

Research**Routine Cytology of Nipple Discharge in Breast Diseases**Ahmed M Abdel Modaber^{1*} Ahmed Hammad¹ and Vusal Aliyev²¹General Surgery Department, Faculty of Medicine, Mansoura University, Egypt²General Surgery Department, Emsey Hospital, Istanbul, Turkey**Abstract****Background**

Nipple discharge (ND) is the third most frequent complaint of patients visiting a breast clinic, being the presenting symptom in 4-7% of cases. Additionally, it accounts for 6-7% of breast surgical indications. It has been questioned whether discharge color correlates to histological diagnosis. Traditionally, pathologic ND is evaluated by cytological examination of fluid smears. The management of pathological nipple discharge has caused somewhat of a diagnostic dilemma, with both physiological and pathological etiologies proving difficulty to differentiate. Physiological nipple discharge, often a feature upon Breast manipulation, is typically considered bilateral and emanating from multiple ducts. At least three different approaches have been used to assess the usefulness of nipple discharge cytology in detecting breast disease. Historically, nipple discharge cytology has been reported as a poorly sensitive yet highly specific screening tool in the detection of carcinoma amongst patients with nipple discharge. The impact of the rising incidence of breast disease has led to the demand for diagnostic tests that are not only accurate but also quick, cheap and cost effective.

Objective

To evaluate the benefit of routine cytology of nipple discharge in early diagnosis of breast diseases.

Methods

This study was carried out on 500 female patients presented with nipple discharge. Lactating females were excluded from the study. patients were followed up for a minimum of 3 months and a maximum of 18 months on monthly basis regarding follow up of the discharge and follow up of the breast as regard appearance of any breast lump or any changes. Every patient was subjected to full history taking, complaints, general examination, vital signs, systemic examination, local breast examination, examination of the discharge and discharge cytology.

Conclusion

Nipple discharge in most patients is due to benign causes. One method of investigation is not sufficient for the diagnosis of the cause of nipple discharge even in the benign cases, but correlation between physical examination, radiological and pathological investigations must be present.

Key Words: Cytology; Nipple Discharge; Breast**Introduction**

Nipple discharge is regarded as one of the three most common presenting complaints in women attending a breast clinic; the other two complaints being breast pain and the finding of a lump [1].

Nipple discharge accounts for 3-5% of patients with breast symptoms, and the underlying causes could be numerous and varied [2].

The most common causes of pathologic nipple discharge is a benign papilloma (48,1% of cases) followed by duct ectasia (15-20%). The least likely, but significant is carcinoma (10-15% of cases) [3]. Evaluation of patients with pathological nipple discharge includes history, physical examination, mammography, sonography, cytology, ductography and most recently ductoscopy [4].

Ductography or ductoscopy is used to diagnose any intraductal pathology and to preoperatively localize the intraductal lesion to be resected [5].

Mammary ductoscopy is a safe and effective procedure that offers advantages of high lesion localization rate and intraoperative guidance, therefore negating the need for a pre-operative ductogram [6].

Microdochoectomy or major duct excision performed for nipple discharge resulted in a low rate of malignancy on excision. Conservative management of non-bloody nipple discharge can be considered in patients with no other clinical or radiological signs of malignancy [7].

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Historically, Nipple Discharge cytology has been reported as a poorly sensitive (sensitivity range of 11-27 %) yet highly specific (specificity range of 81-96 %) screening tool in the detection of carcinoma amongst patients with nipple discharge [8].

This study aimed at understanding the role of cytology in early detection of breast cancer and to identify patients with pathological nipple discharge and to avoid unnecessary diagnostic surgical intervention in patients with physiological nipple discharge.

Patients and Methods

This study was carried out on 500 female patients presented with nipple discharge in 20-month period from January 2012 to September 2013. Lactating females were excluded from the study. patients were followed up for a minimum of 3 months and a maximum of 18 months on monthly basis regarding follow up of the discharge (increase , decrease , disappear .localized to single duct or any change in the colour or the type of the discharge) and follow up of the breast as regard appearance of any breast lump or any changes.

Inclusion criteria

- All female present in outpatient clinic complaint or not complaint of breast disease
- After menarche (more than 15 years old)

Exclusion Criteria

- Male
- No.nipple discharge even after tried to express the nipple
- Female refused to participate in the study
- Congenital retracted nipple
- Lactating female

Methods

Every patient was subjected to:

- Full history taking
- Complaints
- General examination including consciousness level, bilt, weight, decubitus, gait and mental status.
- Vital signs including temperature, pulse, blood pressure, respiratory rate
- Systemic examination
- Local breast examination
- Discharge cytology for all cases

Statistical analysis: Data was summarized as mean \pm standard deviation

(SD) for continuous variables. Continuous variables (or parameters) were non-parametrically analyzed by the Mann-Whitney U test. Categorical variables were compared using the χ^2 test or Fisher's exact test where appropriate. Pearson coefficient was used for correlation. All statistical data were generated using JMP 5.0.1 (SAS Institute, Cary, NC) and Prism 6.02 (GraphPad Software, Inc., La Jolla, CA, USA).

Results

In the present study, the age of patients presented with nipple discharge ranged from 15 years to 60 years with a mean age of 39.6 ± 11.8 years. Whereas, the highest incidence (29.8%) of nipple discharge occurred in the age group 40-<50 years. Four hundred twenty nine cases (85.8%) were married. Meanwhile, 71 patients (14.2%) were single. One hundred thirty nine patients (27.8%) were in the post-menopausal period. Pre-menstrual females were 361 (72.2%), irregular cycles were recorded in 54 patients (10.8%). The majority of the patients (n=429, 85.8%) had at least one baby, while only 14.2% (n=71) of the females were nulliparous. About half of the patients (n=249, 49.8%) were using contraceptive methods; 160 patients (32%) were using intrauterine contraceptive devices (IUD), 60 patients (12%) were using oral contraceptive pills, and 29 patients (5.8%) were on contraceptive injection. Only 2.6% (n=13) of the female patients had a family history of breast cancers in their relatives (table 1).

Breast lump was found in 78 cases (15.6%). This was associated with skin changes in 22 cases (4.4%). From the total 500 patients, 192 patients (38.4%) were complaining of Mastalgia (table 2).

Also table (2) had shown that in 100 patients (20%), the discharge was spontaneously released, while in 400 patients (80%) the discharge occurred on areolar and periareolar squeezing. In 119/500 patients (23.8%), the nipple discharged from uni-orifice and in 381/500 patients (76.2%) the nipple discharged from multi-orifice. About 59% of the studied patients complained from unilateral discharge, while 41% of them complained from bilateral discharge. In the majority of the patients, the discharge was intermittent in course (88.8%) and it was persistent in 11.2% of the cases.

Regarding discharge color and consistency, 10 patients (2%) presented with milky discharge, 30 patients (6%) presented with creamy discharge, 226 patients (45.2%) presented with serous discharge, 85 patients (17%) presented with serosanguinous discharge, 111 patients (22.2%) presented with sanguinous

Table 1. Demographic characteristics of overall enrolled women (n=500):

	Overall (n=500)	
Age groups (years) No. (%)		
<20	19	3.8
20-<30	94	18.8
30-<40	128	25.6
40-<50	149	29.8
50-60	110	22.0
Mean ±SD	39.6±11.8	
Range	15-60	
Marital status, No. (%)		
Single	71	14.2
Married	429	85.8
Menstrual status, No. (%)		
Pre-Menopausal	361	72.2
Regular cycle	307	61.4
Irregular cycle	54	10.8
Post-Menopausal	139	27.8
Parity status, No. (%)		
Nulliparous	71	14.2
Parous	429	85.8
Contraceptive method, No. (%)		
No	251	50.2
IUD	160	32.0
Pills	60	12.0
Injection	29	5.8
Family history, No. (%)		
No	487	97.4
Yes	13	2.6

Table 2. Breast changes and nipple discharge characteristics of overall enrolled women (n=500):

	Overall (n=500)	
	No.	%
Breast lump		
Absent	422	84.4
Present	78	15.6
Skin changes		
Absent	478	95.6
Present	22	4.4
Mastalgia		
Absent	308	61.6
Present	192	38.4
Discharge release		
Spontaneous	100	20.0
Squeezed	400	80.0
Orifice		
Uni-orifice	119	23.8
Multi-orifice	381	76.2
Laterality		
Unilateral	296	59.2
Bilateral	204	40.8
Persistency		
Persistent	56	11.2
Intermittent	444	88.8
Discharge color and consistency		
Milky	10	2.0
Creamy	30	6.0
Serous	226	45.2
Serosanguinous	85	17.0
Sanguineous	111	22.2
Purulent	38	7.6

Table 3. Cytological results characteristics of overall enrolled women (n=500):

	Overall (n=500)	
	No.	%
Nipple discharge cytological features:		
Galactorrhea	10	2.0
Inflammatory cells	60	12.0
Fibrocystic disease	231	46.2
Fibrocystic disease with duct ectasia	110	22.0
Fibrocystic disease with duct papilloma	41	8.2
Duct papilloma	29	5.8
Malignant cells	19	3.8
Cytological classification:		
Unsatisfactory	70	14.0
Benign	411	82.2
Malignancy	19	3.8

Table 4. Correlation between cytological classification and the studied variables:

Variables	Pearson Correlation Coefficient	P-value (2-tailed)
Age	.403	<0.0001**
Marital status	.113	0.011*
Contraceptive history	-.154	0.001**
Menstrual history	.309	<0.0001**
Family history	.361	<0.0001**
Parity	.063	0.160
Breast lump	.321	<0.0001**
Skin changes	.344	<0.0001**
Mastalgia	-.057	0.201
Laterality	-.053	0.240
Discharge release	-.013	0.777
Orifice	-.144	0.001**
Color and consistency	.212	<0.0001**
Persistence	-.011	0.803

*Significant correlation at p-value <0.05, **highly significant correlation at p-value <0.01.

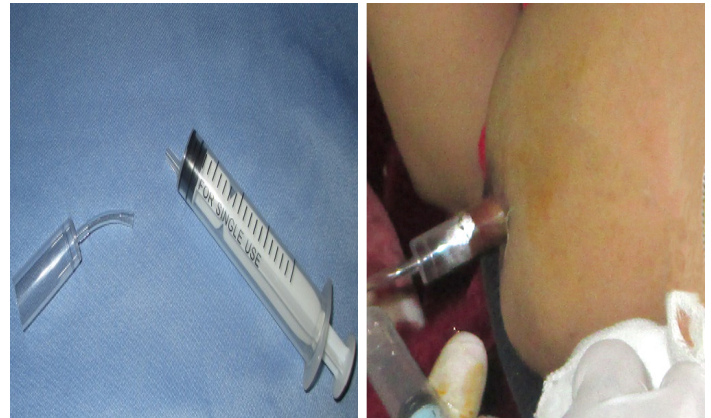
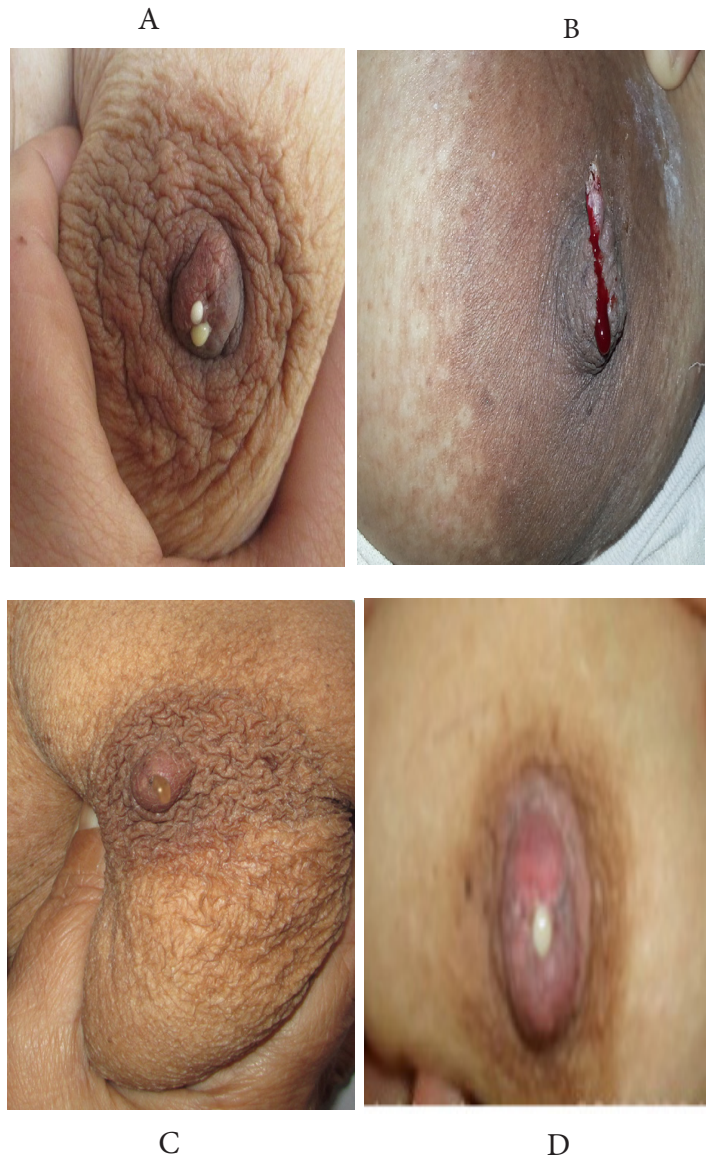


Fig. 1

Collection of nipple Discharge in one patient



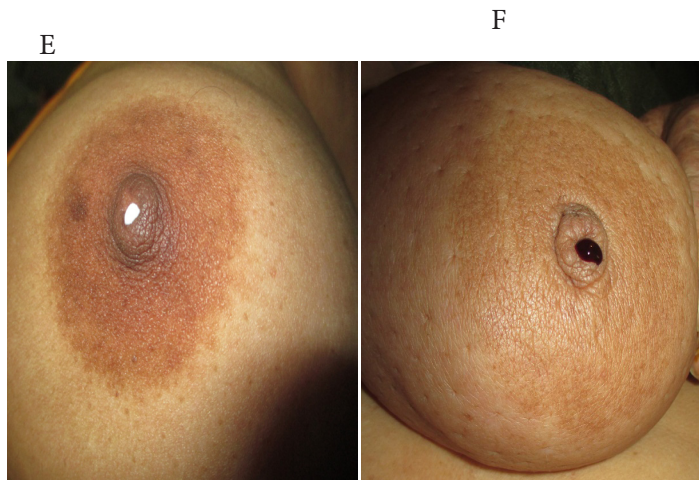


Fig.2

Patients presented with a-greenish nipple discharge from multiple ducts, b- bloody, c- serous, d- creamy white, e-milky, f- sero-sanguineous nipple discharge.

Discussion

Nipple discharge of the breast is a common complaint. Between 5% and 10% of women presenting for routine examination will report spontaneous nipple discharge, and as many as 80% of women will experience at least one episode of nipple discharge during their reproductive years [9].

Although most nipple discharges are caused by benign conditions such as papillomas and duct ectasia, up to 15% of patients with nipple discharge may have an underlying malignancy [10].

Although clinical presentation alone may help distinguish between benign/physiological and suspicious/pathological nipple discharge, further evaluation is often needed to help rule out an underlying malignancy [11].

There is no consensus on the diagnostic approach to evaluating patients with pathologic nipple discharge. Workup may include endocrinologic testing, mammography, ultrasound, magnetic resonance imaging, ductography, ductoscopy, and cytology [12].

The gold standard diagnostic and therapeutic approach for patients with pathological nipple discharge is surgical duct excision [13].

The challenge for the breast surgeon and the logical approach is to identify patients with pathological nipple discharge in the clinical setting and to avoid unnecessary diagnostic surgical intervention in patients with physiological nipple discharge [14]. The clinical utility of cytological examination of nipple discharge preparations is controversial. Nipple discharge preparations should be interpreted in light of the clinical and radiologic findings [15,16].

In our study, the age of patients presented with nipple discharge ranged from 15 years to 60 years with a mean age of 39.6 ± 11.8 years. These findings

coincided with the results of Gulay et al. [17], who had studied 448 women with nipple discharge. The age of their patients ranged between 16 and 65 years with a mean age of 42 years.

In agreement with our results, Dolan et al. [15] found that the median age of their patients was 43 years. Their primary outcome was also similar to our study, as their aim was to assess the potential association of the characteristics of nipple discharge with the risk of underlying carcinoma and evaluate the efficacy of duct cytology in identifying this risk.

In our study we found that 22% of our patients had age ranged from 50-60 years. A higher mean age was found by Jeffrey [18]; Kooistra et al. [16] and Morrogh et al. [9].

The first study, Jeffrey [18], recorded the data of 35 cases with nipple discharge, the mean age of these patients was 54 years (range; 26-74 years), the second study, Kooistra et al. [16], examined 618 patients with median age of 50 years (range; 20-86years) and the third study.

These differences between the mean age of the studied patients in our study and the previous studies may be due to the fact that they included a higher number of elderly (geriatric patients) and post-menopausal women in their studies than in our study. For example, Morrogh et al. [9] reported that 280 (67.3%) of their patients were post-menopausal women.

Our study showed that 139 patients (27.8%) were in the post-menopausal period. Premenopausal females were 361 (72.2%). But, it is interesting to note that the highest incidence of nipple discharge in our patients occurred in the age group around 50 years which was approximately 30%.

A comparable results about the frequency of post-menopausal women was found by Cheung and Alagarantnam [19], they documented that 26 (25%) of their patients with nipple discharge were in post-menopausal period.

Our data indicated that only 2.6% (n=13) of the female patients had a family history of breast cancers in their relatives.

Similarly, Morrogh et al. [9] found that the family history of ipsilateral breast cancer among their patients was 4.3%.

In our results, breast lump was reported in 78 of our cases (15.6%). This was associated with skin changes in 22 cases (4.4%). From the total 500 patients, 192 patients (38.4%) were complaining of Mastalgia.

Similar observations were found in the study performed by Dolan et al.(15), they reported that the presentation of nipple discharge was associated with additional symptomatology. These symptoms included mastalgia (28%, 88/313), nipple skin changes (4%, 12/313), and the presence of a lump (14%, 45/313).

Also our results had shown that in the minority of our patients (n=100; 20%), the discharge was spontaneously released, while in the majority of our patients (n=400; 80%), the discharge released with areolar and periareolar squeezing. About 59% of the studied patients complained

from unilateral discharge, while 41% of them complained from bilateral discharge.

In the study performed by Jeffrey [18], the discharge was spontaneous in 6 cases (17%), and provoked in 29 cases (83%). The discharge was unilateral in 21 cases (60%), bilateral in 14 cases (40%).

In the same way, Dolan et al. [15], found that the minority of their patients had active (spontaneous) nipple discharge (96/313; 31%). The nipple discharge was unilateral in 78% (245/313) of cases and bilateral in 22% (68/313) of cases. Also the majority of cases in Morrogh et al. [9] study had unilateral discharge, where the discharge was unilateral in 379 cases (91%).

This research observed that in 119/500 patients (23.8%), the nipple discharged from uni-orifice and in 381/500 patients (76.2%) the nipple discharged from multi-orifice. In the majority of the patients, the discharge was intermittent in course (88.8%) and it was persistent in 11.2% of the cases.

In contrast, Morrogh et al. [9] found that the nipple discharged from multi-duct in 200/416 (48.1%). The nipple discharge was persistent in 70.2% of the cases.

Regarding discharge color and consistency, 10 patients (2%) presented with milky discharge, 30 patients (6%) presented with creamy discharge, 226 patients (45.2%) presented with serous discharge, 196 patients (39.2%) presented with bloody discharge (85 patients (17%) with sero-sanguineous discharge and 111 patients (22.2%) with pure sanguineous(bloody) discharge) and 38 patients (7.6%) presented with purulent discharge.

These findings were also observed by Leis(20), he found that milky discharge was present in 3% of 644 cases with nipple discharge, creamy discharge in 4% of the cases, serous discharge in 42%, serosanguinous in 26%, sanguinous in 18%, and purulent in 7%. Similarly, Dey and Dhar(21) had observed in a study of 80 cases of nipple discharge that the discharge was serous in 29 cases (36.25%) and bloody in 33 cases (41.25%).

The same was documented by Dolan et al.(15), they reported that the discharge was milky in 9% (27/313) of cases, serous in 42% (130/313) of cases, bloody in 44% (137/313) of cases, and purulent in 6% (19/313) of cases.

Comparable results were observed by Morrogh et al. [9]. They reported that the nipple discharge was whilt/milky discharge in 26 patients (6.3%), clear/serous/pink discharge in 125 patients (30%), bloody discharge in 224 patients (53.8%), and green/brown discharge in 41 patients (9.9%).

Regarding the cytological evaluation for nipple discharge, galactorrhea was observed in 10 cases (2%) of cases. Twenty percent (n=60) of the studied females showed inflammatory cells only in their nipple discharge. Both galactorrhea and inflammatory cells classified as unsatisfactory category. The majority of cases (n=411, 82.2%) showed benign lesions; in the form

of fibrocystic disease in 231 cases (46.2%), fibrocystic disease with duct ectasia in 110 cases (22%), fibrocystic disease with duct papilloma in 41 cases (8.2%), and duct papilloma in 29 cases (5.8%). Nineteen cases were positive for malignant cells (3.8%).

The incidence of malignant cells in our study was comparable to Dunn et al. [22] study. They studied 393 women with nipple discharge, of which 19 (4.8%) had malignant smear cytology.

A little higher incidence of carcinoma was observed by Funge et al. [23] (15 cases; 9%).

Moreover, a similar incidence of benign lesions was reported by Funge et al. (23,24) (85%) including; duct papilloma in 78 cases (44%), duct ectasia in 31 cases (18%), fibrocystic disease in 25 cases (14%) and other (9%).

There were significant positive correlations between malignancy and higher age of the patients, married women, IUD use, postmenopausal women, and positive family history of breast cancer, presence of breast lump, presence of skin changes, uni-orifice discharge release, and serous or sero-sanguineous discharge.

We acknowledge the limitations of this study. Nipple discharge characteristics, such as color, uni- or bilaterality and spontaneity were obviously subjective. Moreover, these and other variables vary greatly in time in a substantial portion of nipple discharge patients. This may also clarify the many contradicting results in this field of research.

In conclusion, nipple discharge smearing and its cytological examination may had some complementary diagnostic value. Therefore, its routine use for detection of nipple discharge-related breast pathology should be reconsidered carefully. Nipple discharge cytology may usefully redirect patient management in some cases.

Conclusion

Nipple discharge in most patients is due to benign causes.

Spontaneous bloody, unilateral, single duct discharge needs a work up and thorough evaluation. Most of these patients may require surgery to rule out carcinoma.

As routine investigations, every woman presented with nipple discharge should undergo exfoliative cytology because it has a sensitivity of 66.67% and a specificity of 100%. Other investigations will depend upon type, laterality of the discharge, whether the discharge is uniorificial or multiorificial and associated with lump or not.

One method of investigation is not sufficient for the diagnosis of the cause of nipple discharge even in the benign cases, but correlation between physical examination, radiological and pathological investigations must be present.

Regular follow up of the patient is important whether the patient is managed conservatively or surgically to check the efficacy of the treatment.

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