Pathological Nipple Discharge: A Comparison between Breast Ultrasound and Mammography

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Abstract:

Background: Nipple discharge is a relatively common complaint of females in reproductive age and after menopause.

Objectives: The aim of this study was to compare the radiological findings of mammography and ultrasound in women with pathological nipple discharge (PND) of different etiology.

Methods: Mammography and ultrasound were done for a total of 50 patients attending the breast clinic in Oncology Teaching Hospital in Baghdad complaining from PND. Ultrasound guided fine needle aspiration was performed for all cases, and histopathology was available for eleven cases.

Results: The mean age for the women included in the study was 45.3 ± 10.4 years. Ultrasound was able to provide clues for a possible underlying cause for all PND whereas mammography was negative in 54%. Ultrasound was more sensitive in diagnosing malignant breast lesions associated with PND (85.7%) but less specific (88.3%) as compared with mammography which had (71.4%) sensitivity and (90.6%) specificity. Negative predictive value of ultrasound and mammographywere 97.4% and 95.1% respectively.

Conclusion: Ultrasound is essential to complete PND workup, particularly when mammography is normal, to rule out the possibility of neoplastic changes and to provide clues for non-neoplastic etiology that may guide the management.

Keywords: nipple discharge, ultrasound, mammography, pathological nipple discharge

Background:

Nipple discharge is the third most common complaint of women visiting breast clinics after breast pain and lumps (1). Overall nipple discharge prevalence is approximately 5-10%; a quarter of which are actually galactorrhea (non-lactational milky discharge) (2). Suspicions nipple discharge represents 3-7% of all breast related surgical interventions (3), however associated breast cancer diagnosed in only 5% mostly due to carcinoma *in situ* (4, 5). Suspicious nipple discharge is usually spontaneous, unilateral, persistent, serous, or bloody whereas non-spontaneous, bilateral and milky, green or dark color discharge originating from many ducts are rarely caused by cancer (6).

The usual work up of nipple discharge starts with proper history and physical examination to identify the pathological discharge form physiological one. In addition to patient age, the nature of the discharge such as the time of onset, duration, quantity and color are important information to consider. Additionally, family history of breast cancer and absent history of recent pregnancy or trauma further characterized risk groups. Inspection of the nipple and areola helps to exclude local nipple lesion from true nipple discharge (2). The evaluation of discharge color appears more accurately by putting drops of it on a gauze (2). Nipple discharge cytology is recommended for pathological discharge because it is an unexpansive noninvasive test with variable sensitivity; however the test has limited positive predictive value 50-68% (7-9). Thus radiological evaluation is recommended for all pathological nipple discharge.

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The role of mammography in diagnosing a breast lesion is well established. It is usually the first imaging method requested in evaluating PND when the woman is older than 40 years; however, its efficacy in capturing intraductal lesion, the most common cause of pathological nipple discharge, is low (2). The role of high resolution ultrasound (US) is complementary in nipple discharge workup. It is capable of diagnosing tiny solitary intraductal papilloma (10), can better characterize a mammographic identified lesion and confirm its malignant potential by using US guided biopsy (11). ACR recommended US as an initial examination for nipple discharge if the woman have had a recent mammography, pregnant or 30 years old and younger (12). Nonetheless, even in this young age group, mammography may be complementary if the initial ultrasound shows a suspicious features or genetic predisposition is confirmed such as BRCA mutation. This study is designed to compare the radiological findings of mammography and US in women with PND to stand on US sensitivity and accuracy in evaluating breast lesions associated with nipple discharge alone and in combination with mammography.

Patients and methods:
This was a cross sectional study approved by the Ethical Committees of Baghdad college of medicine and Oncology Teaching Hospital. A total of 50 women with PND visiting the breast clinic in the Training and Referring Center for Early Detection of Breast Diseases located in Oncology Teaching Hospital/ Baghdad were recruited in the period between 1st Dec 2016 to the end of June 2017after giving an informed written consent. Demographic data were collected by reviewing patients records as summarized in table (1). All of the patients were evaluated by mammography and ultrasonography. Fine needle aspiration (FNA) was performed for all cases, and 11 of them had undergone surgical removal and had histopathological results.
Radiological examination Bilateral breast US was performed by a consultant radiologist. In supine position, breast nipple and axilla were scanned with a high-resolution linear probe (7-12 MHZ, GE Volsun E6, US). Multiple images in different planes were obtained on grayscale US; dilated ducts site, caliber and presence and characteristics of intraductal mass were assessed. Breast Imaging-Reporting and Data System (BI-RAD) score was given for each case.
Bilateral mammography with 2 standard views craniocaudal (CC) and mediolateral oblique (MLO) was performed with Siemens 3000 nova. Symmetry, mass characteristic, LN presence and BI-RADS score were reported for each case.

Statistical analysis:
Data analysis was performed using Statistical Package for Social Sciences (SPSS) version 20 computerized statistical software; Descriptive statistics presented as (mean ± standard deviation) and frequencies as percentages. Multiple contingency tables conducted and variables and Fishers exact test was used when more than 20% of expected variable was less than 5. One way ANOVA analysis was used to compare between more than two means. ROC curve analysis was used to detect the borderline validity measures. In all statistical analysis, level of significance (p value) set at ≤ 0.05.

Results
The mean age of the patients was 45.3±10.4 years. Almost two third of the patients with PND in our cohort were middle age (40-59 years); 56% of them were premenopausal and 26% reported a positive family history for breast cancer (Table 1). Bloody and colorless discharge constituted more than half of the cases. Associated pain was expressed by 40% and a mass was palpable in only 18% of the patients (Table 1).

Table 1 Patients demographics and characteristics.

Parameter	No.	%
Age		
< 40yr	14	28
40-59yr	32	64
≥ 60yr	4	8
Menstrual status		
Premenopausal	28	56
postmenopausal	22	44
Family history of breast cancer		
Positive	13	26
Negative	37	74
Nipple discharge color		
White	8	16
Colorless	14	28
Yellow	11	22
Brown	1	2
bloody	16	32
Associated pain		
Present	20	40
Absent	30	60
Palpable mass		
Present	9	18
Absent	41	82

All patients with PND had ductal dilatation by US. The dilatation was mild and central in most of cases as shown in (Table 2A, Figure 1A). Peripheral dilation, the more clinically important, was seen in 18%, Figure 1B. Ductal dilatation was the only US finding in Sixteen out of fifty (32%) of the cases. On the other hand, 27/50 (54%) of the mammography

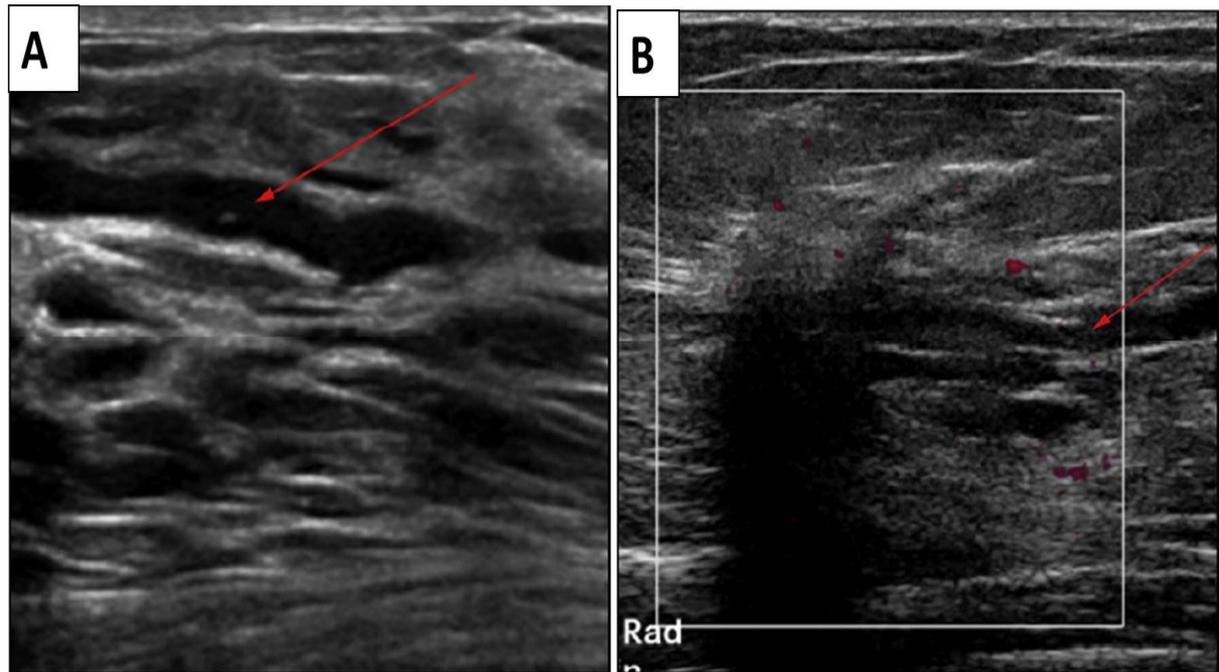performed for these women were completely normal
(Table 2B).

Figure 1 A) Ultrasound demonstrates dilated retro areolar ducts containing anechoic fluid and minimal hypoechoic debris (arrow) in a 44-year-old woman with history of a prolactinoma and bilateral nonbloody spontaneous nipple discharge. No intraductal mass is identified. B) Hypoechoic intraductal mass with adjacent ductal dilation (arrow) in 53- year-old woman with bloody nipple discharge. FNA revealed positive for malignancy.

A breast mass was seen in US of 10/50 (20%) of the cases, four (8%) were BI-RADS V and six (12%) were BI-RADS IV (Table 2A), whereas mammography identified a mass(s) in only 7 cases, three (6%) were BI-RADS V, three (6%) were BIRAD IV and one (2%) was BI-RADS III (Table 1B).

Table 2 Imaging findings in patients with nipple discharge by A) Breast ultrasound; B) Mammography.

A) Ultrasound			B) Mammography		
Finding	No	%	Finding	No	%
Duct dilatation			Normal	27	54
Mild	32	64			
Moderate	16	32			
severe	2	4			
Site of Duct dilatation			Asymmetry		
Central	17	34	*Focal*	11	22
Peripheral	9	18	*global*	2	4
Central and peripheral	24	48			
Intraductal lesion			calcification	1	2
Present	17	34			
Absent	33	66			
Mass			Mass borders		
Present	10	20	Well circumscribed	4	8
Absent	40	40	Ill defined	3	6
Change architecture			Bilateral small well circumscribed opacities	4	8
Present	7	14			
Absent	43	86			
LN			LN		
Present	18	36	Benign	3	6
Absent	32	64	Malignant	0	0
BIRADS (U) I	0	0	BIRADS (M) I	27	54
II	23	46	II	9	18
III	16	32	III	5	10
IV	7	14	IV	4	8
V	4	8	V	5	10

Furthermore, US detected 17/50 (34%) intraductal BI-RADS III-IV lesions (Table 2A), 8/17 (47%) of them appeared as focal asymmetry by mammography and 2/17 (12%) as a mass. Out of these intraductal lesions, FNA cytology/histopathology diagnosed 3 (18%) intraductal papillary neoplasm, 2 (12%) malignant lesions, 6 (35%) duct ectasia and 6 (35%) inflammatory process (table 3).

Table 3 The association of final histo/cytological diagnosis with ultrasound, mammography BI-RADS categories and nipple discharge color.

Diagnostic method	Total	Malignancy No. (%)	Papillary neoplasm No. (%)	Duct ectasia No. (%)	Fibrocystic changes No. (%)	Inflammatory process No. (%)
Ultrasound						
BIRADS IV , V	11	7 (100)	0 (0)	0 (0)	1 (50)	3 (9)
BIRADS II, III	39	0 (0)	3 (100)	7 (100)	1 (50)	28 (91)
Mammography						
BIRADS IV , V	9	6 (86)	0 (0)	0 (0)	1 (50)	2 (6)
BIRADS I, II,III	41	1 (14)	3 (100)	7 (100)	1 (50)	29 (94)
Discharge color						
Bloody	16	5 (71)	2 (67)	1 (14)	2 (100)	6 (19)
Non-bloody	34	2 (29)	1 (33)	6 (86)	0 (0)	25 (81)
Total	50	7 (100)	3 (100)	7 (100)	2 (50)	31 (100)

All FNA confirmed malignant lesions were seen as suspicious BI-RADS IV and V by US as compared to 86% by mammography. Significant association was seen between US BI-RADS IV and V and malignant cytological impression P=0.002. Mass detection in particular showed highly significant association P< 0.001 with cytology prediction of malignancy. Similarly, mammography BI-RADS IV and V showed a higher significant association with positive for malignancy cytology P<0.0001, yet no specific feature had a significant association with malignant cytological impression than the others.
When the color of the nipple discharge was correlated with final US and mammography BI-RADS and cytological impression, a significant association was seen between bloody nipple discharge and higher BI-RADS (US) 7/ 16 (44%), P=0.01, five of them were confirmed to be malignant by FNA (Table 4). On the other hand, only two out of 11 patients with yellow nipple discharge had suspicious BI-RADS IV and V US both of which proved to be malignant by FNA. None of the white, colorless or brown color discharges associated with malignant lesion by cytology. There was no significant association observed between nipple discharge color and mammography or cytological impression P= 0.1 and 0.09 respectively.

Table 4 The association of nipple discharge color with ultrasound, mammography and FNA findings.

Diagnostic modality	No (%)	White No (%)	Colorless No (%)	Yellow No (%)	Brown No (%)	Bloody No (%)
Ultrasound						
BIRADS II and III	39 (78)	8 (100)	13 (93)	9 (82)	0	9 (56)
BIRADS IV and V	11 (22)	0	1 (7)	2 (18)	1 (100)	7 (44)
Mammography						
BIRADS II and III	41 (82)	8 (100)	13 (93)	9 (82)	1 (100)	10 (24.4)
BIRADS IV and V	9 (18)	0	1 (7)	2 (18)	0	6 (66.7)
FNA result						
Benign	43 (86)	8 (100)	14 (100)	9 (82)	1 (100)	11 (69)
Malignant	7 (14)	0	0	2 (18)	0	5 (31)
Total	50	8 (100)	14 (100)	11 (100)	1 (100)	16 (100)

The negative predictive value of US in detecting malignancy amongst patients with nipple discharge was slightly higher than mammography (97.4% vs 95.1) and associated with higher sensitivity of US (85.7% vs 71.4%). The specificity of mammography, however, was higher (90.6% vs 88.3%) (Table 5).

Table 5 The predictive values of breast ultrasound, mammography.

Predictor	No	Malignancy (%)	No malignancy (%)	Predictive value
Ultrasound				
BIRADS IV , V	11	6 (54.5)	5 (45.5)	PPV 54.5%
BIRADS II, III	39	1 (2.6)	38 (97.4)	NPV 97.4%
Mammography				
BIRADS IV , V	9	5 (54.5)	4 (45.5)	PPV 55.5%
BIRADS I, II,III	41	2 (2.6)	39 (97.4)	NPP 95%

Discussion

Radiology is an important step in the work up of pathological nipple discharge. Along with cytology, it can provide a clue to the underlying pathology and prompt the right management. We have shown that only 20% of PND in our cohort were of neoplastic etiology, all of which were readily predicted by US whereas mammography missed 3 intraductal papillary neoplasm and 1 malignant lesion.

Additionally, BI-RADS classification of ultrasonography was significantly associated with the final cytology results which is consistent with the results of Gokhale et al. (13). Several other studies highlighted the sensitivity of breast US in identifying neoplastic changes associated with nipple discharge. Nevertheless, mammography remained the first line of investigation recommended due to its specificity and ability of detecting in situ carcinoma (1, 14).

Furthermore, and in agreement with previous Iraqi and American studies (15-17), we found that US was not only sensitive in detecting malignant and papillary neoplasm, but it also provided helpful information in non-neoplastic conditions such as duct ectasia and fibrocystic lesions explaining the reason for the abnormal nipple discharge which assure the patient and reduce recurrent unnecessary consultation (17, 18). This support the importance of US breast scan in patients with PND whenever mammography is negative.

Although it showed a high specificity in predicting breast cancer, mammography failed to show any changes in 24 cases which depicted at least ductal dilatation agreeing with previous reports (19-21), 66% of which were peripheral dilatation. Central (retro- areolar) dilatation in most of the cases are secondary to benign process (22), by contrast many studies stressed the role of US in detecting tumors within or adjacent to a peripheral dilated duct (22).

We, similar to other studies (23-25), have also shown that bloody nipple discharge is the most common discharge associated with neoplastic conditions. Bloody nipple discharge has shown a significant association with BI-RADS IV and V breast US.

In conclusion, US is an important radiological modality to complete the evaluation of PND particularly when mammography is normal. This would rule out the possibility of neoplastic changes and provide clues for non-neoplastic etiology that guide the management, assure the patient and reduce repeated unnecessary consultations.

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افرازات الحلمة: مقارنة بين التصوير الشعاعي للثدي والموجات فوق الصوتية

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الخلفية: افرازات الحلمة هي شكوى شائعة نسبيا بين الإناث في سن الإنجاب وبعد انقطاع الطمث.

الهدف: الهدف من هذا البحث هو مقارنة النتائج من التصوير الشعاعي والتصوير بالموجات فوق الصوتية في النساء اللاتي يعانين من إفرازات الحلمة المرضية لأسباب مرضية مختلفة.

المرضى و طرق البحث: تم إجراء التصوير الشعاعي للثدي والموجات فوق الصوتية لإجمالي 50 مريضة من اللواتي يراجعن المركز التدريبي المرجعي للكشف المبكر عن امراض الثدي واللاتي يشكين من إفرازات الحلمة المرضية. تم إجراء رشفة بالابرة الدقيقة تحت ارشاد الموجات فوق الصوتية الموجهة لجميع الحالات، وكانت نتائج الفحص النسيجي متوفرة لإحدى عشرة حالة.

النتائج: تمكن التصوير بالموجات فوق الصوتية من تقديم دليل عن السبب الكامن المحتمل لجميع إفرازات الحلمة المرضية في حين كان التصوير الشعاعي للثدي سلبيًا بنسبة 54٪. وكانت الموجات فوق الصوتية أكثر حساسية في تشخيص آفات الثدي الخبيثة المرتبطة بإفرازات الحلمة المرضية (85.7٪) ولكن أقل تحديدا (88.3٪) مقارنة مع التصوير الشعاعي للثدي الذي له (71.4%) حساسية و (90.6٪) خصوصية. كانت القيمة التنبؤية السلبية للموجات فوق الصوتية 97.4٪ ، بينما كانت للتصوير الشعاعي للثدي 95.1٪ .

الاستنتاج: الموجات فوق الصوتية ضرورية لإكمال التحري عن اسباب افرازات الحلمة المرضية خاصة عندما يكون التصوير الشعاعي للثدي سلبي لاستبعاد إمكانية حدوث تغييرات ورمية خبيثة كما انه يقدم أدلة على المسببات غير الورمية التى ممكن ان توجه مسار العلاج

كلمات مفتاحية: افرازات الحلمية المرضية, سونارالثدي , ماموكرام . تصوير الثدي الشعاعي.