Nipple Discharge

3

Jill R. Dietz

3.1 Introduction

Nipple discharge is the presenting complaint of approximately 5% of women seeking medical care for a breast problem [1, 2]. While the majority of these patients will have a benign process, nipple discharge can be the sole presenting sign of cancer in 1 % of patients [3]. Historical reports suggest malignancy rates up to 24 % [4] in these patients, but with improved imaging and overall earlier detection, current rates are 3–7 % [5]. The evaluation and treatment of nipple discharge vary greatly in practice and in the literature, causing confusion for both patients and physicians. Differentiating between physiologic and pathologic nipple discharge is critical in order to identify patients in need of a diagnostic work-up and treatment plan.

3.2 Anatomy and Physiology

A review of the anatomy and physiology of the human mammary ductal system and nipple anatomy is helpful in understanding the etiology of nipple discharge. There has been a resurgence of attention to nipple anatomy secondary to the popularity of nipple-sparing mastectomy. There are rarely terminal ductal lobular units (TDLUs) in the nipple itself so it is more often a conduit for discharge than the source of primary cancer [6].

The female breast has approximately 15–20 lobes that radiate from the nipple. Each lobe is comprised of glands (lobules) and branching milk ducts. The breast milk is produced in the TDLUs, which empty into a branching ductal network that leads to the proximal duct. The proximal ducts converge toward the areola and empty into the nipple. The mammary ducts are lined by actively dividing epithelial cells that slough on a regular basis. The nipple orifices of nonlactating women are usually blocked by a keratin plug that prevents the leakage of normal ductal secretions.

During pregnancy, the ductal system proliferates and secretions are produced in response to large increases in estrogen, progesterone, and prolactin (which is released by the anterior pituitary gland). After parturition, lactation is promoted by persistently elevated levels of prolactin, and rapidly declining levels of estrogen and progesterone. The nursing infant causes further release of prolactin via the suckling reflex, thus stimulating milk production. These same hormones that promote and sustain breast-feeding can also contribute to physiologic nipple discharge in nonlactating women. Pathologic discharge is caused by a growth or proliferation of the mammary ductal epithelial lining.

3.3 Definition

Nipple discharge is fluid that flows or is expressed from the mammary ducts and is present in a small percentage of women. Nipple secretions are found within the ductal system and are by-products of the epithelial cells that are undergoing cellular turnover. These physiologic secretions are generally not evident to most women because they are blocked by the keratin plug and eventually reabsorbed. Goodson and King found secretions, or nipple aspirate fluid (NAF), in up to 81.2 % of asymptomatic women by using a suction aspirating device [7]. Studies have confirmed that the ability to aspirate nipple secretions is influenced by age, race, parity, and hormonal status but is successful in the majority of patients [8, 9]. Although nipple secretions are considered normal, the mammary ducts are the origin of most breast cancers, making the fluid secreted by the ducts a point of interest for researchers.

Many studies have been done on aspirated nipple secretions examining cellular changes and biochemical composition [8, 10–12]. NAF contains cholesterol and other steroids, estrogens and other hormones, immunoglobulin,

J.R. Dietz (✉)
Surgery, University Hospitals Seidman Cancer Center,
3909 Orange Place, Suite 4400, Beachwood, Bentleyville,
OH 44122, USA
e-mail: jill.dietz@uhhospitals.org

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Fig. 3.1 Classic presentation of physiologic nipple discharge

lactose, fatty acids, and alpha-lactalbumin. Exogenous compounds such as caffeine, nicotine, pesticides, and other drugs are also found in nipple secretions. Lang and Kuerer have compiled an extensive list of compounds found intraductally by various studies [13]. The color of NAF, which can vary from white to dark green, is related to the cholesterol, lipid peroxide, and estrogen content [14]. The normal cellular make up of NAF consists of foam cells, a few epithelial cells, and other cells of hematogenous origin [15].

When secretions become abundant or persistent enough that they discharge spontaneously from the duct orifice, they are known as nipple discharge. Nipple discharge is generally categorized as "physiologic" or "pathologic" discharge. Physiologic discharge can be caused by exogenous or endogenous hormones, medications, direct stimulation, stress, or endocrine abnormalities. Although the cause of the hormonal influence may be pathologic, as is the case with prolactinoma, the ductal system itself has no abnormality, so the resultant discharge is classified as physiologic. Most physiologic discharge is bilateral, nonspontaneous, and involves multiple ducts. These characteristics result from the central effect of an outside influence on the breast. The color of the discharge can vary from milky to yellow, gray, brown, or dark green depending on the composition and cause of the physiologic discharge. As with NAF, darker-colored discharges are associated with higher levels of estrogens and cholesterol [16] (Fig. 3.1). Because there is rarely an intraductal pathologic abnormality involved with this type of discharge, localization procedures, breast biopsies, or surgeries are not necessary.

Pathologic nipple discharge or PND is caused by an abnormality of the duct epithelium. It is typically unilateral and from a single duct. The discharge is spontaneous or at least easily expressible. The patient often notices the discharge after a warm shower that likely removes the keratin plug. The pathologic lesion often causes ductal obstruction and dilatation so that the fluid which collects in the duct is subsequently released when the plug is removed or the duct is expressed. The color of the discharge is usually clear, serous, or bloody, although pathologic nipple discharge can present as other colors (Fig. 3.2). This type of discharge tends not to be affected by the menstrual cycle or hormonal status. While some women seek care when they first notice the discharge, many will delay until the discharge becomes socially embarrassing or bloody. Although the majority of these women will have a benign etiology for their nipple discharge, all patients with PND need a thorough evaluation to rule out malignancy as the source.

3.4 Incidence

Approximately, 5 % of women presenting for breast care have a complaint of nipple discharge [17, 18]. The incidence is likely underreported since many women do not seek medical care for this symptom. Women who have physiologic discharge, an otherwise normal exam and normal imaging, have a very low chance of having a malignancy [19, 20].

Patients with nipple discharge have a higher relative risk for cancer than the asymptomatic population. While the vast majority of patients with pathologic nipple discharge have benign proliferative lesions as the etiology, breast cancer is found to be the cause of the nipple discharge in 4–21 % of cases [1, 3, 21–27]. Those patients with nipple discharge associated with a mass or skin change have an even higher

Fig. 3.2 Classic presentation of pathologic nipple discharge

relative risk of cancer. One study showed that the incidence of carcinoma for patients with discharge and a mass was 61.5 % as compared to 6.1 % for patients with discharge alone [2].

While most patients with pathologic nipple discharge have normal mammograms, many studies have shown that an abnormal mammogram in patients with pathologic nipple discharge is associated with an increased risk for cancer [21, 27–30]. As should palpable masses, suspicious radiologic findings should be evaluated by stereotactic or core needle biopsy prior to duct excision. This will diagnose a malignancy in some patients, allowing for definitive surgical treatment. If minimally invasive biopsy is not available, then the mammographic abnormality will need to be evaluated at the time of duct excision.

Bloody or guaiac positive discharge also increases a person's risk of cancer, although most cases of bloody nipple discharge are benign, and cancer has been found to be the cause of discharge of milky and serous fluid [3]. A recent report showed that the malignancy rate for bloody PND was 14 % compared to 6 % for nonbloody discharge [31]. Advanced age or postmenopausal status, imaging abnormality, and mass have also been shown to increase the risk of breast cancer being the cause of the pathologic discharge [25].

The number of breast cancer cases presenting as nipple discharge has dropped over the last few decades. Copeland's series of patients in the 1950s reported that 25 out of 67 (37 %) patients with nipple discharge had breast cancer [32] whereas more recent studies of patients undergoing duct excision for pathologic nipple discharge tend to have cancer rates between 5 and 10 % [19, 25, 26]. The decrease in the incidence of cancer presenting in this way is likely due to the earlier detection of breast cancer with improved imaging techniques and increased screening, which shifts diagnosis to earlier stage disease. Another possibility is that minimally invasive biopsy of imaging and clinical abnormalities is being performed to establish a preoperative cancer diagnosis, thus moving these patients out of the category of women undergoing surgical biopsy for the diagnosis of nipple discharge.

Even though the most significant cause of nipple discharge is cancer, most cases have a benign etiology. Many studies do not differentiate the exact histology of benign lesions, although it is clear that papillomas or papillomatosis are responsible for a large percentage of pathologic nipple discharge. Other reported causes are duct ectasia, epithelial hyperplasia, and fibrocystic changes [3, 21, 28]. Localizing techniques increase the diagnostic yield of duct excision: The percentage of proliferative lesions increases, while fewer cases of duct ectasia and fibrocystic changes are found. This suggests that there is a proliferative ductal process accounting for most, if not all, cases of pathologic nipple discharge [25, 26, 29].

3.5 Characteristics and Etiology

Discharge from the nipple can present as a spectrum of signs, from a tiny opaque drop during breast examination to alarming bloody discharge that stains the patients clothing. The presentation and history are important in categorizing the discharge as either "physiologic" or "pathologic." Even though some causes of bilateral multiduct discharge are from a pathologic source, such as a pituitary adenoma, the effect is central and not the result of a ductal abnormality. These

Table 3.1 Characteristics of pathologic and physiologic nipple discharge

Characteristic	Physiologic	Pathologic
Laterality	Bilateral	Unilateral
#Ducts	Multiple	One
Spontaneity	Expressed	Spontaneous
Color	Multicolored, milky, gray, green, brown, yellow	Bloody, serous, clear
Consistency	Sticky, thick	Watery, copious

Table 3.2 Causes of nonpathologic nipple discharge

Hormonal
Pregnancy/postlactational
Mechanical stimulation
Galactorrhea
Duct ectasia
Bloody discharge of pregnancy
Infection (Zuska's disease)
Montgomery gland discharge
Fibrocystic change

discharges are better categorized as physiologic or "non-pathologic" discharge. This grouping system is helpful in determining both the evaluation and treatment necessary for that patient. Table 3.1 shows the classic presentation of each type of nipple discharge.

Physiologic nipple discharge has various presentations and etiologies. Table 3.2 reviews the most common causes of nonpathologic nipple discharge. Over 75 % of nipple discharges are physiologic in nature and do not require surgical intervention [1]. The evaluation and treatment of physiologic nipple discharge should be focused on identifying the external factor that is stimulating the breasts.

Galactorrhea is physiologic discharge from the nipple that resembles breast milk but occurs in a patient who is not lactating. The discharge is a thin, watery milk-like substance that usually arises from both breasts. The most common scenario is a postpartum woman who continues to discharge from one or both breasts long after she has stopped breast-feeding. She may have some concern regarding the discharge and may attempt to repeatedly express the fluid. The continued stimulation of the nipple causes further discharge perpetuating the cycle. Other sources of nipple stimulation such as the friction of clothing, or nipple involvement during intimacy, can also aggravate the symptom. Again, explaining to the patient the likely etiology of the discharge and reassurance is usually sufficient.

Thin, milky discharge can occur around menarche and menopause when the breasts are exposed to extreme hormonal variation. The discharge is self-limited and simply requires reassuring the patient. Nipple discharge can also be seen in newborns as a result of maternal hormones that cross the placental barrier prior to parturition. After delivery, the precipitous drop in estrogen and progesterone levels associated with the high neonatal prolactin levels causes stimulation of the infant's breast tissue. This discharge, commonly referred to as "witches' milk," lasts only a few weeks [33].

Galactorrhea can result from an increase in prolactin levels. Most often, the levels are elevated due to medication, although the most significant cause is a pituitary adenoma that secretes prolactin. Prolactinoma should be expected if the patient has the classic triad of symptoms: amenorrhea, galactorrhea, and infertility. The tumor arises from the anterior pituitary gland and can become quite large causing symptoms of diplopia from compression of the optic chiasm. If a prolactinoma is suspected, a prolactin level should be drawn, which will be abnormal (>30 ng/mL). Screening nipple discharge patients with prolactin levels is not cost-effective, considering fewer than one in one thousand cases are due to a pituitary adenoma [34]. If a tumor is found, it can be successfully treated with a dopamine agonist, which will also eliminate the discharge. Occasionally, surgical excision of the tumor may be necessary.

Other rare causes of galactorrhea are listed in Table 3.3 along with the categories of medications that have been known to cause nipple discharge [35]. Thoracic surgery or chest trauma has been reported to cause nipple discharge. The injury stimulates the afferent thoracic nerves and the hypothalamic-pituitary axis resulting in increased prolactin release, which in turn stimulates nipple discharge [36].

Opalescent physiologic discharges, which are multicolored and nonserous, emanate from one or both breasts and usually from multiple ducts. The discharge may only be evident with vigorous expression by the patient, or may be very easily expressed and copious. Creamy white, tan, or yellow discharge may present next to a duct producing a brown, dark green, or blackish discharge. Although this type of discharge is often alarming to the patient because the dark color is assumed to be blood, it is quite unlikely for it to be associated with an intraductal lesion. A tissue test, where the discharge is placed on a thin white tissue, often results in absorption of the drop, which then proves the discharge is green. It can be difficult to differentiate green discharge from guaiac positive discharge on hemoccult testing. When duct excision is done for this type of discharge, histology often shows normal breast tissue, duct ectasia, or fibrocystic changes. Most patients with physiologic discharge are willing to be followed after being reassured of its benign

Table 3.3 Causes of galactorrhea (hyperprolactinemia)

Physiologic:
Postlactational
Mechanical stimulation
Chest wall abnormalities
Chest trauma or surgery
Burns
Herpes zoster
Spinal cord injury
Tumors
Pituitary
Hypothalamic tumors
Craniopharyngiomas, meningioma
Ectopic prolactin (bronchogenic carcinoma)
Acromegaly
Metabolic
Chronic renal failure
Hypothyroidism
Cushing's disease
Idiopathic
Medication induced
Lactogenic drugs
Estrogens, progestins, androgens
Long-term opiate use (e.g., morphine, cocaine)
Anesthetics
Phenothiazines (e.g., Compazine®, Thorazine®)
Antidepressants (e.g., Elavil®, Prozac®, Paxil®)
Monoamine oxidase inhibitors (e.g., Nardil®, Parmate®)
Antipsychotics (e.g., Clozaril®)
Antihypertensives (e.g., Aldomet®, Calan®)
Butyrophenones (e.g., Haldol®)
Thioxanthenes (e.g., Navane®)
Benzodiazepines (e.g., Valium®)
Other prescribed drugs (e.g., Tagamet®, INH, Danocrine, Reglan®)

nature. On a rare occasion, the patient may request surgery to eliminate copious discharge. If the discharge is associated with pain and fibrocystic changes, the patient should be informed that it is not likely that the surgery will decrease her pain. It may also result in decreased nipple sensation and the inability to breast-feed, particularly if bilateral excisions are performed. If an underlying cause for the nipple discharge can be identified, then it can be addressed, such as a medication change or cessation of hormones.

Communication of cysts with ductal structures appears to be responsible for nipple discharge in some instances. In these situations, the cyst, often presenting as a mass, may disappear with the onset of discharge. Whenever a patient presents with nipple discharge and an associated mass, the mass must be evaluated. In this case, aspirated cyst fluid characteristics will likely correlate to the nipple discharge, and no further evaluation is necessary. A ductogram may show communication with the cyst. Although this is an interesting finding, a ductogram is not necessary if there is clinical evidence that the cyst is related to the discharge. If the problem persists, many patients prefer excision to control the discharge.

Some breast infections present with purulent and malodorous nipple discharge. This condition is treated like other breast infections. Large abscess cavities may be apparent and should be drained. Cellulitis in association with nipple discharge may be indicative of a deep abscess cavity. If it is unclear whether an abscess has formed, an ultrasound may be useful. Otherwise, conservative treatment with an antibiotic that has adequate gram-positive coverage is an appropriate initial therapy. The discharge itself may be a useful source to test for microbiology and sensitivities. Zuska's disease is a condition of chronic periareolar abscess with sinus formation and can result in intermittent nipple discharge and infection. Excision of the entire ductal system on the effected side, including the sinus tract, is often associated with the fewest recurrences [37]. Because this problem occurs almost exclusively in smokers, major duct excision in this setting is also associated with a higher incidence of ischemic necrosis and other complications. A smoking cessation program may reverse this cycle of chronic infection or at least decrease the complications if duct excision is performed.

Duct ectasia is a condition, which results in poor emptying of ductal secretions, stagnation, and inflammation of the ducts. The associated nipple discharge can present spontaneously or require vigorous expression to elicit a thick, white discharge. Bilateral, multiduct involvement varying in color is the most common presentation. The drainage is thought to be secondary to increased glandular secretions due to chronic inflammation [38].

Fibrocystic disease: Several series report that fibrocystic disease is a common histologic finding in many duct excision specimens from patients with pathologic nipple discharge. Series using localization techniques have very high proliferative lesion retrieval rates, which suggest that most cases of pathologic discharge are caused by intraductal abnormalities and not fibrocystic change [25, 29, 39]. In cases where fibrocystic change or normal breast tissue is reported, it is important to ensure that all the excised tissues are analyzed or that the correct tissue was excised. Some papillomas are only 1–2 mm in size and could easily be missed with the sampling error of serial sectioning. A high suspicion for a missed proliferative lesion should remain when the histologic diagnosis of fibrocystic change is reported for duct excision specimens.

Occasionally, women who are in their third trimester of pregnancy or who are postpartum will experience bloody nipple discharge. While it is common to have a milky

discharge at this time, bloody discharge is rare, often unilateral, and may be expressible from multiple ducts. The bloody discharge is often noted after an abrupt increase in breast size associated with the pregnancy. In women, who have asymmetrical breast growth during pregnancy, bloody nipple discharge is more often associated with the larger breast [40]. The bloody discharge can accompany normal lactation and is often found during pumping. She may be concerned about breast cancer or the blood harming her nursing infant. The bleeding is usually minimal and self-limited and is unlikely to cause a problem for the nursing infant. The majority of case reports describe resolution of bleeding by the third month after delivery. Cytologic evaluation of nipple discharge in pregnant or postpartum patients often reveals abnormal appearing cells that are the result of normal epithelial changes during lactation. These cells may be falsely interpreted as arising from cancer; therefore, cytologic examination of this discharge must be interpreted with caution. This bloody discharge during pregnancy and lactation is an unusual circumstance in which it may be reasonable to postpone or at least delay further evaluation. It must be appreciated that if the discharge is associated with a mass or persists as a unilateral, single duct discharge, then further evaluation is needed.

Montgomery gland discharge presents from the large areolar sebaceous glands known as Montgomery's tubercles and is not truly the nipple discharge. This type of discharge usually occurs at times of extreme changes in hormonal status such as menarche or menopause. The discharge has characteristics of physiologic discharge as it is commonly found coming from many glands and is either serous or opaque in nature. This type of discharge requires reassurance unless infection occurs. In this case, antibiotic therapy and, occasionally, excision of the infected gland are indicated. There are rare reports of duct communication to the Montgomery glands causing nipple discharge. This presents as pathologic discharge from the tubercle of the areola [41].

Nipple discharge in the male patient is treated similar to that in females. Puberty in adolescents, and the same drugs and medical conditions that stimulate gynecomastia in men can cause nipple discharge. The evaluation should include mammography in addition to careful history and physical examination. Any suspicious mass or mammographic abnormality should be biopsied. In one study of 6200 patients, Leis found that 5 out of 24 (20.8 %) men diagnosed with cancer had nipple discharge as the presenting symptom. Evaluation is mandatory for male patients with PND, especially when associated with a mass, because of the increased risk of cancer and decreased survival rate of male patients with invasive breast cancer [21].

Table 3.4 Causes of pathologic nipple discharge

Papilloma
Papillomatosis
Papillary cancer
Ductal carcinoma in situ
Invasive ductal carcinoma
Ductal epithelial hyperplasia
(?) Cysts/fibrocystic disease/duct ectasia

Pathologic nipple discharge is caused by an intraductal abnormality and is therefore typically a unilateral finding. Although it is possible for the pathology to involve more than one ductal system, the typical presentation is consistent discharge from a single duct orifice. The discharge can be watery clear, serosanguinous, dark brown old blood, or bright blood. Occasionally, reports of carcinoma with other types of discharge, such as milky, have been reported, but this is distinctly unusual [20, 42]. Table 3.4 reviews the common etiologies of pathologic nipple discharge.

Papilloma: (Fig. 3.3) A large percentage of pathologic nipple discharge is attributed to papillomas or papillomatosis. Papillomas are often found centrally in the subareolar region. Solitary papillomas arise from the larger ducts compared to the smaller, often multiple papillomas, which are more peripherally located and arise from the TDLUs. Peripheral papillomas can occur bilaterally and have a higher recurrence rate after excision than the solitary central variety. Multiple, peripheral papillomas present with pathologic nipple discharge less frequently than central papillomas [36, 43].

In the past, there has been much controversy over whether papillomas are premalignant. It is generally accepted that central, solitary papillomas have little malignant potential although they should be completely excised to avoid recurrence [44]. In contrast, papillomas arising in small, more peripheral ducts can be associated with cancer. Ohuchi reconstructed ductal excision specimens from patients with pathologic nipple discharge and found that cancer was associated with 37.5 % of peripheral papillomas but not with central papillomas [45]. Hou et al. showed that 70 % of malignancies found on duct excision for nipple discharge were located over 2 cm from the nipple [46]. Patients with nipple discharge, who are found to have peripheral lesions on ductography, should be considered for a preoperative localizing procedure to guide the surgeon during surgical biopsy. These patients should also have careful follow-up since the risk of recurrence or development of cancer is higher than that for central lesions [4].

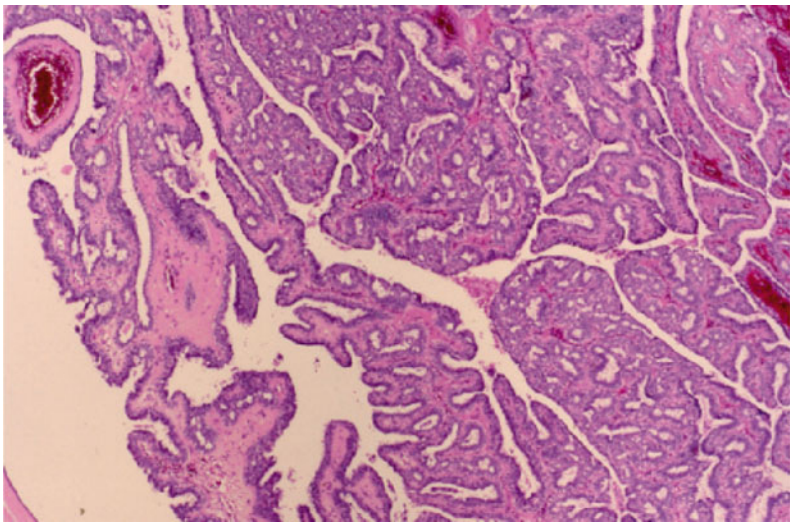

Fig. 3.3 Histologic section through an intraductal papilloma showing the vascular stroma with epithelial lining

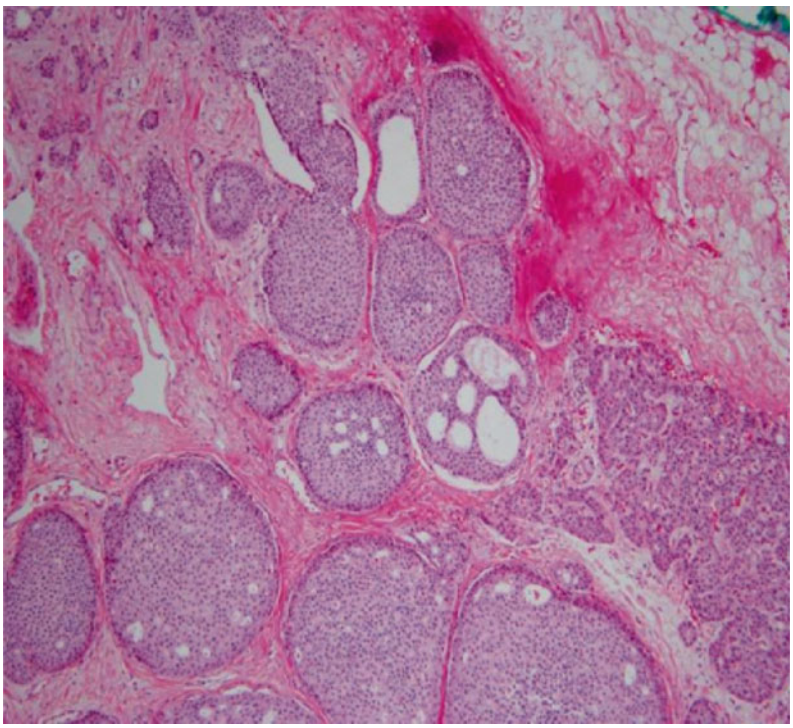

Fig. 3.4 Histologic representation of ductal carcinoma in situ

Carcinoma: (Fig. 3.4) One percent of all breast cancers present with nipple discharge as the only symptom [3]. Approximately, one in ten cases of pathologic nipple discharge will have cancer as the etiology and the incidence increases if the discharge is bloody. The rationale for investigation in patients with pathologic nipple discharge is to rule out cancer as the source. While there are a number of diagnostic tests available that correlate with the malignant potential of a lesion, no single test can rule out carcinoma, so duct excision is recommended. Imaging abnormalities or suspicious clinical findings should be worked up and biopsied to assist in establishing a diagnosis.

3.6 Diagnostic Evaluation

Many diagnostic tests are available to evaluate patients with nipple discharge. Before embarking on any of these, a full history must first be taken, including the patient's age, gynecologic and sexual history, and use of medication and hormones. Pertinent medical history such as previous endocrine problems or chest trauma should also be ascertained. The characteristics of the discharge must be noted, including laterality, spontaneity, number of ducts involved, color, and consistency. PND is a clinical diagnosis based on presentation. Physical exam should include a breast exam, assessing for palpable masses, lymphadenopathy, skin changes, and nipple inversion or lesions. The information obtained from a careful history and a confirming physical exam will frequently lead to a diagnosis and limit the tests needed prior to duct excision.

3.7 Mammography

If it is determined that the patient has physiologic nipple discharge, no additional procedures are needed. Mammography is reserved for patients in the appropriate age group and risk categories if physiologic discharge is the presenting symptom. All patients with pathologic nipple discharge should undergo mammographic evaluation regardless of age. Still, mammography is often normal in cases of discharge associated with cancer. Fung found that only 2 out of 15 patients with cancer causing nipple discharge had mammograms suggestive of malignancy [47]. Mammography might identify a separate or associated lesion that may alter the course of management. Mammographic abnormalities associated with nipple discharge increase the likelihood of a malignancy [28]. If a mammographic abnormality is visualized, this finding takes precedence and a stereotactic or ultrasound-guided core biopsy should be performed. If a minimally invasive biopsy is not done, then a needle localization excisional biopsy should be performed at the duct excision to include the imaging abnormality.

3.8 Ultrasound

Ultrasound has been used for patients with pathologic nipple discharge to view dilated ducts. This technique has also been used with saline lavage of the discharging duct to dilate and obtain cytology from the duct under echographic guidance [48, 49]. Chung compared ultrasound to ductography and found that ultrasound is superior for defining small 0.5 cm lesions and to evaluate multiple ductal systems. Ultrasound-guided localization of the lesion is particularly helpful in cases of failed cannulation during ductography. Ductography remains superior to ultrasound for visualizing the extent of abnormality within a ductal system and for detection of microcalcifications [50, 51]. The addition of US to ductography has the highest sensitivity and specificity; however, even if both of these tests are negative, malignancy cannot be excluded [52].

High-resolution ultrasound is performed at 13–15 MHz and has a higher sensitivity for the diagnosis of intraductal pathology than conventional ultrasound (75 vs. 30 %). Although it has a lower specificity than conventional ultrasound performed at 7.5 MHz, high-resolution ultrasound appears to be better for evaluating proximal ducts [53, 54] (Fig. 3.5). If an identified peripheral lesion can be visualized

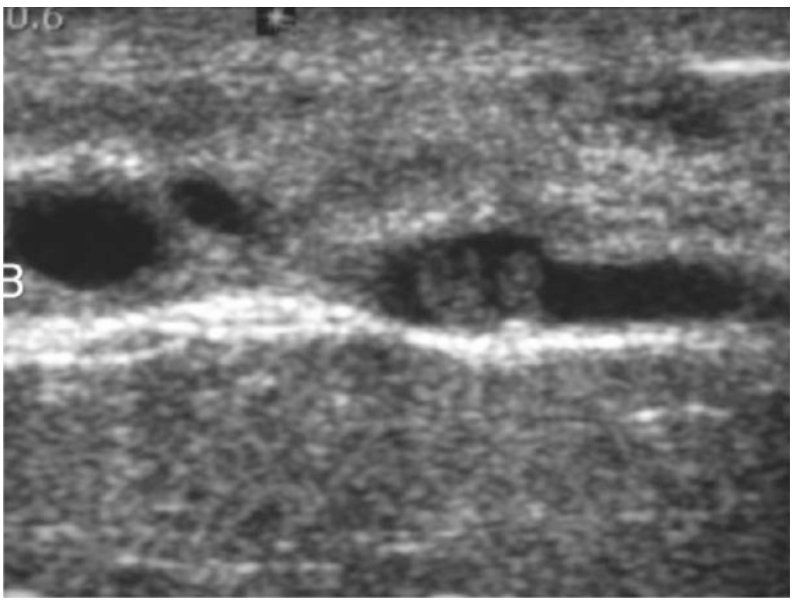

Fig. 3.5 Ultrasound of a dilated duct showing an intraductal lesion

by ultrasound, needle localization or ultrasound-guided fine needle aspiration (FNA) may be performed. The sensitivity of cytologic examination of ultrasound-guided FNA is only 50 %; however, duct excision is warranted to remove the lesion [55]. Two recently published studies looked at patients with nipple discharge who underwent ultrasound-guided percutaneous Mammotome excision of their intraductal abnormalities. Both of these studies report that 95 % of patients were discharge free after the procedure. Thorough pre-biopsy work-up and patient selection are critical for this procedure to be successful [56, 57].

3.9 MRI

Magnetic resonance imaging is being used more often as an additional diagnostic tool for breast diseases. It is particularly useful in young women with dense breast tissue where more conventional tests such as mammography and ultrasound have a lower sensitivity. MRI has a higher sensitivity than standard ductography but still cannot reliably differentiate benign from malignant disease [58–60]. MR can be helpful if other localizing techniques such as ductoscopy or ductography are not available [61]. MR ductography has been developed as an additional tool for patients with pathologic nipple discharge and can be useful for identifying the extent of the disease. While expense is an issue, it is not as invasive as conventional ductography and does not have the problem of failed cannulation. Fusion imaging of MR ductography and contrast-enhanced MR mammography can provide useful information on the extent of disease, and size and shape of the lesion. This is helpful for resection planning and in suspected cancer cases where breast conservation will be attempted [62–64].

3.10 Occult Blood

Testing nipple discharge for occult blood has been evaluated in many studies. Bloody or heme-positive discharge has been associated with an increased incidence of cancer. In one large series, discharge was tested for occult blood using a Bililabstix reagent strip. All patients with the eventual diagnosis of cancer tested positive even though less than half were grossly bloody [3]. Since there are reports of cancers identified in nonbloody discharge, if the discharge is characteristically pathologic, it should be evaluated even if it is hemoccult negative.

3.11 Cytology

Many physicians will send nipple discharge for cytologic evaluation. In a large screening study where cytology was performed on over 20,000 patients with nipple discharge, only 0.2 % patients were either positive or suspicious for malignancy. In this same series, 61 of 404 detected cancers had nipple discharge. In these 61 cases, cytology findings were as follows: 24 negative, 18 positive, 7 suspicious, and 12 atypical for a sensitivity of 60.7 % [65]. The ability to detect malignancy by cytologic examination of nipple discharge ranges from 45 to 82 % [20, 21, 66–68]. Nipple discharge cytology has a 0.9–2.6 % false-positive rate [21, 68] (Fig. 3.6).

A recent study from the CAP Interlaboratory Comparison Program queried pathologists with a brief history and slides of nipple discharge. The results indicated a high 12.8 % false-positive rate and a 3.4 % false-negative rate, confirming the difficulties in relying on cytologic results in this condition [69]. Cytology alone should not be used to

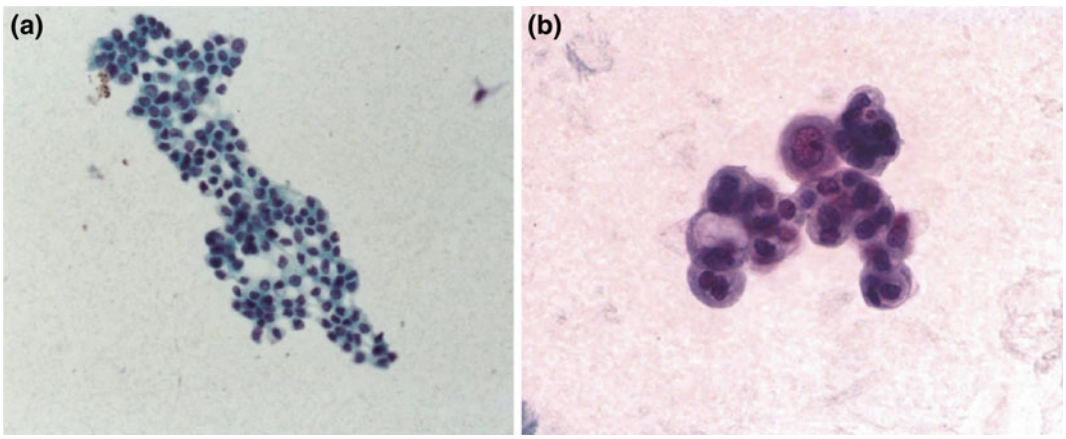

Fig. 3.6 **a** Nipple discharge cytology showing benign ductal cells and proteinaceous material. **b** Nipple discharge cytology showing malignant cells

determine if surgical excision is necessary because of the high false-negative and false-positive rates. In cases of positive nipple cytology and mammographic changes suggestive of malignancy, a diagnostic surgical procedure may be justified [70]. If the mammographic abnormality is biopsied preoperatively and a cancer diagnosis is established, then a thorough work-up and definitive diagnosis can be performed. For patients with pathologic nipple discharge and no mass or mammographic abnormality, a biopsy should be done regardless of cytologic findings.

Cytology examination is not recommended for pregnant patients due to the difficulty in differentiating normal from abnormal proliferative changes. Positive cytology in cases of pathologic nipple discharge or nipple lesions can be helpful, but in cases in which the clinical evaluation is suspicious without positive cytology or if cytology is positive without a corresponding high level of clinical suspicion, tissue biopsy is required. A negative cytology report in the setting of clinical nipple discharge could erroneously reassure the patient who still needs further evaluation.

3.12 Biochemical Markers

Several researchers have addressed the role of biochemical markers in nipple discharge in an attempt to diagnose breast cancer. Certain LDH isoenzyme levels have been found to be elevated in the nipple discharge of patients with breast cancer. The test is relatively simple and inexpensive but is associated with a false-negative rate in cases where a cancer is in another area of the breast and not associated with the discharge [71]. Immunoassays for CEA have been done using small nitrocellulose-backed disks placed on the nipples of cancer patients. Nipple secretions from 94 % of the patients with cancer had significantly higher levels of CEA than from those without cancer. This difference was not apparent in healthy controls [72]. Several studies of NAF and abnormal discharge using immunoassays for CEA show similar trends whereas others show no difference [73–75]. Using a modified breast pump to obtain NAF, Sauter found that decreased levels of prostatic specific antigen (PSA) were associated with an increased breast cancer risk [9]. In a recent study, Liu found that basic fibroblast growth factor (bFGF) from nipple fluid was significantly increased in breast cancer patients over controls [76]. Sauter's group has also looked at proteomic analysis of ductal fluids using SELDI-TOF mass spectrometry showing differential expression between women with and without breast cancer [77]. These tests using nipple discharge or secretions may aid in the diagnosis of breast cancer and are promising for future screening and diagnosis but are currently not accurate enough to rule out carcinoma or negate the need for biopsy in patients with nipple discharge.

3.13 Ductal Imaging

Ductography or galactography has proven useful for preoperative localization of intraductal lesions [78, 79] (Fig. 3.7). Due to the significant false-negative rate, however, the decision to operate should not be based solely on the ductogram results [23]. The ability of ductography to distinguish between benign and malignant disease remains limited [51, 80]. A recent study reported an increase in the

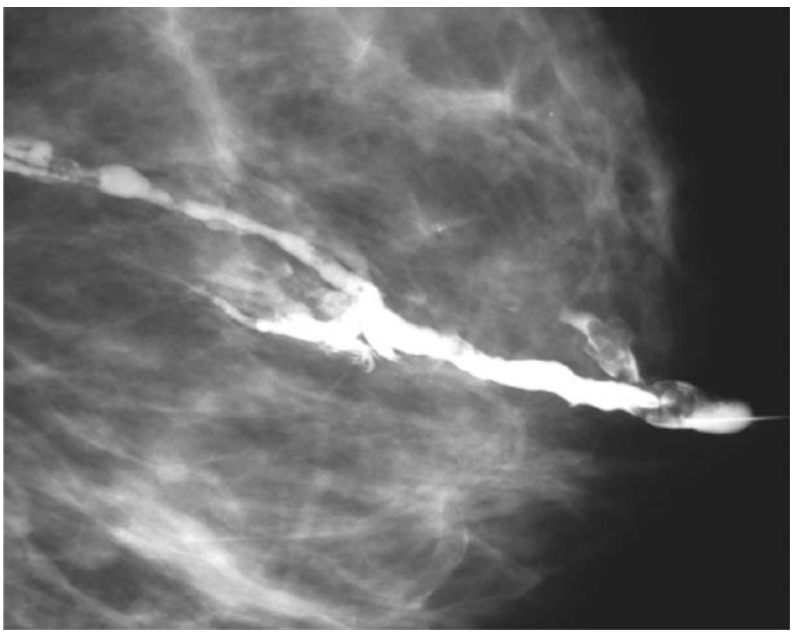

Fig. 3.7 Ductogram showing the typical lobulated appearance of a benign intraductal papilloma

duct excision yield of neoplastic growths from 67 to 100 % by using preoperative ductography [79]. This procedure is easily performed by inserting a 30-gauge blunt-tip needle into the discharging duct orifice and instilling 0.1–1.5 mL of water-soluble contrast. Mammograms are taken in two views and will show a filling defect or duct cutoff in most circumstances [22]. In cases where the ductal lesion is far from the nipple, ductography can be combined with preoperative needle localization to assist the surgeon with the excision [79, 81]. Other techniques combine preoperative ductography with methylene blue dye injection to assist the surgeon in removing the lesion [79, 82].

Standard ductography via the nipple is not possible in many patients who have had previous duct surgery with retained or new duct lesions or for patients who have dilated ducts that cannot be accessed through the nipple. In these cases, percutaneous ductography has been described using ultrasound guidance. This procedure allows for identification and localization of the lesion to assist with surgical excision [83].

3.14 Surgical Evaluation and Treatment

Surgery for pathologic nipple discharge can be less than satisfying procedure. Duct excision is typically performed blindly because the intraluminal pathology cannot be visualized directly during surgery. Duct excision can cause decreased sensation to the nipple and prevent the ability to breast-feed depending on the extent of dissection. The surgeon must judge the amount of tissue to be excised so as to assure adequate removal of the lesion without unnecessary destruction of normal breast tissue. Benign or normal pathology findings could result from not excising the lesion, from the pathologist not identifying the lesion within the specimen, or possibly from a truly negative pathology.

Various techniques for surgical removal of the mammary ducts have been described. A major duct excision removes all or most of the subareolar ductal tissue through either a circumareolar or radial incision [21, 84]. Traditionally, this approach was used for pathologic nipple discharge prior to the availability of localizing procedures. It is still useful in cases of copious physiologic discharge for which the patient requests surgery or for cases where localizing attempts are unsuccessful or show multiple duct involvement. After the incision is made, the ducts are encircled and tied off as they enter the nipple. The subareolar tissue is coned out for several centimeters to remove all apparent ductal tissues. The recurrence rate of nipple discharge after this procedure is very low, although the proliferative lesion retrieval rate is less than for more directed techniques [19]. The circumareolar incision and more extensive subareolar tissue resection necessary to perform a major duct excision may disrupt the nerve supply to the nipple and leave the patient with numbness, nipple retraction, and the inability to nurse on that side. Care must be taken to avoid cautery burn to the undersurface of the nipple to limit the possibility of nipple necrosis [84].

A more limited or segmental duct resection can be performed by cannulating the discharging duct with a probe. The tissue is removed from around the probe deep within the breast. The goal is to remove an entire ductal system from the nipple to the terminal duct-lobular unit. This is useful in cases where localizing attempts have failed and the location of the lesion is unknown or for deep lesions. A circumareolar incision is commonly made in the quadrant of the discharging duct [85]. A flap is created undermining to the nipple, and the dilated or blue duct is encircled. It is important to dissect into the nipple to remove the proximal duct tissue to prevent recurrent discharge [84]. A useful adjunct to this procedure is preoperative ductography combined, if necessary, with needle localization for a deep abnormality. The proximal duct is removed with the assistance of a probe or blue dye while the deep lesion is identified by excising the tissue around the localizing wire [81]. Duct excision using a lacrimal probe guide has the advantage of identifying the proximal portion of the discharging duct. The probe may, however, enter the wrong duct at a bifurcation or be unable to be advanced to the level of pathology.

Microdochectomy is a procedure, which removes the abnormal duct while preserving surrounding normal breast tissue [25, 86]. The technique involves identifying and cannulating the discharging duct preoperatively by ductography. Blue dye is then injected into the abnormal ductal system through the cannula placed during the preoperative ductogram. The duct is dissected from the nipple toward the deeper ducts removing only the blue-stained duct tissue. This technique is described with a transareolar incision, which is a radial incision through the nipple, or a small curvilinear incision within the areola or at the areolar edge can be used as well [78, 87]. This technique has the benefit of removing the discharging duct while preserving the normal ducts in an effort to limit sensation loss and retain the ability to breast-feed.

3.15 Mammary Ductoscopy

Mammary ductoscopy allows for direct visualization of the intraductal lesion by passing a small endoscope through the nipple into the ductal system after the duct orifice is dilated. This technique is becoming more widely used especially in cases of pathologic nipple discharge and reports the highest proliferative lesion rates of all localizing techniques [29, 88–91]. The visual component alone of ductoscopy cannot

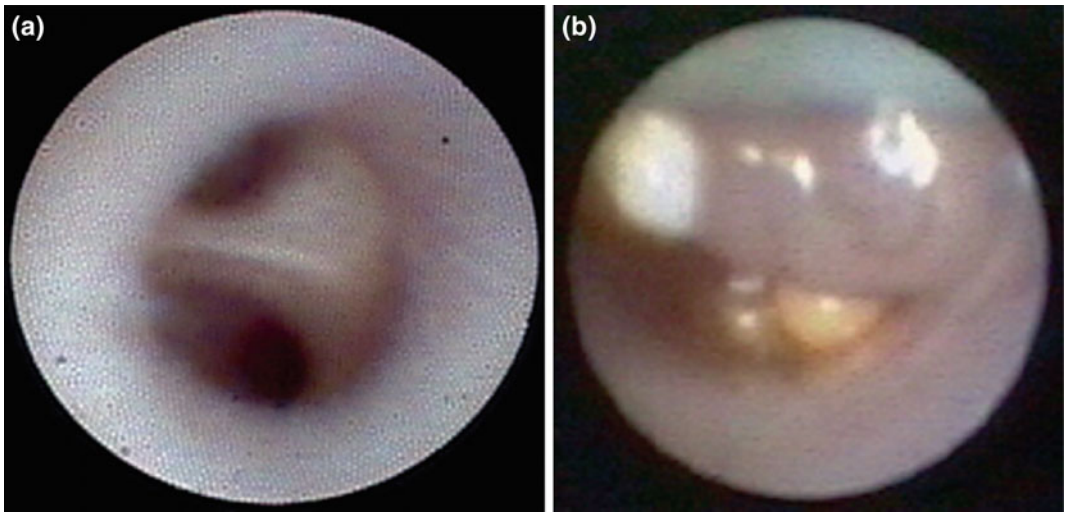

Fig. 3.8 Intraductal images through the mammary ductoscope. **a** Normal duct bifurcation. **b** Intraductal papilloma

adequately differentiate benign from malignant lesions [92]. Other studies show excellent sensitivity (98 and 96 %) with ductoscopy and cytology or intraductal biopsy, which can help with planning resection [39, 93].

The ability to enter the ductal system and directly visualize ductal abnormalities has distinct advantages. The intraductal pathology can be visualized during the time of surgical excision and the scope itself can direct the surgeon to the lesion (Fig. 3.8). Intraoperative visualization of the lesion enables adequate removal of the abnormality while preserving surrounding normal tissue. Ductoscopy enables the surgeon to identify the abnormality within the specimen and assists the pathologist in locating the lesion [94]. Mammary ductoscopy may limit the extent of surgery necessary to excise intraductal pathology, as well as help in identifying the lesions to be removed including lesions within the nipple itself, which can be left behind, and multiple deeper lesions, which occur in 25 % of cases, more accurately [29]. Intraductal biopsy tools are becoming available, which will provide histology samples of intraductal pathology [95]. A recent study used such tools to successfully remove 22 of 26 intraductal papillary lesions in an office setting. Short-term follow-up showed no recurrent discharge in these patients. [96] A recent Japanese study successfully removed 24 lesions in 75 patients with PND (29.3 %) negating surgical excision. One patient is subsequently developing DCIS and one developed recurrent discharge from multiple papillomas [97].

3.16 Follow-up

Anywhere from 5 to 20 % of duct excision cases will turn out to be malignant. As preoperative evaluation becomes more thorough, and malignant cases are identified preoperatively, this number declines. The treatment of breast cancer presenting as nipple discharge has traditionally been mastectomy. Many series suggest that intraductal cancer presenting as nipple discharge is more extensive and has a higher recurrence rate than DCIS in other areas of the breast [46, 98–100]. Ito found that in 26 patients with nonpalpable breast cancer associated with nipple discharge that were treated with duct-lobular segmentectomy, only one patient had microscopic residual disease found in the follow-up mastectomy specimen. These findings suggest that segmental duct resection is an adequate surgery for nonpalpable cancers presenting with nipple discharge [101]. If cancer is found at the time of duct excision for PND, then MRI may be useful for determining the extent of disease. Reexcision, which is often needed to obtain clear margins, will also help determine residual disease.

Carcinoma of the ipsilateral breast following duct excision has been reported in a number of series [3, 28, 46]. Many of these patients were found to have benign disease or no pathologic diagnosis at the original surgery. In these cases, it is likely that the lesion causing the discharge was not removed during the first procedure. These cancers typically present as masses rather than recurrent nipple discharge

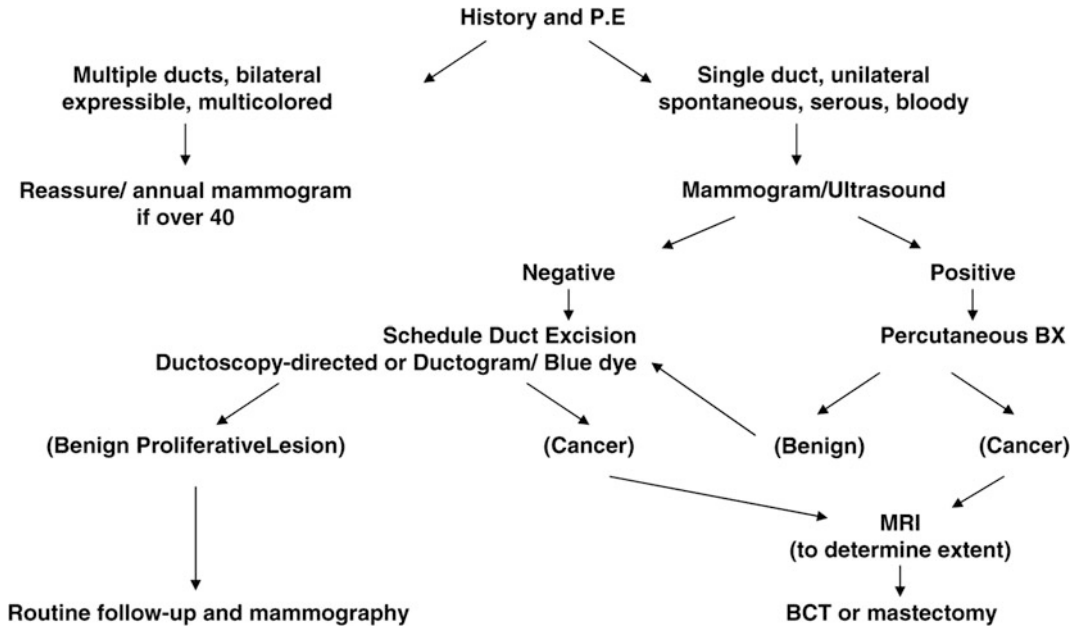

Fig. 3.9 Algorithm

because of the interruption of the ductal system at the time of the original duct excision. Close follow-up is essential for patients with nipple discharge in which no proliferative lesion was seen on analysis of the specimen, and for patients with peripheral papillomas. Patients undergoing breast conservation who have in situ carcinomas as the cause of their nipple discharge should also have postoperative radiation therapy and close mammographic and clinical follow-up [46].

Nipple discharge, in the majority of patients, is physiologic and usually does not require further evaluation. Spontaneous, clear or bloody, single duct discharge should be worked up with imaging modalities and most of these patients need excision to rule out carcinoma. While technology is rapidly advancing and we have many options available for ductal evaluation, none of these can satisfactorily rule out malignancy as the cause of the discharge. There are a few reports that suggest surveillance in patients with PND and negative extensive work-up is feasible; however, most studies advocate for excision [102–105]. Therefore, at this time, excision of the affected duct is still considered standard of care. The preoperative and excisional techniques you will utilize in this patient population will depend somewhat on the availability of equipment and expertise at your institution. It is clear, however, that localized excisions result in a greater lesion identification rate. Figure 3.9 illustrates the algorithm used at University Hospitals Seidman Cancer Center for the evaluation of nipple discharge. As imaging and biopsy techniques become more advanced, many nipple discharge patients will be able to forgo surgical excision altogether without compromising their diagnosis.

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