Implications of nipple discharge in Hong Kong Chinese women

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A B S T R A C T

Introduction: There are no recent data on nipple discharge and its association with malignancy in Hong Kong Chinese women. This study reported our 5-year experience in the management of patients with nipple discharge, and our experience of mammography, ultrasonography, ductography, and nipple discharge cytology in an attempt to determine their role in the management of nipple discharge.

Methods: Women who attended our Breast Clinic in a university-affiliated hospital in Hong Kong were identified by retrospective review of clinical data from January 2007 to December 2011. They were divided into benign and malignant subgroups. Background clinical parameters and investigative results were compared between the two subgroups. We also reported the sensitivity, specificity, and positive and negative predictive values of the investigations that included mammography, ultrasonography, ductography, and cytology.

Results: We identified 71 and 31 patients in the benign and malignant subgroups, respectively. The median age at presentation for the benign subgroup was younger than that of the malignant subgroup (48 vs 59 years; P=0.003). A higher proportion of patients in the malignant subgroup than the benign subgroup presented with blood-stained nipple discharge (87.1% vs 47.9%; P=0.002). Mammography had a specificity of 98.4% and positive predictive value of 66.7%; ultrasonography had a specificity of 87.0% and negative predictive value of 75.0%. Cytology and ductography were sensitive but lacked specificity. Ductography had a negative predictive value of 100% but a low positive predictive value (14.0%). Clinical variables including age at presentation, duration of discharge, colour of discharge, presence of an associated breast mass, and abnormal sonographic findings were important in suggesting the underlying pathology of nipple discharge. Multiple logistic regression showed that blood-stained discharge and an associated breast mass were statistically significantly more common in the malignant subgroup.

Conclusions: In patients with non–blood-stained nipple discharge, a negative clinical breast examination combined with negative imaging could reasonably infer a benign underlying pathology.

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New knowledge added by this study

- Blood-stained nipple discharge and an associated breast mass at presentation could suggest a higher chance of malignancy.

Implications for clinical practice or policy

- A period of watchful waiting is a reasonable alternative to surgical intervention in patients with inferred benign pathology.

Introduction

Nipple discharge is a relatively uncommon complaint in the Hong Kong Chinese women. According to a study in 1997, nipple discharge constituted 1.5% of all presenting complaints for women who attended a breast clinic in Hong Kong.[1] On the contrary, nipple discharge accounted for up to 4% to 7% of all presenting symptoms in other studies.[2,3] This may be better explained by the unique Chinese culture and help-seeking pattern rather than a true disease pattern. With this understanding, any clinical survey will probably underestimate the prevalence of nipple discharge in Chinese women. When patients approach health care professionals because of nipple discharge, not only is it important to differentiate malignant from benign causes of nipple discharge, it is also a valuable opportunity to promote breast health awareness.

Numerous studies have demonstrated the relationship between breast cancer and nipple discharge, with malignancy reported in up to 9.3% to 21% of all patients who present with nipple

香港華籍女性乳頭溢液的預示

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引言：近代文獻中未有關於香港華籍女性乳頭溢液以及其相關惡性腫瘤的資料。本研究報告我們5年來處理有關乳頭溢液病例的經驗，並回顧乳房X光造影、超聲檢查、乳管造影和乳頭溢液細胞學檢查的病例，從而確定這些檢測在乳頭溢液治療過程中的角色。

方法：回顧分析2007年1月至2011年12月期間，所有到香港一所大學教學醫院的乳房護理診所求診的病人的臨床資料。我們把病人分為良性和惡性腫瘤兩組，然後比較兩組的背景臨床資料和檢查結果，並報告乳房X光造影、超聲檢查、細胞學和乳管造影檢查的敏感性、特異性，以及其陽性和陰性預測值。

結果：良性和惡性腫瘤兩組分別有71例和31例。良性腫瘤組別的病人年齡中位數顯著低於惡性腫瘤組別（48歲比59歲；P=0.003）。惡性腫瘤組別中有較多患者的乳頭有血性溢液（87.1%比47.9%；P=0.002）。乳房X光造影的特異性98.4%，陽性預測值66.7%；超聲檢查的特異性87.0%，陰性預測值75.0%。細胞學和乳管造影檢查的敏感度高，可惜缺乏特異性。乳管造影檢查的陰性預測值有100%，但其陽性預測值偏低（14.0%）。患者年齡、溢液持續期、溢液顏色、是否有相關的乳房腫塊和異常的超聲檢查結果，對於反映乳頭溢液的潛在病理狀況相當重要。多元邏輯迴歸分析顯示惡性腫瘤組別中，患者的乳頭有血性溢液和相關乳腺腫塊的情況明顯較多。

結論：對於無出現乳頭血性溢液的患者，如果其臨床乳腺檢查和造影顯像均為陰性時，便可合理地推斷患者屬良性腫瘤的病例。

discharge.[4,5] The most challenging role of breast surgeons is to accurately identify these patients. Notwithstanding, controversy persists about the value and accuracy of individual investigative tools for nipple discharge.[6]

There are no recent data on nipple discharge and its association with malignancy in Chinese women in Hong Kong. The primary aim of this study was to report our recent experience in the management of patients with nipple discharge in a single surgical centre. The secondary aim was to report our experience of individual investigative tools in an attempt to determine their role in the management of nipple discharge.

Methods

We retrospectively reviewed the clinical data of patients who attended our Breast Clinic in Queen Mary Hospital, a university-affiliated hospital in Hong Kong, for nipple discharge from January 2007 to December 2011. Potential subjects were identified when diagnosis coding 611.79 (other signs and symptoms in breast) was entered into our Clinical Management System, which is a territory-wide computer-based medical record system designed for use in public hospitals, and also from the prospective database of the Division of Breast Surgery, The University of Hong Kong.

Data extraction and coding were performed by the first author (WM Kan) and included duration of follow-up until December 2011, age at presentation, history of breast condition, and laterality and duration of nipple discharge before first consultation. Clinical variables included colour of nipple discharge, single- or multiple-duct discharge, associated symptoms, mammographic and ultrasonographic imaging results, as well as ductogram and cytology results. Pathology results were recorded for patients who underwent surgery or biopsy.

In order to make a meaningful comparison, we divided patients into malignant and benign subgroups. The malignant subgroup was defined by malignant pathology on a surgically resected specimen. The benign subgroup was defined by benign pathology of a surgically resected or biopsy specimen, or clinical non-progression after more than 2 years of follow-up. Patients who did not undergo surgery or biopsy and who were followed up for less than 2 years were excluded (Fig).

In the first part of our study, we compared the background clinical variables and investigative results between the two subgroups. In the second part of our analysis, we reported the sensitivity, specificity, positive predictive value, and negative predictive value of individual investigative tools.

For the purpose of this analysis, we also classified the results of clinical examination, mammography, ultrasonography, and cytology as 'test positive' or 'test negative' for underlying malignancy. Presence of a palpable breast mass (regardless of mobility) was considered a positive result and no palpable breast mass a negative result. For mammographic findings, microcalcifications were considered a positive result. For ultrasonography, a detectable mass was 'test positive' for underlying malignancy; non-solitary dilated ducts, cysts, and normal ultrasonogram were regarded as 'test negative'. For ductogram results, dilated ducts, irregularity, and the presence of ductal filling defects were considered positive. For cytology, 'atypical', 'suspicious', and 'malignant' were considered a positive test, and 'benign' as negative. This study was done in accordance with the principles outlined in the Declaration of Helsinki.

Statistical analysis

R version 3.0.2 (the R Foundation) and the SPSS (Windows version 14.0; SPSS Inc, Chicago [IL], US) were used for data analysis. To determine the differences between subgroups, Wilcoxon rank sum test and Fisher's exact test were used for numerical data and categorical data, respectively. Multiple logistic regression was performed to examine the odds ratios of the factors. Backward selection through likelihood ratio test with removal of P value of 0.1 was conducted for model selection. Variables in univariate analysis with a P value of <0.1 were

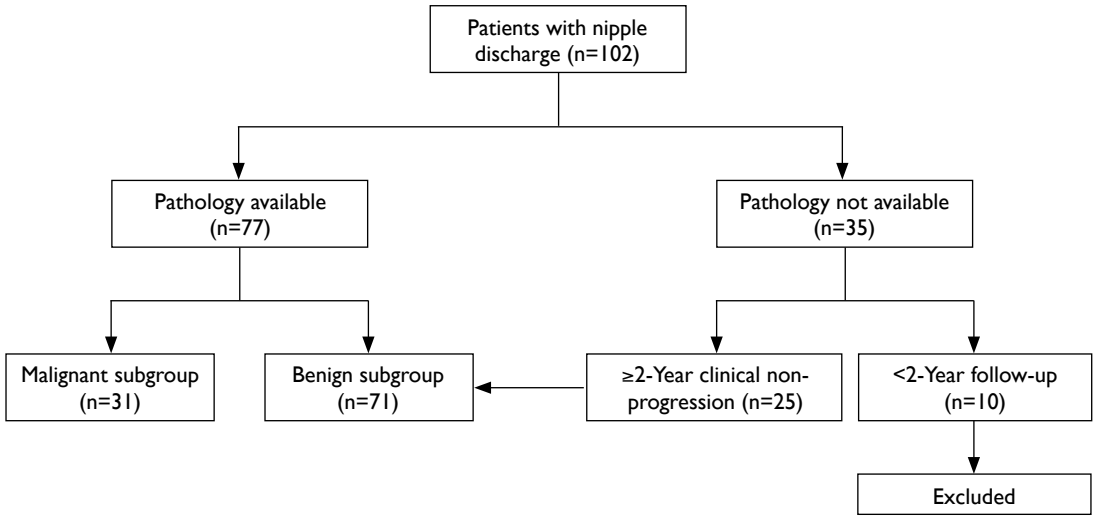

FIG. Algorithm for patient selection

included in the full model. A P value of <0.05 was considered statistically significant.

Results

Table 1 summarises the first part of our analysis. We identified 102 patients who presented to our Breast Clinic during the study period. They had either a tissue diagnosis or had been followed up for longer than 2 years without tissue diagnosis. There were 31 and 71 patients in the malignant and benign subgroups, respectively.

The median age at presentation of the benign subgroup was significantly younger than the malignant subgroup (48 vs 59 years; P=0.003). The median interval between onset of nipple discharge and first presentation was significantly longer in the benign subgroup than in the malignant subgroup (13 vs 4 weeks; P=0.002).

Comparing the two subgroups, a larger proportion of patients in the malignant subgroup presented with blood-stained discharge (87.1% vs 47.9%; P=0.002) and had a breast mass at presentation (46.7% vs 7.0%; P<0.001). For the individual investigative modalities, with the exception of ultrasonography, neither mammography, ductography nor cytology showed any statistically significant difference between the malignant and benign subgroups.

Table 2 summarises the second part of the study. We calculated the sensitivity, specificity, and positive and negative predictive values of mammographic, ultrasonographic, cytological, and ductographic findings. There were 83, 95, 27, and 46 patients who underwent mammography, ultrasonography, cytology, and ductography, respectively. The positive and negative predictive values of cytology were 41.2% and 80.0%, respectively. Ductography had a sensitivity of 100%, specificity of 7.5%, positive predictive value of 14.0%, and negative predictive value of 100%.

Multiple logistic regression analysis with backward selection was performed. Covariates with a P value of <0.1 were included in the full model (Table 1). By likelihood ratio test and removal of variables with a P value of >0.1, duration of nipple discharge, colour of nipple discharge, mastalgia, and associated mass remained in the final model (Table 3).

Compared with serous, milky and brownish discharge, patients with blood-stained discharge had a significantly higher risk for malignancy (odds ratio=13.368; 95% confidence interval, 1.926-92.809). In addition, compared with patients having no symptoms, those with a breast mass had a significantly higher risk for malignancy (odds ratio=14.648; 95% confidence interval, 3.155-68.000) [Table 3].

Discussion

A methodologically ideal study of nipple discharge would require every patient to undergo the same investigations and also surgery for final pathology. This, however, would be unethical. For patients who opted for non-operative management of nipple discharge, our retrospective study considered 2-year clinical non-progression a reasonable surrogate for benign breast pathology.

Clinical variables

Women in the malignant subgroup were significantly

TABLE 1. Bivariate analysis of tumour type (benign or malignant) and other clinical parameters

Variable*	Median (range) or No. (%) of patients		P value (Fisher's exact/ Wilcoxon rank sum test)
	Malignant (n=31)	Benign (n=71)	
Duration of follow-up (weeks)	129 (9-261)	173 (7-266)	0.190
Age at presentation (years)	59 (36-91)	48 (24-87)	0.003
History of malignancy in contralateral breast	1 (3.2)	3 (4.2)	1
Laterality of nipple discharge (unilateral / bilateral)	29 (93.5) / 2 (6.5)	56 (78.9) / 15 (21.1)	0.085
Duration of nipple discharge before consultation (weeks)	4 (1-26)	13 (1-520)	0.002
Colour of nipple discharge			
Serous	3 (9.7)	22 (31.0)	0.002
Milky	1 (3.2)	8 (11.3)	
Brownish	0	7 (9.9)	
Blood-stained	27 (87.1)	34 (47.9)	
Single / multiple duct (n=82)			
Single duct	10 (71.4)	59 (86.8)	0.222
Multiple duct	4 (28.6)	9 (13.2)	
Associated symptoms (n=101)			
No symptoms	14 (46.7)	58 (81.7)	<0.001
Mastalgia	2 (6.7)	8 (11.3)	
Breast mass	14 (46.7)	5 (7.0)	
Mammogram (n=83)			
Microcalcifications	2 (9.5)	1 (1.6)	0.156
Normal	19 (90.5)	61 (98.4)	
Ultrasonogram (n=95)			
Normal	4 (15.4)	34 (49.3)	<0.001
Cyst	11 (42.3)	5 (7.2)	
Dilated ducts	5 (19.2)	21 (30.4)	
Mass	6 (23.1)	9 (13.0)	
Ductogram (n=46)			
Normal	0	3 (7.5)	0.900
Dilated ducts	2 (33.3)	9 (22.5)	
Irregularity	1 (16.7)	7 (17.5)	
Filing defect	3 (50.0)	21 (52.5)	
Cytology (n=27)			
Benign	2 (22.2)	8 (44.4)	0.383
Atypical	5 (55.6)	8 (44.4)	
Suspicious	2 (22.2)	1 (5.6)	
Malignant	0	1 (5.6)	

* Data were missing for some patients

TABLE 2. Sensitivity, specificity, and positive/negative predictive values of different modalities

	Mammography (microcalcifications with or without a mass) [n=83]	Ultrasonography (mass) [n=95]	Cytology (atypical, suspicious, and malignant) [n=27]	Ductography (dilated ducts, irregularity, and filling defect) [n=46]
Sensitivity	9.5%	23.1%	77.8%	100%
Specificity	98.4%	87.0%	44.4%	7.5%
Positive predictive value	66.7%	40.0%	41.2%	14.0%
Negative predictive value	76.3%	75.0%	80.0%	100%

TABLE 3. Multiple logistic regression of factors associated with malignancy

	Odds ratio	95% Confidence interval	P value
Duration of nipple discharge before consultation	0.969	0.920-1.020	0.227
Colour of nipple discharge (ref: serous / milky / brownish)			
Blood-stained	13.368	1.926-92.809	0.009
Associated symptoms (ref: no symptoms)			
Mastalgia	8.004	0.698-91.741	0.095
Breast mass	14.648	3.155-68.000	<0.001

older at presentation than their benign counterparts. This was in agreement with the fact that physiological nipple discharge is more common in younger pre-menopausal women. Caution should be exercised in postmenopausal women who present with nipple discharge and the possibility of malignancy investigated before concluding a benign pathology.

With respect to the colour of nipple discharge, underlying benign and malignant causes had a different pattern. Benign pathology was more likely to be associated with non–blood-stained discharge (n=37, 52.1%), whereas malignant pathology was more likely to be associated with blood-stained discharge (n=27, 87.1%). This is not pathognomonic but did reach statistical significance.

The differentiation between multiple-duct and single-duct discharge showed no association with underlying pathology.

Mammography and ultrasonography

As shown in Table 2, mammography had a higher specificity of 98.4% and positive predictive value of 66.7% but a disappointingly low sensitivity of 9.5%. Therefore, a normal mammogram did not confidently exclude malignancy. On the other hand, breast ultrasonography had a specificity and negative predictive value of 87.0% and 75.0%, respectively. Mammography was routinely offered to patients who presented with nipple discharge. Complementary breast ultrasonography was also arranged, especially for younger Asian women with denser breasts on mammography.[7] In our experience, complementary ultrasonography increases the overall sensitivity and negative predictive value compared with mammography alone.

Nipple discharge cytology

Opinion is divided on the value of cytological examination. While some studies report a complementary diagnostic value and recommend its routine use,[8,9] others report it has little such value and advise against its routine use.[10]

Of the 102 patients, 36 had demonstrable nipple discharge at consultation with a sample collected for examination. Of these 36 specimens, only 27 showed a sufficient number of cells to make a cytological diagnosis. Nonetheless, we attempted to analyse its accuracy. The sensitivity and specificity of cytological examination were 77.8% and 44.4%, respectively. Its positive predictive value was disappointingly low at 41.2% and its negative predictive value was 80.0%. The diagnostic value of this investigation was limited as not every patient had demonstrable nipple discharge and not every specimen contained adequate cells for testing. Nonetheless, this investigation is minimally invasive so was always performed if there was demonstrable nipple discharge, although it rarely affected the clinical decision or plan of management.

Ductography

The value of ductography is debatable. While some studies have validated the diagnostic value of preoperative ductography in differentiating benign and malignant pathology,[11,12] others doubt its value.[13] Rather than differentiating benign and malignant pathology, we used preoperative ductogram to aid in the localisation of non-palpable lesions.[14,15] The sensitivity was 100% whereas the specificity was low at 7.5%, with a positive predictive value of 14.0% and a negative predictive value of 100%.

Magnetic resonance imaging

Magnetic resonance imaging was not included in our routine evaluation of patients with nipple discharge although we acknowledge its value in the detection of carcinoma in these patients. It has an exceptionally high sensitivity for both invasive and in-situ carcinoma.[16] Its routine use in patients with a breast lesion is nonetheless limited by its relatively low specificity of 72% (95% confidence interval, 67%-77%).[17] The role of magnetic resonance imaging in patients with nipple discharge has been extensively validated,[18-21] suggesting that it may detect or exclude the presence of carcinoma with a high degree of certainty. Magnetic resonance imaging may be considered when all other available strategies are inconclusive.

Microdochectomy

Emerging evidence suggests that neither clinical variables nor preoperative investigations reliably distinguish benign and malignant pathology so duct excision should be offered to every patient with nipple discharge.[22-26] We offered microdochectomy to patients with no palpable breast lesion based on two indications: clinical or radiological suspicion, or a patient's wish to stop nipple discharge by surgery. It is likely that offering microdochectomy to all patients with nipple discharge would result in over-treatment as the final pathology was benign in most cases. In patients with negative clinical examination and negative imaging findings, a period of watchful waiting with regular follow-up is a reasonable alternative to surgical intervention.

The association of blood-stained discharge with malignancy is controversial. Morrogh et al[24] reported that haemorrhagic discharge did not indicate malignancy or high risk, and non-haemorrhagic discharge did not exclude malignancy. In our study, we showed that blood-stained discharge was associated with malignancy but was not pathognomonic.

On the other hand, presence of an associated breast mass was a significant finding. This may be because it is the most common presenting symptom of breast cancer, and its incidence rises with age.

Limitations

Our study had several limitations. First, as data collection was retrospective, there might have been inconsistent or incomplete recording of clinical findings. Study subjects might not be representative and some data for importable variables might have been missing. No blinding during information extraction or coding could be achieved as it was performed by the first author. Second, the small sample size limited the power of our study although this could in part be due to the relatively conservative culture and help-seeking pattern of Hong Kong Chinese women. The unequal arm size also limited the interpretation of statistical significance of comparisons. Third, our assumption of 2-year clinical non-progression as benign pathology might have underestimated the true incidence of malignancy in our group of patients. Lastly, the small number of adequate cytology specimens limited meaningful analysis of this investigation. As the sample taken for cytology is usually small, it will affect the sensitivity.

Conclusions

Clinical variables including age at presentation, duration and colour of discharge, presence of an associated breast mass, and abnormal sonographic findings were important in suggesting the underlying pathology of nipple discharge. Only blood-stained nipple discharge and an associated breast mass remained in the multiple logistic regression and were statistically significant. In patients with non–blood-stained nipple discharge, as well as a negative clinical breast examination and imaging, we may infer an underlying benign pathology. Further prospective studies with a larger sample size are advocated.

Declaration

All authors have disclosed no conflicts of interest.

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