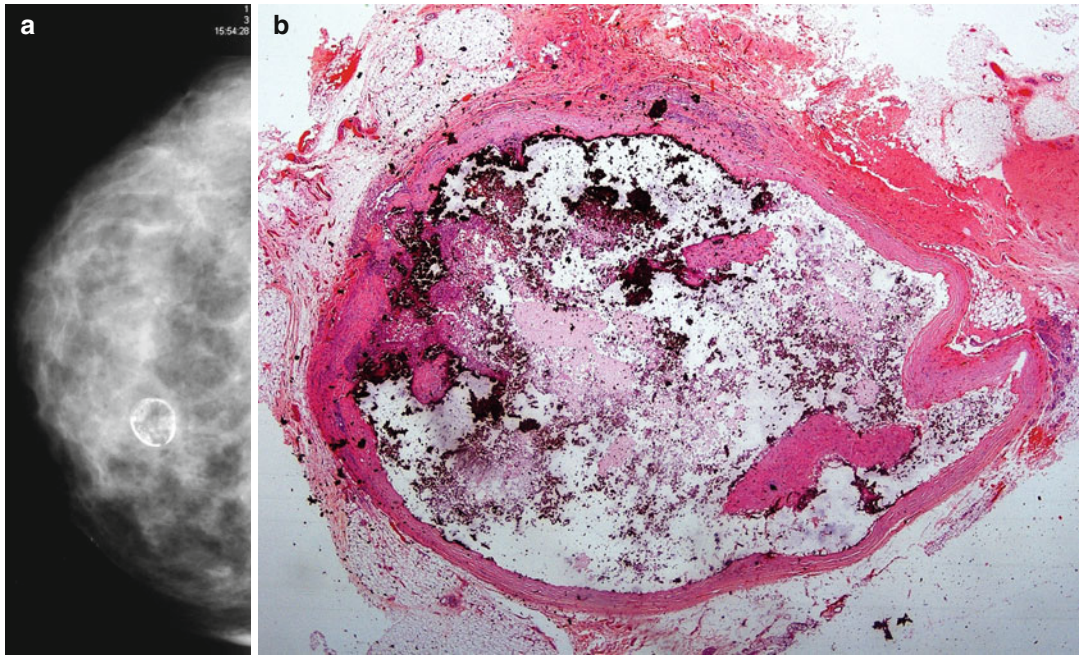


Fig. 13.3 (**a**) The mammogram shows a ring of calcification due to previous fat necrosis in a patient who presented symptomatically. (**b**) The histology shows a fibrous wall surrounding amorphous dystrophic calcification. (**c**) Higher magnification highlights the amorphous dystrophic calcification

Fig. 13.3 (continued)

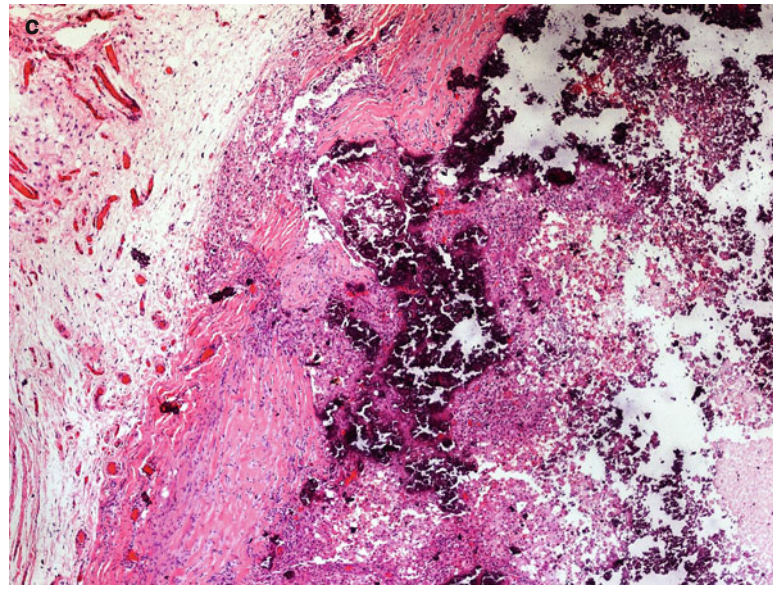
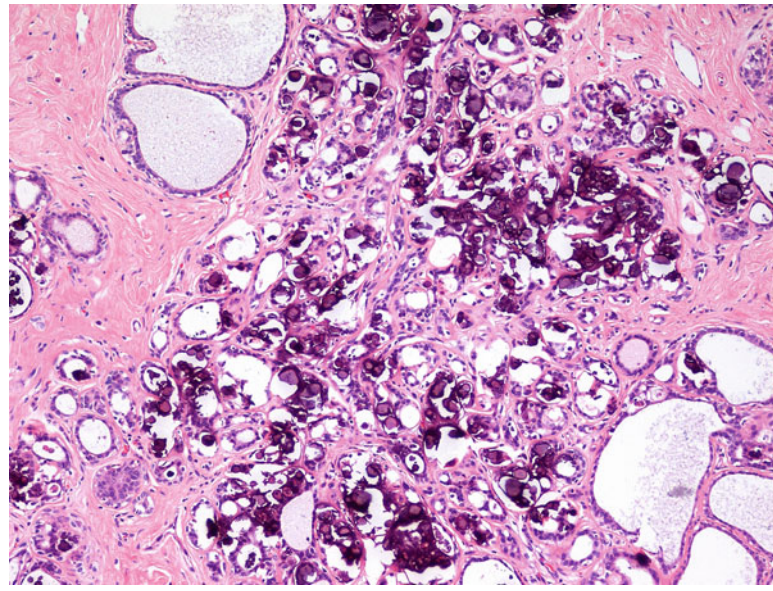


Fig. 13.4 Psammomatous microcalcification usually presents in benign lesions such as sclerosing adenosis



lesions contained calcium phosphate, eight contained calcium oxalate only and six had both forms of calcification. When calcium oxalate was present in isolation, the associated lesion was benign. Radiologically, calcium phosphate had a medium- to high-density appearance, whereas calcium oxalate had an amorphous, low- to medium-density appearance. Other low-density patterns of calcifications were also associated with benign epithelium. The authors suggested that it was feasible to manage patients with low-density microcalcification conservatively, as some of this could be calcium oxalate. However, the number of patients with this pattern of calcification was too small for clinical application.

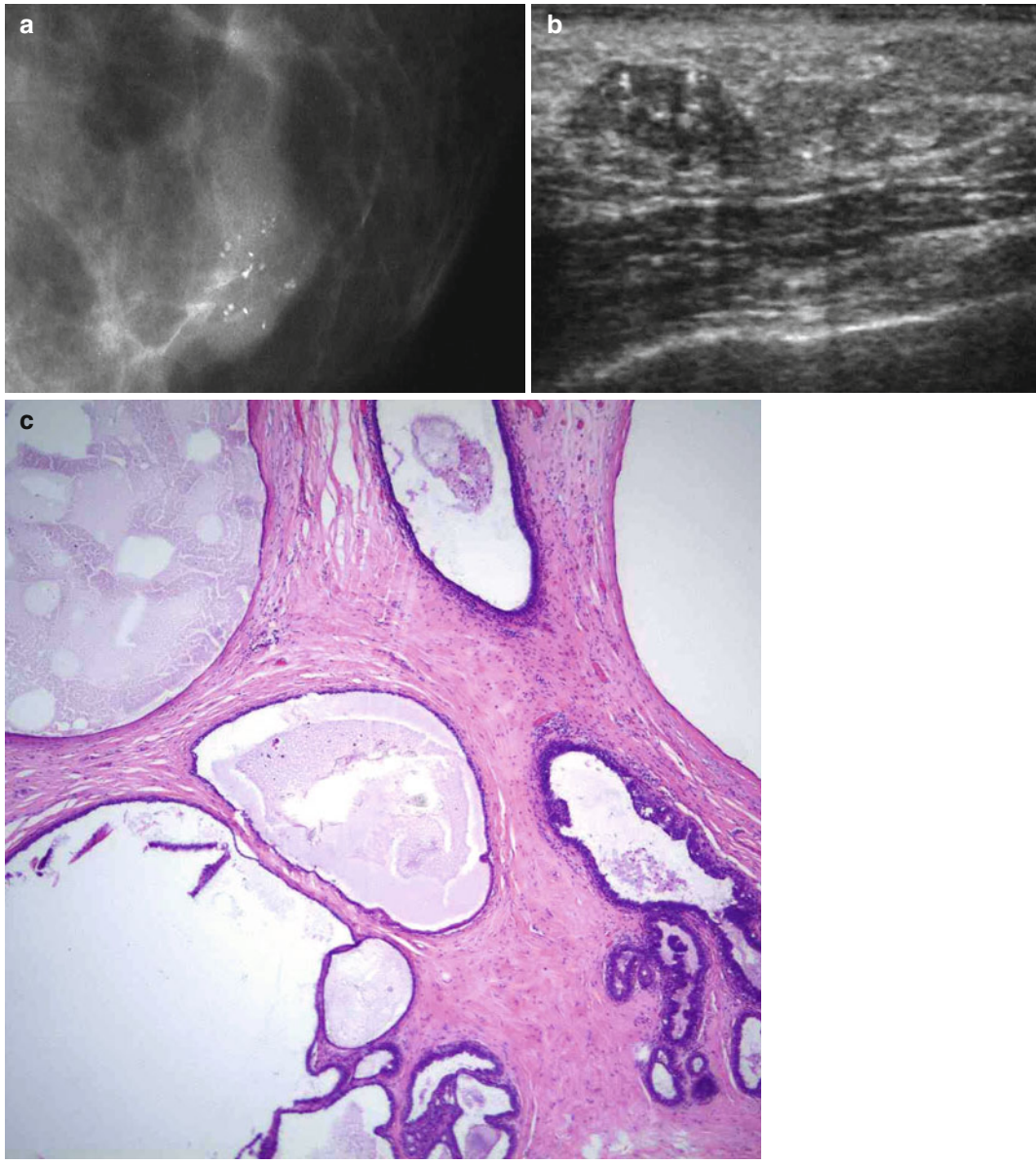
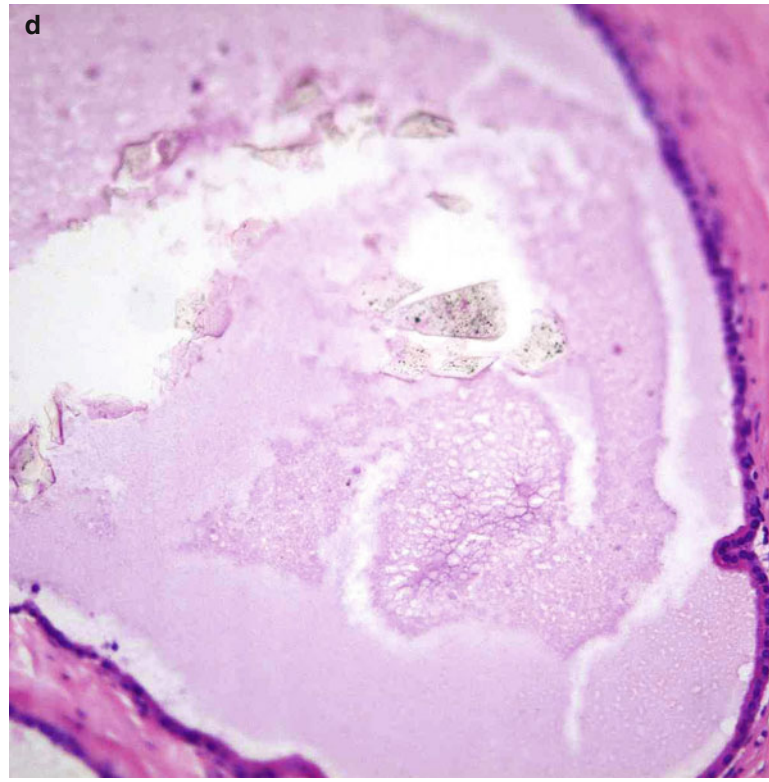


Fig. 13.5 (**a**) Magnified focus of mammographically detected tissue density associated with calcification in a 54-year-old woman. (**b**) Ultrasound shows a cystic lesion with foci of calcification. (**c**) The histology shows fibrocystic change with ducts lined by attenuated epithelium. The calcification is not histologically apparent. (**d**) At high magnification, irregular 'colourless' fragments of calcification (weddellite) can be seen in the lumen of the cyst. (**e**) Polarising microscopy highlights refractile calcium typical of weddellite (calcium oxalate). This is a common cause of lack of microcalcification in biopsies if the pathologist does not use polarising light. (**f**) The dilated duct contains the type of secretions that would crystallise to weddellite. Usual ductal hyperplasia is present in the background. (**g**) A different case of calcium oxalate with colourful display on polarising microscopy

Fig. 13.5 (continued)



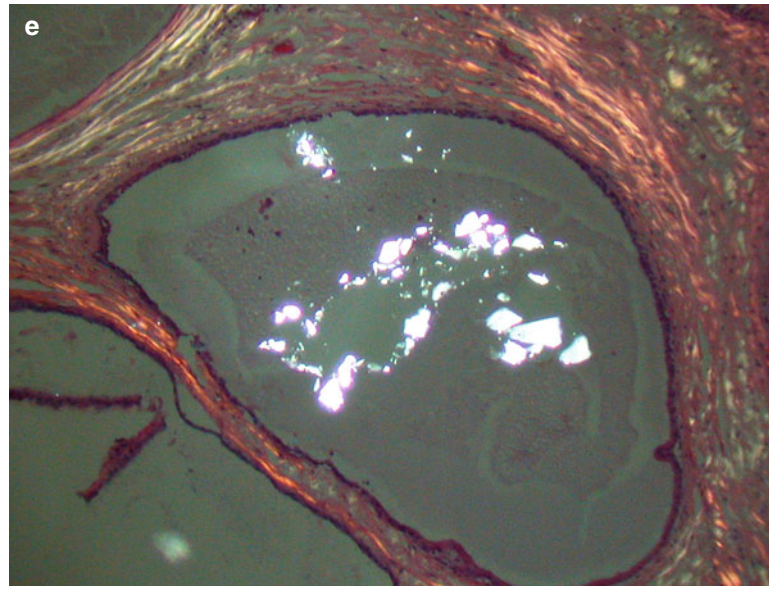
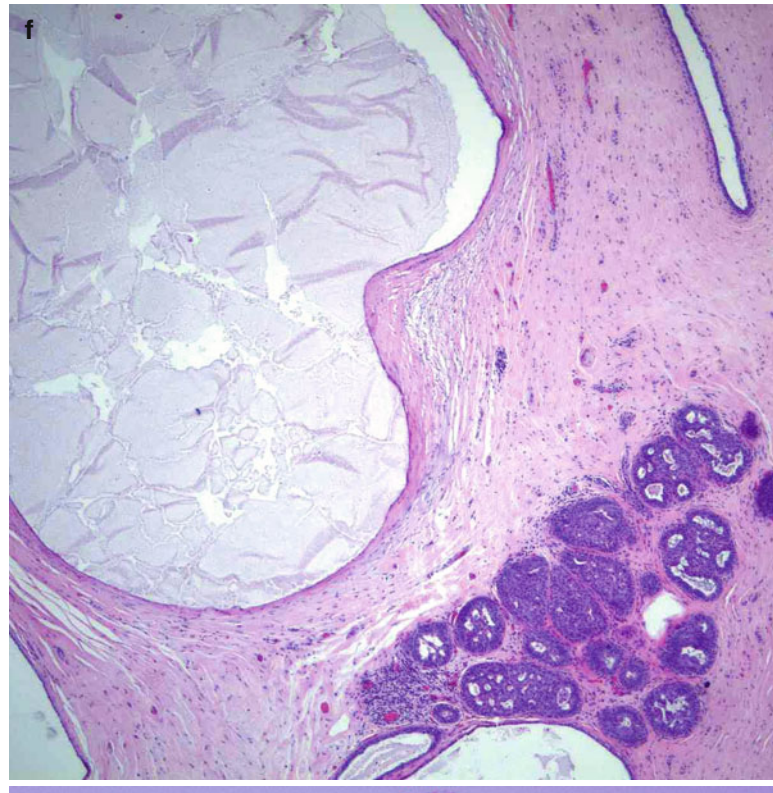
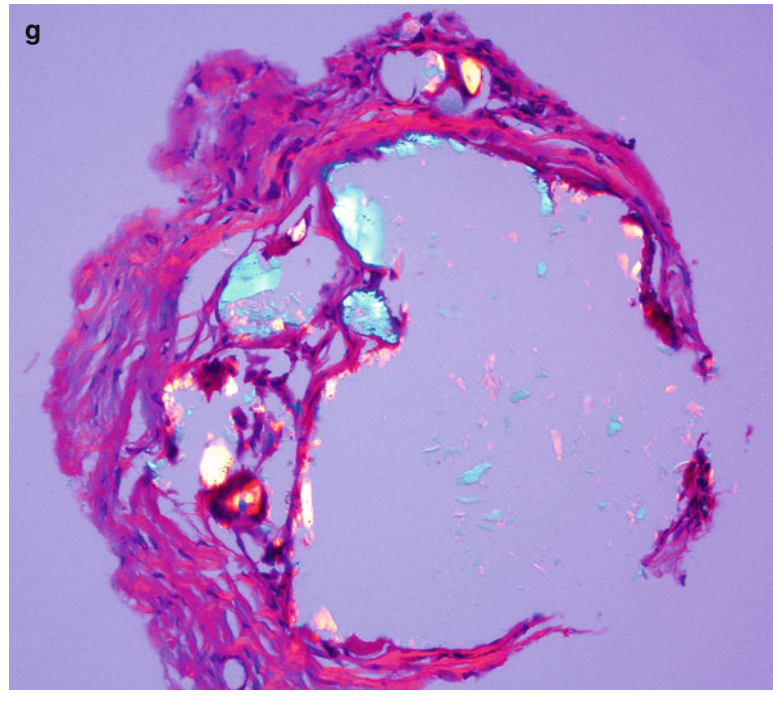


Fig. 13.5 (continued)





13.4 Vascular Calcification

Vascular calcification is one of the easily recognised forms of breast calcification. Also termed Monckeberg's calcification, this process can affect other arteries in the body. Breast arterial calcification is a degenerative age-related change most common in old women (Nielsen and Holm 1985). Mammographically, arterial calcification characteristically exhibits tram-like serpentine patterns and tends to be bilateral (Fig. 13.6). The calcification affects the media of the artery (Fig. 13.7).

Diabetes mellitus and hyperlipidaemia have been reported with high prevalence in women with breast arterial calcification (Moskowitz and Verani 1976). Breast arterial calcification has been associated with increased risk of cardiovascular mortality in women over 50, especially if these women had concomitant diabetes mellitus (Kemmeren et al. 1998). Separately, Leinster and Whitehouse (1987) found that there was no association of breast calcification with systemic hypertension, and hormone replacement therapy appeared to lower the incidence of calcification. Metastatic breast calcification as well as vascular calcification has also been reported in patients on renal dialysis (Evans et al. 1992).

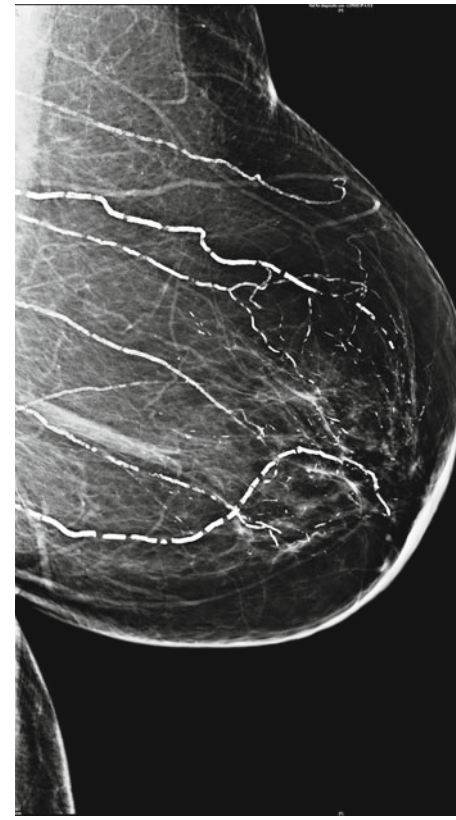


Fig. 13.6 Typical serpentine vascular calcification in a 69-year-old woman. The mammogram was otherwise normal

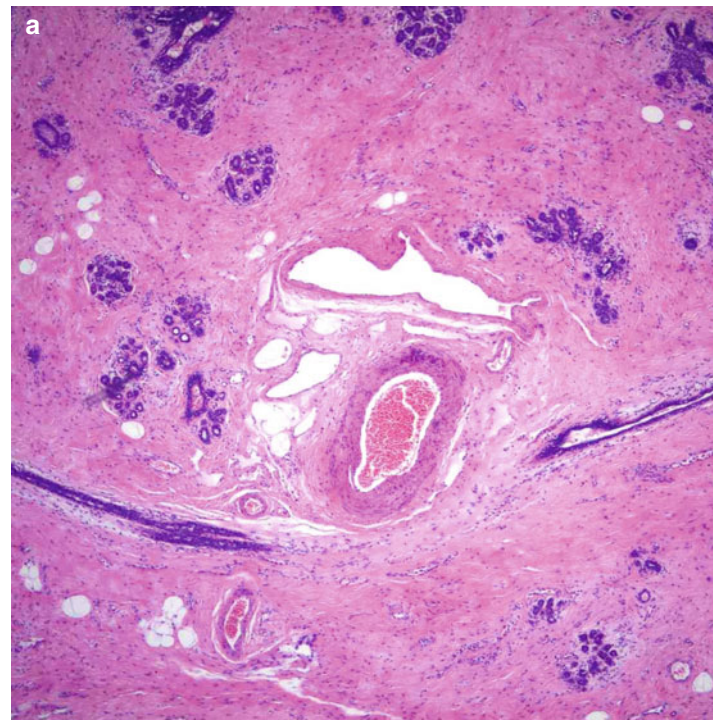
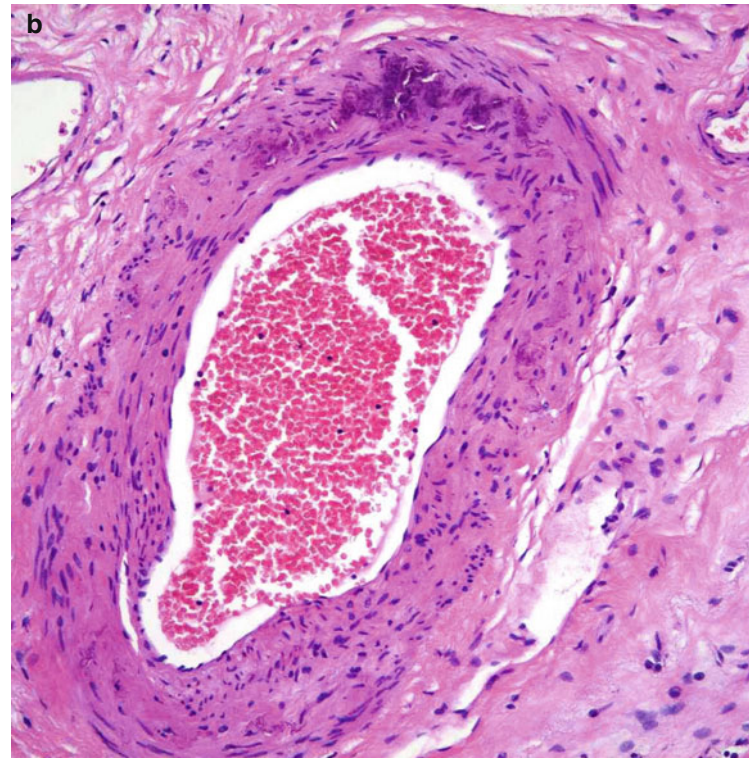


Fig. 13.7 (**a**) Incidental vascular calcification in a 54-year-old woman with lobular calcification due to pregnancy-like changes (see Fig. 10.8). (**b**) The calcification typically involves the media of the artery

Fig. 13.7 (continued)



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Non-epithelial Lesions

14

Learning Points

- PASH is a benign localised mesenchymal/stromal proliferative lesion with possible hormonal aetiology.
- PASH is characterised by slit-like spaces resembling capillaries within a dense fibrous stroma.
- PASH cells show myofibroblastic differentiation and express progesterone receptors.
- PASH has an excellent prognosis and in most cases local excision is sufficient.
- Fat necrosis of the breast is usually due to trauma.
- Presence of fibrosis in fat necrosis with associated architecture distortion can simulate malignancy.
- Cyst formation, calcification and haemosiderin deposition can occur at a later stage in fat necrosis.
- Localised fibrosis often presents as a non-calcified mass on radiological imaging and the diagnosis should be accepted on needle core biopsy if there is radiological concordance.
- MRI is useful in assessing postsurgical scarring to exclude malignancy.
- Haemosiderin deposition can mimic calcification mammographically.

14.1 Pseudoangiomatous Stromal Hyperplasia

14.1.1 Aetiology and Pathogenesis of PASH

Pseudoangiomatous stromal hyperplasia (PASH) was first described by Vuitch et al. in 1986. The authors described the tumorous, histological and ultrastructural features of PASH in nine premenopausal women. The women presented with unilateral breast masses. PASH is a benign proliferative lesion of the stroma whose aetiology and pathogenesis are ill-understood (Virk and Khan 2010). Leon et al. (2002) believed the proliferation originated from mammary fibroblasts and proposed the term nodular myofibroblast hyperplasia of the mammary stroma which indicates its true histogenesis. The stromal hyperplasia in PASH is due to exaggerated, aberrant responsiveness of the mammary myofibroblasts to hormonal stimuli, either endogenous or exogenous. The main hormone implicated is progesterone. The nuclei in PASH are progesterone receptor (PR) positive, whereas expression of oestrogen receptors (ER) is variable (Anderson et al. 1991). Powell et al. (1995) also reported expression of PR in 36 % (5/14) and ER in 12 % (2/14) cases of PASH. Further hormonal basis for this lesion is supported by the fact that half of postmenopausal women with tumorous PASH were on hormone

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_14, © Springer-Verlag Berlin Heidelberg 2014

replacement therapy (HRT) and occurred in men with gynaecomastia (Powell et al. 1995; Anderson et al. 1991). The origin of the slit-like spaces is unknown but on electron microscopy the spaces are lined by an incomplete layer of spindle cells joined through cell junctions or occasionally by tight junctions (Vuitch et al. 1986).

14.1.2 Clinical Features of PASH

PASH can affect any women between the age of 12 and 75 years, but with a predominance in postmenopausal women (Vuitch et al. 1986; Powell et al. 1995; Ferreira et al. 2008). PASH is also seen in men with gynaecomastia (Milaneze et al. 1998). PASH may be detected as an incidental finding on microscopic examination or palpable slow growing breast mass. On examination tumorous PASH is a solitary firm, painless mass mimicking a fibroadenoma but may also enlarge rapidly to mimic a malignant tumour with bilateral diffuse enlargement of the breasts (Yoo et al. 2007). The differential diagnoses of PASH include low-grade angiosarcoma, myofibroblastoma, fibroadenoma and mammary hamartoma (Virk and Khan 2010).

14.1.3 Radiological Features of PASH

There are no specific radiological features for PASH. Mammographically PASH consists of a well-circumscribed round to oval density without calcification (Polger et al. 1996). On ultrasonography, PASH exhibits a solid, well-circumscribed, homogenous, hypoechoic mass; the mass may be ill-defined or hyperechoic. MR imaging reveals isointense mass on T1-weighted gradient echo images and may show linear reticular 'lace-like' pattern on axial T2-weighted images due to slit-like spaces in PASH (Mercado et al. 2004; Yoo et al. 2007).

14.1.4 Pathological Features of PASH

Tumorous PASH varies in size from 0.6 mm to 12 cm (Powell et al. 1995; Ferreira et al. 2008; Polger et al. 1996). Sasaki et al. (2008) documented a 20 cm mass in a 36 year old woman. Macroscopically tumorous PASH is round to oval, well-circumscribed with a rubbery texture. The outer surface is smooth and un-encapsulated. The cut surface has a homogenous solid appearance with a grey white appearance and occasional cysts (Mercado et al. 2004). Histologically, PASH is characterised by dense fibrous stroma separated by complex anastomosing of slit-like spaces (Fig. 14.1). The spaces are lined by discontinuous spindle cells. The stroma lacks cytological atypia and there is no mitotic activity. The epithelium of the lobules and ducts may be unremarkable or may show ductal epithelial hyperplasia with apocrine metaplasia (Virk and Khan 2010). In gynaecomastia, there may be associated epithelial proliferative change. Needle core biopsies have been reported to have 83 % sensitivity in diagnosing PASH (Wieman et al. 2008). Cytology is not helpful in making a diagnosis of PASH (Virk and Khan 2010).

On immunocytochemistry, the spindle cells lining the slit-like spaces are positive for myofibroblastic markers, CD34, Vimentin and smooth muscle actin (SMA) (Vuitch et al. 1986; Powell et al. 1995). The cells are negative for cytokeratin, S100 protein and endothelial markers such as Von Willebrand factor antigen and CD31.

14.1.5 Management of PASH

There is no additional specific treatment if PASH is found incidentally in specimens excised for other lesions. Excision with adequate close margin is recommended treatment for tumorous PASH. Diffuse PASH may require wide excision of the breast or mastectomy for cosmetic reasons or for persistent pain and discomfort (Virk and Khan 2010). The recurrence rate after excision ranges from 0 % to 22 % (Powell et al. 1995; Ferreira et al. 2008; Wieman et al. 2008). The recurrence can occur in the ipsilateral or contralateral breast. There is no established medical treatment for PASH, although tamoxifen has been reported to have induced complete resolution of bilateral PASH (Pruthi et al. 2001). Overall the prognosis of PASH is excellent and is not considered a premalignant lesion or risk factor for malignancy (Virk and Khan 2010).

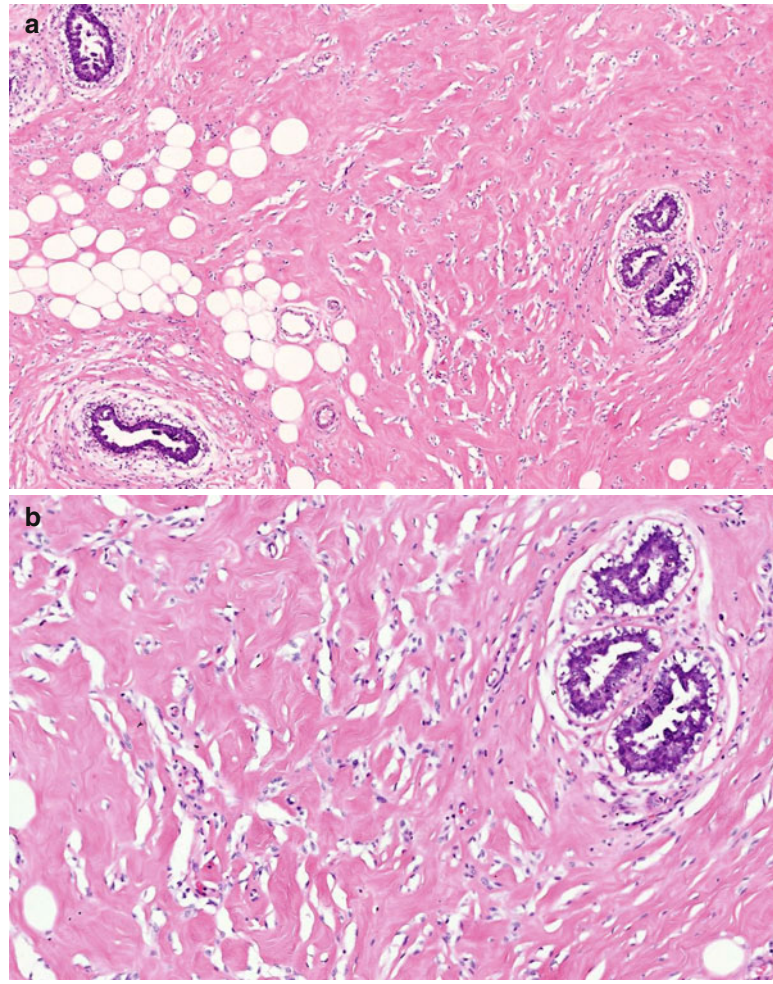


Fig. 14.1 (**a**) PASH is a common finding in gynaecomastia; arbotive male breast lobules are surrounded by dense hyalinised stroma with numerous slit-like spaces. (**b**) At high magnification, the slit-like spaces are irregular, resemble capillaries but without red blood cells. The slit-like spaces are partly lined by discontinuous spindle cells

14.2 Fat Necrosis

14.2.1 Pathogenesis of Fat Necrosis

Mammary fat necrosis is an important benign lesion because of its ability to mimic cancer both clinically and mammographically. Fat necrosis is associated with trauma, especially in women with pendulous breasts. However, a history of trauma is present in only up to 65 % of cases (Bilgen et al. 2001). Other causes of fat necrosis include seat-belt trauma, cyst aspiration, needle core biopsy, lumpectomy, radiation therapy, reduction mammoplasty, breast reconstruction with transverse rectus abdominis myocutaneous flap and removal of implant and anticoagulant therapy (Hogge et al. 1995; DiPiro et al. 1995).

Microscopically, fat necrosis is caused by sterile inflammation resulting from leakage of fatty acids from the adipocytes, leading to a polymorph, lymphocytic and macrophage infiltrate with associated giant cell reaction. Saponification by blood and tissue lipases leads to formation of vacuoles surrounded by macrophages. Clinically, fat necrosis can present with a firm and fixed lump, with or without skin or nipple retraction. Lanyi (1986) succinctly illustrated stages in the pathogenesis of fat necrosis as follows:

1. Lesion phase – damage to the fat cells with leakage of the neural fat.
2. Absorption phase – lipophages remove the liberated neutral fat leading to formation of fat vacuoles with macrophage, plasma cell and other inflammatory cell infiltrate.

3. Repair phase – increasing numbers of fibroblasts follow the absorption phase, walling off a cavity with a dense capsule or scar formation. Calcium salts or haemosiderin deposition may occur in the fibrosis. The calcification of the oil cyst may exhibit an eggshell appearance.

14.2.2 Radiological Features of Fat Necrosis

Fat necrosis is not an uncommon lesion. In Lanyi's series (1986) of 1,044 consecutive mammograms, he identified 90 liponecrotic microcysts, which constituted 8.6 % of the mammographic lesions. The mammographic appearance of the fat necrosis depends on the stage of the lesion. In the early stages, fat necrosis produces an ill-defined radiolucent mass (Heywang-Köbrunner et al. 2001).

When liponecrotic cysts develop, they are usually microcysts and rarely macrocysts (Lanyi 1986). The microcysts are usually 2–3 mm and exhibit a central lucency surrounded by punctate or amorphous calcification of the peripheral rim. Frequently the cysts are solitary but multiple clusters can also occur. These lesions are difficult to examine histologically because the calcium shatters under the microtome blade.

Calcification in fat necrosis can appear pleomorphic and clustered. Mammographic magnification may be necessary to highlight some ring-forms, which are features of benignity (Heywang-Köbrunner et al. 2001). Branching, rod-like or angular microcalcifications in fat necrosis may be indistinguishable from carcinoma (Bassett et al. 1978). Ruptured cysts in fibrocystic change and duct ectasia also cause fat necrosis with excessive scarring. Fat necrosis can produce stellate or spiculate lesions, which again closely resemble carcinoma (Meyer et al. 1978).

DiPiro et al. (1995) followed up five women who sustained fat necrosis from seat-belt injuries. At 1–2 months following the breast injury, the mammograms showed thin-walled fat-density cysts in a linear distribution, and in less dense breasts there was an associated 2–3 cm band of increased density. The latter was not apparent in more dense breasts. By 3–4 months after the injury, the lipid cysts and contusions were less apparent and a line of fibrosis had developed. On ultrasound, the lipid cysts were smoothly marginated and anechoic or hypoechoic. Parenchymal calcification may develop 3.5–4 years later.

In a larger study, Bilgen et al. (2001) evaluated the mammographic and ultrasonic appearances and evolution of fat necrosis in 94 patients with a total of 126 lesions between them. This was a retrospective study, which involved women aged between 37 and 68 years (mean 46.4 years). Fifty-eight patients had a history of trauma caused by surgery, motor vehicle injury, a kick or pinching. In 61 patients the lesions were clinically palpable. Histological diagnosis was confirmed in 28 lesions and in the remaining 89 the diagnosis was made on the basis of mammographic and sonographic appearances. Of the 114 lesions apparent mammographically, 26.9 % (34) were radiolucent oil cysts with or without curvilinear calcification; 12.6 % (16) were round opacities; 12.8 % (20) had asymmetric opacity or heterogeneity of the subcutaneous tissues; calcification of dystrophic pattern was present in 26.9 % (34) and clustered pleomorphic pattern in 3.9 % (5); 3.9 % (5) had suspicious speculated masses and mammography was negative in 9.5 % (12). Of the 112 lesions confirmed sonographically, 14.2 % were solid masses; 16.6 % were anechoic cysts with posterior acoustic enhancement; 15.8 % were anechoic cysts with posterior acoustic shadowing due to mural calcification; 11.1 % were cystic lesions with internal echoes; 3.9 % were cystic masses with mural nodules; 26.9 % had increased echogenicity of subcutaneous tissues; and 11.1 % were not apparent on ultrasound. These sonographic features of fat necrosis were similar to those reported by Soo et al. (1998). Bilgen and colleagues followed up the patients for at least 3 years with yearly mammography. In five patients with mammographic calcification, two had surgical excision because the calcification had increased. In another patient with nodular opacity and dystrophic calcification, this disappeared at 4 years of follow-up. Of the 34 radiolucent cysts, 21 had mural calcification on initial mammography. Of the remaining 13 oil cysts, five developed curvilinear calcifications

within 2–3 years. Six of 16 round opacities disappeared and eight were excised. Nineteen of the 34 calcified lesions remained stable with time, but 11 of these became very coarse and developed features of typical fat necrosis calcification. Four of the five spiculated masses were excised. On sonographic follow-up, the most common finding was a return to normal of the subcutaneous tissue echogenicity and formation of small cysts. Solid lesions remained solid but reduced in size, whereas complex lesions evolved to become cystic. This study revealed a wide spectrum of radiological features of fat necrosis and the authors indicated that it was possible to follow-up patients and reduce the amount of surgical intervention. However, the radiological features illustrated in this detailed study are so varied that each patient with possible fat necrosis should be treated individually with appropriate clinical, mammographic and histological biopsy results.

The repair stage in fat necrosis as advocated by Dr Lanyi is illustrated in the mammogram with an oil cyst showing eggshell calcification of the wall (Fig. 14.2). However, this calcification was not confirmed on histology, even with polarising light. Instead there is prominent haemosiderin deposition within the wall which simulated calcification on mammography. In the late stages of fat necrosis, haemosiderin deposition and fibrosis predominate (Taboada et al. 2009).

MRI features of fat necrosis are variable and can mimic malignancy. Calcifications are sometimes seen on MRI as signal voids. Fibrosis may be seen as architectural distortion with or without spiculated margins. Fibrosis may appear as high, intermediate or low signal on T1-weighted images. Necrotic fat usually shows low signal on T1-weighted MRI and may be due to its haemorrhagic and inflammatory content (Taboada et al. 2009).

14.2.3 Pathological Features of Fat Necrosis

Fine needle aspiration cytology of fat necrosis consists of foamy lipid-laden macrophages in an amorphous background. Other inflammatory cells include lymphocytes and polymorphs, macrophages and giant cells depending on the stage of the lesion (Fig. 14.2h). The histology again depends on the stage of the lesion. In the late stages cystic degeneration may occur resulting in a cavity containing fat. The oil cyst will be surrounded by fibrosis and calcification can also be noted in the wall. However, in this case haemosiderin deposition was present in the wall (Fig. 14.2e–g). Haemosiderin has been documented to mimic calcification on mammographic examination (Yam et al. 2001). Fat necrosis occasionally elicits a florid granulomatous reaction (lipophagic granuloma) (Fig. 14.2d–e). In the early stages, foamy lipid-laden macrophages predominate (Fig. 14.3). The needle core biopsy was obtained at follow-up mammography for previous surgery and radiotherapy for breast cancer.

14.3 Focal Fibrosis

Focal fibrosis is also termed fibrous tumour or fibrous mastopathy. Azzopardi (1979) disputed whether fibrosis of the breast is a pathological entity. He believed that fibrosis is a normal process of stromal involution and, in the presence of an excisional lump, pathologists may not find it ‘easy to tell a surgeon that the 2 or 3 cm lump he had clearly palpated in the breast is normal’. He cautioned pathologists not to strain themselves too far in search of non-existent disease. Despite Azzopardi’s reservations, fibrosis of the breast can present as either a clinical lump or a mammographically detected lesion (Minkowitz et al. 1973; Barnard et al. 1988). Barnard and colleagues (1988) identified four lesions (1.8 %) in 224 mammographically detected, histologically confirmed benign lesions. The histological criteria for fibrous breast disease were the presence of breast tissue containing irregular zones of fibrosis extensively replacing epithelial elements.

With increased use of mammography for both symptomatic and screen-detected lesions, focal breast fibrosis is not rare. The lesion typically occurs in premenopausal women. This entity should be recognised for accurate mammographic

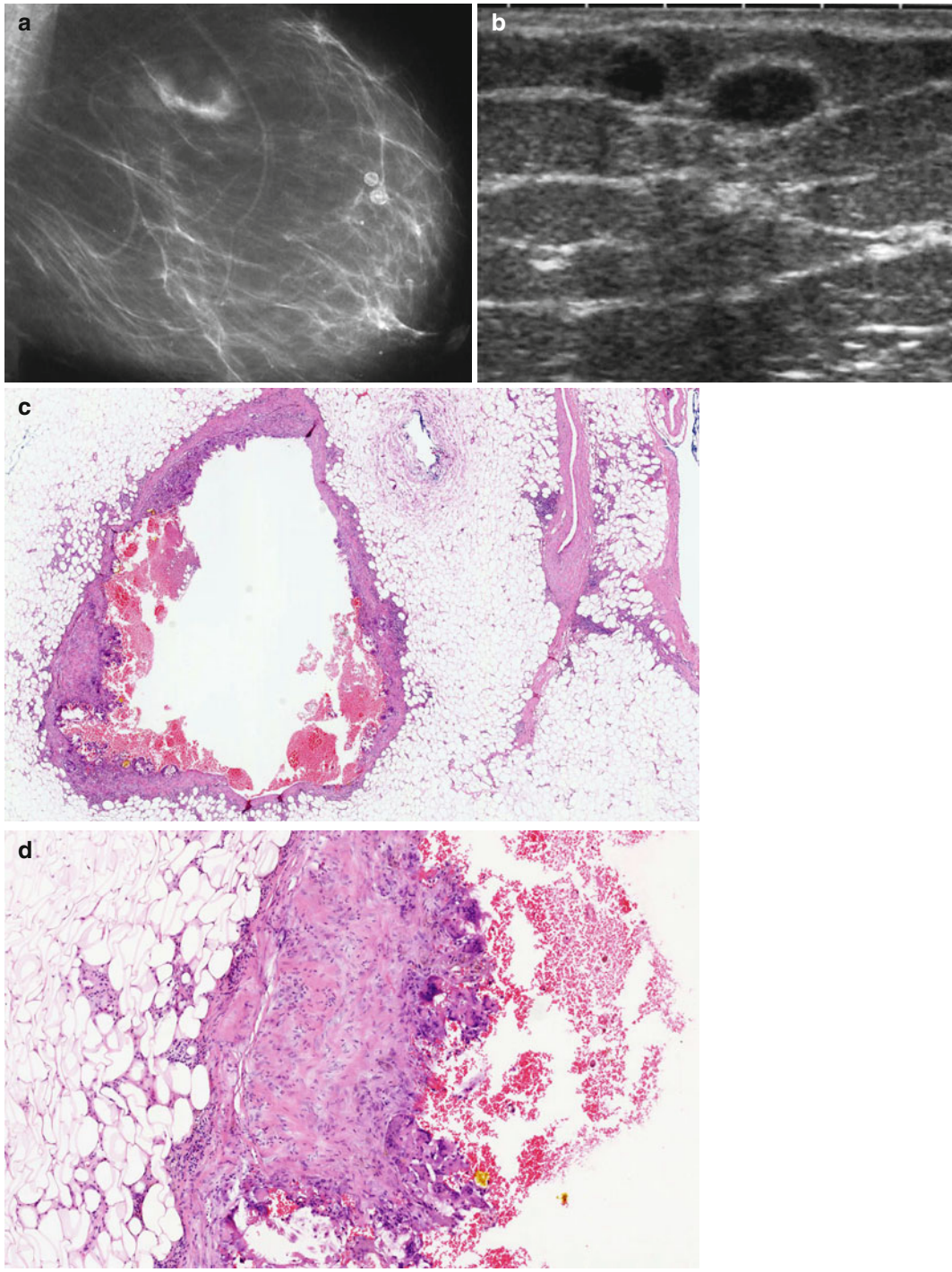
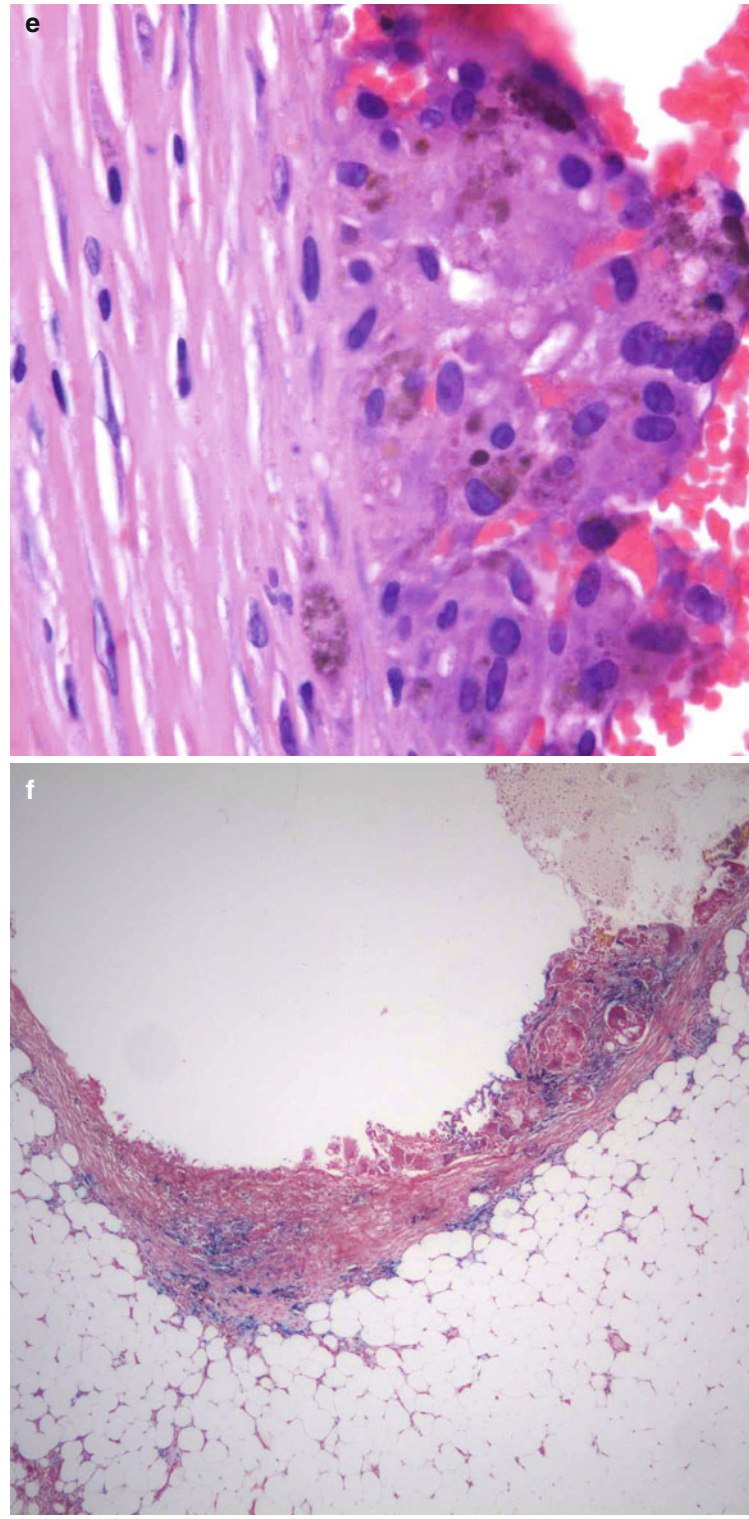


Fig. 14.2 (**a**) The mammogram from a 60-year-old woman shows characteristic eggshell 'calcification' in two oil cysts due to fat necrosis. (**b**) The oil cysts are highlighted in the ultrasound images. (**c**) The histology shows an oil cyst containing blood surrounded by a thick fibrous wall. There is no histological calcification. (**d**) At high magnification, the wall is lined by multinucleate giant cells characteristic of a lipogranuloma. (**e**) The multinucleate giant cells contain brown haemosiderin. (**f**) The haemosiderin deposition is highlighted within the wall with the Prussian blue stain. (**g**) High magnification of the haemosiderin granules within the fibrous wall which mimicked mammographic calcification (see also Fig. 14.5). (**h**) Away from the cyst wall, there is fat necrosis associated with chronic inflammation and foreign body giant cell reaction

Fig. 14.2 (continued)



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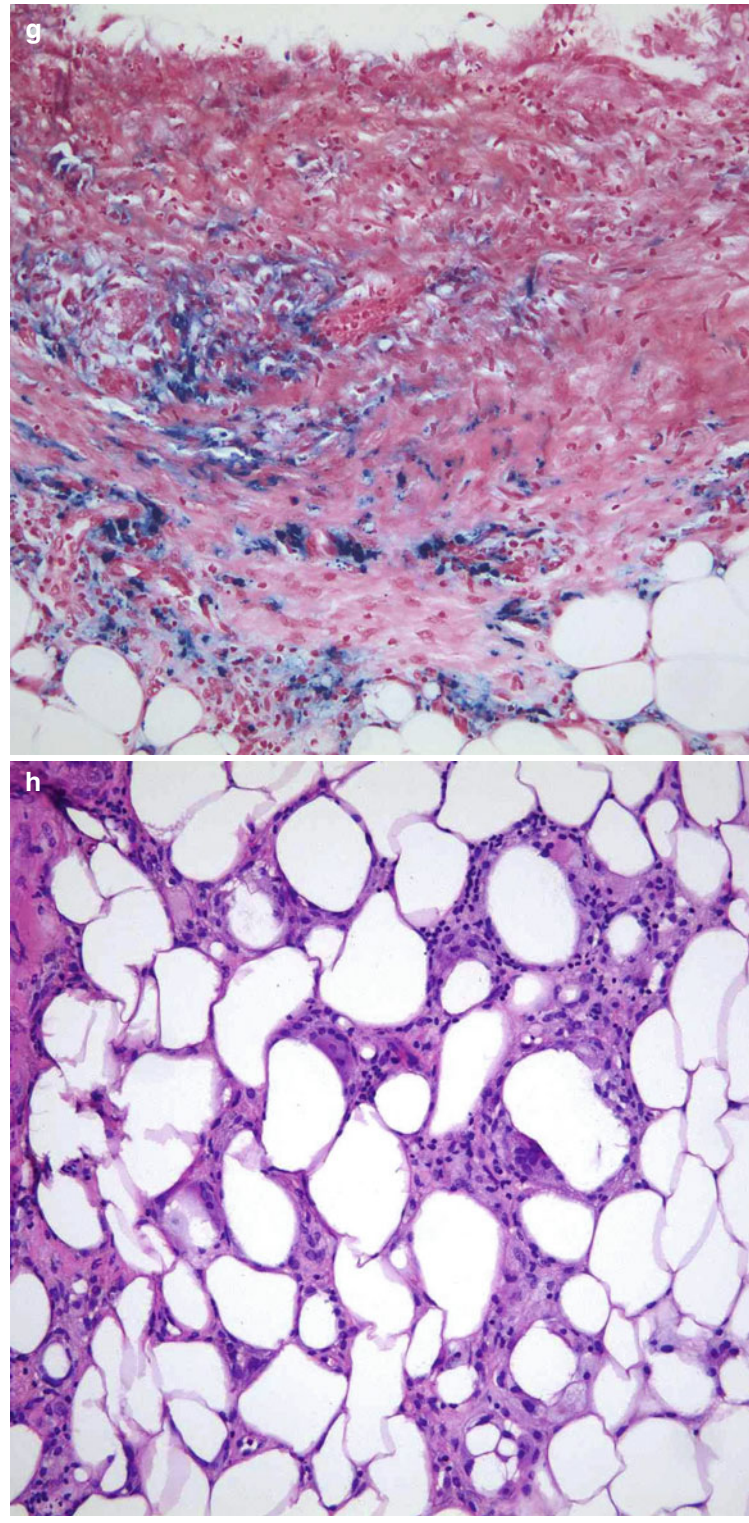


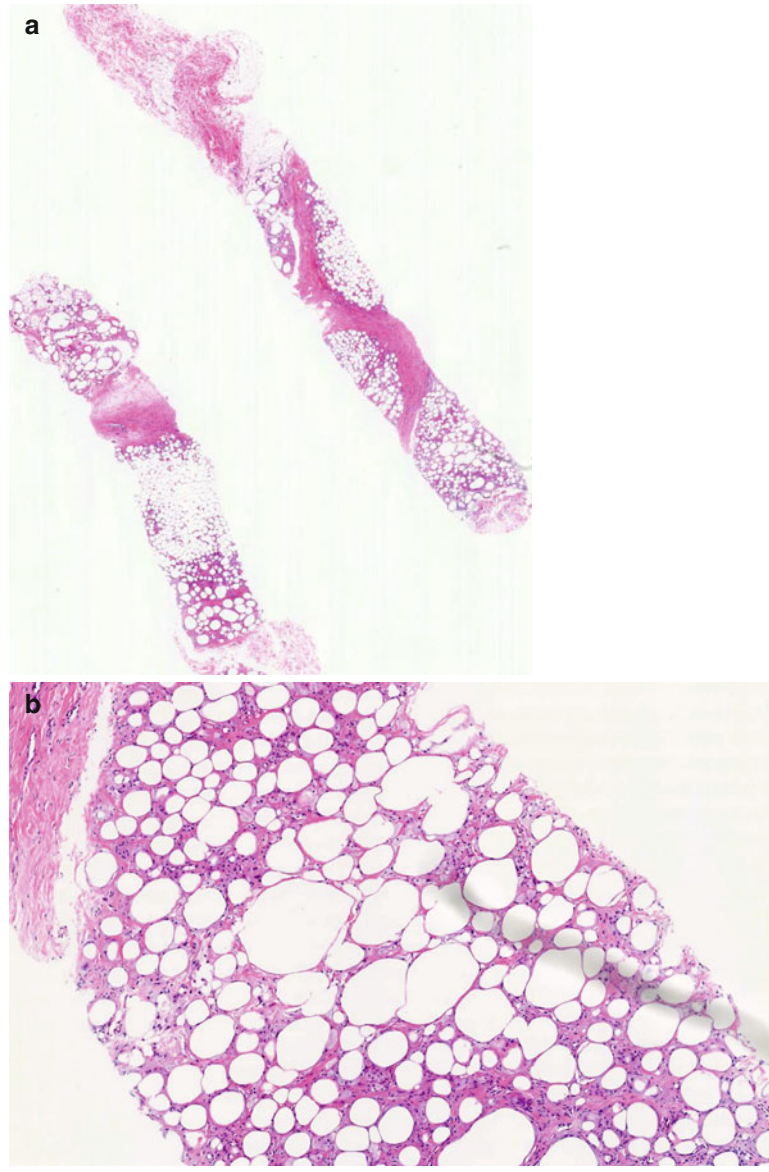


Fig. 14.3 (**a**) Mammography following previous surgery and radiotherapy for breast cancer was suspicious of recurrent disease. The needle core biopsies show fibrosis and fat necrosis. (**b**) At high magnification, the fat necrosis is characterised by variation in the size of the adipocytes and accumulation of foamy lipid laden macrophages in the stroma

histological concordance on needle core biopsies and to avoid unnecessary excisional biopsies. Two separate studies from the USA carried out mammographic and histological assessment of this entity. Although the results of radiological and pathological correlations are different, the two studies concurred in that focal fibrosis of the breast is a distinct entity.

Venta et al. (1999) carried out a retrospective review of 610 needle core biopsies and revealed the histological diagnosis of focal fibrosis in 89 (15 %) specimens and 50 (8 %) biopsies revealed focal fibrosis in the absence of calcification or other pathological diagnosis, constituted the basis of the study. Mammographically, focal fibrosis presented as a mass in 34 (68 %), architectural

distortion in six (12 %) and asymmetric density in five (10 %) patients. Focal fibrosis was mammographically occult in five (10 %) patients. On sonography, 36 (72 %) patients with focal fibrosis exhibited three echo texture patterns, namely, hypoechoic, isoechoic and centrally echogenic with peripheral hypoechoic rim. The sonographic margins were circumscribed in 21, lobulated in ten and ill-defined in five lesions. Histologically, the lesions had three morphological patterns: perilobular, septal and haphazard fibrosis. Correlation with radiological features showed that septal and perilobular fibrosis most often presented as hypoechoic or centrally echogenic masses, whereas haphazard fibrosis was associated with architectural distortion. The authors concluded that focal fibrosis often presented as a non-calcified mass on mammography or sonography, and the presence of fibrosis in a needle core biopsy should be accepted if concordant with the radiological features. Marginal spiculation should prompt an excisional biopsy.

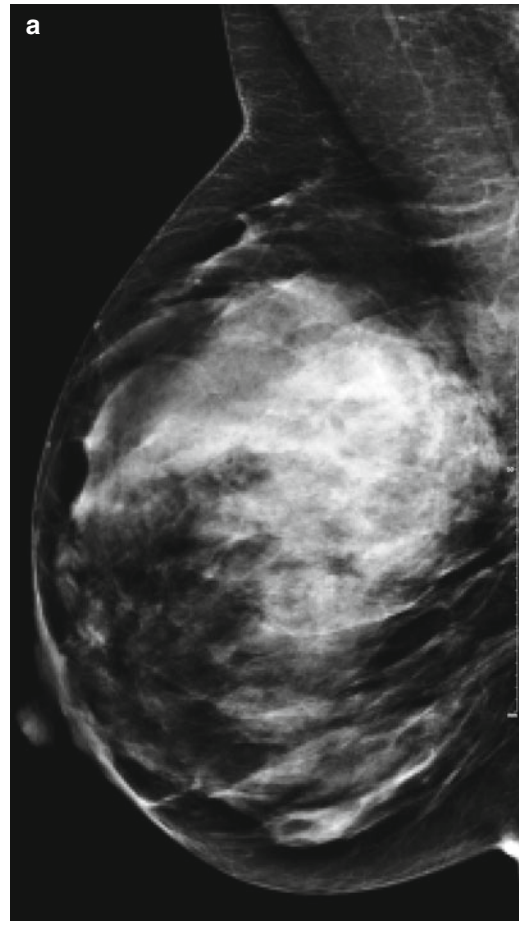
In a larger series, Revelon et al. (2000) reviewed 1,268 surgical excisional and 796 percutaneous breast biopsies to assess the prevalence and radiological and histological features of focal fibrosis of the breast. Forty-four (2.1 %) of the lesions met the criteria of focal breast fibrosis. Thirty-seven (84 %) of the 44 lesions were mammographically detected and had the following features: six (14 %) were circumscribed masses, two (5 %) lobulated masses, one (7 %) microlobulated masses, 11 (25 %) obscured masses, two (5 %) architectural distortion and 15 (34 %) asymmetric densities. Seven palpable lesions were mammographically occult. Thirty-three of the 44 lesions were evaluated by ultrasound and 25 (76 %) were visible. Twenty (80 %) of the 25 lesions were well-defined and hypoechoic, three (12 %) were ill-defined and two (8 %) showed marked shadowing without a visible mass. Histological examination revealed mass-like fibrosis in 17 (39 %) of the lesions, 14 (32 %) had nodular fibrosis, 12 (27 %) had haphazard fibrosis and one (2 %) had septal fibrosis. Unlike Venta and colleagues (1999), Revelon did not find morphologic correlation between the radiological and pathological features of focal breast fibrosis. However, the authors accepted that fibrosis of the breast was a distinct entity with varying radiological features and, if present in a needle core biopsy, should be accepted as the diagnosis provided there is radiological–pathological concordance.

The mammographic and histological features of focal fibrosis are illustrated in Fig. 14.4. The patient presented with a suspicious lump which was on mammography and ultrasound was graded as R3. The needle core biopsy was reported as fibrosis only (B2) because of the clinical–radiological–pathological discordance, the patient underwent local excision. The specimen was 40×35×35 mm and weighed 16.5 g and had diffuse, white rubbery cut surface with no haemorrhage or necrosis. The histology showed an area of fibrosis which was well demarcated from the normal breast tissue (Fig. 14.4b). Another section consisted of fibrous tissue only which was present on the margin (Fig. 14.4c). On high magnification the fibrosis has a scar tissue-like appearance surrounding atrophic ducts and lobules (Fig. 14.4d). The adjacent breast contained benign lesions such as an evolving radial scar, fibrocystic change and columnar cell change.

The cause of focal fibrosis is unclear and this should not be confused with fibrosis of diabetic mastopathy, which is a distinct entity. Transforming alpha beta (TGF-beta) is emerging as a key mediator of the fibrotic process in patients undergoing radiotherapy for breast cancer (Li et al. 1999). TGF-beta stimulates fibroblast proliferation, migration and extracellular matrix synthesis. It may be useful in the future to study the role, if any, of TGF-beta in the genesis of focal fibrosis of the breast. There is no known risk of breast cancer associated with fibrosis (Fitzgibbons et al. 1998).

14.4 Postsurgical Scarring

Postsurgical scarring occurs in breasts that have undergone surgery for either benign or malignant lesions. In the latter, the main difficulty is to differentiate the scarring from recurrent disease. Mammographic scarring of breast tissue presents as a spiculated lesion or architectural distortion. Scars do not usually have a central mass when seen on mammography (Heywang-Köbrunner



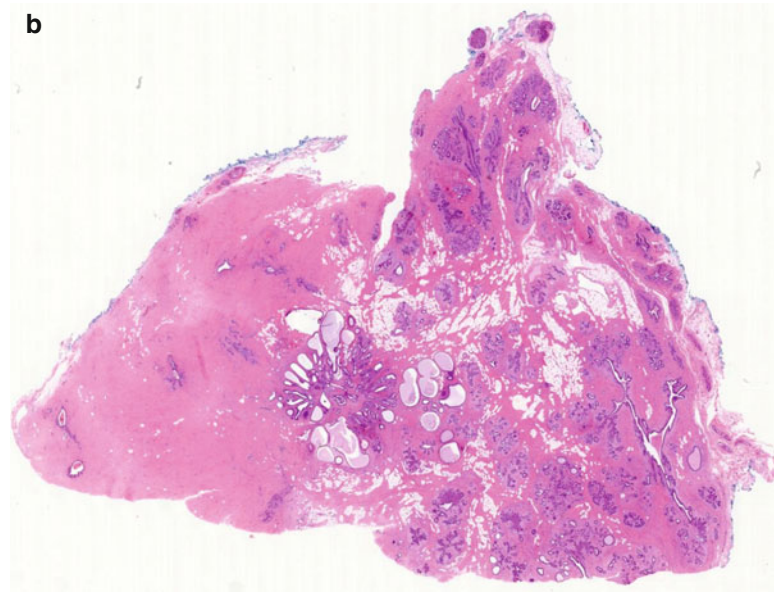


Fig. 14.4 (**a**) A mammogram for a 41-year-old woman who presented with a palpable lump, she had no history of diabetes mellitus and the lesion was radiologically graded as R3 and the needle core biopsy showed fibrosis only (B2). (**b**) The histology of the excision specimen showed an area of fibrosis well demarcated from the normal breast tissue; note the evolving radial scar. (**c**) Another field shows a large area of fibrosis containing atrophic ducts and lobular units. (**d**) At high magnification the lesion shows atrophic benign ducts and lobular units surrounded by fibrosis with scar tissue appearance

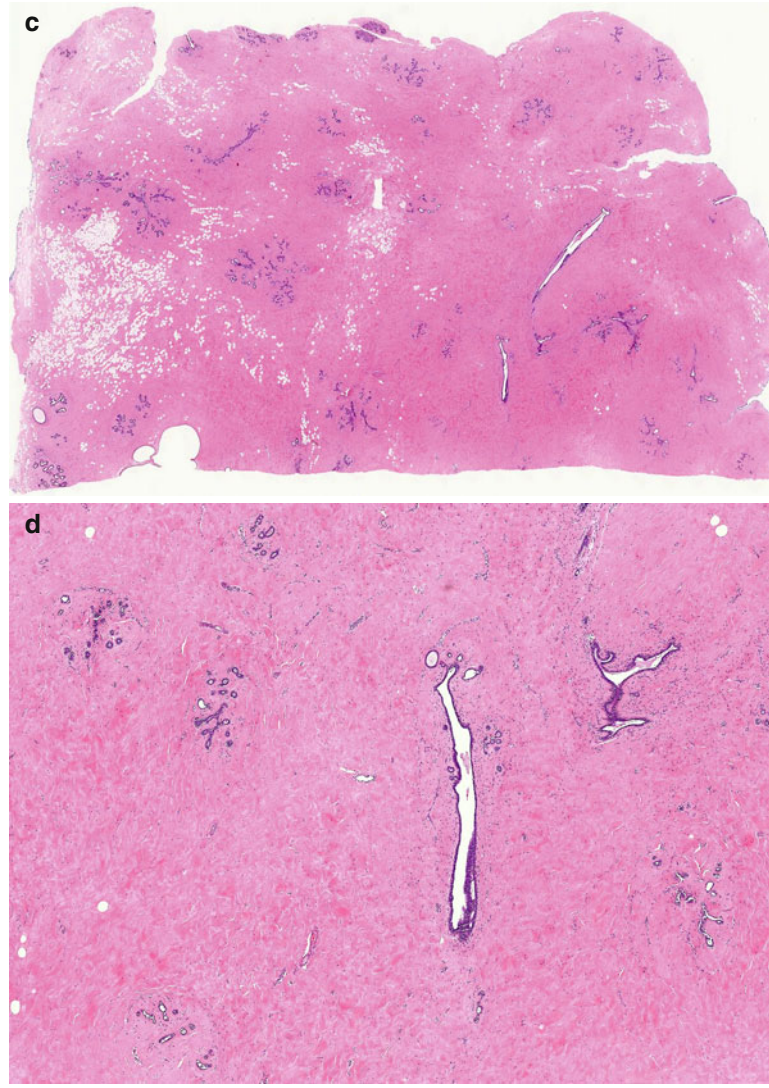


Fig. 14.4 (continued)

et al. 2001). However, appropriate radiological projections and further assessments are appropriate to exclude cancer.

Dystrophic calcification can also occur in a scar; this can be pleomorphic and may not be easily distinguished from malignant calcification. When assessing scars, suture microcalcification should also be taken into consideration. Sonographic features vary with the stage of the scarring but in the late stage, which usually causes concern, there are hypoechoic features with or without acoustic shadowing. Magnetic resonance imaging is usually useful in the follow-up of scars to exclude recurrence because cancers enhance (Heywang-Köbrunner et al. 2001).

The histology of scar tissue is also variable. In the early stages, there is a fresh haemorrhage,

inflammatory cells, fat necrosis and foreign body giant cell reaction to suture material. The cellularity of the scar tissue also varies with the age of the lesion. In the early stages, the collagen fibres show fibroblasts with plump nuclei and old scars show prominent hyalinisation. Haemosiderin deposition can also be prominent. It is unusual for haemosiderin to present as mammographic calcification (Fig. 14.5) but this has been reported in the literature (Yam et al. 2001). In this report the authors devised a computer programme which distinguishes mammographic calcification from haemosiderin deposition.

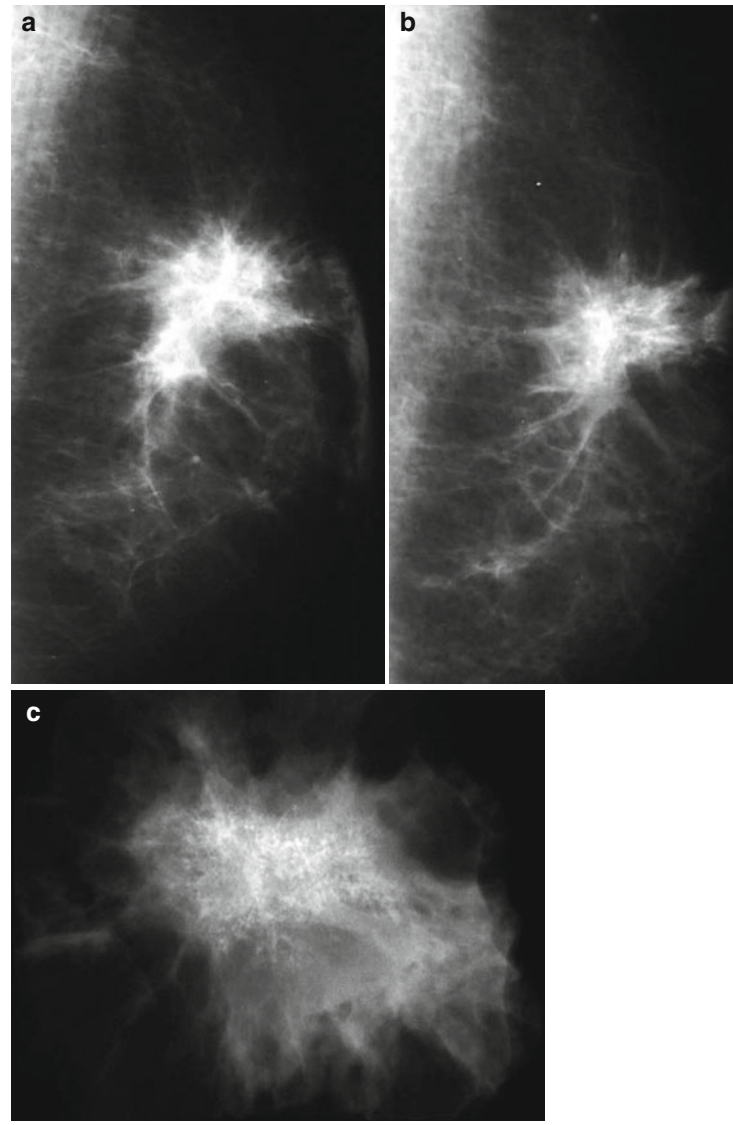
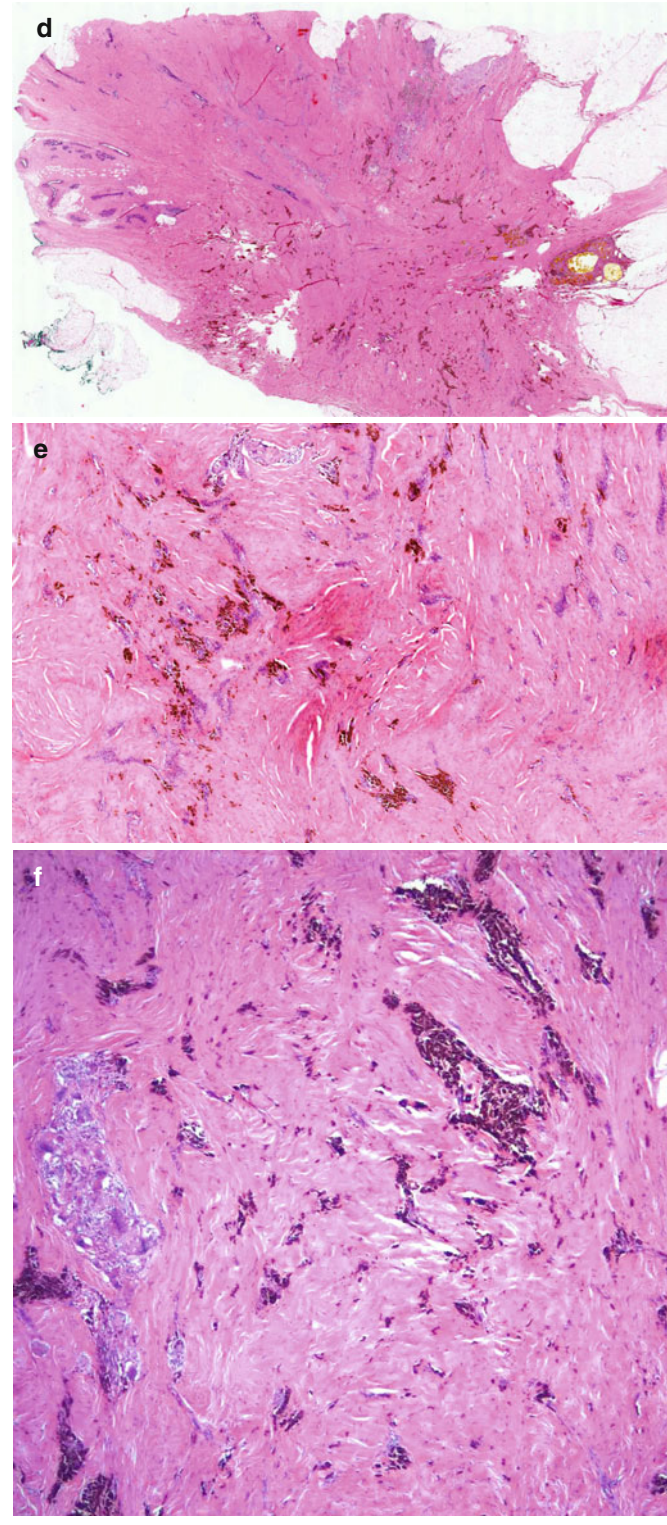


Fig. 14.5 (**a**) A mammogram was taken a year after surgery for carcinoma in a 63-year-old woman. The scarring exhibits a roughly stellate configuration. There is no calcification. (**b**) Follow-up mammogram, 2 years post-surgery. Although the scarring is less dense than the previous year (**a**), there is punctate microcalcification. It was not possible to exclude malignancy. (**c**) The calcification, highlighted better in the specimen X-ray, is quite diffuse. (**d**) Whole-mount section of hyalinised scar tissue with extensive haemosiderin deposition, which simulated microcalcification in the X-rays. (**e**) Medium power magnification of the scar. (**f**) This field shows scarring associated with foreign body giant cell reaction to suture material and haemosiderin deposition. (**g**) High magnification to highlight the haemosiderin granules

Fig. 14.5 (continued)



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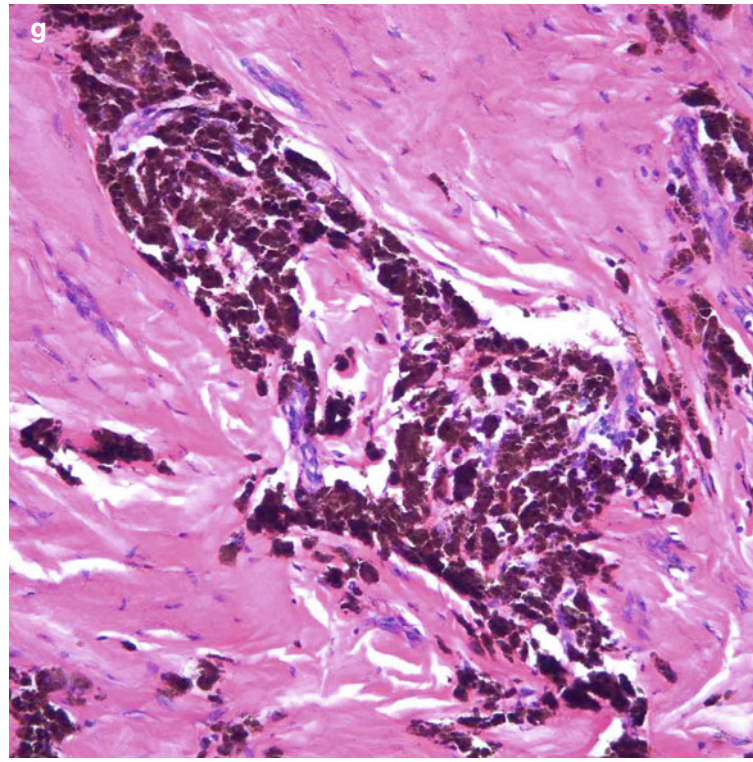

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Male Breast Lesions

15

Learning Points

- Gynaecomastia occurs due to altered oestrogen–androgen imbalance.
- Physiological gynaecomastia occurs during neonatal and pubertal periods.
- Pathological gynaecomastia affects older men and has multifactorial causes.
- Drugs and chronic illness promote the production/utilisation of oestrogens resulting in gynaecomastia.
- Systemic and genetic factors promote the production of aromatase which converts androgens to oestrogens.
- Gynaecomastia increases the risk of male breast cancer

15.1 Prevalence of Gynaecomastia

Gynaecomastia is a benign enlargement of the male breast due to glandular tissue proliferation manifesting as palpable firm mass. It is the most common reason for men attending the Breast Clinic. Gynaecomastia affects men of all ages. In two separate studies, gynaecomastia was detected in 36 % of healthy young men and 57 % of healthy older men on physical examination (Nuttall 1979) and more than 70 % of hospitalised elderly men (Niewoehner and Nuttal 1984). Autopsy studies reported the presence of gynaecomastia in 40–50 % of unselected cases (Andersen and Gram 1982).

Gynaecomastia has three peaks during a life span, thus: during neonatal period, during puberty and in older men. It is estimated that 60–90 % of infants have transient gynaecomastia due to transplacental transfer of maternal oestrogens. Neonatal gynaecomastia regresses completely by the end of the first year (Bembo and Carlson 2004). Gynaecomastia recurs in puberty when it affects 48–64 % of boys. It may affect boys as young as 10 years old and peaks between 13 and 14 years, followed by a decline in late teens (Bembo and Carlson 2004). The highest prevalence is men aged between 50 and 80 years (Nuttall 1979; Niewoehner and Nuttal 1984).

15.2 Causes of Gynecomastia

15.2.1 Altered Oestrogen–Androgen Balance

Gynaecomastia occurs due to an imbalance between oestrogen and androgens in favour of oestrogens or from increased sensitivity of the breast tissue to normal circulating oestrogen levels (Glass 1994). The imbalance is between the stimulating effect of oestrogen and the inhibitory effect of androgen (Ansstas et al. 2012). Oestrogens stimulate ductal epithelial

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_15, © Springer-Verlag Berlin Heidelberg 2014

proliferation, ductal elongation and branching, proliferation of periductal fibroblasts and increase in vascularity. The response to exposure of the male breast to oestrogens is similar to that of female breast (Braunstein 1993). Oestrogen production in men results from peripheral conversion of androgens (testosterone and androstenedione) to oestradiol and estrone through the action of aromatase mainly in the muscle, skin and adipose tissue (Ansstas et al. 2012). The second and small source of oestrogens is the testes. Altered oestrogen and androgen balance can be physiological, pathological or a genetic abnormality.

15.2.2 Physiological Gynecomastia

Neonatal gynaecomastia occurs in 60–90 % of infants due to transfer of maternal and placental oestrogen (Bembo and Carlson 2004). The second phase of physiologic gynaecomastia occurs at puberty and affects up to 60 % of boys (Bembo and Carlson 2004). At puberty there is a surge of luteinising hormone (LH) and follicle stimulating hormone (FSH) in conjunction with growth hormone and insulin-like growth factor-1 which stimulate testosterone production in Leydig cells. Oestrogen levels increase threefold, peaking earlier than testosterone concentrations and eventually increase to 30-fold (Niewoehner and Schorer 2008). It is uncertain whether gynaecomastia occurs due to delayed testosterone production, temporary increase in aromatase activity, varying sensitivity to oestrogen or a combination of these factors.

Gynaecomastia increases with age because free testosterone levels decline and obesity becomes more common (Nuttall 1979). In an unselected group of hospitalised men, the prevalence of gynaecomastia correlated with a high body mass index (Niewoehner and Nuttal 1984).

15.2.3 Pathological Gynaecomastia

Although gynaecomastia is idiopathic in 50 % of the patients (Einov-Bacher et al. 2004; Glass 1994), pathologic gynaecomastia is caused by an increase in the production of oestrogen or decrease in the production of testosterone in conjunction with increased aromatisation (Ansstas et al. 2012). Several drugs also induce gynaecomastia.

Decreased androgen action occurs with the following:

(i) Decreased production
(ii) Increased sex hormone binding globulin (SHBG), which binds testosterone and thus favours greater peripheral oestrogen action
(iii) Androgen receptor antagonist

Increased oestrogen action occurs with the following:

(i) Increased aromatisation of androgens to oestrogens
(ii) Increased androgenic precursors (dehydroepiandrosterone (DHEA) and androstenedione
(iii) Increased SHBG which binds testosterone and thus favouring greater peripheral oestrogen action
(iv) Oestrogen receptor agonist (Ansstas et al. 2012)

Primary hypogonadism due to mumps orchitis, trauma, cytotoxic chemotherapy or a congenital abnormality such as Klinefelter's syndrome are associated with an oestrogen–androgen imbalance leading to gynaecomastia. The reduced levels of testosterone increase the levels of serum luteinising hormone (LH). The excess LH stimulates the aromatase enzyme in testicular Leydig cells to produce more oestrogen from testosterone. Furthermore, peripheral aromatisation of the adrenal androgens androstenedione to oestrogen remains unaffected (Ansstas et al. 2012; Bembo and Carlson 2004). Eighty percent of patients with Klinefelter's syndrome develop gynaecomastia.

Secondary hypogonadism due to hypothalamic or pituitary abnormality is a rare cause of gynaecomastia. These patients have low LH production resulting in reduced testosterone and oestradiol in the testis, but the aromatisation of the adrenal cortex androgens continues (Ansstas et al. 2012; Bembo and Carlson 2004).

Several tumours, benign and malignant, are associated with gynaecomastia. Leydig cell tumour of testis, 90 % of which are benign, secretes oestradiol which suppresses LH leading

to reduced serum testosterone. Excess oestradiol also stimulates SHBG which preferentially binds testosterone and thus reduces free testosterone paving the way for increased oestradiol activity (Bembo and Carlson 2004).

Human chorionic gonadotropin (HCG)-producing tumours are associated with gynaecomastia. HCG has similar action to LH and stimulates the Leydig cells to produce oestradiol. Several tumours secrete HCG, namely, testicular germ cell tumours, lung, liver and gastric cancer (Bembo and Carlson 2004). Several drugs induce gynaecomastia, the most well-known being diethylstilbestrol for treatment of advanced prostate cancer (Moore et al. 1945). Other drugs which induce gynaecomastia and their mode of action are listed in Table 15.1.

Other conditions associated with gynaecomastia include chronic renal failure, cirrhosis of the liver, hyperthyroidism and malnutrition (Hershkovitz and Liberman 2002; Ansstas et al. 2012; Niewoeher and Schorer 2008). Men with end-stage renal disease may have reduced testosterone and elevated gonadotropin hormones resulting in breast development. Gynaecomastia in cirrhosis occurs due to reduced catabolism of androgens which are converted to oestrogens in the peripheral tissue. Hyperthyroidism increases aromatase activity and levels of SHBG. SHBG binds androgens more avidly, allowing higher free levels of oestrogens to act on the peripheral tissue such as the breast. Malnutrition and starvation reduce gonadotropin hormones and testosterone levels and on refeeding the production of oestradiol outpaces the rise in gonadotropin hormones and testosterone, resulting in gynaecomastia.

Table 15.1 Drugs associated with gynaecomastia

Low androgen levels: inhibition of testosterone synthesis
Ketoconazole, metronidazole, gonadotropin releasing hormone agonists (chronic) and antagonists, spironolactone, chemotherapy (cytotoxic drugs)
Low androgen levels: inhibition of testosterone action
Androgen receptor blockers-bicalutamide, flutamide, nilutamide, spironolactone, eplerenone, cyproterone
5 α reductase inhibitors – finasteride, dutasteride
H_2 blockers and proton pump inhibitors – cimetidine, ranitidine, proton pump inhibitors; marijuana
High androgen levels resulting in high oestrogen levels
Androgen administration- excessive testosterone replacement, anabolic steroids, androgen containing contraceptives; human chorionic gonadotropin
High oestrogen levels or oestrogen action
Oestrogen administration, occupational exposure to oestrogen, oestrogen containing creams or cosmetics, isoflavones
Phytoestrogens – cosmetics, soy products, beer, tea tree oil, lavender oil
Oestrogen action – diethylstilbestrol, clomiphene, phenytoin, digitalis
Other or multifactorial
Angiotensin-converting enzyme inhibitors, alcohol, amiloride, amiodarone, amphetamines, calcium channel blockers, ciclosporin, diazepam, growth hormone, highly active antiretroviral therapy, heroin, methyldopa, isoniazid, reserpine, risperidone, theophylline, tricyclic antidepressants (increase prolactin levels)

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15.2.4 Genetic Alterations in Gynaecomastia

As previously alluded to, gynaecomastia results from an imbalance in oestrogen and androgen activity on the male breast tissue. Aromatase cytochrome P45019 (aromatase CYP19) activity is important in maintaining this balance. The cytochrome P450 enzyme converts androgens androstenedione and testosterone to oestrone and oestradiol, respectively (Czajka-Oraniec et al. 2008). The conversion takes place mainly in skin adipose tissue and bone and in men with gynaecomastia in the breast stromal cells (Simpson et al. 2002; Binder et al. 2005). Czajka-Oraniec and colleagues (2008) reported a high level of CYP19 polymorphisms in men with gynaecomastia when compared to the controls, suggesting that this may contribute to gynaecomastia. Furthermore, aromatase excess syndrome which causes familial prepubertal gynaecomastia, a rare autosomal dominant inherited condition, occurs due to excess oestrogen caused by increased

aromatase activity (Shozu et al. 2003; Binder et al. 2005). The condition appears to be due to heterozygous inversion or polymorphism of the p450 aromatase gene (Ansstas et al. 2012). The human p450 aromatase gene is located on chromosome 15q21 (Clen et al. 1988).

15.3 Clinical Features of Gynaecomastia

Pseudogynaecomastia or lipomastia (fatty breast) common in obese men must be distinguished from true gynaecomastia. In true gynaecomastia, there is a firm discrete subareolar tissue or diffuse fibroglandular tissue that resembles female breast (Bembo and Carlson 2004). Gynaecomastia can be unilateral or bilateral. Unilateral gynaecomastia is more common in the left than the right breast (Bannayan and Hajdu 1972). Gynaecomastia is often asymptomatic and discovered as incidental finding during examination. It may also present with pain and tenderness especially if the condition is of acute onset (Bembo and Carlson 2004).

The effects of altered oestrogen–androgen imbalance in inducing gynaecomastia are most felt acutely in men taking diethylstilbestrol for treatment of prostate cancer. The male breast contains receptors for oestrogen, progesterone and androgens. Oestrogen stimulates duct development and progesterone stimulates alveolar development in the presence of the permissive anterior pituitary hormones: LH, FSH and growth hormone (Niewoehner and Schorer 2008).

15.4 Radiological Features of Gynaecomastia

There are three main mammographic appearances of gynaecomastia, namely, nodular, dendritic and diffuse. Nodular gynaecomastia appears as a fan-shaped density radiating from the nipple; it may be symmetrical or more prominent in the upper outer quadrant. The density usually blends gradually into the surrounding fat but may be more spherical (Cooper 1994; Dershaw 1986; Michels et al. 1977; Chantra et al. 1995). Pathologically, a nodular pattern on mammography correlates with florid gynaecomastia which is characterised by hyperplasia of the intraductal epithelium within a loose stroma and surrounding oedema (Appelbaum et al. 1999). The other mammographic appearance of gynaecomastia is the dendritic pattern (Michels et al. 1977). This consists of a retro-areolar soft tissue density with prominent extensions that radiate into the deeper adipose tissue. The pathological features of the dendritic pattern consist of ductal proliferation within a dense stroma, so called fibrous gynecomastia and is a feature of longstanding disease (Appelbaum et al. 1999; Chantra et al. 1995). The third mammographic pattern of diffuse glandular gynaecomastia has a mammographic appearance of a heterogeneous dense female breast (Appelbaum 1997; Wershaw 1986; Chantra et al. 1995).

Appelbaum and colleagues (1999) carried out a mammographic review of 65 patients with gynaecomastia. In 61 patients with histologically proven gynaecomastia, 47 (77 %) of cases were classified as nodular, 12 (20 %) dendritic and 2 cases (3 %) as diffuse glandular. The mammographic appearances of male breast cancer are different from gynaecomastia. In male breast cancer, the density tends to be in the subareolar location (see Sect. 15.7) but occasionally eccentric. The margins may be well defined, ill-defined or speculated. The cancer may be round, oval or irregular and is frequently lobulated. Calcification, when present, is coarser and frequently rod shaped when compared to that seen in female breasts (Appelbaum 1999; Cooper 1994; Wershaw et al. 1993). Gynaecomastia can mask the presence of breast cancer.

The nodular pattern of gynaecomastia described by Appelbaum and colleagues (1999) is illustrated in Fig. 15.1 in a patient on diethylstilbestrol for prostatic cancer. There is a soft tissue density behind the nipple with radiation of fibrous strands into the surrounding fatty tissue. The mammograms also show excess fat which makes the volume of breasts tissue almost equivalent to that of female breasts. He subsequently underwent bilateral mastectomy.

Mammography is the main modality used to assess gynaecomastia in older men and

sonography is used mainly to assess prepubertal gynaecomastia (Welch et al. 2004). To obtain a better perspective of the sonographic abnormalities in gynaecomastia, Dialani and colleagues (2010) retrospectively reviewed sonographic features of 153 men with gynaecomastia in conjunction with the mammographic images. In this cohort, 38 men presented with pain, 95 men with a lump, 17 men with pain and a lump and three men with nipple discharge. A total of 219 sonographic images were performed consisting of 66 bilateral (132 breasts) and 87 unilateral. Masses were reported in 73 % of the 219 (33 %) images, and 146 breasts had no masses. The sonographic images were categorised into four patterns:

(i) Nodular – discrete round or oval hypoechoic area in the retro-areolar region
(ii) Poorly defined – vague hypoechoic area in the retro-areolar region
(iii) Flame shaped – irregular hypoechoic area with extensions into the surrounding tissue
(iv) Increased anteroposterior (AP) depth at the nipple defined as greater than 1 cm depth of breast parenchyma at the nipple (which may be isoechoic, hypoechoic or hyperechoic)

In this study Dialani and colleagues (2010) reported the presence of 73 (33 %) masses, of which 20 (27 %) were nodular; 20 (27 %) poorly defined and 33 (45 %) flame shaped. All masses were retro-areolar with 57 (78 %) hypoechoeic, 54 (73 %) avascular, 60 (82 %) parallel to the chest wall and 47 (64 %) without posterior enhancement or shadowing. Of the 146 (67 %) images without masses, 141 (97 %) had increased AP depth at the nipple. The authors concluded that gynaecomastia is a clinical diagnosis and mammography was the primary imaging modality. However, if mammography was declined (as this may be quite uncomfortable in men with smaller breasts than women) or mammography is inconclusive, sonography should be utilised, and it is important to recognise

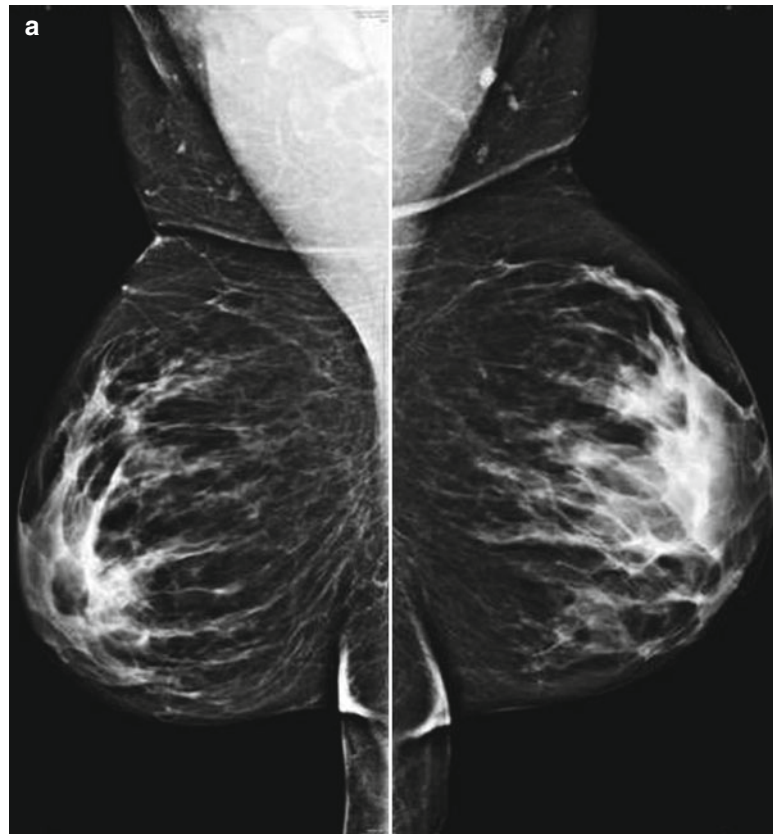
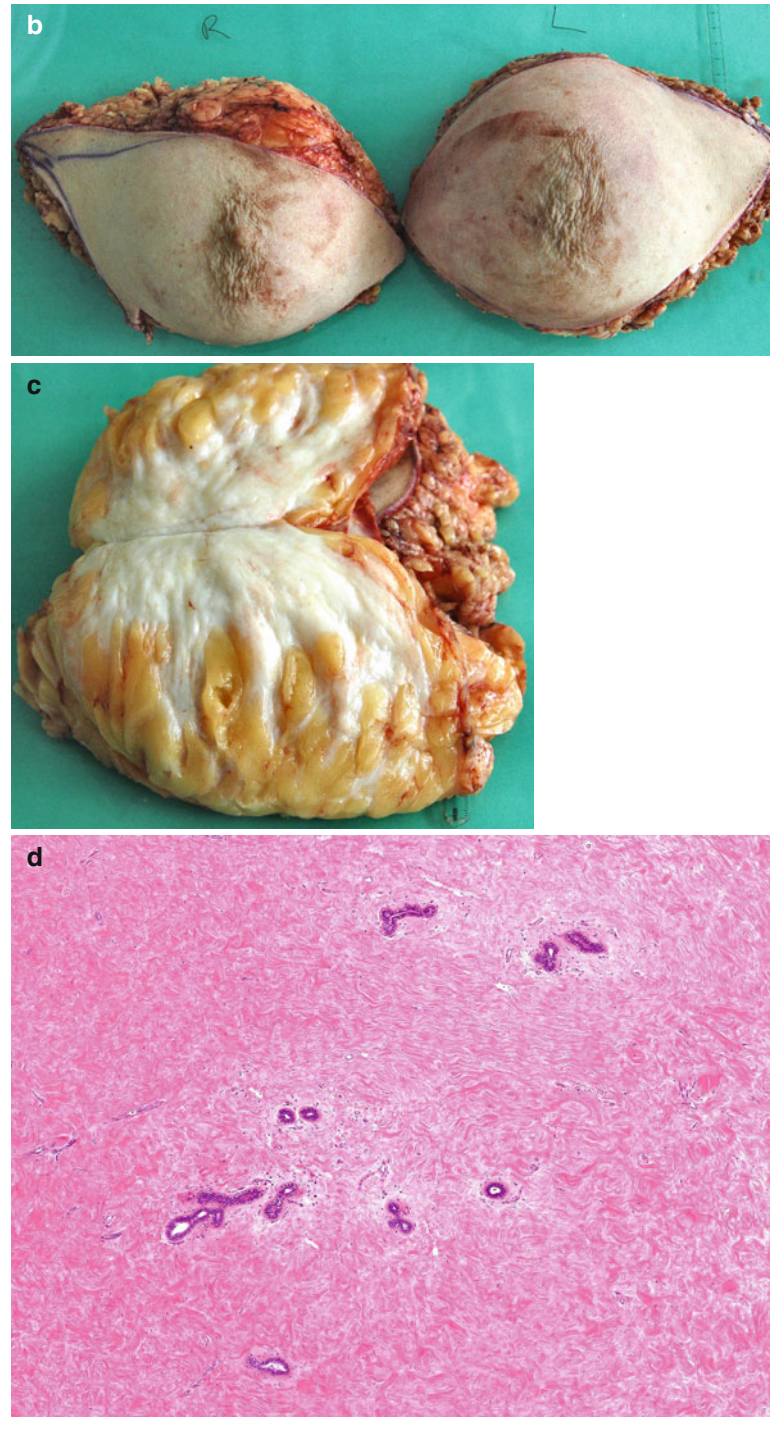


Fig. 15.1 (**a**) Mammography in patient with bilateral gynaecomastia showing central dense tissue behind the nipple which radiates into the surrounding fibrofatty tissue. (**b**) He subsequently underwent bilateral mastectomy. (**c**) The cut surface has a white fibrous texture with no haemorrhage or necrosis. (**d**) The histology consists of dense hyalinised stroma with characteristic male abortive TDLUs. Hyalinised stroma indicates gynaecomastia present for a long duration

Fig. 15.1 (continued)



the various sonographic patterns of gynaecomastia to avoid unnecessary biopsies.

15.5 Pathological Features of Gynaecomastia

Gynaecomastia is either bilateral or unilateral. In the later, it is not clear why one breast should respond to oestrogen stimulation and not the other. A patient on stilboestrol for prostate cancer had bilateral gynaecomastia and underwent bilateral mastectomy. The right breast weighed 1,288 g and the left 1,043 g, weights normally expected of female breasts (Fig. 15.1b). The cut surface had a white rubbery tissue, radiating from the nipple and fanning out into the surrounding fatty tissue (Fig. 15.1c). The histology showed hyalinised fibrous stroma containing abortive TDLUs typical of male breast (Fig. 15.1d). Hyalinised fibrosis indicates gynaecomastia of long duration. The TDLU appear atrophic and there are no luminal secretions. The patient may have stopped the stilboestrol at the time of surgery.

Another patient had unilateral gynaecomastia (Fig. 15.2). He did not have any imaging investigations. The mastectomy specimen showed diffuse replacement of the beast tissue by white fibrous tissue with a rubbery texture. On microscopic examination there is epithelial hyperplasia with abortive male TDLUs and luminal secretions surrounded by stroma with features of PASH.

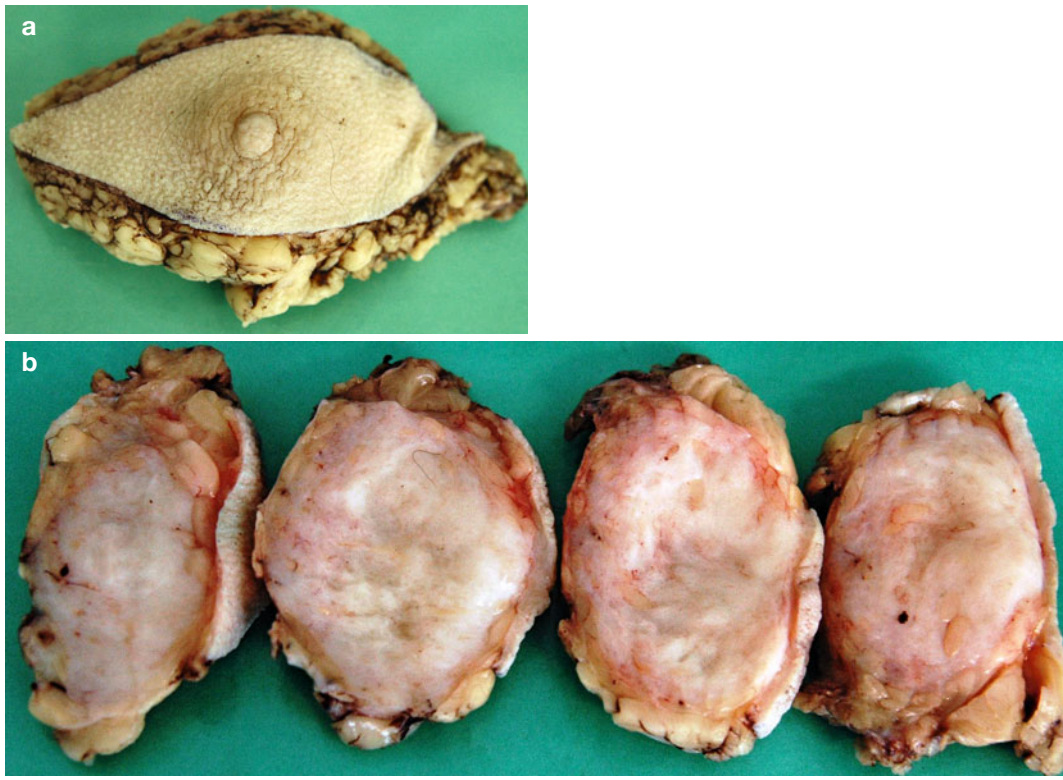


Fig. 15.2 (**a**) Mastectomy for unilateral gynaecomastia in a patient with liver disease. (**b**) The cut surface shows diffuse rubbery white tissue involving the whole breast. This patient had no imaging investigations. (**c**) The histology consists of stroma containing abortive male TDLUs. (**d**) At high magnification there is epithelial hyperplasia and luminal secretions in the background of stroma with features of PASH

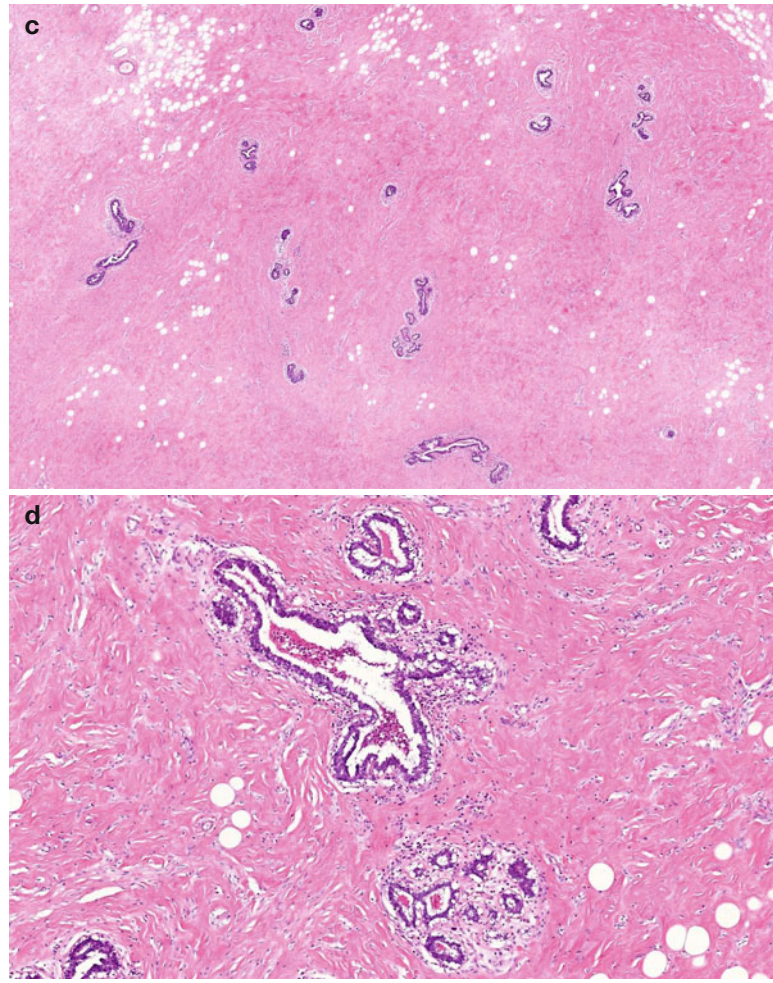


Fig. 15.2 (continued)

15.6 Treatment for Gynaecomastia

Physiological gynaecomastia required no treatment as this resolves spontaneously. Drug-induced gynaecomastia will resolve if the offending drug is withdrawn, especially if of recent onset. Testosterone replacement in hypogonadal men can be beneficial, but long-standing fibrotic gynaecomastia is unlikely to respond (Niewoehner and Schorer 2008).

Treatment with tamoxifen reduces pain and breast volume in 40–80 % of boys with pubertal gynaecomastia and men with prostate cancer treated with androgen receptor blocker bicalutamide (Boccardo et al. 2005). Local radiation and tamoxifen can also be used to treat men with bicalutamide-induced gynaecomastia (Perdona et al. 2005). Surgery is the treatment of choice for gynaecomastia causing persistent pain or embarrassment. The aims of surgery are to remove abnormal breast tissue,

restoring the normal breast contour and reducing pain. Subcutaneous mastectomy is required for removal of glandular tissue and redundant skin and pain relief (Niewoehner and Schorer 2008).

15.7 Gynaecomastia and Male Breast Cancer

Male breast cancer represents approximately 1 % of all cases of breast cancer in the developed countries, but in sub-Saharan Africa, 7–14 % of breast cancer occurs in men (Niewoehner and Schorer 2008). High oestrogen states which induce gynaecomastia are also a risk factor for breast cancer. Patients with Klinefelter's syndrome who develop testicular failure shortly after puberty have a 58-fold risk of developing breast cancer compared to normal males, with an absolute risk that approaches 3 % (Swerdlow et al. 2005). In a separate nested case control study of 41 Swedish men who developed cancer after treatment for prostate cancer, the risk was higher in men treated with oestrogen than in other survivors of prostate cancer (Karlsson et al. 2006).

Family history of breast cancer also increases the risk of male breast cancer. BRCA2 is associated with the risk of both breast and prostatic cancer. Male carriers of BRCA2 have a cumulative risk for breast cancer of 7 % by the age of 80 (Niewoehner and Schorer 2008). Ashkenazi Jews have a higher prevalence of BRCA1 and BRCA2 and of increased risk of male breast cancer than the general population (Struewing et al. 1997).

A man presented with unilateral nipple retraction (Fig. 15.3). The mammographic appearances of gynaecomastia are distinctly different from those of male breast cancer. The mammogram of the left breast shows an irregular speculated subareolar density which is clearly malignant. The ultrasound shows an irregular shadow fanning out from the nipple which corresponds to the whole mount section of the cancer on histological examination.

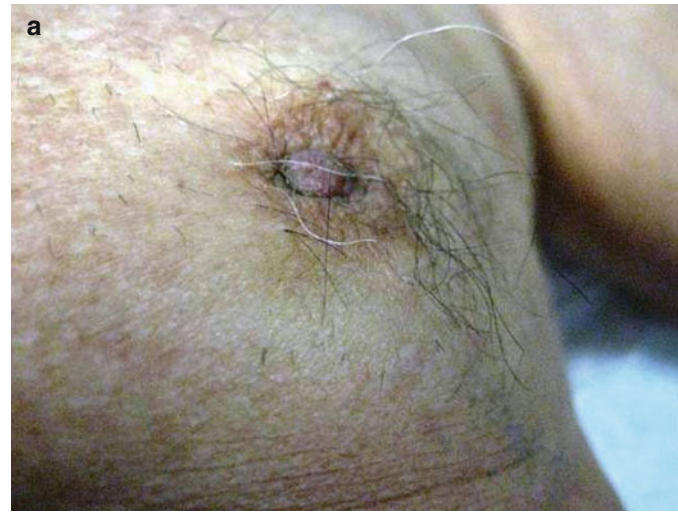


Fig. 15.3 (**a**) A man presented with nipple retraction of the left breast due to breast cancer. (**b**) The mammogram showed a localised subareolar soft tissue density, which is different from gynaecomastia. (**c**) The ultrasound revealed an irregular malignant speculate mass. (**d**) The whole mount histological section shows invasive carcinoma which corresponds to the ultrasound image

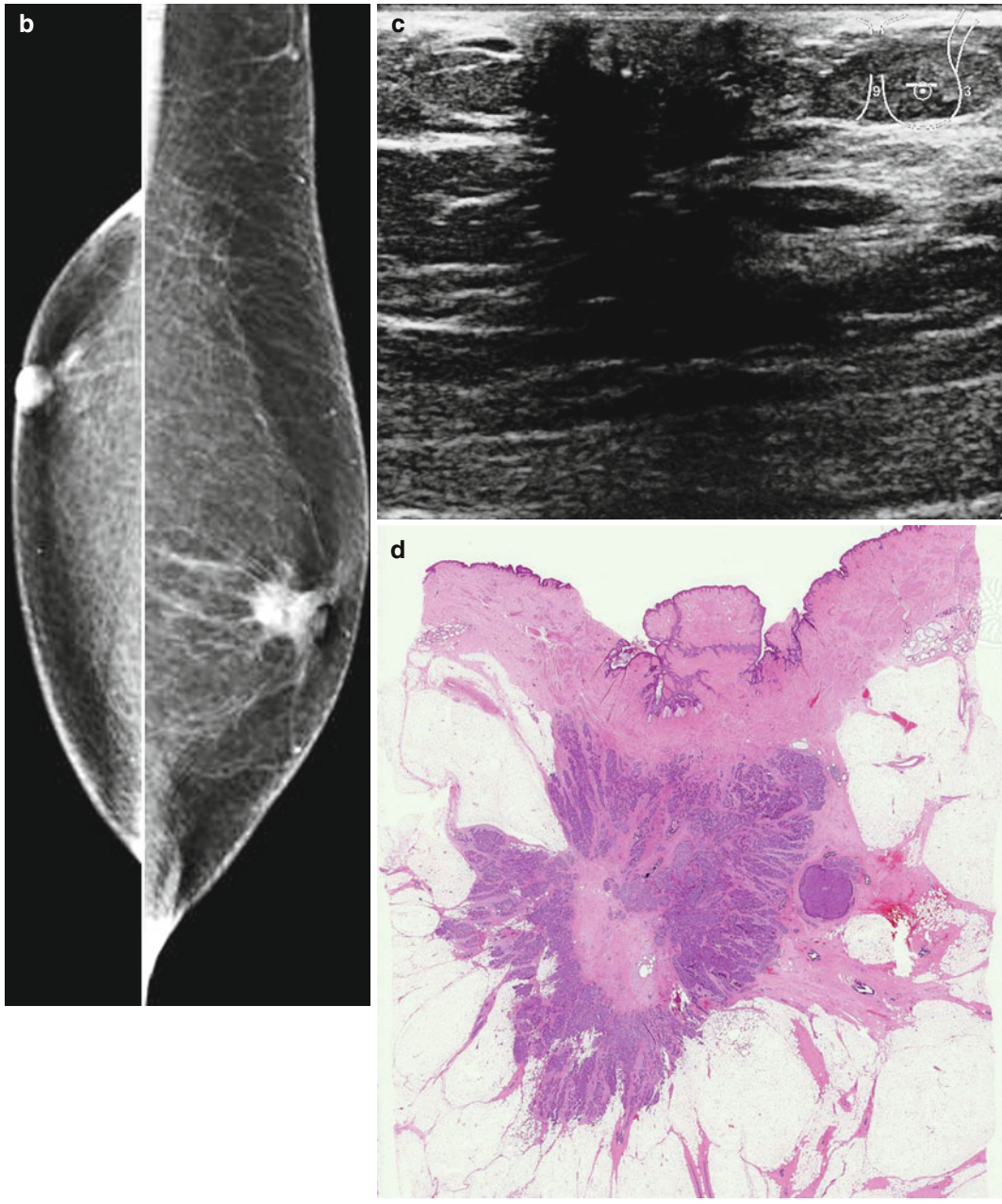


Fig. 15.3 (continued)

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Risk Assessment in Benign Breast Lesions

16

Learning Points

- Accurate assessment of risk of breast cancer due to benign breast lesions is affected by previous use of different terminology.
- Accurate risk assessment is essential in counselling women at risk of developing breast cancer.
- Risk assessment is important in decision-making with regard to screening programmes, prophylactic treatment and surveillance of women at risk.
- Age, family history, menstrual history, parity and any previous surgery for breast disease are taken into account when assessing risk of developing cancer.
- Alcohol increases the risk of breast cancer by increasing serum oestrogens concentration.
- Future risk assessment models should include the mammographic and pathological results of benign breast disease.

16.1 The Concept of Risk Assessment in Benign Breast Lesions

Benign breast lesions can present symptomatically or mammographically detected through screening programmes. Risk assessment is important for both the clinician and the patient to assist in making decisions regarding screening, prophylactic treatment and surveillance. Because of widespread use of mammography, clinically silent benign lesions are now easily detected, leading to pathological assessment to exclude the presence of malignancy. Fine needle aspiration cytology, needle core biopsies and excision biopsies are the methods used to confirm benignity and allay patient anxiety. When a woman has a diagnosis of benign breast disease, more often than not she wishes to know what is the likelihood of the benign lesion predisposing to cancer at a later stage. With some conditions, such as fat necrosis, duct ectasia or hyalinised fibroadenoma, the clinician can reassure the patient confidently that there is no risk of developing cancer. However, some benign proliferative lesions confer an increased risk of subsequent malignancy, although in most cases the risk is very small. These conditions require careful explanation to the patient, not to alarm them but to encourage compliance with follow-up. The advantage of assessing the possible risk of progressing to malignancy in benign disease is that regular clinical and radiological follow-up can detect malignancy at an early, potentially curable stage.

Risk assessment is based on epidemiological studies, which combine demographic factors and pathological features of the benign lesions. However, accurate risk assessment of benign breast lesions can be hindered by the differences in terminology used in different publications as illustrated in the previous chapters with columnar

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9_16, © Springer-Verlag Berlin Heidelberg 2014

cell lesions being a typical example. Until recently, most benign lesions were clinically and pathologically classified under the collective term 'fibrocystic disease' (Page et al. 1978; Love et al. 1982; Hutter et al. 1986). Although attempts have been made to standardise classification of benign lesions, inter- and intraobserver variation among pathologists when classifying atypical proliferations can reduce or increase the perceived risk of subsequent malignancy of a particular proliferative lesion.

Because of the above confounding factors, the actual incidence of benign breast disease is also variable, Ernster (1981). In a case-controlled study in Greater Boston, Cole et al. (1978) reported the incidence of benign breast disease to be 89.4 and 32.8 per 100,000 women for 'fibrocystic disease' and fibroadenoma, respectively. In Western Australia, Fleming et al. (1982) reported benign breast disease to be 420.2/100,000 women. The breast lesions in the latter study were classified into 'benign mammary dysplasia' and fibroadenoma. Prior to the introduction of the terminology which unified benign breast disease, the above conflicting figures would place the clinician in a difficult position as to which publication to believe. A woman with a mixed benign breast disease (busy breast) will no doubt have a higher risk of developing cancer than a woman with fibroadenoma.

16.2 Defining Risk and Related Terms

16.2.1 Definition of Risk

There is no readily available medical literature on the definition of risk and most useful information is in industry or technology-based publications. Fischhoff and Watson (1984) outlined in their essay the controversies around defining risk. They stated that 'risk is a focal topic in the management of many activities and technologies'. For that management to be successful, an explicit and accepted definition of the term 'risk' is essential. Although this essay is on risk in general with regard to day-to-day industry and technology, it is applicable to assessing the risk for breast cancer or any other disease process because they further explain that 'the choice of definition can affect the outcome of policy debates and allocation of resources'. They also highlight the technical distinction between objective and subjective risk, the former being a product of scientific research, public health statistics, experimental studies, epidemiological surveys and probabilistic risk analysis. In contrast, subjective risk is the public perception of that research. They also highlight the effects of comparing different scientists which can affect the relative riskiness of technologies. This is clearly illustrated in this book when different authors assess the relative risk of ADH, which ranges from 4 to 13 times that of the general public depending on which publication one reads (Dupont and Page 1985; Palli et al. 1991). However, in this paper Fischhoff and Watson do not provide the reader the definition of risk but highlight various factors to consider in assessing risk for any situation, which is also applicable to breast cancer. The factors the authors evaluated include the following:

(i) Objective and subjective nature of the risk.
(ii) Dimension of the risks, as risk is not a single consequence, e.g. in giving prophylactic tamoxifen to patients with ADH one should consider whether the risk of breast cancer outweighs the risk of endometrial cancer or death from thromboembolism.
(iii) Taking into consideration summary statistics, which in benign breast disease several publications have done to evaluate the risk associated with different proliferative lesions of the breast.
(iv) Willingness to count delayed effect of the risk, i.e. the evaluating of the risk is not bound by time as illustrated by the Gail Model which assesses risk in women aged 35–90 years of age. Furthermore, does circumventing one risk exposes individuals to another risk, e.g. use of prophylactic tamoxifen above.
(v) The event should be one which threatens people's health and safety sufficiently to raise concern, i.e. concern over developing breast cancer with risk of dying from the disease.

There is no definition of risk in the National Cancer Institute online dictionary of medical words. The online Oxford Dictionaries (British and World English) define risk as 'a situation involving danger'. A better definition of risk is provided in online business dictionary which provides 'a probability or threat of damage, injury, liability, loss or any other negative occurrence that is caused by external or internal vulnerabilities, and that may be avoided through pre-emptive action' (Business Dictionary). The dictionary provides several examples of risks including that on cancer which is described as the consequence and probability of a hazardous event or phenomenon, i.e. the risk of developing cancer is estimated to be an incremental probability of developing cancer over a lifetime as a result of exposure to potential carcinogens.

16.2.2 NCI Dictionary of Cancer Terms Relative Risk

Risk assessment for breast cancer is divided into relative risk and absolute risk. The National Cancer Institute Dictionary of Medical Terms (NCI Dictionary of Cancer Terms) defines relative risk as 'a measure of risk of a certain event happening in one group compared to the risk of the same event happening in another group'. In cancer research, relative risk is used in prospective (forward looking) studies such as cohort studies and clinical trials. A relative risk of one means there is no difference between two groups in terms of their risk of cancer based on whether or not they are exposed to a certain substance or factor or how they respond to two treatments being compared. A relative risk of greater than one or of less than one usually means that being exposed to a certain substance or factor either increases (relative risk greater than one) or decreases (relative risk less than one) the risk of cancer or that the treatments being compared do not have the same effect, also called the 'risk ratio'.

Most relative risk estimates are from longitudinal studies and have been derived under the assumptions that the woman's relative risk remains constant over time. However, it is possible that the relative risk of individual patients varies with age or the time since the original biopsy. To illustrate this point, Dupont and Page (1985, 1989) demonstrated that the relative risk of developing breast cancer in women with atypical hyperplasia and proliferative disease without atypia (PDWA) is greatest during the first 10 years of follow-up. Women with PDWA who remain disease-free after 10 years will no longer be at risk of breast cancer when compared with women of a similar age group without PDWA. Similarly, the relative risk of breast cancer in women with atypical hyperplasia is halved if they remain cancer-free for 10 years following the initial biopsy. This supports the notion that atypical hyperplasia may not be an obligate precursor of breast cancer and that the lesion may progress to breast cancer, remain static or regress over a period of time. However, the absolute risk of women with atypical hyperplasia remained constant over a period of 17 years of follow-up (Dupont and Page 1985). The clinical significance of this time-dependent analysis is that, depending on other factors, it will allow women with atypical hyperplasia to be closely followed up during the first 10 years of diagnosis. If the woman has not developed cancer at 10 years or more during follow-up, she can be reassured that her risk is now closer to that of the general population than it was at the time of the diagnosis of atypical hyperplasia, although the absolute risk per year has remained the same.

16.2.3 Absolute Risk

The National Cancer Institute Dictionary of Cancer Terms (NCI Dictionary of Cancer Terms) defines absolute risk as 'a measure of risk of a certain event happening'. In cancer research, it is the likelihood that a person who is free of a specific type of cancer at a given age will develop that cancer over a certain period of time. For example, a woman of 35 years of age with no known risk factors for breast cancer has an absolute risk of developing breast cancer over a lifetime of 90 years of about 13.5 % meaning one out of every seven women will develop breast cancer by the age of 90.

Absolute risk is more informative than relative risk and can be determined over time intervals of 10–20 years when the corresponding relative risk estimates have been accurately determined (Dupont and Plummer 1996). To the patient, it is more important to know that the absolute risk of developing breast cancer if one had ADH is 10 % over a period of 10–15 years than to be told the relative risk of developing cancer is four times that of the general population. Although absolute values give a more accurate assessment of risk, they require lengthy follow-ups of large numbers of patients with similar risks (Dupont and Page 1989). For this reason, patient management is usually based on estimation of relative risk.

16.2.4 Risk Factors

For the probability of an event to occur, the individual must be exposed to a risk factor. This is another term which is not clearly defined in medical literature. As explained by Dr Brian Burt at the Department of Epidemiology (University of Michigan), the literature is unclear whether risk factors should be truly causal, i.e. a link in the aetiological chain or whether it is more peripherally associated with an outcome (Burt BA Definitions of risk). This statement is pertinent to benign breast lesions where it is not always clear whether the presence of a proliferation will directly metamorphose into breast cancer or it is just a marker of the likelihood that cancer will develop at some point in the woman's lifetime.

In the dictionary of epidemiology, risk factor is defined as 'an aspect of personal behaviour or lifestyle, an environmental exposure, or an inborn or inherited characteristic which on the basis of epidemiological evidence is known to be associated with health-related condition(s) considered important to prevent' (Last 2001). Some examples cited as risk factors for cancer are age, a family history of certain cancers, use of tobacco products, being exposed to radiation or certain chemicals, infection with certain viruses or bacteria and certain genetic changes. This definition is wider and more inclusive when compared to the National Cancer Institute definition which defines risk factor as 'something that increases the chance of developing a disease'.

An equally informative definition of risk factor is that provided by Dr Beck (1998) which states that 'a risk factor is an environmental, behavioural or biological factor confirmed by temporal sequence, usually in longitudinal studies, which if present increases the probability of a disease occurring, and if absent reduces the probability'. Risk factors are part of the causal chain. Once disease occurs, removal of a risk factor may not result in a cure. Dr Beck (1998) explains that this definition is more specific as there is

(a) Emphasis on the temporal sequence of exposure before outcome.
(b) The acceptance that a risk factor is part of the causal chain.
(c) The acceptance that risk factors are involved in disease onset, not necessarily in future progression or resolution.

The definition by Dr Beck is clearly applicable for ADH as risk factor for breast cancer in that

(a) This proliferation has to be there before development of cancer.
(b) ADH is considered part of causal chain to breast cancer because of the shared genetic alterations between ADH, DCIS and invasive cancer.
(c) ADH is involved in onset but not the progression of cancer as other growth factors are involved.

16.2.5 Risk Marker

If some risk factors in breast cancer are part of the causal chain, this raises the question what is a risk marker? The dictionary of epidemiology (Last 2001) defines a risk marker as 'an attribute or exposure that increases the probability of occurrence of disease or specified outcome'. This would apply to a lesion such as ALH which some consider to be a marker of rather than a causal factor of invasive breast cancer because the resultant breast cancer and can be either ductal or lobular and affect both breasts. In contrast, ADH is considered to be a causal link in the pathogenesis of breast cancer and is also a modifiable risk factor, i.e. a determinant that can be modified by intervention, thereby reducing the probability of disease (Dictionary of Epidemiology, Last 2001).

There is evidence that prescribing prophylactic tamoxifen to women with ADH reduces the risk of developing cancer, however, the same applies to ALH (Chuba et al. 2005).

16.3 General Risk Factors for Breast Cancer

16.3.1 Genetic Factors

Assessment of risk factors for breast cancer can be divided into those individuals who have a familial predisposition because they carry a genetic mutation such as BRCA1 and BRCA2 and those without a mutation (Parmagiani et al. 1996). Five to ten percent of breast cancer occurs as a result of genetic predisposition caused by a mutation in a single cancer susceptibility gene which confers considerable risk (Vogel and Bevers 2003). Features of familial breast cancer include

- Breast cancer in two or more relatives from the same lineage
- Early age at diagnosis (<50 years of age)
- Bilateral disease
- Multiple primary tumours (breast and ovarian)
- Group of features consistent with a genetic syndrome
- Male breast cancer
- Ashkenazi Jewish ancestry
- A relative with a mutation in a known cancer susceptibility gene.

BRCA1 gene and BRCA2 genes which predispose to hereditary breast and ovarian cancer account for 81 % and 14 % of hereditary breast cancer, respectively (Ford et al. 1998). Other genetic syndromes associated with familial breast cancer include Cowden syndrome, Li-Fraumeni syndrome, ataxia-telangiectasia heterozygotes and Peutz–Jeghers syndrome (Vogel and Bevers 2003). The UK NICE recently recommended the use of tamoxifen for chemoprevention in women with high risk of developing cancer due to familial predisposition (June 2013). In addition to the above risk factors the NICE Guidelines include

- Sarcoma in a relative younger than 45 years of age
- Glioma or childhood adrenocortical carcinomas
- Complicated patterns of multiple cancers at a young age
- Very strong paternal history (for relatives diagnosed at younger than 60 years of age on the father's side of the family)

16.3.2 Hormonal Factors

Hormonal changes play an important role and reduce or increase the risk of breast cancer in an individual. Early menarche (<12 years), late menopause (>55 years), nulliparity or first born child after 30 years and current use of oral contraceptives are associated with increased risk of breast cancer (Vogel and Bevers 2003). The risk is due to the high levels of circulating oestrogens.

Earlier studies published conflicting evidence as to whether hormone replacement therapy (HRT) is associated with an increased risk of breast cancer or not (Dupont et al. 1999). The presence of oestrogen and progesterone receptors in the breast tissue makes it sensitive to circulating hormonal therapy. A meta-analysis of 51 international case control and cohort studies found no appreciable increased risk of breast cancer in women on short-term oestrogen replacement therapy of less than 5 years, (Manson and Martin 2001). However, long-term use of oestrogen replacement therapy (>5 years) was associated with an increased risk of 35 %. A separate study by the Writing Group for Women's Health Initiative Investigators, reported an increased risk of 26 % in women on combination HRT (2002).

A multicentre study involving over one million women, in which 9,364 women developed cancer and 637 women died from breast cancer, Beral and the Million Women Study Collaborators (2003) observed that current users of HRT were more likely than 'never users' to develop cancer (adjusted RR = 1.66, 95 % CI = 1.58–1.75, $P < 0.0001$) and to die from breast cancer (RR = 1.22, 95 % CI = 1.00–1.48, $P = 0.05$). The risk of breast cancer was increased much more with combined oestrogen and progesterone preparations than with oestrogen only and other preparations. Long duration of HRT use, up to 10 years, was also associated with an increased risk. Based on these findings, it may be clinically advantageous to assess the

parenchymal density of the women before they commence HRT and offer shorter interval screening periods for those with a significant increase in parenchymal density while on HRT. This may detect women with early cancer when this is potentially curable. Selective oestrogen-receptor modulators (SERMs) such as tamoxifen and raloxifene may be an alternative to HRT for women at risk for breast cancer (Vogel et al. 2010).

16.3.3 Alcohol as a Risk Factor

There is accumulating evidence that alcohol intake is associated with increased risk of breast cancer (Vogel and Bevers 2003; Longnecker 1994; Longnecker et al. 1995; Rosenberg et al. 1993). The following mechanisms have been implicated:

- Induces increased levels of circulating oestrogen
- Stimulates hepatic metabolism of carcinogens such as acetaldehyde
- Facilitates transport of carcinogens into the breast tissue
- Stimulates pituitary production of prolactin
- Modulates cell membrane integrity with an effect on carcinogenesis
- Aids production of cytotoxic protein products
- Impairs immune surveillance
- Interferes with DNA repair
- Promotes production of toxic congeners
- Increases exposure to toxic oxidants
- Reduces intake and bioavailability of protective nutrients

Coutelle and colleagues (2004) demonstrated that oral intake of alcohol in women with alcohol dehydrogenase 1C*1 allele, which rapidly metabolises alcohol to produce increased levels of acetaldehyde have increased levels of serum estradiol. The women with this alcohol dehydrogenase genotype were 1.8 times more at risk of developing breast cancer than women without the genotype (95 % CI 1.431–2.330, $p<0.001$). Thus, individuals with this genotype increase their risk of breast cancer if alcohol is consumed in excess, resulting in increased blood oestrogen concentration.

In a previous study, Wright et al. (1999) proposed that metabolism of alcohol produced reactive oxygen species which induce carcinogenic mutations and damage to DNA predisposing to breast cancer. The amount of alcohol consumed is directly proportional to the risk of breast cancer. Drinking 10 g of alcohol (one drink daily) is associated with relative risk of 1.09 when compared to non-drinkers. Increasing alcohol consumption to 30–60 g/day (2–5 drinks) increased the relative risk of breast cancer to 1.41 when compared to non-drinkers (Smith-Warner et al. 1998). Alcohol consumption in individuals with family history of breast cancer increases the RR of developing breast cancer to 2.45 (Vachon et al. 2001). The risk is similar for beer, wine and liquor (Smith-Warner et al. 1998).

16.3.4 Other Risk Factors for Breast Cancer

Other factors associated with increased risk of breast cancer are old age and high body mass index (BMI), but there is no evidence that diet and exercise influence the occurrence of breast cancer (Vogel and Bevers 2003). As already illustrated in the previous chapters, different types of benign proliferative disease confer varying degrees of risk of subsequent breast cancer and these will be summarised in this chapter.

16.4 Radiological Risk Factors

16.4.1 Wolfe's Breast Parenchymal Patterns

John Wolfe highlighted the concept of breast cancer risk based on mammographic parenchymal patterns, and most of the publications on this subject were in 1976. Age, pregnancy, thyroid hormone levels, endogenous and exogenous hormones can influence breast parenchymal appearances. Wolfe classified the appearance of the breast parenchyma into four categories irrespective of vasculature, presence or absence of masses, calcifications, parity, family history of

breast cancer or age of the patients. He noted four breast parenchymal patterns, which he classified as follows:

N1 = Normal, consisting of mostly fat (fatty breasts).

P1 = Consists of mostly fat but in the subareolar area or other quadrant, there is a linear pattern of prominent ducts.

P2 = Breast parenchymal with more prominent duct pattern. The ducts exhibit a triangular disposition in the central portion of the breast. This pattern involves more than a quarter of the breast volume.

DY (for 'dysplasia') = Generalised increase in the density of the breast parenchyma with or without prominent ducts.

The exact histological features of 'dysplastic' breast tissue are not clear from Wolfe's original study (Wolfe 1976a). However, Wellings and Wolfe (1978) carried out a radiological and pathological correlation of tissue from the different parenchymal patterns. This included subgross analysis of the excised breast tissue. The histological features of the different parenchymal patterns were reported as follows:

N1 = Fat, delicate vascular elements, fibrous bands containing normal lobules

P1 = Increased periductal and perilobular fibrosis. The lobules were normal

P2 = Increase in fibrosis with 'moderate epithelial atypia'

DY = Marked fibrosis. 'Overt atypical' lobules and incidental cysts present.

16.4.2 Parenchymal Patterns and Risk of Breast Cancer

When Wolfe (1976b) assessed the different radiological parenchymal patterns in relation to the risk of breast cancer, the incidence of detecting cancer in the N1, P1, P2 and DY parenchymal patterns was 0.1, 0.4, 1.7 and 2.2 %, respectively, indicating that dense breast carried the highest risk of harbouring malignancy. Based on these results, the risks of the parenchymal patterns were assessed as follows: N1 = minimal risk, P1 = moderate risk, P2 = significant risk, DY = highest risk.

In a subsequent report, Wolfe (1976c) followed up 995 women who had undergone mammography over a period of 15 years (range 5–15 years). All women had presented symptomatically (age range 30–49 years). The study reported that breasts initially classified as N1, P1 or P2 rarely changed their parenchymal density with age. In contrast, breasts classified as DY mostly regressed to P2, which is still a high-risk category, with some breasts regressing to P1 or N1. These changes occurred between 35 and 50 years. In a similar but separate study, Wolfe et al. (1987) reported that most breast cancers occurred in the P2 breast, with decreasing frequency in the DY, P1 and N1 parenchymal patterns. In this case-controlled study of 160 women who had presented symptomatically (mean age 53 years), the RR of developing breast cancer was 3.3 in women who had P2 or DY patterns when compared with women who had N1/P1 patterns. Black women had a higher risk of 5.2 when compared with white women with an RR of 2.3 for the P2 and DY parenchymal patterns. Women younger than 53 years had a lower RR of 2.8 compared with 3.8 for women older than 53 years if their mammograms exhibited the P2 and DY parenchymal patterns.

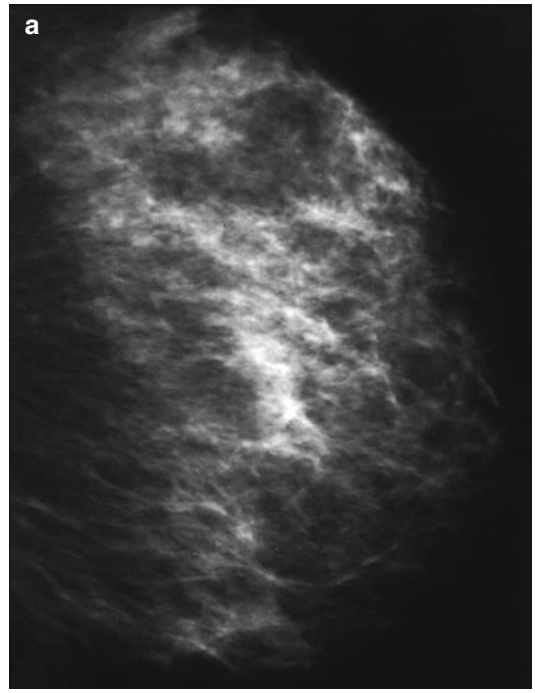
In a separate study, Saftlas and colleagues (1991) assessed parenchymal density in women undergoing screening mammography. The authors reviewed mammograms that were taken 4 years prior to diagnosis of breast cancer to determine whether increased mammographic density was predictive of breast cancer risk. The median ages of the women were 54 and 53 for the study cases ($n = 266$) and controls ($n = 301$), respectively. This study applied planimetry to assess the percentage of mammographic density and this had a better predictive value than Wolfe's parenchymal patterns. The odds ratios (OR) of breast cancer increased steadily with increasing breast density ($P < 0.0001$). The breast cancer OR were 1.7 for women with 5–24.9 % parenchymal density, 2.5 for women with 25–44.9 % parenchymal density, 3.8 for women with 45–64.9 % parenchymal density and 4.3 for women with densities over 65 %. These OR were irrespective of other breast cancer risk factors such as family history of cancer or age at first parity.

Byrne et al. (2001) assessed the histological features of benign breast disease and mammographic density of the breast in a case-controlled study of 347 women who developed breast cancer and 410 women without breast cancer. Adjusting for mammographic density, the OR for subsequent cancer for atypical hyperplasia was 2.1. In contrast, adjusting for benign breast histology, the OR for increased breast density of >75 % was 3.8. Women with non-proliferative benign breast disease and increased breast density of >75 % had an OR of 5.8, whereas women with breast density of less than 50 % and atypical hyperplasia had an OR of 4.1.

Previously, Friedenreich and colleagues (2000) assessed the mammographic density of fibroglandular tissue as a risk factor for subsequent malignancy in the screening age group. They assessed women who attended the Alberta Screening Programme in Canada. The women were asymptomatic, aged between 50 and 69 years and attended for breast screening biannually. The aim of the study was to determine whether women with histologically proven benign breast disease had a radiologically identifiable increase in breast tissue density. The study compared 165 biopsy-proven benign diseases with 217 women who had no histological evidence of proliferative breast disease. The proliferative benign disease was classified into multiple papillomas, radial complex sclerosing lesion, nodular adenosis, sclerosing adenosis, usual hyperplasia (moderate or florid), ADH and ALH. The mammographic content of fibroglandular tissue was assessed as follows: (1) fatty, (2) >0–<25 %, (3) 25–50 %, (4) 50–75 %, (5) >75 %. The women also responded to a questionnaire on demographic factors, which included smoking and dietary habits, menstrual and reproductive history, physical fitness, hormone usage and family history of benign proliferative breast disease. When all the demographic and radiological features were assessed, the authors found that women with increased fibroglandular density on mammography of >25 % had an increase in benign proliferative disease when compared with women with less than 25 % of fibroglandular tissue (OR = 1.91; 95 % CI = 1.24–2.94). Most studies that assessed benign breast disease for the potential risk of malignancy were based on symptomatic patients. The study by Friedenreich and colleagues should pave the way for prospective follow-up studies, which should combine demographics, radiological and histological features of benign proliferative disease to accurately prognosticate the risk factors in the screening age group. In a separate study, Boyd et al. (2000) reported a high prevalence of benign epithelial hyperplasias associated with increased mammographic densities of over 75 %. The benign epithelial hyperplasias were in turn risk factors for malignancy. The findings were comparable to those of Saftlas and colleagues (1991).

The association of breast cancer risk with increased breast tissue density has not been universally supported by other investigators (Mendell et al. 1977; Moskowitz et al. 1980; Arthur et al. 1990). In the UK Trial for Early Detection of Breast Cancer in Nottingham, Arthur and co-workers (1990) examined breast tissue from 119 women with a histological diagnosis of fibrocystic change with epithelial hyperplasia or in situ carcinoma. Women attending routine breast cancer screening were used as controls. The Nottingham study reported that the Wolfe patterns were related to the distribution of fibrous and adipose tissue in the breast interlobular stroma and appeared to have no relationship to the epithelial parenchymal content. Based on these findings, the authors concluded that radiological densities of P2 and DY patterns did not correspond to high-risk epithelial proliferations.

Despite the variation in the reports regarding the significance of breast tissue density as a risk factor for breast cancer, there is a growing evidence that increased breast tissue density may be a risk factor for subsequent malignancy. It is not clear whether the increased risk of malignancy associated with dense breasts is due to masking of small cancer because mammographic interpretation of dense breast is difficult, or whether mammographic density is an independent risk factor (Fig. 16.1). However, there is evidence that including mammographic density as a risk factor minimally improves the predictive accuracy of the Gail Model (Tice et al. 2006).



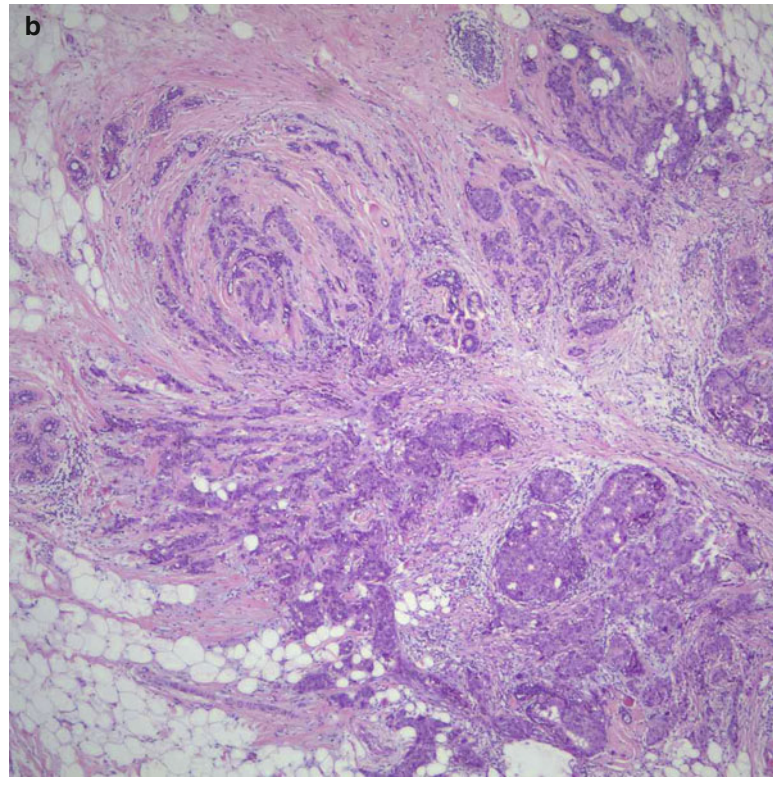
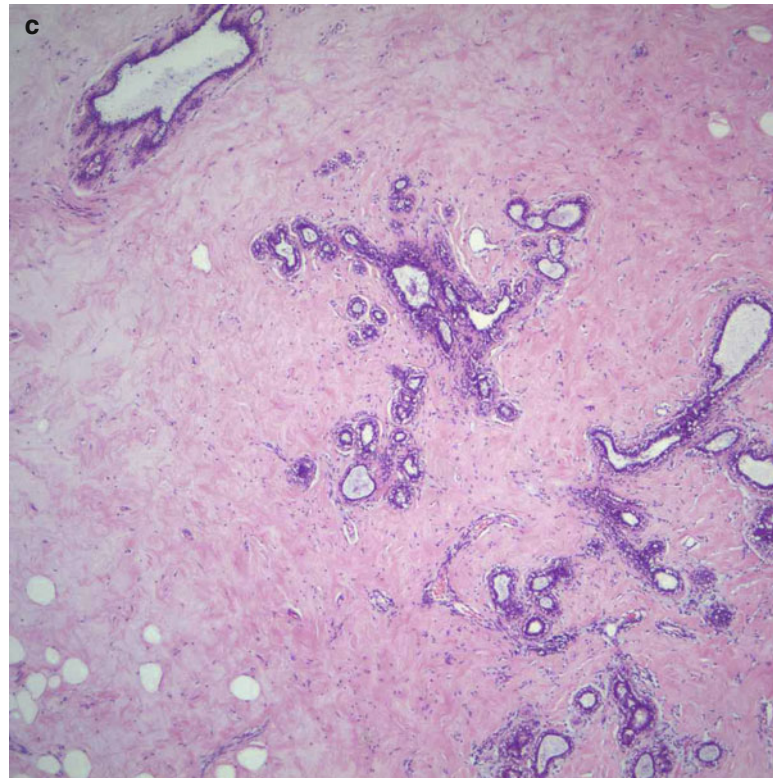


Fig. 16.1 (**a**) This mammogram illustrates moderately dense breast in a 45-year-old patient who presented symptomatically with ill-defined tender lumpiness in the left breast. There is no discrete lesion in mammograph. (**b**) Although there was no definite lesion on mammography, the patient requested to have the 'lump' excised. An incidental grade 3 carcinoma was identified on histology. (**c**) The rest of the breast tissue showed widespread fibrosis with atrophic duct–lobular units with areas of fat infiltration. There was no significant benign epithelial proliferation to explain the increased mammographic density

Fig. 16.1 (continued)



16.4.3 Effect of Hormone Replacement Therapy on Breast Density

Sterns and Zee (2000) assessed the effects of HRT on mammographic density when they compared the mammographic density of HRT users and non-users in 1,232 postmenopausal women attending their breast-screening clinic. This study showed that there was no difference in parenchymal density between postmenopausal women taking HRT and those who were younger than 55 years and not taking HRT. After the age of 55, the parenchymal density was reduced in non-users and remained at the pretreatment level in the majority of women taking HRT. However, in 8 % of the women, there was a reported increase in parenchymal density after HRT was commenced. The authors concluded that any adverse effect of HRT on the breast would have an impact on the epithelium and this may be reflected in the mammographic density.

16.5 Pathological Risk Factors

To assist in risk assessment, Dupont and Page (1985) classified benign breast disease into non-proliferative disease, proliferative breast disease without atypia and atypical hyperplasia. This is a useful concept for the pathologist, because once the benign disease has been categorised, it is easier to assign the associated risk of malignancy. As the pathologist plays a vital role in assessing the risk in benign breast disease to assist in the management of the patient, it is crucial that stringent criteria are applied in classifying benign proliferative disease. Inaccurate diagnosis of a high-risk lesion would subject women to unnecessary anxiety associated with frequent follow-ups, whereas misclassification into a low-risk lesion would miss women who require follow-up. In addition to inter- and intraobserver variation in the classification of benign breast disease, some breasts contain more than one significant epithelial proliferation and this can also make risk assessment difficult.

Benign disease can be classified as either markers or precursors of malignancy. Precursors of malignancy can also be considered premalignant lesions. Page (1986) defined a premalignant lesion as a condition whose natural history involves the evolution to malignancy, in the sense of threat of dealing with death. Page and Dupont (1990) further classified premalignant conditions into those already committed to progress to invasive carcinoma, such as ductal carcinoma in situ and indicators or markers of increased risk. The latter includes various benign proliferative diseases. At this juncture it is therefore appropriate to summarise the RR of the various benign lesions discussed in the previous chapters and where appropriate provide management strategy.

16.5.1 Relative Risk of Benign Breast Lesions and Their Management

The summary of RR of various proliferative lesions will be based on discussion in previous chapters but also on the review of high-risk benign breast lesions by Kiluk and colleagues (2007) who also provided management strategies. Kiluk's paper provides a pragmatic approach to high-risk benign breast lesions as it offers the clinicians management options to discuss with the patient.

16.5.1.1 Usual Ductal Hyperplasia (UDH)

The relative risk (RR) of usual ductal hyperplasia (UDH) ranges from 1.5 to 2 (Dupont and Page 1985), and the risk is independent of other risk factors such as family history (Wang J et al. 2004; London et al. 1992). Diagnosis of UDH without atypia on core biopsy does not require surgical excision unless there is clinical, radiological and pathological discordance. Therefore, these patients do not need chemoprevention or regular screening (Kiluk et al. 2007).

16.5.1.2 Intraductal Papillomas

Papilloma is classified into large central solitary lesions or multiple peripheral micropapillomas. When atypical hyperplasia (within or surrounding the papilloma) is excluded, the RR of a solitary papilloma is 2.04–2.1 compared to 3.01–3.54 with micropapillomas (Page et al. 1996; Lewis et al. 2006). When there is associated atypia within the papilloma, the RR increases from 5.1 to 13.1 for solitary papillomas and from 4.4 to 7.0 for micropapillomas (Page et al. 1996; Lewis et al. 2006). In addition to increased risk of breast cancer, the finding of papillary lesion in a needle core requires exclusion of papillary DCIS or intracystic papillary carcinoma. Use of myoepithelial cell immunocytochemistry such as smooth muscle actin, CK5/6 and p63 are useful, but generally the papillary lesion requires excision biopsy to exclude underlying malignancy.

16.5.1.3 Radial Scar

Jacobs et al. (1999) reported the RR of a single radial scar in women with non-proliferative benign breast disease to be 2.5 and this increases to 4.3 with multiple radial scars. The presence of atypical hyperplasia increased the RR from 2.5 in women with single radial scars to 8.4 when multiple radial scars were present. Sanders et al. (2006) reported an overall RR of 1.11 in women with radial scars without proliferative disease, which increased to 1.14 when proliferative disease without atypia was present and to 2.14 if atypia was present. Furthermore, identification of a radial scar on radiological assessment and on biopsy requires excision, to exclude invasive cancer. Radial scars mimic invasive carcinoma radiologically and can also harbour invasive cancer at the periphery of the fibroelastic core.

16.5.1.4 Sclerosing Adenosis

Sclerosing adenosis carries an RR of 1.5–3.7 of subsequent invasive cancer (Jensen et al. 1989; Bodian et al. 1993). The risk increases to 5.5 if there is atypia associated with the sclerosing adenosis (Gill et al. 2003). The diagnosis of sclerosing adenosis on core biopsy is usually accurate for circumscribed masses, non-palpable indistinct masses or clustered microcalcification that excision is not usually required if there is pathological–radiological concordance (Gill et al. 2003).

16.5.1.5 Fibroadenomas

There is conflicting evidence with regard to the risk of subsequent breast cancer in patients with fibroadenomas. McDivitt et al. (1992) reported an RR of 1.7 in women with fibroadenomas. Subsequently Dupont et al. (1994) reported an RR of 2.17 in patients with simple fibroadenomas and risk increased to 3.10 in patients with complex fibroadenomas. However, in a follow-up study, the above authors (Carter et al. 2001) reported that the presence of atypia within a fibroadenoma cannot predict the presence of atypia in the adjacent breast parenchyma. They also found that atypia confined to a fibroadenoma did not incur a clinically meaningful risk of future breast carcinoma greater than fibroadenoma alone. Sklair-Levy et al. (2008) reported a prevalence of 16 % of complex fibroadenoma in 400 fibroadenomas which occurred in older women and there was a low incidence of malignancy. They suggested that complex fibroadenomas could be managed conservatively.

16.5.1.6 Atypical Hyperplasia

Depending on which publication one reads, the risk of developing breast cancer with a diagnosis of atypical ductal hyperplasia has been reported as 2.4, 4.3 and 13 (Marshall et al. 1997; Page et al. 1985; Palli et al. 1991). However, a comprehensive study by Page and colleagues (1985) gives a better perspective risk associated with atypical hyperplasia of the breast. The authors reported RR of 4.3 in women with ADH which elevated to 8.9 in women with family history of cancer. ALH was associated with an RR of 4.2 which elevated to 8.4 in women with family history of breast cancer.

All patients with ALH or ADH diagnosed on needle core require excisional biopsy to exclude a high-grade lesion as cancer has been found in 31 % of the excision specimens in patients with ADH, 16 % with ALH and 25 % with LCIS (Margenthaler et al. 2006). Patients with atypical hyperplasia benefit from taking tamoxifen, a selective oestrogen receptor modulator (SERM) as a chemopreventive strategy to reduce the risk of cancer. The Breast Cancer Prevention Trial (BCPT) instigated by the National Cancer Institute, in collaboration with the National Surgical Adjuvant Breast and Bowel Project (NSABP-1) randomised 13,388 women at risk of developing cancer based on the Gail Model with an RR of ≥1.66 or had LCIS to tamoxifen and placebo for 5 years. Tamoxifen reduced the risk of invasive breast cancer by 49 % compared to the placebo group. The risk of breast cancer was also reduced in women with LCIS (56 %) and atypical hyperplasia (86 %) (Fisher et al. 1998). Tamoxifen preferentially decreased the incidence of oestrogen-receptor positive cancers, a common finding in atypical hyperplasia and LCIS. There was also 50 % reduction in the incidence of non-invasive carcinomas in the tamoxifen arm.

16.5.1.7 Lobular Carcinoma In Situ (LCIS)

LCIS and ALH are now collectively classified as lobular neoplasia because morphologically, immunohistochemically and genetically the cells are identical (Lu et al. 1998; Lakhani et al. 2006). There is considerable debate as to whether classical LCIS is considered a marker for increased malignancy or a precursor of invasive cancer. This only applies to classical LCIS and not pleomorphic LCIS which are morphologically and biologically different.

Based on the data collected from the Surveillance, Epidemiology and End Results (SEER), Chuba and colleagues (2005) reported that there was no difference between the incidence rates of invasive breast cancer in the ipsilateral and contralateral breast when LCIS was reported in one breast. The authors therefore concluded that LCIS was a marker of the risk of malignancy for which close follow-up may be considered adequate. By using comparative genomic hybridisation (CGH), Lu et al. (1998) found alterations in chromosomes 6, 16, 17 and 22 in similar frequency in LCIS and ALH. These findings were confirmed in a separate study which reported loss of 16 p in both invasive lobular carcinoma (ILC) and LCIS (Hwang et al. 2004). The loss included the focus for E-cadherin gene (16 q.22.1) which is associated with loss of E-cadherin immunocytochemistry staining. Hwang and colleagues (2004)

also reported gain of 1q in both ILC and LCIS. Based on these molecular findings, O'Malley (2010) suggested that lobular neoplasia behaves both as risk indicator for subsequent carcinoma as well as a non-obligate precursor. Furthermore, invasive lobular carcinoma is reported more often in the ipsilateral breast with lobular neoplasia and most of the cancers are ILC supporting the concept of a precursor lesion (Page et al. 2003). Page and colleagues (1991) reported the relative risk of LCIS to be ten times that of the general population with absolute risk of 17 % at 15 years.

There is a general agreement among clinicians that the diagnosis of lobular neoplasia in a needle core biopsy requires an excision biopsy to exclude high-grade lesion (Gao et al. 2010; Reis-Filho and Pinder 2007; Margenthaler et al. 2006). No further action is required if lobular neoplasia is an incidental finding in the specimen excised for other abnormality (O'Malley 2010). If appropriate the patient should be counselled for chemoprevention (Chuba et al. 2005).

Kiluk and colleagues (2007) produced an algorithm of the management of high-risk benign breast lesions which combines the pathology of the benign breast lesions and the Gail model so as to stratify patients into those who require intensive follow-up with or without chemoprevention and routine follow-up.

Table 16.1 summarises the relative risks discussed in this chapter and others, where known discussed in the other chapters. There is very limited information on recently described lesions such as columnar cell lesions and mucocele-like lesions.

Table 16.1 Published relative risk factors of various benign breast lesions

Lesion	Relative risk	Reference
Apocrine adenosis	Not known	–
ADH (no family history)	4.3	Page et al. 1985
ADH (with family history)	9.7	Page et al. 1985
Atypical hyperplasia + Ca^{++}	6.5	Dupont and Page 1985
ALH (no family history)	4.2	Page et al. 1985
ALH (with family history)	8.4	Page et al. 1985
Blunt duct adenosis	2.08	Shaaban et al. 2002
CLL without atypia	1.5	Boulos et al. 2008
CCL with atypia/FEA	20.2	Verschuur Maes et al. 2011
Calcification, NOS	1.8	Dupont and Page 1985
Cyst, NOS	1.5	Dupont and Page 1985
DCIS	8–10	Fitzgibbons et al. 1998
Dense breasts	3.3	Wolfe et al. 1987
Duct ectasia	None	Fitzgibbons et al. 1998
UDH	1.5–2.0	Dupont and Page 1985
Fat necrosis	None	–
Fibroadenoma, simple	1.7–2.17	McDivitt et al. 1992; Dupont et al. 1994
Fibroadenoma, complex	3.1–3.7	McDivitt et al. 1992; Dupont et al. 1994; Carter et al. 2001
Focal fibrosis	None	Fitzgibbons et al. 1998
LCIS	8–10	Fitzgibbons et al. 1998
Micropapillomas (multiple) without atypia	3.01–3.54	Page et al. 1996; Lewis et al. 2006
Micropapillomas with atypia	4.4–7.0	Page et al. 1996; Lewis et al. 2006
Papillary apocrine hyperplasia	1.2	Page et al. 1996
Papilloma, solitary without atypia	2.04–2.1	Page et al. 1996; Lewis et al. 2006
Papilloma, solitary with atypia	5.1–13.1	Page et al. 1996; Lewis et al. 2006
Microglandular adenosis	Not known	–

(continued)

Table 16.1 (continued)

Lesion	Relative risk	Reference
Mucocele-like lesion	Not known	–
Radial scar (single)	2.5	Jacobs et al. 1999
Radial scar (multiple)	4.3	Jacobs et al. 1999
Radial scar + atypical hyperplasia (single)	3.5	Jacobs et al. 1999
Radial scar + atypical hyperplasia (multiple)	8.4	Jacobs et al. 1999
Sclerosing adenosis, NOS	1.5–3.7	Jensen et al. 1989; Bodian et al. 1993
Sclerosing adenosis with ADH	6.5–6.7	Gill et al. 2003; Jensen et al. 1989

Significant risk is considered to be more than twice that of the general population
ADH atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *DCIS* ductal carcinoma in situ, *LCIS* lobular carcinoma in situ, Ca^{++} calcification, *NOS* not otherwise specified

16.6 Models for Assessing Risk of Breast Cancer

Cancer risk prediction models are useful in planning intervention trials, assisting in creating benefit-risk indices, estimating the population burden of disease, identifying individuals at high risk, designing population prevention strategies and improving clinical decision-making (including genetic counselling) (Freedman et al. 2005). Several models are utilised to assess women and men at risk of developing breast cancer and the models in current use (mostly in the USA) are discussed below.

16.6.1 The Gail Model

The Gail Model is the most commonly used tool to assess the risk of breast cancer. The Gail Model is based on a study of 2,852 white women and 3,146 controls of white women who were assessed for the family history of breast cancer in the first-degree relatives, age of menarche, age at first child birth and history of previous benign breast disease (Gail et al. 1989). The model is an interactive tool designed by scientists at the National Cancer Institute at the National Surgical Adjuvant Breast and Bowel Project (NSABP) to estimate the woman's risk of developing breast cancer and is available online at http//brca.nci.nih.gov.brc. The modified version of the tool was validated during the Breast Cancer Prevention Trial (Fisher et al. 1998). The modified Gail Model includes the following:

- Results from African-American women
- Number of first-degree relatives
- Number of previous biopsies
- History of hyperplasia

The individual's estimated 5-year and lifetime risks (up to the age of 90 years) are calculated and compared to women of the same age and race who are at average risk of developing breast cancer (National Cancer Institute website). Increased risk is defined as a 5-year risk of 1.66 % or greater. A relative risk of 1.66 % was the cut-off point used in the Breast Cancer Prevention Trial for women to qualify for chemoprevention with tamoxifen (Constantino et al. 1999). Vogel and Bevers (2003) advocate that the majority of women undergoing breast screening and mammography should be evaluated for breast cancer risk using the Gail Model but not women under the age of 35 as the use of tamoxifen in women less than 35 has not been evaluated. Women less than 35 years with a family history of breast cancer should be referred for genetic risk assessment and counselling. Vogel and Bevers (2003) further advocate that the model should not be used for women over the age of 85 as the risks of the use of tamoxifen outweigh the risk of breast cancer.

When Evans and Howell (2007) evaluated the Gail Model, they reported that the model was limited by the inclusion of only first-degree relatives which resulted in underestimating risk

in 50 % of families with cancer in the paternal lineage. Furthermore, the Gail Model does not take into account the age of onset of breast cancer of the affected relative. In a separate study Pankiratz and colleagues (2008) reported that the Gail model significantly underestimated the risk of breast cancer in women with atypical hyperplasia.

16.6.2 The Claus Model

The Claus Model was developed using data from the Cancer and Steroid Hormone Study, a nested population-based case–control study between 1980 and 1982, using breast cancer patients enrolled in the Surveillance, Epidemiology and End Results (STEER) Project (Claus et al. 1991). The original model only assessed data on patients with family history of breast cancer and this was later modified to include data on ovarian cancer (Claus et al. 1991, 1993). The Claus Model includes data on family history of first- and second-degree and age of onset of the cancers. Assessing individuals with this data will most likely identify people with BRCA1 and BRCA2 mutations. When they evaluated the Claus model, Evans and Howell (2007) reported that the major limitation of the Claus Model is that it does not assess other risk factors such as hormonal and reproductive factors and history of previous breast biopsies.

16.6.3 Tyrer-Cuzick Model

The Tyrer-Cuzick Model is also known as the IBIS because it was based partly on the data derived from the International Breast Intervention Study (Tyrer et al. 2004). The model integrated family history, surrogate measures of endogenous oestrogen exposure and history of benign breast disease in a comprehensive fashion. When compared to the other models, the Tyrer-Cuzick Model scored very high because the model's algorithm includes the likelihood of BRCA1 and BRCA2 mutations (Evans and Howell 2007; Amir et al. 2003). In a separate study the Tyrer-Cuzick model was reported to significantly overestimate the risk of breast cancer in women with atypia and individual risk estimates showed poor concordance between predicted risk and invasive breast cancer development (Boughey et al. 2010).

16.6.4 BRCAPRO Model

The Breast Cancer Program (BRCAPRO) was designed by Parmigiani and colleagues (1996) at the Institute of Statistics and Decision Sciences, Duke University USA (Cyrillics Software Website). The model calculates the probability of a particular family member carrying a germ-line mutation of the BRCA1 and BRCA2 genes. The method applies to both men and women, but the proband is mostly women. The calculations are incorporated into the Cyrillics Software which applies Bayesian rules to calculate the probability of mutation in an individual with a family history of breast cancer. The model incorporates published BRCA1 and BRCA2 mutation frequencies, cancer penetrance in mutation carriers, cancer status (affected, unaffected and unknown) and age of consultee's first-degree and second-degree relatives. Bayesian methods are based on strict mathematical foundations, providing a coherent methodology which makes it possible to incorporate relevant information, and solves many of the difficulties faced by conventional statistical methods. The Bayesian paradigm is based on the interpretation of probability as a conditional measure of uncertainty which closely matches the use of the word 'probability' in ordinary language. For this reason the Bayesian methods can be applied to complex scientific reporting (Bernardo).

The advantage of using the BRCAPRO is that it includes information on both affected and unaffected relatives. It also provides estimates for the likelihood of finding either BRCA1 mutation or BRCA2 mutation in a family. The model gives the option of using estimates of mutation frequencies from three independent populations: two unselected populations based on data published by Claus et al. (1996) and Ford et al. (1998) and one on Ashkenazi Jewish population published by Struewing et al. (1997). However,

the model does not include the other non-genetics risk factors. When the BRCAPRO model was compared with other models, the model produced the least accurate breast cancer estimation and predicted only 49 % of the breast cancer that actually occurred in a screened group of 1,900 women studied by Evans and Howell (2007).

16.6.5 BOADICEA Model

Investigators in Cambridge UK used segregation analysis to derive a susceptibility model – the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model in which susceptibility is explained by mutations in BRCA1 and BRCA2 together with a polygenic component reflecting the joint multiplicative effect of the multiple genes which individually have small effects on breast cancer risk (Antoniou et al. 2004). The authors reported that the overall familial risks of breast cancer predicted by the model are close to those observed in epidemiological studies. The predicted prevalence of BRCA1 and BRCA2 mutations among unselected cases of breast and ovarian cancer was also consistent with observations from population-based studies. The predictions in this study were closer to the observed values using the Claus and BRCAPRO models. Predicted mutation probabilities of cancer risks can be derived from this model.

16.6.6 Revalidation of Models for Assessing Breast Cancer Risk

In a prospective study, Evans and Howell (2007) assessed the goodness to fit and discriminatory accuracy of the above models using data from 1,933 women attending the Family History Evaluation and Screening Programme in Manchester, UK of which 52 developed cancer. The Gail, Claus, Tyrer-Cuzick and BRCAPRO models were applied to the women with a mean follow-up of 5.27 years to estimate the risk of breast cancer. The authors reported that the Tyrer-Cuzick model was the most consistently accurate model for prediction of breast cancer. The Gail, Claus and BRCAPRO models all significantly underestimated risk, particularly in women with a single first-degree relative affected with breast cancer. The Tyrer-Cuzick model was accurate in this subgroup. Conversely all models accurately predicted risk in women with multiple relatives affected by breast cancer, i.e. two first degrees and one first-degree relative plus two other relatives. This implies that the effect of a single-affected first-degree relative is higher than may have been previously thought. The authors commented that the Gail model is likely to underestimate the risk in this group as it does not take into account the age at breast cancer in the affected relative, and most women in Evans and Howell's study in single first-degree relative category had a relative diagnosed at younger than 40 years of age. The BRCAPRO and Tyrer-Cuzick models were the only models to accurately predict risk in women with a family history of ovarian cancer, which confirmed that ovarian cancer had a significant effect on breast cancer. Furthermore Evans and Howell (2007) reported that the Gail, Claus and BRCAPRO models all significantly underestimated risk in women who were nulliparous or whose first live birth occurred after the age of 30 years. The Gail model appeared to increase the risk with pregnancy before the age of 30 years in a familial setting. In addition, the Gail, Claus and BRCAPRO models underestimated risk in women whose menarche occurred after the age of 12; but the Tyrer-Cuzick model accurately predicted risk in these subgroups. These results suggest that age at first live birth has an important effect on breast cancer risk, while age at menarche may have a lesser effect. Evans and Howell (2007) warned the risk of modifying models to adapt for new risk factors without prospective revalidation in an independent dataset as this can lead to erroneous prediction.

Amir and colleagues (2010) designed a flow chart to assist the clinician as to which model to use depending on whether the patient has a family history of breast cancer or not. Gail and Mai (2010) were concerned that clinicians may disregard taking into account other information and just use the flow charts.

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Index

C.N. Chinyama, *Benign Breast Diseases*,
DOI 10.1007/978-3-642-41065-9, © Springer-Verlag Berlin Heidelberg 2014