

CLINICOMORPHOLOGICAL STUDY OF NIPPLE DISCHARGE AND ITS ROLE IN DIAGNOSING UNDERLYING BREAST MALIGNANCY

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ABSTRACT

Background: Nipple discharge is the third most common complaint in patients attending cytology clinic. The assessment of nipple aspiration fluid is a simple, non-invasive and cost effective method of screening for underlying breast malignancy. This study aims to evaluate the spectrum of breast lesions associated with nipple discharge and to assess the diagnostic accuracy of nipple discharge cytology in predicting breast malignancy. **Materials and Methods:** A cross-sectional study was conducted over 5 years from January 2020 to December 2024. Sociodemographic and clinicoradiological data were recorded. Imprint smears from nipple discharge and fine needle aspiration cytology smears from any associated lump were analyzed. Reporting and categorization were done according to the *International Academy of Cytology (IAC) Yokohama System* for reporting breast cytopathology. **Result:** A total of 48 cases presenting with nipple discharge were evaluated. The mean age of presentation was 43 years. Malignant nipple discharges occurred predominantly in women above 45 years of age ($p < 0.005$). Benign lesions were observed in 34 cases (70.8%), most commonly fibrocystic disease while 14 cases (29.2%) were malignant, most of which presented with bloody discharge (50%), followed by serous discharge (35.7%). Seven (07) of these 14 malignant cases were biopsy-proven intraductal carcinomas. **Conclusion:** Nipple discharge cytology is mandatory, especially in the screening for breast cancers. All the pathological nipple discharge, especially in women above 45 years should compulsorily be evaluated to rule out malignancy. Newer modalities can increase the diagnostic accuracy and reliability.

INTRODUCTION

Nipple discharge as a presenting complaint is seen in 4-7% of patients with varied breast lesions. 50% of the patients are in their reproductive age group. Physiological nipple discharge is bilateral and arising from multiple ducts seen during pregnancy and lactation. In the absence of recent pregnancy, similar discharge can be seen in galactocoele or galactorrhea. These are milk filled cysts or persistent milk secretion, often resulting from excessive levels of estrogen or prolactin.^[1] Nipple discharge encompasses a wide spectrum of breast lesions and commonly reflects underlying hormonopathy.^[2] They are generally benign, mostly comprising of intraductal papilloma and duct ectasia with incidence of 35-56% and 15-20% respectively. It is also seen in

benign epithelial hyperplasia with or without atypia and in Paget's disease. The literature studies suggest carcinoma cases presenting as nipple discharge can range from 5-33%, often associated with underlying mass and skin changes.^[3-7] Cytologic evaluation of pathological nipple discharge (PND) is a simple, non-invasive, and inexpensive out patient diagnostic approach. Cytological findings aid in differentiating benign from malignant lesions, especially when interpreted in conjunction with clinical and radiological examination.^[3] In this background the present study is undertaken to evaluate the spectrum of breast lesions presenting with nipple discharge and to know the incidence of carcinoma of breast among these cases.

MATERIALS AND METHODS

A cross-sectional study was conducted in Department of Pathology over a period of 5 years from January 2020-December 2024. The study was approved by Institutional ethics committee and adheres to the guidelines of World Medical Association Declaration of Helsinki. All patients presenting to cytopathology section with complaints of nipple discharge with or without underlying lump were included in the study. Sociodemographic data, clinical and radiological findings were retrieved from case files of Medical Records Department. Imprint smears of nipple discharge were prepared. In cases where underlying lump was present, FNAC was performed and smears were prepared. All smears were stained with Leishman stain and H and E stain. The reporting was done and further classified as per the IAC Yokohama System for Reporting Breast Fine-Needle Aspiration Cytopathology.^[8] This system categorizes the breast FNAC into 5 categories based on the risk of malignancy.

I: Insufficient/inadequate

II: Benign

III: Atypical

IV: Suspicious of malignancy

V: Malignant

Statistical analysis was carried out using descriptive and inferential methods. Frequency tables, mean, standard deviation, percentage, sensitivity, specificity, PPV and NPV were calculated. The Fisher's exact test was used to determine statistical significance.

RESULTS

In the study period, breast FNAC constituted 16.2% of the total FNAC. Of these 48 cases (3.5%) presented with history of nipple discharge. All patients were female, age ranging from 16 to 79 years, with mean age being 43 years. 26 of the 48 cases (54.1%) had history of underlying breast lump along with nipple discharge. [Table 1]

A total of **26 cases (54.1%)** had a history of an underlying breast lump in association with nipple discharge, while **18 cases (37.5%)** presented with nipple discharge as the sole complaint. Among the latter group, **16 cases** revealed cytological features consistent with *fibrocystic disease* and other benign breast lesions, corresponding to **Category II** of the *IAC Yokohama System*. The remaining **two cases** were non-diagnostic due to scant cellularity.[Table 2]

Benign Lesions : A total of 34 cases(70.8%) were diagnosed as benign. The most common among benign lesion was fibrocystic disease[Fig 1C &D], accounting for 15 cases (44.1%), followed by benign breast disease in 9 cases (26.5%) and inflammatory lesions in 5 cases (14.7%). One (01) case of Intraductal papilloma showed papillary fragments of ductal cells with stromal core and scant bare nuclei[Fig 2A& B]; this case presented with bloody

nipple discharge. A 28-year-old female with history of milky discharge diagnosed as galactocoele, characterized by presence of granular amorphous background, cyst macrophages and lipid micelles[Fig 1A&B]. We encountered three cases of duct ectasia which presented in central quadrant as a subareolar cord-like mass, two with serosanguineous discharge and one with serous discharge. On cytology, few ductal epithelial cells with chronic inflammatory cells of lymphocytes, few histiocytes and cyst macrophages were seen[Fig 2C].

Malignant lesions : A total of 14 cases (29.2%) were diagnosed as Ductal carcinoma and cytology showed dyscohesive cell clusters exhibiting nuclear pleomorphism, high N:C ratio with prominent nucleoli [Fig 2D]. Few Singly dispersed malignant cells with intact cytoplasm were also seen. Seven (50%) presented with bloody nipple discharge, five (35.6%) with serous, one (7.2%) with purulent and one (7.2%) with serosanguineous type. Histopathological correlation was available in eight cases, all of which were diagnosed as invasive ductal carcinoma, no special type (IDC-NOS), showing SBR Grade II and TNM Stage II. All were estrogen receptor (ER) and progesterone receptor (PR) positive, with Ki-67 indices ranging from 40% to 80%. The remaining six cases were lost to follow-up. Among the 14 malignant cases, 12 (85.7%) occurred in women aged 45 years and above, in comparison only 8 benign lesions were observed in this age range. This association was statistically significant with p value of <0.05 by Fisher's exact test.

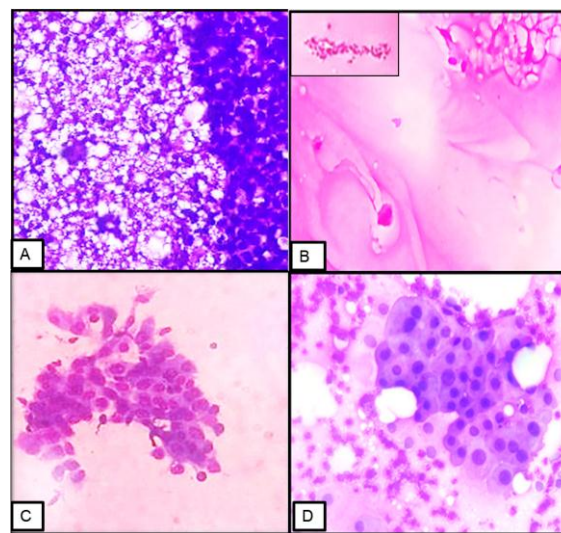


Figure 1: A and B: Leishman-stained and hematoxylin and eosin (H&E)-stained smears of Galactocoele showing lipid micelles and cyst macrophages (40x). Inset shows ductal epithelial cells dispersed in a proteinaceous background.

C and D: Leishman-stained smears of Fibrocystic disease of the breast showing cohesive clusters of apocrine epithelial cells with granular cytoplasm (40x).

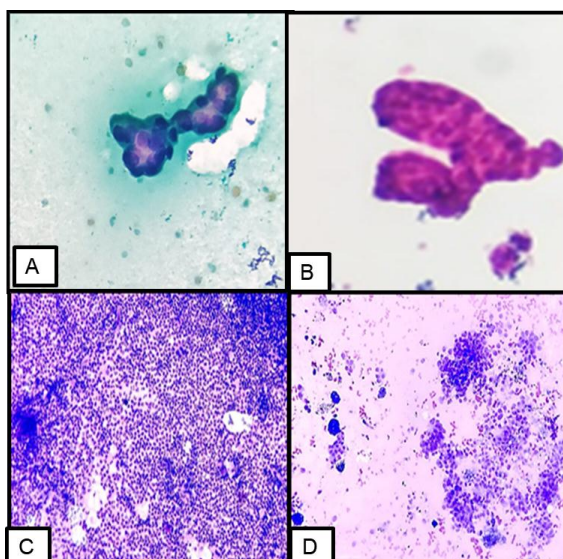


Fig 2: **A** Pap-stained smear showing papillary and fragments of ductal epithelial cells against a background of cyst macrophages and proteinaceous material suggestive of papilloma (40x). **Fig B** H & E stained smears of papilloma showing branching papillary fragments (40x). **Fig C:** Leishman-stained slides showing sheets of neutrophils with occasional squamous cells suggestive of inflammatory lesions (10x). **Fig D** showing ductal carcinoma with loose cohesive clusters of malignant cells against a background of hemosiderin laden macrophages (10x).

Table 1: Patient Demographics and Characteristics of Nipple Discharge

Parameters	Benign (N, %)	Malignant (N, %)	P Value
≥ 45 years	08	12	<0.0000(S)
<45 years	27	01	
Unilateral	27	14	0.08(NS)
Bilateral	07	00	
Bloody	04	07	0.10(NS)
Serosanguineous	06	01	
Serous	17	05	
Milky	03	00	
Purulent	04	01	

Table 2. Clinical Features

Sl. No	Clinical Features	N, %
1	Nipple discharge	18, 37.5%
2	Lump + Nipple discharge	26, 54.1%
3	Lump + Nipple discharge + Cyclical mastalgia	02, 04.2%
4	Lump + Nipple discharge + Lymph node enlargement	02, 04.2%
Total		48, 100%

Table 3: Correlation between Nature of Nipple Discharge and Cytological Diagnosis

Sl. No	Final Diagnosis	Nature of discharge					TOTAL n, %
		Serous	Serosanguineous	Bloody	Milky	Purulent	
1	Benign breast disease	06	01	01	01	-	09, 18.7%
2	Duct ectasia	01	02	-	-	-	03, 06.3%
3	Fibrocystic disease	09	03	02	01	-	15, 31.3%
4	Galactocoele	-	-	-	01	-	01, 02.1%
5	Papilloma	-	-	01	-	-	01, 02.1%
6	Inflammatory lesion	01	-	-	-	04	05, 10.4%
7	IDC	03	01	07	-	01	12, 25.00%
8	IDC + LN mets	02	-	-	-	-	02, 04.1%
Total		22	07	11	03	05	48, 100%

Table 4: Correlation with IAC Yokohama System of Reporting Breast Cytopathology

Sl. No	Categories	Description	Nature of discharge					TOTAL
			Serous	Serosanguineous	Bloody	Milky	Purulent	
1.	C2	Benign	17	06	04	03	04	34,70.8%
2.	C5	Malignancy	05	01	07	-	01	14, 29.2%
Total			22	07	11	03	05	48, 100%

DISCUSSION

There have been various studies on nipple discharge of breast since the 19th century. The first reported study was by Adair et al, in 1932 who emphasized the value of microscopic examination of breast secretion.^[9] Another report published in 1946 by Jackson and Severancea on the cytologic study of nipple secretions proposed the importance of cytologic study of breast secretion for the detection of silent papilloma.^[10] Saphirs and Papanicolaou have studied the exfoliative cytology of breast secretions to detect the malignant cells in its preclinical stage. In their studies, they concluded that cytological examination of breast secretions is always mandatory to rule out malignancy.^[11] Nipple discharge, is the second most common symptom following the presence of a lump. It can be the result of either physiologic or pathologic causes. Drugs, metabolic conditions such as hyper- and hypothyroidism, pituitary adenoma with elevated prolactin levels, and hormonal fluctuation resulting from pregnancy or lactation are among the physiologic causes of nipple discharge. Approximately 3% of malignant breast lesions are associated with an abnormal nipple discharge.^[12] Nipple aspiration fluid (NAF), a non-invasive aspirate of the intramammary ductal system is being studied increasingly, to detect the presence of biomarkers of breast cancers. NAF-derived biomarkers act a tool in the detection of breast carcinogenesis at its earliest stage, even before the lump can be seen in imaging studies. It also acts as diagnostic tool for imaging especially when imaging is not advisable (such as during pregnancy and breastfeeding). Hence the ongoing research activities will shed a light on its clinical implications.^[13] This study is to determine the underlying cause of nipple discharge, if it's an ominous sign that can indicate malignancy. To determine physiological or pathological nipple discharge based on single duct or multiple ducts are difficult. Radiological investigations and evaluation of intraductal system using ductoscopy have proved little reliable to differentiate between physiological and pathological nipple discharge. Exfoliate cytology with FNAC of the underlying mass can provide reliable information in this regard.^[14] During the study period of 5 years, 48 cases presented with nipple discharge. All the cases were females with a mean age of 43 years. The age range of patient was 16-79 years. A study done by Gupta et. al., reported that age was not useful in diagnosing the nature of breast lesion.^[15] However, we found a positive correlation with increased risk of

malignancy in patients beyond 45 years. This was concordant with the study done by Dolan et al., who also reported increased risk of malignancy in age above 50 years.^[16] All the cases presenting with bilateral nipple discharge were benign whereas malignant cases presented with unilateral nipple discharge, which were either serous or bloody in nature. This proves the dictum that pathological nipple discharges usually arise from single duct and hence are usually unilateral.^[3] Dr. State in his review of three types of nipple discharge, stated that until otherwise proved the bloody nipple discharge must be seen as the cause of underlying cancer.^[17] This was concordant with study by Gupta et. al., who inferred that the cases of papilloma, suspicious for malignancy and cytologically malignant cases presented with unilateral single duct discharge and were bloody or watery in nature.^[15] However, in our study neither the nature of discharge nor the laterality of the lesion showed any statistical significance. Dolan et al., in their study reported increased risk of carcinoma in patients presenting with bloody nipple discharge as compared to non-bloody nipple discharge.^[16] Li et al., in their meta-analytical study suggested that variation in the method of obtaining the nipple discharge, may have a substantial effect on heterogeneity of nipple discharge. Traditional method that is followed is exfoliative cytology by squeezing the nipple. However, the breast malignancy located in the peripheral ducts and the ones that are small in size may not be express significant material by this traditional method.^[18] Nature and appearance of ND gives an indication of underlying pathology. Most of the benign cases in our study presented with serous and milky discharge while malignancy had bloody discharge, seen in 50% of cases. This was similar to the studies conducted by Pritt et al.^[19] Literature study reveals unilateral ND are malignant. Pathological nipple discharges usually arise from single duct and hence are usually unilateral.^[20] In our study, all cases presenting with bilateral nipple discharge were benign (100%) and 50% of unilateral ND cases were malignant. Gupta et. al. in his study inferred that cytologically malignant cases presented with unilateral single duct discharge and were bloody or watery in nature.^[15] Dolan et al study reported increased risk of carcinoma in patients presenting with bloody nipple discharge as compared to non-bloody nipple discharge.^[16] Bloody discharge was seen in 11 cases of which seven were malignant in our study. Cytologically 34 cases were benign (70.8%), 14 (29.2%) were malignant similar to studies conducted by Gupta et al and Morrogh et al.^[15,21] Of the 14

cytologically diagnosed malignancy, seven cases were proven on histopathology and presented with an underlying lump. Morrogh et al., in their study suggested that surgical duct excision should be the gold standard to rule out underlying malignancy in cases of pathological nipple discharge.^[21] In our study, there were 14 cases were of cytologically diagnosed malignancy, which were proven on histopathology in seven of the cases. These cases presented with an underlying lump. Hence the cytological diagnosis of a case of malignant nipple discharge has high specificity and positive predictive value of 100%, which corroborates with study done by El. Daly et al.^[22]

CONCLUSION

The cytological examination of the cases presenting with nipple discharge is mandatory. It is a part of triple assessment of breast examination which also includes clinical examination and radiological investigation. It serves as a valuable, simple, and non-invasive diagnostic tool, especially in women above 45 years of age presenting with unilateral nipple discharge, where the risk of malignancy is higher.. It attributes to the overall assessment of patient. Emerging technologies and newer modalities for the analysis of nipple fluid cytology must be utilized to increase the diagnostic accuracy and reproducibility.

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