Damayanti, the beloved of Prince Nala, being adorned by her companions. Guler miniature, circa 1780 A.D. Reproduced by the courtesy of Dr. Karan Singh.

An algorithm for the management of nipple discharge is provided, and translational research initiatives related to the intraductal approach to breast carcinoma are summarized.

Breast Ductal Secretions: Clinical Features, Potential Uses, and Possible Applications

Julie E. Lang, MD, and Henry M. Kuerer, MD, PhD, FACS

Background: *Nipple discharge accounts for approximately 5% of visits to a breast specialist surgical practice and may be encountered as the chief complaint by many other types of physicians. The vast majority of breast cancers originate in the ductal system, which prompted interest in the evaluation of the intraductal approach to breast cancer. Ductoscopy, nipple aspiration, and ductal lavage have emerged as innovative fields of study that may have clinical applications.*

Methods: *We performed a literature search of published manuscripts using the keywords nipple discharge, breast ductal secretions, and intraductal approach. We also report our single-institution experience in managing nipple discharge.*

Results: *We present our institutional algorithm for the management of nipple discharge. The possible etiologies of nipple discharge and the appropriate workup are reviewed. Three evolving minimally invasive techniques for the evaluation of high-risk patients include ductoscopy, nipple aspiration, and ductal lavage. Nipple aspiration and ductal lavage fluid may be assayed for cytology, genomic, gene expression, and proteomic studies. Several different translational approaches are being undertaken to investigate the local microenvironment associated with the development and progression of breast carcinoma.*

Conclusions: *Nipple aspiration fluid and ductal lavage offer the opportunity to study the local microenvironment of the ductal system, which is where most breast cancers originate. These powerful approaches to biomarker analysis could be applied to the prevention and treatment of breast cancer.*

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Abbreviations used in this paper: NAF = nipple aspiration fluid.

Background

Nipple discharge accounts for about 5% of breast-related complaints. It is an alarming symptom to the patient and her healthcare providers due to concern for potential breast cancer. However, fluid can be elicited from the nipple by gentle manipulation in the majority of women, regardless of age or health status.

Nipple discharge is classified as benign or pathologic on the basis of its clinical characteristics. Benign nipple discharge is typically considered to be bilateral and nonspontaneous (occurring after manipulation of the breast), and it emanates from multiple ducts. Benign discharge varies in color from white to yellow to green to brown/black and is thought to be caused by apocrine glandular secretion of the breasts.[1] Pathologic nipple discharge is typically considered to be unilateral, persistent, and spontaneous, and it arises from a single duct. Nipple discharge that is clear, serous, serosanguineous (pink), or bloody is associated with an increased risk of carcinoma.[2,3] Benign nipple discharge is considered physiologic, whereas pathologic nipple discharge is associated with an increased risk of malignancy. Although nipple discharge usually has a benign etiology, previous studies have found the incidence of breast carcinoma to be between 9.3% and 21.3% in women with pathologic nipple discharge.[2,4-7] Furthermore, an increased risk of carcinoma has also been reported in women in whom nipple discharge is associated with a palpable mass or related imaging abnormality.[3,8,9]

Surgical treatment is indicated for nipple discharge for eliminating the symptom and for diagnostic purposes to rule out breast carcinoma. In this article we review the causes of nipple discharge as well as the workup and management of nipple discharge, including indications for surgical treatment. We also consider applications of the intraductal approach to evaluation of potential breast malignancy via modalities such as nipple aspiration, ductal lavage, and duct endoscopy.

Etiologies of Benign Nipple Discharge

The causes of nonsurgically treated nipple discharge can generally be grouped into four different etiologies: (1) physiologic causes, (2) pathologic endocrine causes (failure of normal prolactin inhibition of release or increased prolactin production or release), (3) pharmacologic causes resulting from the use of certain medications, and (4) idiopathic causes (Table 1). Galactorrhea is bilateral milky-fluid production not associated with pregnancy. In general, the idiopathic category accounts for 50% of patients presenting with galactorrhea.

Physiologic causes of nipple discharge include lactation in the peripartum period. However, it is important to counsel patients that regardless of age, parity, or menopausal status, breast secretions may be elicited from the majority of women by manual stimulation of the nipple. Patients who present with nonspontaneous nipple discharge should be reassured that this is a normal, benign process. Any spontaneous discharge should be reported to the clinician.

Prolactinomas are the most common secretory tumor of the anterior pituitary and may cause bilateral or unilateral galactorrhea. Primary hypothyroidism causes hyperprolactinemia secondary to increased production. Rarely, bronchogenic carcinomas can result in ectopic production of prolactin. Several hypothalamic disorders can result in increased prolactin release including head trauma, encephalitis, and hypothalamic infiltration (sarcoid) or tumors.

Several drugs can cause increased levels of prolactin and galactorrhea. The most common drugs include (1) psychoactive drugs (phenothiazines, tricyclic antidepressants, selective serotonin reuptake inhibitors, haloperidol, and anxiolytics), (2) antihypertensive medications (calcium channel blockers, alpha-methyldopa, reserpine, and opiates), (3) gastrointestinal drugs (metoclopramide, cimetidine, famotidine, ranitidine), (4) anesthetics, (5) amphetamines or marijuana, and (6) estrogens (conjugated estrogen and medroxyprogesterone acetate, oral and injectable contraceptives).

It is important to note that in rare cases, patients with nipple discharge considered to be clinically benign in character (milky or green) may actually harbor a malignancy. All patients should undergo physical examination and appropriate breast imaging consisting of mammogram and/or ultrasound as clinically indicated.

Patients with pathologic nipple discharge are at a higher risk for breast carcinoma; yet, as previously stated, the majority of these patients do not have a breast cancer. Other potential causes of pathologic nipple discharge are all benign conditions, including those listed

Table 1. — Causes of Nonsurgically Treated Nipple Discharge

Physiologic
Peripartum period
Manual stimulation of the nipple(s)
Pathologic (endocrine abnormalities)
Pituitary adenoma
Primary hypothyroidism
Ectopic production of prolactin (bronchogenic carcinoma)
Hypothalamic disorders
Pharmacologic
Psychoactive drugs
Anti-hypertensive medications
Gastrointestinal medications
Opiates
Oral contraceptives or estrogen replacement therapy
Idiopathic

Modified from Kuerer HM, Cabioglu N. Nipple discharge and ductal secretions. In: Singletary SE, Robb GL, Hortobagyi GN. *Advanced Therapy of Breast Disease*. 2nd ed. Hamilton, London: BC Decker, Inc; 2004. Modified with permission.

in the benign etiology section as well as trauma, duct ectasia, proliferative breast disease, and intraductal papilloma. Solitary papillomas without atypia are not considered to have malignant potential. However, the presence of multiple papillomas (greater than 5 within a localized segment of breast), atypia, or papillomatosis is associated with an increased risk of breast cancer.[10] Patients with pathologic nipple discharge are typically considered surgical candidates due to the potential for diagnosing a malignancy.

Diagnosis, Workup, and Treatment of Pathologic Nipple Discharge

The standard workup for patients presenting with nipple discharge includes a thorough history and physical examination in addition to a complete breast imaging evaluation. Imaging studies allow potential localization and characterization of the lesion in question, with the option of percutaneous image-guided biopsy to achieve a tissue diagnosis. Typically, mammography and ultrasound are used to identify mass lesions responsible for nipple discharge. Additionally, magnetic resonance imaging (MRI) may be useful in the workup of pathologic nipple discharge when lesions cannot be localized with mammography or ultrasound.[11] While MRI has been preliminarily studied for this indication at a few centers, it is not generally part of the workup. When nipple discharge is determined to be of benign etiology, duct excision may also be indicated to eliminate discharge when bothersome to the patient.[4] In the absence of a mass or other lesion identified with breast imaging, the conventional surgical approach has been to perform major duct or lacrimal probe-guided excision. However, a histopathologic etiology is not always found on major duct or lacrimal probe-guided excision, which raises the possibility that the causative lesion might have been left in situ.[12] Diagnostic ductography allows preoperative determination of the number, location, and extent of any underlying lesions. Preoperative use of ductography with methylene blue injection to localize lesions has been shown to increase the likelihood that a specific pathologic lesion will be found at surgery.[13]

Minimally Invasive Techniques for Evaluation of High-Risk Patients

Operative Breast Endoscopy

Studies suggest that 5 to 12 independent ductal lobular systems drain directly to the skin surface of the nipple, while approximately 20 ducts taper to within 1 mm of the skin surface and are therefore less directly accessible.[14-16] Every segmental duct branches sequentially, ultimately forming the terminal duct-lobular unit. It is believed that the vast majority of premalignant and malignant breast lesions arise in the epithelial lining of the ductal lobular units,[14,17,18] which is the rationale for the intraductal approach to detect cancerous and precancerous lesions of the breast.[19]

Several investigators have reported their experience with operative breast endoscopy for the evaluation and management of pathologic nipple discharge.[20-24] They have used ductoscopy to identify the abnormal appearing duct for surgical resection. Investigators at the Cleveland Clinic Foundation have shown that this technique can negate the need for preoperative galactography in some patients.[20] Furthermore, when routine operative endoscopy is performed for patients with bloody nipple discharge, the extent of proliferative disease accounting for the pathologic discharge is much greater than what would normally be resected using classic blind resection of tissue behind the areola.[21] One particular advantage of ductoscopy is that the technique permits evaluation of breast ducts deep to the nipple areolar complex, offering a means of assessment of deeper ducts remote from the nipple. This is especially useful in cases in which the patient has normal central ducts with malignancy involving the deeper mammary ducts remote from the nipple. At this point, the use of breast endoscopy is just beginning to be utilized by specialists in breast disease at certain academic centers. It is currently unclear whether this technique will prove to be of clinical utility and thus used more often in clinical practice or whether it will be an interesting passing technique based on developing miniature endoscopic technology. Advocates contend that ductoscopy may allow a more accurate means of identification of intraductal lesions,[22] and critics argue that many of these findings are benign or would be typically present in the planned surgical field.[24] Additionally, few breast specialists are currently trained in endoscopic techniques of the breast, and current ductoscopy equipment does not allow for a two-channeled approach with direct visual guidance for biopsy of suspected intraductal lesions. The potential role for breast endoscopy in the evaluation of intraductal lesions and the early detection of breast cancer requires further investigation before it can be widely adopted into practice.

Nipple Aspiration

Analysis of the biochemical and cellular contents of breast ductal fluid has recently gained interest for its potential to noninvasively study the local microenvironment associated with the development and progression of breast carcinoma.[25-28] Potential drawbacks to the evaluation of ductal fluid include failure of the involved duct to produce fluid and failure of the fluid specimen to contain sufficient cellular material for analysis. Interest in nipple aspiration has been renewed partly because a simple hand-held, externally placed suction cup can be used to quickly obtain a concentrated fluid fraction of breast secretions in most women.[29] Although much of the earlier groundbreaking work was performed with either healthy volunteers or women with benign breast disease,[26,30] we and other groups believe that comparing the ductal fluid characteristics of a breast containing a known carcinoma to the healthy contralateral breast might be a practical method to identify clinically relevant tumor markers that could be useful in risk stratification, diagnosis, treatment monitoring, and detection of recurrence.

To investigate this hypothesis, we initiated a prospective trial and enrolled 65 patients with primary invasive breast cancer and measured soluble HER-2/neu in nipple aspiration fluid (NAF) samples from the breast with cancer and the normal contralateral breast and in the serum.[31] We chose to measure the extracellular domain of the HER-2/neu tyrosine kinase growth factor receptor because the identification and characterization of this molecule seems to be one of the most significant and clinically relevant developments in our understanding of breast cancer biology and treatment.[32] In this study, the mean NAF volume obtained and the mean NAF protein concentration were found to be no different in the normal vs the affected breast (62.4 µL vs 60.4 µL and 140.9 mg/mL vs 107.8 mg/mL, respectively). Mean serum HER-2/neu level was 4.36 ng/mL (range 0–16.8 ng/mL), nearly 50 times less than the mean NAF HER-2/neu level from all patients and all breasts (209.2 ng/mL, range 1.0–3,480.0 ng/mL). NAF HER-2/neu levels were significantly correlated between breasts for each individual patient (r = .302, P=.038). HER-2/neu-overexpressing tumors produced significantly more HER-2/neu in the affected breast (653.6 ng/mL) than in the unaffected breast (101.7 ng/mL) or serum (3.46 ng/mL) (P=.016). Therefore, we concluded from this initial study that nipple aspiration is a noninvasive method for detecting tumor-specific relevant molecular changes from ductal fluid.

Breast ductal fluid has been shown to contain a variety of chemical substances and many different proteins (Table 2).[33-55] Substances of exogenous origin found in breast ductal fluids include nicotine, caffeine, technetium, pesticides, orally ingested drugs, and Ames test-positive substances that are indicative of mutagenic agents of undetermined origin,[30,56] thus indicating that the breast ductal epithelium is in contact with exogenously derived substances. Many endogenously derived proteins have also been found in NAF samples including immunoglobulins, estrogen and progesterone, androgens, prolactin, prostate-specific antigen, and carcinoembryonic antigen (Table 2).[27,30,53,56] Perhaps one of the most interesting groups of molecules detected in breast ductal fluid are members of the epidermal growth factor family, which are secreted and act locally and have potent mitogenic effects on human breast cancer cells.[43] Both epidermal growth factor and transforming growth factor-α have been found in NAF samples from healthy premenopausal women, and ErbB-2 (HER-2/neu) has been detected in nipple discharge samples from patients.[45] The extremely high amount of HER-2/neu extracellular domain detected in bilateral NAF samples from patients with unilateral breast cancer in the current study was unexpected. This finding may have important clinical ramifications in light of recent studies regarding expression of this molecule in patients with benign breast disease and in the use of monoclonal-antibody therapy for HER-2/neu-overexpressing breast cancer.

Recently, several groups, including our own, have investigated the use of proteomic profiling technologies as a potential method to identify tumor markers in the NAF.[57-61] This approach is used to identify and quantify protein spectral peaks for comparisons between cancer-bearing breasts and non–cancer-bearing breasts or healthy controls. The recent development of surface-enhanced laser desorption/ionization coupled with time-of-flight mass spectroscopy (SELDI-TOF) allows for both qualitative and quantitative studies of proteomics. The advantages of this approach are that it is high-throughput, requires minimal material compared to conventional electrophoresis-based methods, and analyzes a molecular panel inclusive of posttranslational modifications of protein, which may be an important component of cancer biology. This promising technology is discussed further in another article within this issue.

Several groups have investigated the application of cytology-based approaches to NAF. Although NAF cytology is not a sensitive test for the detection of invasive carcinoma of the breast, it has been demonstrated that the probability of detecting malignant cells in NAF is dependent on the extent of ductal carcinoma in situ (DCIS) and nipple involvement by DCIS.[62] King et al[63,64] demonstrated that patients with NAF cytologic findings of hyperplasia and atypia were 2.5 and 4.9 times as likely, respectively, to develop breast cancer than were women from whom fluid was not elicited.

Several groups have implemented a genomic strategy to investigate NAF for malignant potential. Researchers have successfully extracted cellular DNA from NAF and have demonstrated that this DNA can be amplified by polymerase chain reaction (PCR). The NAF fluid showed loss of heterozygosity and microsatellite instability increasingly in parallel with the extent of disease progression.[65] Methylation of promoter regions of tumor suppressor genes is common in breast cancer and results in oncogenesis by silencing the tumor suppressor genes. Promoter hypermethylation has been demonstrated in NAF of patients with invasive ductal carcinoma and DCIS.[66] NAF may potentially serve as a surrogate for breast tissue in the evaluation of the high-risk patient, permitting many different

Table 2. — Characteristics of Substances Identified in Human Breast Secretions From Women With and Without Carcinoma

Substance	Reference	Number of Subjects	Concentration	Present in Normal Breast	Present in Breast With Cancer	Comments
Basic fibroblast growth factor (bFGF)	Liu et al[33]	10 normal breast 10 breast cancer	0.019 ng/mL[a] 1.717 ng/mL[a]	X	X	NAF bFGF from cancer patients were significantly higher than from the controls.
Carcinoembryonic antigen (CEA)	Kahana et al[34]	22 benign 4 breast cancer 34 lactating	619 ng/mL[a] 4,600 ng/mL[a] 62 ng/mL[a]	X	X	Patients in this series all had nipple discharge or were lactating.
	Inaji et al[35]	18 benign 15 breast cancer	43 ng/mL[a] >100 ng/mL in 12	X		Patients in this series had nipple discharge. CEA was elevated in breast cancer patients compared with levels in those with benign disease (fibrocystic and papillomas). No correlation of serum CEA levels to discharge levels.
	Mori et al[36]	33 benign 44 breast cancer	<400 ng/mL in 79% >400 ng/mL in 75%		X	Patients in this series all had nipple discharge. Overall accuracy of CEA level >400 ng/mL (78%) in diagnosing non-palpable breast cancer was higher than that obtained for ductography (62%) and cytology (70%).
	Imayama et al[37]	22 normal breast 32 breast cancer	0.6 units 16.2 units	X	X	CEA measured with a disk applied to the nipple. CEA significantly elevated in breast with cancer compared with level in the normal breast of same patient.
	Foretova et al[38]	112 normal breast 4 breast cancer	1,000 ng/mL[b] 2,000 ng/mL[b]	X	X	CEA elevated in NAF of smokers.
	Malatesta et al[39]	15 normal breast 8 breast cancer	310,000 ng/mL[a]	X	X	Concentration of CEA is combined average in 14 women with and without cancer who have type-II NAF.
	Zhao et al[27]	227 normal breast 67 proliferative lesions[c] 44 breast cancer	1,060 ng/mL[b] 1,400 ng/mL[b] 1,830 ng/mL[b]	X	X	CEA levels in NAF from breasts with cancer were significantly higher than were those from normal control breasts.
2,6-Cyclolycopene-1, 5-diol	Chen and Djuric[40]	11 normal breast	34 ng/mL[a]	X		Levels in NAF were consistent with high levels of oxidative stress in the breast.
Cholesterol and cholesterol epoxides	Petrakis et al[41]	150 normal breast	2,200 mg/dL[a]	X		Cholesterol levels were elevated in the NAF compared with plasma and increased with advancing age.
Dehydroepiandrosterone sulphate (DHEAS)	Miller et al[42]	22 normal breast 22 breast cancer	149 µg/m[a] 109 µg/m[a]	X	X	DHEAS levels were much higher in NAF compared with plasma. No significant difference in DHEAS levels were noted between breasts from the same patient or between women with and without cancer.
Epidermal growth factor	Gann et al[43]	18 normal breast	604 ng/mL[a]	X		Levels were similar between breasts in the same patient.

Table 2. — Characteristics of Substances Identified in Human Breast Secretions From Women With and Without Carcinoma (continued)

Substance	Reference	Number of Subjects	Concentration	Present in Normal Breast	Present in Breast With Cancer	Comments
Estrone (E1) and estradiol (E2)	Ernster et al[44]	74 normal breast 7 breast cancer	537–1,793 pg/mL[d]	X	X	E1 and E2 10–20 times higher in breast fluid than in serum. E1 and E2 concentration in NAF not related to phase of the menstrual cycle.
HER-2/neu	Inaji et al[45]	19 fibrocystic 9 breast cancer	21 ng/mL[a] 523 ng/mL[a]		X	Patients in this series had nipple discharge. Two patients with >1000ng/mL HER-2/neu also showed strong staining in the tumor.
	Kuerer et al[31]	65 normal breast 65 breast cancer	102 ng/mL[a] 653 ng/mL[a]	X	X	Values refer to HER-2 levels in breasts with normal levels of HER-2 versus those with over-expressing tumors. Mean serum levels of HER-2 from the patients with cancer were 3.5 ng/mL.
Human glandular kallikrein 2 (hK2)	Black et al[46]	6 normal breast	2,000 ng/L[a]	X		Human glandular kallikrein is a PSA precursor.
8-Isoprostane	Chen and Djuric[40]	11 normal breast	32,110 pg/mL[a]	X		Levels in NAF consistent with high levels of oxidative stress in the breast.
Immunoglobulin (Ig)	Petrakis et al[47]	86 normal breast 12 breast cancer	0.66–16.29 mg/mL[a]	X	X	Ig levels are high in NAF.
	Yap et al[48]	7 normal breast	1.05–237.6 mg/mL	X		IgA concentration in NAF much greater than IgG in NAF.
Lactate dehydrogenase (LDH) isozymes	Kawamoto[49]	63 benign 11 breast cancer	Not stated	X		Description of LDH isozyme patterns in patients with nipple discharge.
Nicotine	Petrakis et al[41]	2 nonsmoker 4 smoker	0 ng/mL[a] 90 ng/mL[a]	X		–
Prolactin	Wynder et al[50]	87 normal breast	40 ng/mL[a]	X		–
	Rose et al[51]	46 normal breast 36 "cystic breast disease"	63.9 ng/mL[a] 136.2 ng/mL	X		Prolactin levels between groups did not differ.
	Malatesta et al[39]	15 normal breast 8 breast cancer	136 ng/mL[a]	X	X	Concentration of cancer prolactin is combined average in 14 women with and without cancer who have type-II NAF.
Progesterone	Rose et al[52]	3 normal breast 29 fibrocystic	48–185 ng/mL[a]	X		Progesterone was markedly elevated in the serum compared with that in NAF.
Prostate-specific antigen (PSA)	Sauter et al[53]	11 normal breast	2,554 ng/g total protein[a]	X		NAF PSA concentration was associated with serum progesterone level.
	Black et al[46]	6 normal breast	77 ng/mL[a]	X		–
	Malatesta et al[39]	15 normal breast 8 breast cancer	48.75 ng/mL[a]	X	X	Concentration of PSA is combined average in 14 women with and without cancer who have type II NAF.
	Zhao et al[27]	227 normal breast 67 proliferative lesions[c] 44 breast cancer	49 ng/mL[b] 22 ng/mL[b] 67 ng/mL[b]	X	X	PSA levels in NAF from breasts with cancer, proliferative lesions, and normal controls were not significantly different.

Continued on page 356

Table 2. — Characteristics of Substances Identified in Human Breast Secretions From Women With and Without Carcinoma (continued)

Substance	Reference	Number of Subjects	Concentration	Present in Normal Breast	Present in Breast With Cancer	Comments
pS2	Harding et al[54]	35 premenopausal 28 postmenopausal	8.5 ng/mg protein[b] 9.1 ng/mg protein[b]	X		pS2 is an estrogen-induced protein. Treatment with tamoxifen lowered pS2 concentration in NAF.
Testosterone	Hill et al[55]	12 normal breast 12 breast cancer	140 ng/dL[a] 40 ng/dL[a]	X	X	Levels significantly higher in breast cancer patients.
Transforming growth factor-α	Gann et al[43]	18 normal breast	2.26 ng/mL[a]	X		Levels similar between breasts in the same patient.
Vascular endothelial growth factor (VEGF)	Liu et al[33]	10 normal breast 10 breast cancer	106 ng/mL[a] 94 ng/mL[a]	X	X	No significant difference in VEGF between controls and cancer patients.

[a] Mean concentration.
[b] Median concentration.
[c] "Proliferative lesions" in this study included ductal carcinoma in situ, lobular carcinoma in situ, and atypical ductal hyperplasia.
[d] Mean ranges of E1 and E2 (reported as the antilogarithms of the means of the logarithms).

Modified from Kuerer HM, Cabioglu N. Nipple discharge and ductal secretions. In: Singletary SE, Robb GL, Hortobagyi GN. *Advanced Therapy of Breast Disease.* 2nd ed. Hamilton, London: BC Decker, Inc; 2004. Modified with permission.

types of cellular, genomic, or proteomic assessment without a biopsy. NAF assessment currently remains a research modality since too few cells are available for definitive cytologic diagnosis.

Ductal Lavage

A major limitation of NAF is that insufficient material is produced for clinical cytopathology, which prompted the development of ductal lavage (DL) to attempt to address this issue. The DL catheter is designed to enable cannulation and sampling of the selected duct via the specimen catheter port with concurrent infusion of 2 to 15 mL of normal saline via a separate port.

In a pilot multicenter study of 507 high-risk patients, Dooley et al[67] reported a median collection of 13,500 epithelial cells per duct via DL compared to 120 epithelial cells per breast with NAF. Four patients not previously known to have breast cancer had abnormal DL findings and subsequently were found to have DCIS on final surgical pathology; only 11 patients went on to have a surgical excision to further evaluate these cytologic findings. The majority of patients in this study underwent DL as an outpatient under local anesthetic. The authors concluded that DL is a safe, well-tolerated procedure that is more sensitive than NAF in the detection of cellular atypia. They suggested DL could be used to sequentially observe the breast epithelium in high-risk individuals in order to risk stratify patients to guide recommendations for chemoprevention. Based on this pilot study, a clinical algorithm for the use of DL was proposed.[68]

Initial studies of DL that correlate cytology results with surgical pathology have found results of DL to be insufficiently accurate for the assessment of patients with known breast cancers.[69,70] Khan et al[69] reported findings of a low sensitivity (17%) for the diagnosis of breast cancer in the setting of a known malignancy in 31 evaluable breast cancer patients. It is unclear if this was due to failure of the involved duct to produce fluid or failure of the fluid to contain cytologically abnormal cells. Reports of chromosomal instability in paired breast surgical and DL specimens[71] and hypermethylation of epithelial cells in DL specimens[28,72] have been published that are similar to studies in NAF. Potential still exists for the use of DL to search for biomarkers to enable early detection of breast cancer.

Treatment Algorithm

We recently reviewed our experience with patients presenting with nipple discharge at our center.[73] During the study period, 146 patients presented to our institution with nipple discharge. Among these patients, 52 had clinically benign discharge and were managed without surgical intervention. Logistic regression analysis identified mammographic abnormalities (relative risk [RR] = 10.47, 95% confidence interval [CI] 2.36 to 46.39, P=.0002) and sonographic (RR = 5.54, 95% CI 1.27 to 25.40, P=.028) as independent factors associated with a malignant diagnosis. Among patients with pathologic discharge, 19 cancers, 62 papillomas, and 13 other benign lesions were identified. In 3 patients with cancer (15.8%) and 30 patients with a papilloma (48.4%), ductography was the only means of identifying lesions to be resected. Patients who underwent ductography-guided surgery (n = 42, 50%) or any surgical procedure including a localization study (n = 66, 78.6%) were significantly more likely than patients who underwent central duct excision alone to have a specific underlying lesion identified (P=.045 and P=.033, respectively). In this study, we concluded that abnormalities on mammography and sonography in patients with nipple discharge should alert physicians to the possibility of a breast cancer diagnosis. In patients with pathologic discharge with normal findings on physical examination and other imaging studies, ductography might be the only means of localizing and resecting breast lesions associated with nipple discharge.

Based on the findings in this study, we developed an algorithm for evaluation and surgical management of patients presenting with nipple discharge (Figure).[73] A few points should be specifically noted. In concordance with most of the large studies,[74-76] we found a low sensitivity of cytology (26.7%) in the detection of cancer among patients with pathologic discharge, although this test did have a high specificity (81.1%) and a high negative predictive value (78.6%). Almost all patients with benign discharge had normal cytology findings. This result suggests that cytology might be useful if combined with other findings but is not by itself sufficient for discriminating between patients with pathologic discharge with and without malignancy. That is, cytological analyses of nipple discharge specimens will not likely change the diagnostic workup and or treatment of patients presenting with nipple discharge. Therefore, this is not a standard component of the workup for nipple discharge at our center. Additionally, when a ductogram shows an abnormality of more than 2 cm from the base of the nipple, we advocate ductography on the day of surgery followed by needle localization of the abnormality to ensure that the lesion is removed during the surgical procedure. On the other hand, we also believe that it is appropriate to follow patients closely rather than perform a relatively

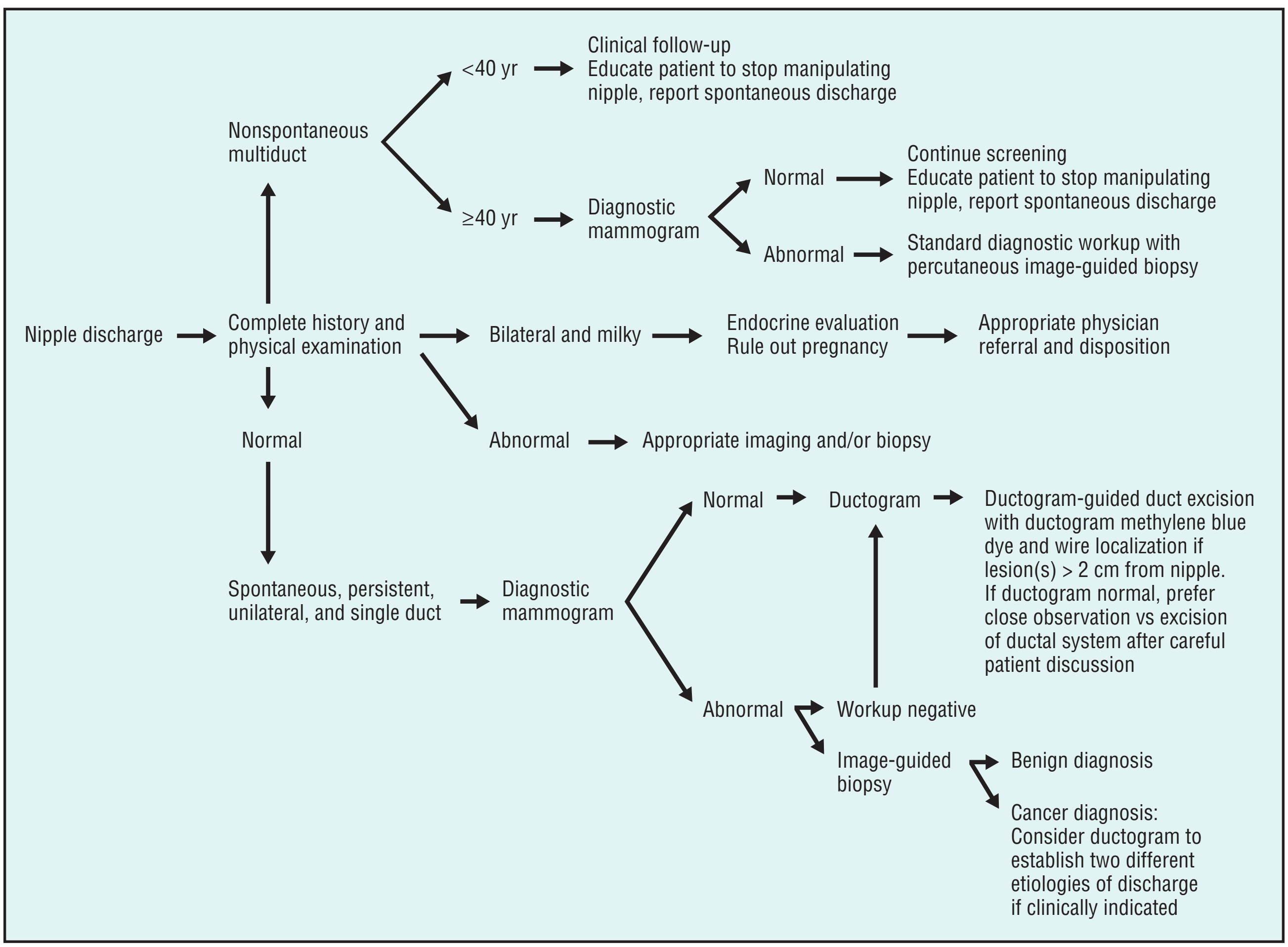

Figure. — M. D. Anderson Cancer Center algorithm for evaluation and surgical management of patients presenting with nipple discharge. Adapted from Cabioglu N, Hunt KK, Singletary SE, et al. Surgical decision making and factors determining a diagnosis of breast carcinoma in women presenting with nipple discharge. *J Am Coll Surg.* 2003;196:354-364. Adapted with permission by Elsevier.

blind central duct exploration and excision when a patient has a normal mammogram and ductogram. A blind central duct excision might eliminate the nipple discharge but does not address the potential underlying pathology. Rather, a blind central duct excision eliminates the ability to monitor the patient's symptomatic discharge, the feature that prompted medical evaluation in the first place.

Although there are many promising investigational approaches to the evaluation of nipple discharge, the clinical role for the techniques of ductoscopy, nipple aspiration, and DL remain to be determined and thus are not incorporated into our institute's algorithm for nipple discharge.

Conclusions

Discrimination between patients with nipple discharge who do and do not require surgery can sometimes be complex and should be based on history, physical examination, and imaging studies (including ductography in cases with suspicious nipple discharge characteristics). Ductography with surgical resection is a useful combination for diagnosis and treatment of patients with nipple discharge and plays a central role in our current algorithm for evaluation and surgical management of patients presenting with nipple discharge. All these strategies are important for identifying a specific causative lesion at surgery and eradicating the underlying cause of the discharge.

The breast is a unique organ in that its microenvironment can be readily accessed and evaluated by aspiration of fluid from the nipple. Ductal fluids contain large amounts of protein. We are beginning to focus our efforts on high-throughput molecular screening of complex biological samples and discovery of biomarkers through advanced protein identification technology, artificial intelligence, and enhanced bioinformatics. As the breasts are a paired organ system, significant differences may be discovered by conducting systematic comparisons of the NAF between them when cancer develops in one breast. The local molecular microenvironment is markedly different from that of the serum as evidenced by the nearly 50-fold increase in HER-2/neu in the ductal fluid compared with that in a concomitantly obtained serum sample. Moreover, in women with HER-2/neu-overexpressing tumors, a distinct elevation of HER-2/neu is detectable in NAF samples from the breast with the tumor compared with the breast without breast carcinoma. Taken together, these results strongly suggest that analysis of paired NAF samples and serum samples from women with breast cancer may be useful as a high-throughput global discovery mechanism for other highly relevant proteins that may be involved in carcinogenesis, progression of in situ disease to invasive carcinoma, monitoring treatment response of breast cancer in the neoadjuvant setting, and serum marker development. Toward this end, our group has used this strategy to identify separate protein species in NAF samples that have unique expression profiles in the breast with the carcinoma relative to the breast without the carcinoma and the serum. The number of separate protein spots detected in NAF samples ranged from 1,280 to 1,649. Substantial qualitative differences were identified between NAF protein expression patterns in the breast with cancer compared with the breast without cancer. The number of protein spots detected in the breast with cancer and not detected in the breast without cancer from the same patient varied from 30 to 202 different proteins. In addition, the number of protein spots detected in the breast without cancer and not detected in the breast with cancer of the same patient varied from 14 to 73 different proteins. We are currently characterizing these expression profiles by multiple techniques. The intraductal approach to breast cancer offers great hope for the identification of other useful markers for evaluation of nipple discharge samples. These powerful approaches to biomarker analysis could be applied to the prevention and treatment of breast cancer.

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