Current Management of Nipple Discharge

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Background and Pathophysiology

Nipple discharge is a relatively common complaint, with a reported incidence of 2–5 % [1] and occurring among 10–50 % of patients with benign breast disease [1, 2]. Typically, the primary concern and initial fear of patients who experience nipple discharge is whether it is due to an underlying breast cancer. The risk of carcinoma among those with nipple discharge has been reported to be between 6 and 21 % [2–10], with some reports including only those patients undergoing an operation, while others do not [3, 7–10]. Nipple discharge can be separated into categories of normal milk production (lactation), galactorrhea (physiologic nipple discharge), or pathologic nipple discharge based on the characteristics of presentation [11].

Lactation occurs as early as the second trimester of pregnancy and can continue for up to 2 years after delivery or cessation of breastfeeding [12]. Lactating women may also have occult or gross blood within their discharge, due to the delicate capillary networks in the developing epithelium [13–15]. Galactorrhea is manifested as bilateral milky nipple discharge involving multiple ducts not associated with pregnancy or recent breastfeeding. Galactorrhea is frequently caused by hyperprolactinemia, which may be secondary to medications, endocrine tumors (i.e., pituitary adenoma), endocrine abnormalities, or a variety of other medical conditions [16].

Pathologic nipple discharge is characterized by a unilateral, spontaneous, persistent discharge from a single duct. Pathologic discharge is not necessarily caused by an underlying carcinoma, and in fact, most pathologic nipple discharge is a result of a periductal mastitis, duct ectasia, or benign intraductal papilloma. Periductal mastitis typically produces multicolored, sticky discharge. Duct ectasia is the result of increased glandular secretions by the lactiferous ducts and results in multi-duct, colored discharge that can often be bilateral. Intraductal papilloma generally produces serous or bloody discharge from a single duct. Other related nipple abnormalities that the clinician should be aware of that can produce symptoms perceived by patients as nipple discharge include Paget's disease of the nipple and subareolar abscess.

The difficulty in managing nipple discharge is that the risk of carcinoma, despite being low [1, 17], cannot be eliminated without surgical duct excision and histologic confirmation. Thus, duct excision in all patients with pathologic nipple discharge has been widely recommended [6, 8, 9, 11, 18, 19]. In addition, although the risk of carcinoma has been reported to be as high as 21 %, most studies examining the risk of underlying carcinoma include only those patients referred to departments of surgery, specialty breast centers [4–6, 20] or

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those patients who underwent duct excision [7–10]. In a broader population of women with nipple discharge, the rate of underlying carcinoma was found to be only 3 % [17], with referral patterns and selection bias likely playing a significant role in the reported incidence of carcinoma among women with nipple discharge. Patients presenting with nipple discharge represent only 1 % of patients with DCIS and <1 % of those with invasive breast carcinoma [17].

Diagnostic Approach to Nipple Discharge

Our current approach to the evaluation and management of patients with nipple discharge is summarized in Fig. 6.1. History taking and physical examination are the first important steps. Older age predicts a higher risk of carcinoma [17, 8, 20] while a personal and family history of breast cancer is not predictive of an underlying cancer etiology [8]. Recent onset of amenorrhea or other symptoms of hypogonadism (hot flashes, vaginal dryness) should prompt consideration of hyperprolactinemia.

The characteristics of the discharge should be obtained and recorded in detail with an attempt to categorize whether it is due to lactation, galactorrhea, or pathologic discharge. The clinician should be sure to understand if the discharge is spontaneous or induced, unilateral or bilateral, the characteristics of the discharged fluid (including volume), the frequency of the discharge, and whether the patient is stimulating his or her nipple to examine for discharge. This latter factor is important as regular self-examination for discharge can produce ongoing, even spontaneous, discharge. Regular self-examination or other forms of breast stimulation can repress the secretion of hypothalamic prolactin inhibitory factor, resulting in hyperprolactinemia and galactorrhea [16].

The physical examination should include careful inspection of the breast skin, nipple, and areola as well as palpation of all the breast parenchyma, including the subareolar tissue and the regional lymph nodes. Care should be taken to examine the nipple for evidence of a central horizontal crease that is associated with duct ectasia, an entity which can also produce nipple discharge. Careful pressure can be exerted at the areolar margin circumferentially to examine for discharge. The discharged fluid can then be inspected for origin from a single or multiple ducts, color, and texture (thin, thick, sticky, etc.).

Hemoccult testing of the discharge is not usually performed, as both serous and bloody discharge can be associated with an underlying breast carcinoma [9, 20]. Cytologic analysis is not regularly performed, as the results of such studies are neither sensitive nor specific for an underlying breast cancer [9, 20–23]. Among patients with biopsy proven carcinoma, 29 % of cytology specimens of the discharge have been reported to show no evidence of carcinoma or atypia [24]. If the patient is found to have subareolar tenderness and periareolar erythema with purulent nipple discharge, this is consistent with a subareolar abscess rather than true nipple discharge. These patients are obviously approached differently and should be treated with an appropriate combination of antibiotics and possible incision and drainage and/or an excision of the subareolar major ducts [25].

Imaging and Laboratory Investigations in Nipple Discharge

There are no radiologic studies that are essential, except for routine screening mammography, when the history and physical examination reveals that the discharge has characteristically benign features (Fig. 6.1). Patients with lactation discharge need no further evaluation, including those with occult or gross blood in the discharged milk. Patients with galactorrhea need no further evaluation for breast carcinoma, but should be evaluated for an underlying cause of hyperprolactinemia including a careful review of medications, review of the patient's history for possible causes of neurogenic stimulation of the nipple-areola complex that would represses the secretion of hypothalamic prolactin inhibitory factor, and review of the history and physical examination for signs or symptoms of pituitary adenoma [16]. One may then perform laboratory

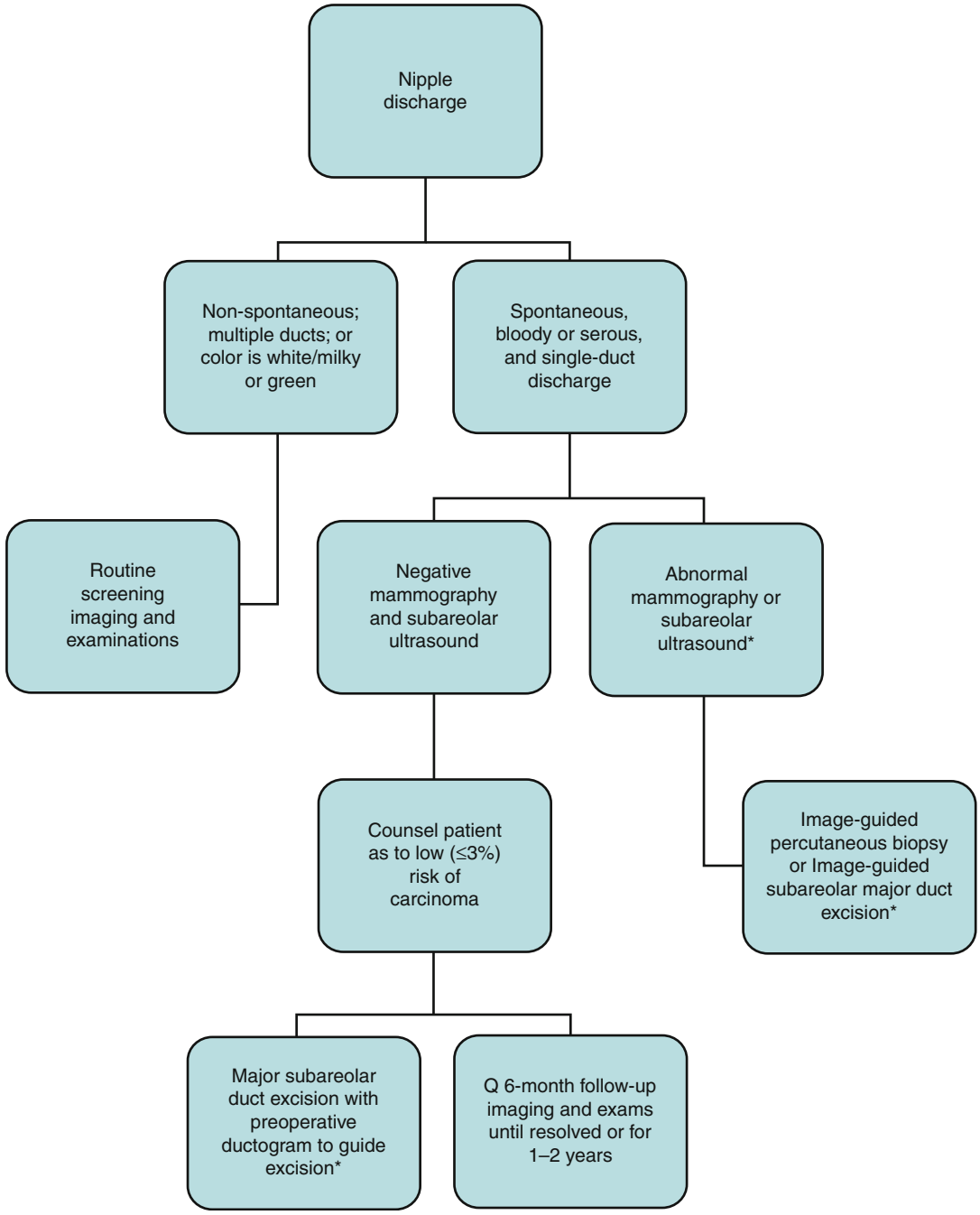

Fig. 6.1 Algorithm for the management of nipple discharge. *If patient plans future breastfeeding, selective duct excision is preferred over major duct excision

workup of the galactorrhea with serum prolactin levels, though the serum prolactin concentration is normal in nearly half of women who present with galactorrhea [26]. Galactorrhea in the absence of hyperprolactinemia is usually not the result of any ongoing disease process.

Table 6.1 Comparative rates of carcinoma risk

Characteristic	Carcinoma rates (%)	*p*
Age ≥50 vs. <50 years	6 % vs. 0 %	0.02
Unilateral vs. bilateral discharge	4 % vs. 2 %	0.49
Spontaneous vs. non-spontaneous	5 % vs. 0 %	0.13
Serous/bloody vs. other discharge	5 % vs. 0 %	0.10
Abnormal vs. normal mammogram	38 % vs. 3 %	<0.01
Abnormal vs. normal ultrasound	12 % vs. 1 %	<0.01
Abnormal vs. normal ductogram	6 % vs. 0 %	0.64

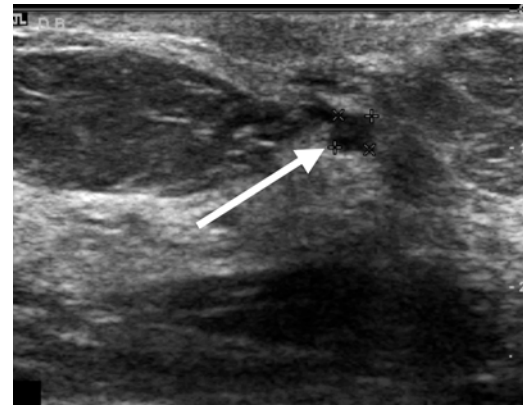

Fig. 6.2 Subareolar ultrasound demonstrating a 0.35 cm intraductal lesion (*arrow*) in a patient subsequently found to have ductal carcinoma in situ upon subareolar duct excision

For those patients with pathologic nipple discharge and without clearly benign features (Fig. 6.1), we proceed to diagnostic mammography (for those 30 years of age and older) and subareolar ultrasound. These imaging modalities have been reported to be able to separate patients with a high risk of underlying carcinoma from those with a low risk (Table 6.1) [17, 6, 8, 9, 11, 20, 27]. The risk of carcinoma with pathologic nipple discharge and an abnormal mammogram, while an uncommon scenario, is as high as 60 %, and the risk with an abnormal ultrasound but normal mammogram is 7 % (Fig. 6.2, Table 6.2) [17].

Ductography can be helpful in the evaluation of pathologic nipple discharge, though the use of subareolar ultrasound in skilled hands greatly minimizes the additional diagnostic yield of ductography. At our institution, we seldom use ductography as a diagnostic tool but rather to provide a "roadmap" as needed for subareolar duct excision once a decision has been made to perform this operation (Fig. 6.1). The primary benefit of ductography is to localize the lesion, especially in the case of multiple and peripheral lesions [4, 20, 28–32]. This allows radiologic guidance, such as wire or radioactive seed localization [33], to be used to direct the major duct excision and be certain that the area/lesion is completely resected.

Of note, ductography has been reported to miss as many as 20 % of ductal lesions, including those of a benign nature [4]. Although the negative predictive value is relatively high (82–91 %) [4, 9, 20, 31], it is still not sensitive enough to exclude the possibility of malignancy. In one series of 163 patients, ductography was associated with a sensitivity of 76 %, a specificity of 11 %, and a positive predictive value of only 19 % [34]. Such performance of this test makes it difficult to justify regularly subjecting patients to a sometimes painful procedure if reliable subareolar ultrasound is available.

The role of ductoscopy in nipple discharge remains to be defined. While this procedure holds some promise, the presence of cancer has been reported to predict unsuccessful ductal cannulation with the ductoscope [27]. Ductoscopy-guided excision, like ductograpy-guided excision, has been reported to increase the yield of atypia or carcinoma in at least one series [35]. Among 114 women in which half the patients were evaluated with ductoscopic guidance and half with surgery alone, the yield of pathologic diagnoses did not significantly differ between the groups [35]. In addition, ductoscopy was technically unsuccessful in 13 % of patients [35]. Currently, we believe that ductoscopy adds little diagnostic value in nipple discharge, with further refinements in instrumentation and technique possibly increasing its usefulness in the future.

While breast MRI may be better than conventional imaging at detecting occult malignancies among patients with nipple discharge [36], others

Table 6.2 Cancer risk by clinical scenario

Clinical scenario[a] – nipple discharge with	*N*	Risk of carcinoma (%)	Risk in other reports
All patients with nipple discharge	204	3	6–21 % [1–6, 13]
Nipple discharge, underwent biopsy	75	9	
Non-spontaneous discharge	49	0	
Bilateral discharge	52	2	
Unilateral, spontaneous, serous discharge from single duct	49	4	
Unilateral, spontaneous, bloody discharge from single duct	60	7	
Unilateral bloody/serous discharge, single duct, and negative mammogram	106	3	3 % [11]
Unilateral bloody/serous discharge, single duct, negative mammogram and negative ultrasound[b]	57	0	3 % [1]
Unilateral bloody/serous discharge, single duct, negative mammogram and abnormal ultrasound	30	7	
Unilateral bloody/serous discharge, single duct, and abnormal mammogram	5	60	13 % [11]

[a]Some patients' characteristics overlap categories
[b]One patient with carcinoma had *bilateral* discharge and a negative mammogram and ultrasound, but she had undergone wire-localized, bilateral subareolar duct excisions 6 months prior at another institution

studies show that most papillomas are MRI-occult which may predict limited sensitivity for otherwise-occult malignancy [37]. In a series of 52 patients with suspicious nipple discharge who were studied with a breast MRI, the sensitivity and specificity for malignancy were 77 and 62 %, respectively [34]. The positive predictive value of MRI in this series was 56 % and the negative predictive value 87 %. Given the low pretest probability of underlying carcinoma for women with nipple discharge, the relatively limited specificity of breast MRI would be expected to produce a significant rate of false positive findings. This combined with the cost of breast MRI makes its current value in this entity limited.

Decision-Making for Biopsy and Subareolar Duct Excision

Once the history and physical examination has eliminated patients with characteristically benign discharge and a normal mammogram and subareolar ultrasound have been obtained, the risk of carcinoma is low. The rate of carcinoma in a 57-patient cohort with these characteristics who underwent subareolar duct excision was 0 % with another 124 patients having no carcinoma with 2-year median follow-up [17]. Other studies have reported an ~3 % risk of carcinoma with a normal physical examination, normal mammogram, and normal ultrasound [20]. When counseled about these low risk levels, most patients choose close clinical follow-up rather than subareolar duct excision.

If patients choose close clinical follow-up, it is appropriate to perform physical examination and subareolar ultrasound every 6 months for 1–2 years or until the discharge resolves, whichever comes first (Fig. 6.1). Many women choose subareolar duct excision for symptom relief if their discharge persists for 1 year or more, regardless of the low risk of underlying carcinoma. The median duration of benign discharge has been reported to be 12 months [20], but nipple discharge has been present in some patients for up to 40 years [17].

For those patients who have an imaging abnormality or who choose to undergo diagnostic subareolar duct excision, a major duct excision is preferable if she does not plan future breastfeeding. Major duct excision has been reported to detect a higher percentage of occult carcinoma than microdochotomy [10], result in fewer patients requiring repeat duct excision [10], and is associated with a 0 % rate of breast cancer diagnosis

over the subsequent 5 years [18]. Unless the targeted lesion is identified by mammogram or ultrasound and is within 2 cm of the nipple, ductography should be considered to identify the position of the lesion with precision. If the lesion is identified by mammography, sonography, or ductography and is greater than 2 cm from the nipple, radiologic localization is appropriate to precisely and effectively resect the offending lesion. For other patients, cannulation of the offending duct with a lacrimal probe intraoperatively is frequently used to guide the excision.

In a series of 192 patients evaluated and treated at our institution utilizing a defined algorithm (Fig. 6.1), 66 % of patients chose to undergo close clinical follow-up rather than subareolar duct excision, including 88 % who did not have an abnormality on mammography or sonography. All patients with carcinoma were found to have an imaging abnormality. Of the patients followed clinically, 20 % eventually chose to have subareolar duct excision due to persistent discharge. Among patients not undergoing subareolar duct excision, 81 % had spontaneous resolution of their nipple discharge.

Conclusion

In conclusion, using a systematic approach to nipple discharge allows the clinician to stratify patients with pathologic nipple discharge into low- and high-risk groups. Low-risk patients can be safely offered close clinical follow-up rather than subjecting all patients with pathologic discharge to operative intervention and additional expensive tests. Patients that are provided with risk-stratification data usually choose to avoid operative intervention when they are found to be at low risk, though 20 % will eventually choose surgery for their persistent symptoms.

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