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Ductography and Microdochectomy: the Diagnostic Procedure of Choice Alongside the Conventional Tools for Nipple discharge

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Abstract

Introduction: Nipple discharge is the presenting complaint in 3-10% of all women with breast-related complaints. It causes considerable anxiety in the modern cancer-conscious woman. Breast surgeons frequently use various tools for diagnosing the underlying cause of nipple discharge. A definitive diagnostic approach is crucial for an accurate diagnosis of the aetiology and exclusion of any malignant breast lesion. The objective of this study was to evaluate diagnostic performances of ductography and microdochectomy and compare these with other conventional diagnostic tools.

Methods: This retrospective study included 153 female patients presenting with significant nipple discharge to "Breast Care Center" from December 2011 to December 2018. Informed consent was taken from all participants. History, clinical examination, relevant imaging, cytology and histology findings of all the patients were recorded in electronic database.

Results: Mean and median age of the cohort were 38.4 years and 35 years respectively. 18 of the 153 patients, had a positive family history for breast cancer which was statistically significant. 3.9% (6/153) patients were eventually diagnosed (cytopathology-1, FNAC-1, ductography-1 & microdochectomy-3) with in situ or invasive malignancies while being evaluated for nipple discharge. Breast ultrasound has sensitivity and specificity of 28.6% (5.1-69.7) & 99.3% (95.7-99.9) respectively at 95% CI in detecting risk lesions. Sensitivity of ductography in detecting risk lesions was 100% (95% CI: 5.4-100) with specificity value of 95.2% (95% CI: 85.8-98.8). Again, microdochectomy has been used as final diagnostic as well as therapeutic tools in the study.

Conclusion: Ductography is a noninvasive imaging modality whereas microdochectomy, although invasive, helps reach a definitive tissue diagnosis. Ductography and microdochectomy together can serve as indispensable diagnostic tools alongside the conventional radiological and histological tools.

Keywords: Breast carcinoma, Ductography, Microdochectomy, Pathological nipple discharge.

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Introduction

Nipple discharge is a troublesome symptom in the women of reproductive age. It is the presenting complaint in 3-10% (2.66% as reported in Bangladesh) of all women with breast-related complaints.[1-3] Although breast cancer rarely presents with nipple discharge (5-12%), it causes considerable anxiety in the modern cancer-conscious woman.[4] While most nipple discharges are physiological or from benign etiology, it is absolutely crucial not to miss the relatively few with underlying malignancies. There has been no clear consensus on clinical and radiological tools that reliably differentiate the benign from the malignant conditions. Breast surgeons frequently use many of the time-tested radiological tools in the assessment of nipple discharge; but with the advent of modern mammographic techniques, the long-abandoned procedure of ductography is posing for a deserving return.[5-8] As the

last resort to confirm the diagnosis or to exclude the underlying cause, microdochectomy can be a viable option of investigation.

Methods

This retrospective study included 153 female patients presenting with significant nipple discharge to "Breast Care Center" from December 2011 to December 2018. History, clinical examination, relevant imaging, cytology and histology findings of all the patients were recorded. For imaging, all cases underwent mammogram and ultrasound of their breasts and axillae as a screening tool by a single radiologist, with the exception of patients aged <35 years who were not suitable for mammographic evaluation. Patients with (a) single duct, serous or bloody spontaneous discharge or (b) multiple duct discharges where sonogram detected location of ectatic duct were opted for ductography. 64 patients met those indications and underwent ductography. Nipple discharge cytology was done in all patients, whereas FNA cytology was done in patients with palpable and/or ultrasound detected lesions. 37 patients with definite indications (described in the results section) underwent microdochectomies. Histological examination was carried out in all surgical specimen obtained from the microdochectomies. All relevant data were stored in the center's electronical patient database software. The data were then exported into Microsoft Excel spreadsheets. Data cleaning and data screening were done to exclude the samples and variables having incomplete and irrelevant data points or errors. Descriptive statistics were obtained through Microsoft Excel's inbuilt options. Data analysis was done in SPSS version 16.0. Fisher's exact test was used to determine statistical significance of association of positive family history with malignancy in this series.

Results

A total of 153 female patients were included in this study. Mean and median age of the cohort were 38.4 years and 35 years respectively (Table 1). Out of the 153 patients, 18 had a positive family history for breast cancer. The association between positive family history and diagnosis of breast malignancy was found to be statistically significant (p=0.04; OR= 16.75; 95% CI: 1.4-195.2).

Table-I

Characteristics		
Sample size (n)		153
Age (years)	Mean ± SD	38.4 ± 11.4
	Median	35
	Range	13-68
Family history	Positive	18/153 (11.8%)
Detection of malignancy		6/153 (3.9%)

Regarding clinical features (Table 2), about one fourth of the patients had bilateral nipple discharge. The 'serous' discharge proportion was twice as many as the 'bloody' discharges. A quarter of all nipple discharges were 'bloody' and the rest were of non- 'bloody' character with varying proportions. Approximately half of the total sample presented with other associated symptoms (e.g. mastalgia, breast lumps etc.) and a majority of them had normal breast examinations.

Table II

Clinical data		
		n (%)
Laterality	Unilateral	118/153 (77.1%)
	Bilateral	35/153 (22.9%)
Duct involvement	Single duct	65/153 (42.5%)
	Multiple duct	88/153 (57.5%)
Color of discharge	Serous	82/153 (53.6%)
	Bloody/serosanguinous	39/153 (25.5%)
	Purulent/yellow	21/153 (13.7%)
	Green/brown/black	11/153 (7.2%)
Associated symptoms		83/153 (54.2%)
Palpation findings	Fine nodular breast	44/153 (28.8%)
	Palpable mass in breast	29/153 (18.9%)
	Focal fibrocystic changes	18/153 (11.8%)
	Normal	62/153 (40.5%)

Cytology of the nipple discharge were done for all patients and 6/153 (3.9%) revealed suspicious findings and 1 (0.65%) was positive for malignant cells. The rest were negative for malignant cells. Fine needle aspiration cytology was performed in 43 (out of 153) patients, out

of which 5 (11.6%) cases showed atypia, 3 (7%) showed suspicious cytology and 1 (2.3%) showed ductal carcinoma.

All patients underwent ultrasound of both breasts and axillae which revealed that approximately 49.7% of the patients had duct ectasia (DE), whereas 26.8% had fibrocystic disease (FCD). An important point to note here is that, 3 patients who had benign findings on ultrasound were later diagnosed with malignancy. Ultrasound was associated with high specificity (99.3; 95% CI 95.7-99.9) but poorer sensitivity (28.6; 95% CI 5.1-69.7) (Table 3). Out of the 153, 64 patients (approx. 42%) underwent ductography. 25/64 (39%) patients were diagnosed with intraductal papilloma, 14/64 (21.9%) had duct ectasia with fibrocystic disease and 7/64 (10.9%) had duct ectasia (DE). 4 patients were found to have atypical findings on ductography and further workup led to diagnosis of malignancy in 1 out of these 4 cases. The diagnostic performances of both ultrasound and ductography are shown in Table III.

Table III

Diagnostic performance of the imaging modalities (breast ultrasound and ductography) in detecting risk lesions

Breast	Sensitivity % (95% CI)	28.6 (5.1-69.7)
ultrasound	Specificity % (95% CI)	99.3 (95.7-99.9)
	PPV % (95% CI)	66.7 (12.5-98.2)
	NPV % (95% CI)	96.7 (92-98.8)
Ductography	% (95% CI)	100 (5.4-100)
Sensitivity	Specificity % (95% CI)	95.2 (85.8-98.8)
	PPV % (95% CI)	25 (1.3-78.0)
	NPV % (95% CI)	100 (92.5-100)

37 patients (out of 153) underwent microdochectomy. The indications for microdochectomy were: a) intraductal papilloma, b) ductal hyperplasia and c) inconclusive ductographic findings. Out of the 37 operated cases, 21(56.8%) were diagnosed to have intraductal papilloma on histological examination (Figure 3). Three (8.1%) patients were found to have ductal carcinoma in situ (DCIS) on histology. Altogether, 6 out of 153 (3.9%) patients were eventually diagnosed with in situ or invasive malignancies while being evaluated for nipple discharge.

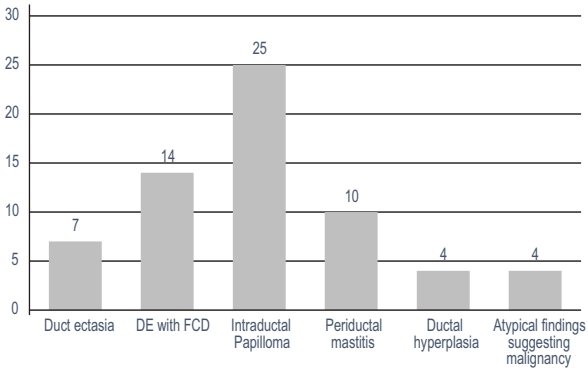

Fig.-1: *USG findings of the patients presenting with nipple discharge. (DE = Duct ectasia, FCD = Fibrocystic disease, IDP = Intraductal papilloma, PDM = Periductal mastitis)*

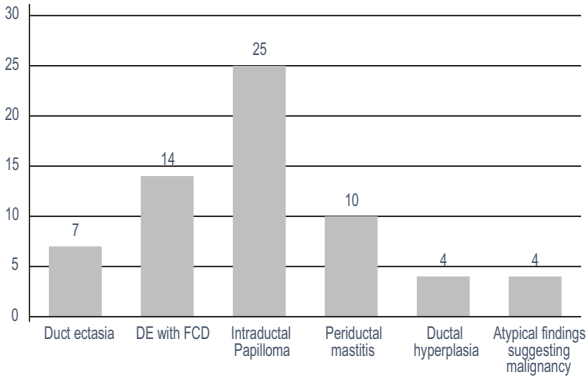

Fig.-2: *Ductography findings of the patients presenting with nipple discharge. (DE = Duct ectasia, FCD = Fibrocystic disease)*

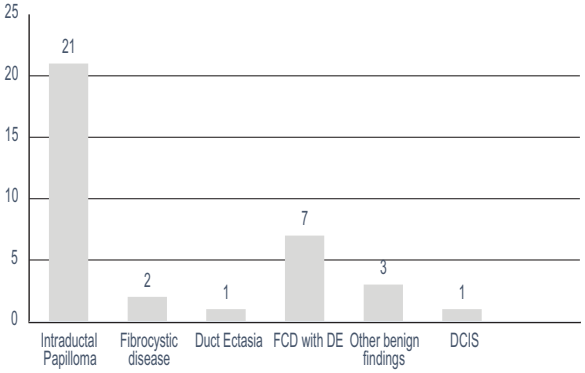

Fig.-3:*Histological examination findings of the patients that underwent microdochectomy. (DE = Duct ectasia, FCD = Fibrocystic disease, DCIS = Ductall carcinoma in situ)*

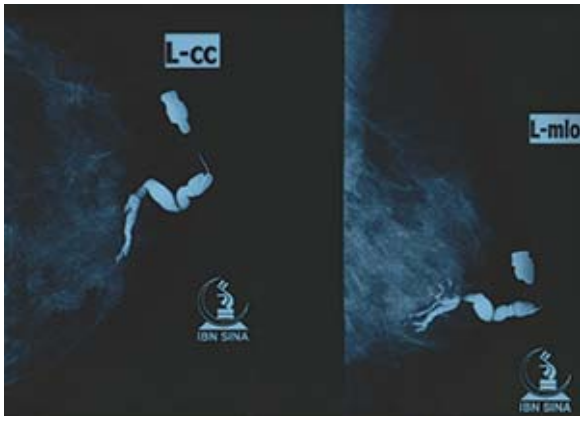

Fig.-4: *Ductography film showing duct ectasia with intraductal papilloma at origin of medial branch of duct at 9 o'clock position in left breast.*

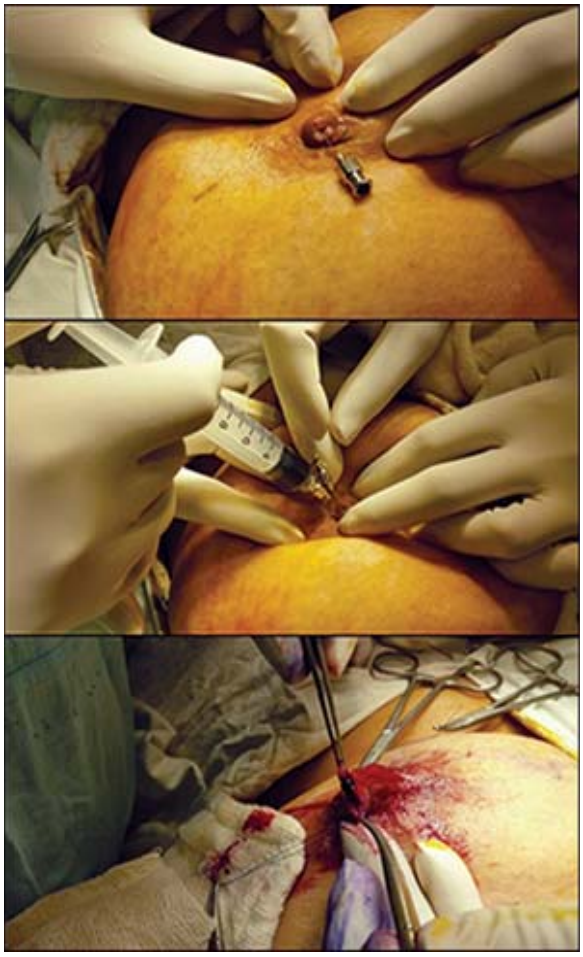

Fig.-6:. *Intraoperative steps of microdochectomy. (a) Duct cannulation. (b) Dye injection through cannula. (c) Identification and excision of affected duct.*

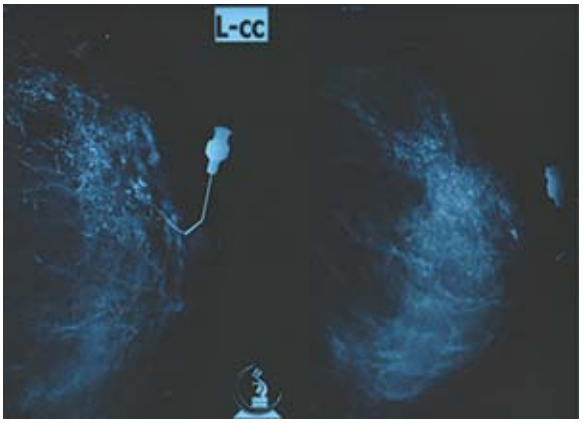

Fig.-5: *Finding suggests malignancy by showing fine linear and branching calcifications in a segmental distribution with rounded lucent area within it and heterogenous breast parenchyma in upper and outer quadrant.*

Discussion

Nipple discharge may be defined as a true direct drainage from the lactiferous duct that appears on the nipple surface.[9] They occur due to various pathologies, which are more commonly benign than malignant. There are some conditions that may be falsely attributed as an etiology for nipple discharges. Some examples include, inverted nipples, eczematoid lesions, traumatic erosions including jogger's nipples, herpes simples, infections, Montgomery gland abscesses, mammary duct fistulas etc.[10,11] To be significant, a discharge should be true, spontaneous, persistent and non-lactational.

Galactorrhea is the inappropriate production of milk in the non-lactating woman. Only one third of women with hyperprolactinemia may have galactorrhea although women with normal prolactin levels may have them too. The nipple discharge in galactorrhea may be spontaneous, bilateral, originating from multiple ducts and having a milky appearance. Etiology can be determined from history of medications, reproductive history, constitutional skin and GI symptoms, neurological symptoms and medical/surgical interventions. Non-galactorrheal nipple discharges occur due to ductal lesions of benign and malignant pathology. These include duct ectasia, fibrocystic diseases, intraductal papilloma, intraductal carcinoma, and invasive (usually papillary) ductal carcinoma.[12] Malignant pathologies can be safely ruled out in the absence of a palpable lump or mammographic abnormality.[10,12]

The color and characteristics of the non-galctorrheal discharge vary according to the etiology. The basic types of nipple discharge that are seen in our daily practice include milky, multicolored (single or a combination of dark green, black, brown etc.), purulent, watery or clear, serous or yellow, serosanguinous or pink and bloody.[10] Nipple discharges are dubbed to be significant if they are spontaneous, and most of them are unilateral and uniductal discharges (except probably in some cases of fibrocystic diseases and duct ectasia). Despite being predominantly of benign origin, an association of the latter four types (mentioned above) with a premalignant or malignant pathology cannot be entirely ruled out without histological examination of tissue obtained through surgery.[10] These are the surgically significant discharges and the main focus of attention in this study. The characteristics of a discharge are not the telltale sign of a particular lesion, but it can guide the clinician towards the right way. Further diagnostic modalities help the clinician approach towards a definitive diagnosis. Standard workup in evaluating the nipple discharge include history, physical examination, mammogram, ultrasound, ductography, nipple discharge cytology, FNA cytology and histological examination of the surgically obtained (often through microdochectomy) pathological specimen.

Ductography, despite remaining quite popular in its early days of emergence as a diagnostic tool, has been abandoned for decades. But with the advent of mammographic techniques, it has been regaining popularity among the clinicians across the world.[6-8,13] Ductography helps in detecting and localising the underlying condition, identifying both central and peripheral lesions, and provides a guidance for surgical excision.[14] Patients diagnosed with duct ectasia or fibrocystic disease through ductography can be treated conservatively avoiding surgery. Without ductography, there remains the risk of inadequate/ incomplete major duct excision and an understaging of the disease extent as a consequence. In our series, most cases detected by ductography were of intraductal papilloma and duct ectasia with or without communicating cysts denoting fibrocystic changes. But possibly the most important of the findings yielded by ductography, was that 4 patients had shown atypical changes suggesting malignancy. Out of the 4, 1 patient eventually was diagnosed with biopsy-proven malignancy. Our estimated sensitivity and specificity (with 95% CI) for ductographies detecting malignant lesions were, 100 (5.4-100) and 95.2 (85.8-98.8) respectively. The specificity was found to have a relatively narrow CI. Conversely, the sensitivity (95% CI) and specificity (95% CI) for ultrasounds detecting malignant lesions were, 28.6 (5.1-69.7) and 99.3 (95.7-99.9), respectively. Baydoun et al. in a retrospective analysis, found that the sensitivity and specificity of ductography, in finding out nipple discharge etiology, were 76% and 72% respectively and those of ultrasound were 73% and 97%. In their analysis, the sensitivity and specificity of ductography and ultrasound combined were 86% and 70%.[15] In another retrospective analysis, Srinivisan et al. showed that the sensitivity and specificity (with CI at 95% level) of ductography in detecting cancer or high risk lesion were 82.8% (64.2, 94.2) and 40.4% (32.9, 48.1) respectively, compared to their noninvasive imaging techniques having values of 58.6 (38.9, 76.5) and 53.8 (46.0, 61.4) respectively.[15] The higher rates in our study may be attributed to the higher expertise of the radiology team in our centre with more than 8 years' experience of our consultant radiologist in performing ductography.

In our centre, we have been looking at microdochectomies in a slightly different light. We have been utilizing the microdochectomy as a diagnostic tool, alongside the therapeutic aspect. There have been multiple case reports of malignant or premalignant (DCIS) breast lesions, in elderly women, being diagnosed solely through microdochectomy while evaluating for nipple discharges.[16,17] In our series, we performed 37 microdochectomies out of which 3 (8.1%) of them had a diagnosis of DCIS on histological examination. Our rate is consistent with Locker et al., who also found a similar 8.2% (8/97) rate in their study.[18] Lanitis et al. reported 8 (10.5%) cases of DCIS yielded from 76 microdochectomies performed over 7 years.[19] On the other hand, Chaudary et al. reported a 16 (5.9%) cases of DCIS diagnosed from microdochectomies performed on 270 patients over the period of 10 years.[20] Microdochectomy can be regarded as both diagnostic and therapeutic. It has the advantage of being less invasive than radical subareolar duct excision carrying lower morbidity. There is less chance of disruption of the ductal anatomy in a microdochectomy as opposed to a major duct excision, which is obviously more destructive in nature. As a result, microdochectomies

yield a better functional outcome in the long run, especially in the younger population. They also offer superiority in terms of diagnostic accuracy compared to major duct excisions. Hou et al. reported that, 70% of breast malignancy patients presenting with nipple discharge had their lesions located >2cm from the nipple.[21] Other literatures report that, up to 20% of the lesions are situated distal to the limits of major duct excision.[22,23] In microdochectomy, up to 5-6cm of the involved duct is excised and the chance of including the lesion within the excised specimen is more than major duct excision. This contributes to the superior diagnostic accuracy of microdochectomy.

One of the important limitations of our study, was the lack of an adequate sample size which resulted from exclusion of many patients who were lost from follow-up in course of investigations. This problem might have led to a possibly skewed distribution of cancer and high-risk patients in our series. There have been some patients who had varying workup protocols, due to their financial limitations or simply, noncompliance rooting from lack of awareness. These flaws might have been responsible for the deviations of diagnostic performances in our study from the published literature. But future prospective study designs with randomization and a control group should alleviate these flaws.

Conclusion

Microdochectomies, despite their invasiveness, can help reach a definite tissue diagnosis. Ductography is yet another noninvasive imaging tool that has been gaining popularity again amongst the clinicians. With adequate supporting data and appropriate technical expertise, the existing nipple discharge workup protocols with conventional diagnostic tools (ultrasonography, mammogram, cytology & FNAC) can be enriched by addition of these diagnostic tools.

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Conflict of interest: None

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