Acta Scientific Women's Health (ISSN: 2582-3205)

Volume 2 Issue 12 December 2020

Research Article

Clinical Significance of Pathological Nipple Discharge as a Single Breast Symptom: A Single-institute Experience

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Received: October 17, 2020

Published: November 28, 2020

Abstract

Background: Nipple discharge is a common symptom which can cause anxiety although usually caused by benign etiologies and only reported as the presenting symptom in 15% of breast cancer cases. The evaluation and management of nipple discharge is diverse and confusing between breast clinics. The aim of this study was to identify clinical characteristics and preoperative examinations which can be used to identify malignancy as the underlying cause of nipple discharge, thereby facilitating patient tailored treatment.

Patients and Methods: We retrospectively reviewed all patients with nipple discharge as a single symptom who attended our institution breast clinic from March 2018 till February 2020. Patients clinical, radiological, lab, pathological, surgical and follow up data were registered.

Results: A total of 148 patients with nipple discharge were reviewed. Discharge was unilateral in 70.3%, Multiductal in 58.1%, bloody in 23% and induced on squeezing in 62.2% of the included patients. the causes of discharge in the operated cases (91 patients) were ductectasia in 47 patients (51.6%), benign papilloma in 28 patients (30.8%) and carcinoma in 12 patients (13.2%){DCIS in 7 patients (7.7%) and IDC in 5 patients (5.5%)}. Regarding discharge characteristics in cancer patients; it was unilateral in 58.3%, uniductal in 66.7%, bloody in 75% and induced in 75% of them.

Conclusion: Pathological nipple discharge is a common breast complain and may indicate serious condition. Although unilateral, uniductal, bloody and induced discharge in patients above 50 years old with abnormal imaging and suspicious pathology are alarming signs of malignancy; non-bloody, bilateral, multiducatl and spontaneous discharge with normal imaging and non-suspicious pathology may still carry the risk of underlying malignancy.

Keywords: Nipple Discharge; Ductectasia; Major Duct Excision; Breast Cancer

Introduction

Nipple discharge is a common presenting symptom in patients attending breast clinics occurring in 3% to 10% of all women breast-related complaints [1,2]. It causes considerable anxiety, although usually physiologic or caused by benign etiologies as nearly 90% of women with nipple discharge have benign disease [2,3]. Nipple discharge has been reported in the literature to be the presenting symptom in breast cancer in up to 15% of cases with great variation (5–15%) [3,4]. Nipple discharge can be physiological milky discharge during pregnancy or lactation (2,4). Pathological causes mostly benign such as galactorrhea which is caused by hyperprolactinemia, thyroid disease or medications inhibiting dopamine, Papillomas which are also benign and may be associated with atypical cells or low grade carcinomas. These can produce bloody or clear discharge in 57% of these patients or duct ectasia in 33% of the patients [5,6]. Malignancy (typically ductal carcinoma in situ) is found in 5–15% of pathologic discharge patients [3,4]. physiological and benign pathological discharge are mostly bilateral, multiductal, not bloody as any color can be seen (clear, grey, yellow, green or brown) and can be stimulated by manipu-

lation of the breast or nipple [5-7], while pathological suspicious discharge is mostly unilateral, uniductal, serous/ clear/bloody, spontaneous and may be associated with a breast mass [8-14]. The evaluation and management of nipple discharge is diverse and confusing between departments and countries [15]. The primary focus of the evaluation of each patient with nipple discharge is to differentiate a benign etiology from a malignancy based on clinical and radiographic assessment in order to save women the risks and discomfort associated with an unnecessary operation and also to detect malignancy in early stage. The aim of the current study was to identify clinical characteristics and preoperative examinations which can be used to identify malignancy as the underlying cause of nipple discharge, thereby facilitating patient tailored treatment. For this; we retrospectively reviewed all cases of patients with nipple discharge as a single symptom who attended our institution breast clinic from March 2018 and February 2020.

Patients and Methods

This retrospective review was conducted on all patients with pathological nipple discharge (Any nipple discharge other than physiological milky discharge during pregnancy or lactation) as a single symptom who attended the breast clinic in the department of Surgery, Medical Research Institute, University of Alexandria, Egypt, during the period between March 2018 and February 2020. All patients were evaluated retrospectively based on medical records in the form of patient's sheet in which all patient's clinical, radiological, lab, pathological, surgical and follow up data were registered. In the current study; we collected the following factors: Age at presentation, smoking, DM, serum prolactin level, previous breast surgery, discharge characteristics {side (unilateral or bilateral), color (clear, colored [green, yellow, white, brown, gray, or reddish brown] or bloody) spontaneous or induced and uniductal or multiductal}, imaging findings, discharge cytology and/ or tissue biopsy from associated mass or lesion detected by imaging, any medical treatment ordered for the current condition, any submitted surgical procedure and the final pathological diagnosis for the surgical specimen in cases who were submitted to surgery. Institutional Research Committee approved the protocol before the study started. Data were fed to the computer and analyzed using IBM SPSS software package version 20.0 (IBM Corp., Armonk, New York, USA). Qualitative data were described using number and percent. Quantitative data (Age) were described using 50 years as classification limit.

Results

We identified 148 patients with nipple discharge as a single presenting symptom. About two thirds of the patients (65.5%) were 50 years old or less. Eleven patients (7.4%) were smokers, thirty-two patients were diabetics (21.6%). Thirteen patients (8.8%) had positive family history of breast cancer. Regarding discharge characteristics; Unilateral nipple discharge was present in 70.3% of patients, Multiductal discharge in 58.1% and the discharge was bloody in 23%. and induced on squeezing in 62.2%. Details of demographic and discharge characteristics are grouped in table 1.

Radiologic imaging was performed in all patients. Ultrasonography alone was done in all patients aged less than 35 years; it was performed in 29 patients (19.6%) while both U/S and mammography were performed in all patients aged 35 years or more. both imaging modality were ordered for 116 patients (78.4%). Breast magnetic resonance imaging (MRI) was performed in 3 patients (2%). MRI was not ordered routinely; it was performed in patients in whom the radiological assessment by U/S and/or mammography needed more clarification. Imaging was normal in 36 patients (24.3%), ductectasia was detected in 98 patients (66.2%), a mass was detected in 12 patients (8.1%) and suspicious microcalcification was detected in two patients (1.4%). Details of imaging methods and findings are collected in table 2.

Hyperprolactinemia was detected in 12 patients (8.1%). Serum prolactin level was not performed routinely; It was done when milky discharge persists in spite of medical treatment.

Regarding the pathological assessment; discharge cytology was performed in all patients except those who had pure milky discharge or minimal clear discharge with normal imaging. It was performed in 118 patients (79.7%) and revealed cystic mastopathy (60.1%), duct papillomatosis (8.8%) and atypical cells (10.8%). U/S-guided biopsy was performed in patients in whom imaging revealed a mass, microcalcification or architectural distortion. U/S-guided biopsy detected hyperplasia in 18 patients (12.2%), atypical cells in 10 patients (6.8%) and carcinoma in two patients (1.4%). The results of pathological assessment are grouped in table 2.

According to our institute protocol for the treatment of patients with nipple discharge; young patients (less than 40 years) with mild clear or colored discharge, normal imaging or mild ductec-

tasia and benign cytology received medical treatment in the form of anti-inflammatory, anti-edematous, antibiotics on need and anti-prolactin when indicated. Patients above 50 years, with abnormal imaging or suspicious pathology, those in whom medical treatment failed for more than 3 months and patients who refused medical treatment from the start or after being treated medically for a short period with no improvement; all of these patients {91 patients (61.5%)} were submitted to surgical treatment in the form of major duct excision (MDE). In the two cases who were diagnosed with carcinoma; one had CBS in the form of central quadrantectomy (suspicious mass was detected by imaging and proved pathologically by U/S-guided FNAC as a malignant mass) and the another one had mastectomy because of microcalcification detected radiologically and extensive DCIS detected by U/S- guided core tissue biopsy. The therapeutic regimens followed are shown in table 3.

Regarding the pathological findings in operated cases; ductectasia was the final pathological diagnosis in 47 patients (51.6%), benign papilloma in 28 patients (30.8%) and carcinoma in 12 patients (13.2%) of the operated cases. The cases with cancer were Ductal Carcinoma In situ (DCIS) in 7 patients (7.7%) and Invasive Ductal Carcinoma (IDC) in 5 patients (5.5%). The pathological findings in operated cases are shown in table 3.

Patients with cancer were totally 12 cases (13.2%): two patients diagnosed before surgery and 10 patients diagnosed after MDE. Eight patients (66.7%) were above 50 years. Two patients were smokers. One fourth of the cases with cancer had positive family history of breast cancer but the data didn't reveal the relative degree. As regard the discharge characteristics; Most of the cancer patients had unilateral (58.3%), uniductal (66.7%), bloody (75%) and induced (75%) discharge. Imaging was normal in 3 patients (25%) and surgery was done either due to the bloody nature of discharge or failed medical treatment. Imaging revealed mass in 4 patients (33.3%), microcalcification in one case (8.4%) and ductectasia in 4 patients (33.3%). As regard the pathological diagnosis before surgery; two patients were diagnosed as carcinoma (16.7%), two patients had cystic mastopathy (16.7%), one patient had duct papilloma (8.3%), sex patients had atypical cells (50%) and one patient had hyperplasia (8.3%). They were detected pathologically either by discharge cytology or U/S-guided biopsy (FNAC or tru-cut core tissue biopsy). The final Pathological diagnosis after surgery detected 10 cases of breast cancer in addition to the 2 cases diagnosed pre-operatively. The total 12 cases were divided as: seven cases (58.3%) were DCIS and five cases (41.7%) were IDC. Details of characteristics of patients with cancer are grouped in table 4.

The cases diagnosed as cancer were managed accordingly. The 2 cases diagnosed pre-operatively: one had CBS in the form of central quadrantectomy (suspicious mass was detected by imaging and proved pathologically by U/S-guided FNAC as IDC) and the another one had mastectomy because of microcalcification detected radiologically and extensive DCIS detected by U/S- guided core tissue biopsy. The remaining 10 cases were 6 cases with DCIS {Three cases had re-excision lumpectomy up to negative margin and Sentinel Lymph Node Biopsy (SLNB) and three had mastectomy and SLNB either due to extensive microcalcification or patient's desire} and 4 cases with IDC (Three had re-excision lumpectomy up to negative margin and SLNB and one had mastectomy and SLNB).

Item	(No./%) (148/100%)
Age ≤50 >50	 97(65.5%) 51(34.5%)
Smokers	11 (7.4%)
DM	32 (21.6%)
Family history of breast cancer	13 (8.8%)
Previous Breast Surgery Benign lump excision Breast abscess incision and drainage	 12 (8.1%) 6 (4. 1%)
Discharge characteristics Side Unilateral Bilateral Extension Uniductal Multiductal Color Clear Colored Bloody Discharging Spontaneous Induced	 104 (70.3%) 44 (29.7%) 62 (41.9%) 86 (58.1%) 53 (35.8%) 61 (41.2%) 34 (23%) 56 (37.8%) 92 (62.2%)

Table 1: Demographic and Clinical Characteristics.

Item	No./% (148/100%)
Imaging	
Methods	
U/S	29 (19.6%)
U/S and Mammography	116 (78.4%)
MRI	3 (2%)
Findings	
Normal	36 (24.3%)
Ductectasia	98 (66.2%)
Mass	12 (8.1%)
Microcalcification	2 (1.4%)
Hyperprolactinemia	12 (8.1%)
Pathological Characteristics	
Cytology	
Cystic Mastopathy	89 (60.1%)
Duct papillomatosis	13 (8.8%)
Atypical cells	16 (10.8%)
U/S guided Biopsy	
Hyperplasia	18 (12.2%)
Atypical cells	10 (6.8%)
Carcinoma	2 (1.4%)

Table 2: Imaging, Hyperprolactinemia and Pathological Characteristics.

Item	No./%
Therapeutic Regimens	148/100%
Medical alone	57 (38.5%)
Medical then Surgical (MDE)	36 (24.3%)
Surgical alone	55 (37.2%)
MDE	53 (35.8%)
CBS	1 (0.7%)
Mastectomy	1 (0.7%)
Pathological findings in operated cases	91/100%
Ductectasia	47 (51.6%)
Papilloma	28 (30.8%)
Carcinoma	12 (13.2%)
DCIS	7 (7.7%)
IDC	5 (5.5%)
Others	4 (4.4%)

Table 3: Therapeutic Regimens and Pathological findings in Operated cases.

MDE: Major Duct Excision; CBS: Conservative Breast Surgery; DCIS: Ductal Carcinoma *In situ*; IDC: Invasive Ductal Carcinoma

Item	(No./%) 12/100%
Age	
≤50	4 (33.3%)
>50	8 (66.7%)
Smokers	2(16.7%)
Family history of breast cancer	3 (25%)
Discharge characteristics	
Side	
Unilateral	7 (58.3%)
Bilateral	5 (41.7%)
Extension	
Uniductal	8 (66.7%)
Multiductal	4 (33.3%)
Color	
Clear	1 (8.3%)
Colored	2 (16.7%)
Bloody	9 (75%)
Discharging	
Spontaneous	3 (25%)
Induced	9 (75%)
Imaging	
Normal	3 (25%)
Ductectasia	4 (33.3%)
Mass	4 (33.3%)
Microcalcification	1 (8.4%)
Pathological Characteristics before Surgery	
Cytology	
Cystic Mastopathy	2 (16.7%)
Duct papilloma	1 (8.3%)
Atypical cells	4 (33.3%)
U/S-Guided Biopsy	
Hyperplasia	1 (8.3%)
Atypical cells	2 (16.7%)
Carcinoma	2 (16.7%)
The final Pathological diagnosis	
DCIS	7 (58.3%)
Invasive Ductal Carcinoma	5 (41.7%)

Table 4: Characteristics of patients with Cancer.

Discussion

For decades; patients with pathologic nipple discharge were counseled to undergo duct excision, however nipple discharge may be caused by benign conditions such as duct ectasia or intraductal papilloma while a small proportion of patients with nipple discharge are found to have a malignancy [6]. Because it has been felt that the risk of carcinoma cannot be excluded without surgical duct excision; surgery has been widely recommended for all patients with pathologic nipple discharge [3,6,12]. The primary aim of the current study was to evaluate each patient with nipple discharge to differentiate a benign etiology from a malignancy based on clinical, radiographic and pathological assessment to save women the risks and discomfort associated with an unnecessary operation and facilitate patient tailored treatment. In the current study; We identified 148 patients with nipple discharge as a single complain then we reviewed the patients from the time of attendance to the breast clinic till complete management. Most of our patients were below 50 years old with unilateral, multi-ductal, colored and induced discharge with negative family history related to breast cancer. Patients above 50 years, with abnormal imaging or suspicious pathology and those in whom medical treatment failed for more than 3 months and patients who refused medical treatment from the start or after being treated medically for a short period with no improvement; all of those patients {91 patients (61.5%)} were submitted to surgical treatment in the form of major duct excision (MDE). In the two cases who were diagnosed with carcinoma; one had CBS in the form of central quadrantectomy (suspicious mass was detected by imaging and proved pathologically by U/S-guided FNAC as a malignant mass) and the another one had mastectomy because of microcalcification detected radiologically and extensive DCIS detected by U/S- guided core tissue biopsy. Duct ectasia was found in more than half of the operated cases (51.6%), while papilloma was the cause in 30.8% of cases. In other series; papilloma was the most commonly seen cause of discharge (up to 57% of cases) while duct ectasia is described in approximately 33% of cases [10]. This difference may be due to low number of patients included in the present study. The prevalence of carcinoma (DCIS and IDC) in present study (13.2%) is not differing from the prevalence described in the literature (5 to 15%) [14,16]. Similar to the study published by Sauter., *et al*. [17] we found most of our cancer patients (66.7%) were above 50 years old but were differing from the results of Røpcke., *et al.* [18] who didnot find any significant correlation between old patients with nipple discharge and increased the risk of carcinoma. In a recent study published in 2018 by Li GZ., *et al.* [19]; two hundreds and eighty patients with pathologic nipple discharge were reviewed using multivariable analysis concluded that age, a palpable mass and abnormal imaging findings were associated with underlying malignancy. Duct excision was found to be reasonable in these patients and in patients without any of these three risk factors; observation rather than duct excision was suggested [19]. We agree with this study regarding age, abnormal imaging, but a palpable mass was not persistent alarming sign. In the current study; in addition to age and abnormal imaging; the bloody unilateral uniductal induced discharge with suspicious pathology are red flags of malignancy. In our study; 75% of cancer patients had bloody discharge which is similar to the several studies and meta-analyses which concluded that bloody nipple discharge is found to be associated with underlying malignancy [20-22] while in one study conducted with Røpcke., *et al.* [18] who did not find a significant association between bloody discharge and invasive cancer. This difference may be due to the low number of cases included in each study as well as the difference in selection criteria [18]. Kan WM., *et al.* [22] published results from a retrospective study on 102 patients with nipple discharge and found through multiple logistic regression that bloody discharge and an associated palpable mass were statistically significantly more common in malignancy, while age, duration of discharge, colour of discharge, palpable breast mass and abnormal sonography all were important in suggesting underlying malignancy; they concluded that non-bloody discharge without a palpable mass and without imaging findings indicate a benign pathology in most cases. Kan WM., *et al*. [22] concluded that no suspicious radiographic findings or palpable masses were described prior to surgery. This is due to the national Danish guideline regarding breast cancer treatment, which dictates that any malignancy related radiographic or clinical finding leads to enrolment in a cancer treatment program, which automatically excluded these patients from the present study on nipple discharge [22]. Therefore, all invasive cancer/CIS found in this study were not visible radiologically or associated with a palpable mass. In the current study; U/S-guided biopsy was performed in patients in whom imaging revealed a mass, microcalcification or architectural distortion. U/S-guided biopsy detected hyperplasia in 18 patients (12.2%), atypical cells in 10 patients (6.8%) and carcinoma in two patients (1.4%). Mammography alone is known to have a sensitivity of 18% in patients with pathological nipple discharge [23] which makes this a diagnostic tool of limited quality regarding intraductal pathologies. Ultrasonography identifies intraductal high risk pathology/invasive cancer in 63%

of cases when performed following a negative mammography in nipple discharge patients [19]. In the present study we didnot depend upon mammography alone. Ultrasonography alone was done in all patients aged less than 35 years; it was performed in 29 patients (19.6%) while both U/S and mammography were performed in all patients aged 35 years or more. both imaging modality were orderd for 116 patients (78.4%). Breast magnetic resonance imaging (MRI) was performed in 3 patients (2%). MRI was not ordered routinely; it was performed in patients in whom the radiological assessment by U/S and/or mammography needed more clarification. The present study has some limitations, which makes conclusions less generalizable. A single center study with a retrospective design and low volume of included case yield less power than a multicenter prospective randomized controlled trial. Furthermore; Comparative studies between cancer and noncancer patients with nipple discharge are needed to identify the risk factors and red flags of malignancy.

Conclusion and Recommendation

Pathological nipple discharge is not uncommon as a single presenting breast complain and it may indicate serious condition. From our reviews: although unilateral, uniductal, bloody and induced discharge in patients above 50 years old with abnormal imaging and suspicious pathology are alarming signs of malignancy; non-bloody, bilateral, multiducatl and spontaneous discharge with normal imaging and non-suspicious pathology may carry the risk of underlying malignancy so we should assess patients with pathological nipple discharge by triple assessment. Again, further multicentric studies with larger volume of cases should be conducted with comparison between cancer and noncancer patients with nipple discharge to identify the risk factors and red flags of malignancy.

Conflict of Interest

The authors declare no conflict of interest or financial ties to conclude.

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