Original Article

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Pathology Section

Papillary Lesions of Breast- A Retrospective Analysis of Cytomorphological Features with Histopathology Concordance

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ABSTRACT

Introduction: Papillary lesions of the breast include a spectrum of entities ranging from benign papilloma to malignant papillary carcinoma. The overlapping morphological features in benign and malignant lesions make their accurate sub categorisation difficult. Definitive surgical management decisions on papillary lesions of breast based on fine needle aspiration cytology report alone is a matter of concern.

Aim: To evaluate the cytomorphological features of papillary lesions of breast and its concordance with histopathology.

Materials and Methods: This retrospective study was conducted in Department of Pathology at Regional Cancer Centre, Thiruvananthapuram, Kerala, India (tertiary cancer centre) from January 2017 to June 2017. Total 28 cases diagnosed as papillary lesions/neoplasm on nipple discharge/fine needle aspiration cytology (FNAC) from January 2014 to December 2016 were reviewed and concordance with histopathology where ever available was analysed. Cytomorphological features that were analysed included cellularity, complex folded and branching epithelial sheets, stromal bare nuclei, cyst macrophages, single cells and atypia.

Results: Total 28 cases of papillary lesions diagnosed by cytology were identified with mean age of 51 years. Out of 28, 22 cases had histopathology concordance. Most common diagnosis in cytology was papillary neoplasm, accurate categorisation into benign or malignant could not be done in cytology in most of the cases. Most common diagnosis in histopathology was carcinoma, in-situ and invasive. Of total 22 cases,16 cases showed true papillae. Majority of the cytomorphological features assessed were statistically insignificant in differentiating benign and malignant lesions. Fifteen cases out of the total 22 cases turned out to be malignant in final histopathology. Out of the total 22 cases wherein histopathology correlation was available, cytology could give a conclusive diagnosis of malignancy in two cases and could give a suggestion of malignancy in seven cases. Out of these nine cases where cytology favoured malignancy, one case turned out to be benign in histopathology while the rest eight cases were malignant. In five cases cytology gave benign diagnosis, one of these turned out to be malignant in histopathology, rest four cases histopathological diagnosis was in concordance with cytology. In eight cases cytology gave an equivocal diagnosis of papillary neoplasm, where further categorisation into benign and malignant category was not possible. Out of these equivocal cases, six turned out to be malignant in histopathology and two were benign.

Conclusion: Cytomorphological features of papillary lesions of the breast are not unique and are inadequate for consistent categorisation into benign and malignant lesions. Excision biopsy with adequate sampling and immunostaining with myoepithelial markers and Oestrogen and Progesterone Receptors (ER and PR) are essential for accurate categorisation of papillary neoplasms of breast.

Keywords: Benign lesions, Malignant lesions, Papilloma, Papillary carcinoma breast

INTRODUCTION

Papillary lesions of the breast include benign as well as malignant entities ranging from papilloma to papillary carcinoma. A preoperative diagnosis in case of breast lumps help in planning definitive surgery. Fine Needle Aspiration Cytology (FNAC) is proven to be highly sensitive in categorising breast lumps into benign or malignant, however this is not true in case of papillary neoplasms [1]. A definite preoperative diagnosis of the benign or malignant nature of these lesions are difficult and is only rarely possible in cytology as there is considerable overlap between the various cytological features in benign and malignant conditions presenting as papillary lesions in breast. This may be because, unlike other carcinomas of the breast even in malignant papillary neoplasms the atypia can be subtle [2]. This study aims to associate cytomorphological and histopathological features of papillary neoplasms of breast diagnosed in the cancer centre so as to determine the limitations in cytology. This will help us to propose a practical approach for management of this group of neoplasms.

MATERIALS AND METHODS

A retrospective analysis of cases reported as papillary lesion/neoplasm on cytology over a period of three years from January 2014 to December 2016 was done in the Department of Pathology of a tertiary cancer centre in South India. Study period was January 2017 to June 2017.

Inclusion and Exclusion criteria: All cases of papillary neoplasms diagnosed on cytology smears in the Department of Pathology of the institute were included in the study. Cases where the slides could not be retrieved from the archival were excluded from the study.

After application of inclusion and exclusion criteria, there were 28 cases, however, histopathology concordance was available for only 22 cases.

Study Procedure

Cytomorphological features of individual cases of papillary lesions diagnosed on cytology smears were analysed by the authors in an attempt to characterise features which may help to further sub categorise these lesions as benign or malignant. The Pap-stained smears were reviewed for cellularity, complex folded and branching epithelial sheets, stromal bare nuclei, cyst macrophages, single cells and cellular atypia. Attempt was made to quantify two of the features namely cellularity and atypia. Thus, smears were categorised into those with low, medium and high cellularity and those with mild, moderate and severe atypia. Rest of the features were assessed as whether present or absent [Table/Fig-1]. The individual cases were associated with the corresponding histopathology where ever available.

Cytological features assessed	Scoring	
Cellularity	Low	+
	Medium	++
	High	+++
Complex folded and branching epithelial sheets	Present	+
	Absent	-
Stromal bare nuclei	Present	+
	Absent	-
Cyst macrophages	Present	+
	Absent	-
Single cells	Present	+
	Absent	-
Atypia	Mild	+
	Moderate	++
	Severe	+++

[Table/Fig-1]: Cytological features assessed.

STATISTICAL ANALYSIS

Statistical Package for the Social Sciences (SPSS) version 11.0 was used. The association between categorical variables were assessed using Fisher's-exact test. The p-value <0.05 was considered significant.

RESULTS

During the three year period from January 2014 to December 2016, of more than 4000 breast cases studied in cytology division, 28 cases diagnosed as papillary lesions/neoplasm on cytology were retrieved. Patients were all females and age ranged from 31 to 78 years, with a mean age of 51 years. The maximum number of patients were in the fourth decade. Histopathology concordance was available in 22 cases. [Table/Fig-2] In six cases histopathology concordance was not available [Table/Fig-3].

Of the 22 cases, where in histopathology concordance was available, a conclusive diagnosis of malignancy was offered in cytology in only two out of 22 cases, both turned out to be malignant in histopathology also. Seven cases, cytology favoured malignancy, six cases turned out to be malignant in histopathology, where as one case was benign, a case of atypical papilloma. In the eight cases which were equivocal in cytology, final histopathology malignant in five and three cases in begin. Of the total 22 cases wherein histopathology concordance was available, the initial cytology diagnosis favoured benign neoplasm in five cases. Of these five cases, four cases turned out to be benign in histopathology. However, one case turned out to be malignant, duct carcinoma in-situ. Thus, cytology had sensitivity of 89%, specificity of 80%, positive predictive value of 89% and negative predictive value of 80% [Table/Fig-4].

Most of the cytomorphological features assessed were not statistically significant in differentiating benign and malignant lesions. Presence of single cells was the only feature wherein statistical significance could be demonstrated (p-value=0.022). Of the 22 cases, six cases showed single cells in smears, five malignant cases and one benign case. Cyst macrophages though considered as a feature to be seen in benign conditions was seen in ten cases of malignancy also (p-value=0.72). Of the 22 cases, stromal bare nuclei, a feature usually seen in benign breast lesions were seen in six cases, three benign and three malignant cases (p-value=0.135). Atypia is a feature commonly associated with malignancy, however only six malignant cases showed severe atypia. Severe cellular atypia was observed in two benign cases also (p-value=0.169). Smears were highly cellular in ten cases of malignancy. Three benign cases also showed high cellularity (p-value=0.685). Complex folded branching papillary structures was present in the smear of thirteen out of 22 cases; eight malignant cases and five benign cases (p-value=0.140). Pseudo papillary structures in fibroadenoma/phyllodes and invasive duct carcinoma Not Otherwise Specified (NOS) led to false diagnosis of papillary neoplasm in cytology [Table/Fig-5].

Age	Cytology diagnosis	Cellularity	Complex folded and branching epithelial sheets	Stromal bare nuclei	Cyst macrophages	Single cells	Atypia	Histopathology
40	Papillary neoplasm	+++	+	-	+	+	+++	IDC
46	Papillary lesion, benign	+++	+	-	+	-	+++	ADH
57	Papillary lesion, benign	++	+	+	-	-	+++	Phyllodes
34	Papillary lesion, benign	+++	+	-	+	-	+	Atypical papilloma
44	Papillary neoplasm? carcinoma	+++	-	-	-	-	+++	Papillary carcinoma
53	Papillary lesion, benign	++	+	-	-	-	+	DCIS, Atypical papilloma
66	Papillary neoplasm	+++	-	-	-	+	+	Atypical papilloma
49	Papillary neoplasm	+++	+	-	+	+	+	Papillary DCIS
43	Papillary neoplasm	+++	+	-	+	+	+	IDC, Atypical papilloma
46	Papillary neoplasm	+++	+	-	+	+	+	IDC, DCIS, Papilloma
55	Papillary neoplasm? Carcinoma	+++	-	-	+	-	+++	IDC
42	Papillary neoplasm	++	-	-	-	-	+	Atypical papilloma
41	Papillary neoplasm with atypia? malignant	++	+	+	-	-	+	Atypical papilloma, DCIS, ADH
43	Papillary carcinoma	+++	-	-	-	-	+++	Papillary carcinoma
49	Complex papillary lesion, benign	+	+	+	-	-	+	Papilloma
43	Papillary neoplasm? carcinoma	++	+	-	-	-	+++	IDC
48	Papillary neoplasm with moderate atypia? malignant	++	+	+	+	-	++	Intraductal papilloma with atypia
65	Papillary neoplasm? carcinoma	+++	+	+	+	-	+++	IDC
75	Papillary neoplasm	+++	-	-	+	-	+	Intracystic papillary carcinoma, Papillomatosis
54	Papillary neoplasm	+	-	-	+	-	-	Papillary DCIS Intraductal papilloma
62	Papillary neoplasm with atypia, malignant	++	-	+	+	-	-	Papillary DCIS
62	Papillary neoplasm? carcinoma	+++	-	-	+	+	+	IDC with papillary pattern

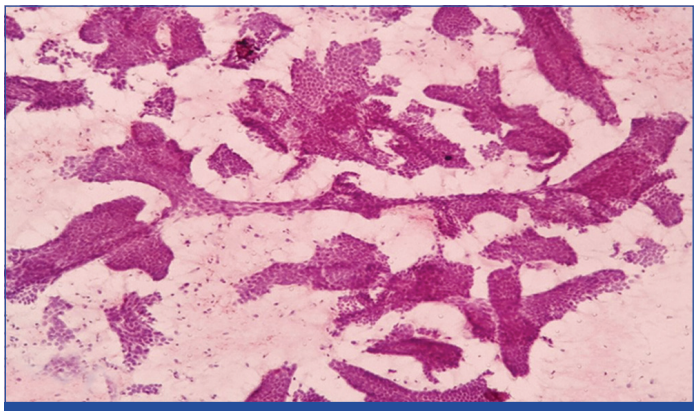
[Table/Fig-2]: Association of cytomorphological features and histopathology features.
IDC: Infiltrating duct carcinoma; DCIS: Duct carcinoma in-situ; ADH: Atypical intraductal hyperplasia

Age	Cytology diagnosis	Cellularity	Complex folded and branching epithelial sheets	Stromal bare nuclei	Cyst macrophages	Single cells	Atypia
78	Papillary neoplasm	+++	-	+	+	-	++
58	Papillary neoplasm	+	-	-	-	-	+
55	Papillary neoplasm	++	-	-	-	-	-
45	Papillary neoplasm	++	-	+	+	-	+
40	Papillary neoplasm	++	-	-	-	-	++
31	Papillary neoplasm	+	+	-	+	-	-

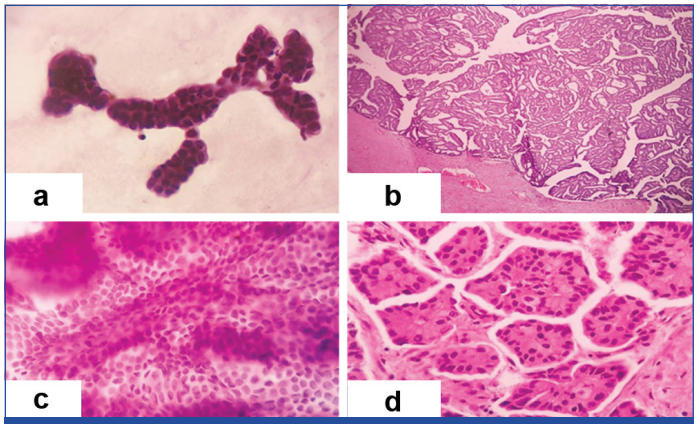
[Table/Fig-3]: Cytological details of six cases where histopathology concordance was not available.

Cytology results	Diagnosis in histopathology	
	Positive	Negative
Positive for malignancy	8 (true positive)	1 (false positive)
Negative for malignancy	1 (false negative)	4 (true negative)
Equivocal (n=8)	6	2
Total	15	7

[Table/Fig-4]: Cytomorphological and histopathology concordance in case of malignancy (In cytology two cases were diagnosed as malignant and seven cases given as suspicious for malignancy; total five cases were diagnosed as benign in cytology). For calculating the sensitivity equivocal cases were excluded



[Table/Fig-5]: Pseudopapillary structures from case of phyllodes tumour (PAP, 100X).



[Table/Fig-6]: a) Papillary structures without atypia from a case of duct papilloma (PAP, 200X); b) Section from a case of intraductal papilloma showing intra ductal proliferation of cells without atypia (H&E, 100X); c) Smear showing papillaroid cluster of cells from a case of papillary carcinoma with minimal atypia (PAP, 200X); d) Section showing papillary carcinoma with micropapillary architecture (H&E, 200X).

DISCUSSION

Papillary lesions of breast include a spectrum of benign and malignant entities. Clinically these lesions usually present with nipple discharge which can be blood stained. They can also present as a palpable mass. These lesions may also get detected incidentally on screening mammograms as retro areolar masses. Radiology cannot accurately differentiate malignant and benign papillary tumours [3].

Cytological categorisation of papillary lesions into benign and malignant is challenging due to diverse cytomorphology like epithelial hyperplasia, atypia, low grade malignancy and neuroendocrine differentiation. The classical features of malignancy like necrosis and absence of myoepithelial cells can also be lacking in malignant papillary neoplasms [4]. There is also overlapping cytomorphological features in smears of papillary lesions and other entities with papillary component [5]. Cytology smears from papillary lesions are characterised by complex branching epithelial sheets, fibro vascular stroma, true papillary fragments with stromal cores, cyst macrophages, single cells, bare nuclei [Table/Fig-6a-d]. Complex branching epithelial sheets are more common than true papillae. These features however are not specific to any particular lesion and can be seen in any papillary lesion, both benign and malignant as well as in some non-papillary lesions like fibroadenoma, phyllodes, atypical intraductal epithelial hyperplasia, infiltrating duct carcinoma, NOS type [6]. In this study also cyst macrophages are observed in both benign and malignant papillary neoplasms, as well as in non papillary lesions like atypical intraductal hyperplasia. Complex branching epithelial sheets in benign, malignant papillary neoplasms and in phyllodes tumour are observed.

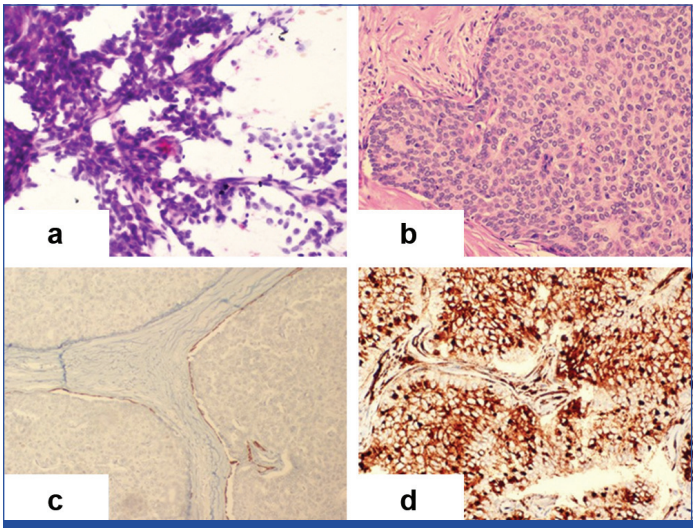
Cellularity and atypia are the usual cytological features of malignancy. However, these features are not that helpful in case of papillary lesions as even benign papilloma can show high cellularity and some degree of atypia and malignant lesions may not always show high degree of atypia [7]. In the present study, atypia was not found to be a reliable feature in categorically differentiating benign and malignant papillary neoplasms. The present study had two benign cases showing high degree of atypia. High cellularity was a feature that was observed more in malignant cases, tencases. However, three benign cases also showed high cellularity. Cyst macrophages, apocrine cells though usually associated with benign conditions can be seen in papillary carcinomas. This is because papillary neoplasm whether benign or malignant can be associated with a cystic component. Dispersal of cells in benign conditions and atypia associated with papilloma with infarction can also mimic malignancy [8,9].

Absence of myoepithelial cells is a criterion commonly used to diagnose malignancy in breast cytology. These cells are usually seen as bare nuclei. However, in the present study, stromal bare nuclei was present in both benign and malignant cases, also in some of our benign cases we could not demonstrate the stromal bare nuclei. Other studies in the literature are of the opinion that more the myoepithelial cells in a smear more the chance of the lesion being benign papillary lesion [9,10]. Some studies in the literature have found features like decreased numbers of bare bipolar nuclei, discohesion and a non cystic background to favour atypical/malignant papillary lesions [11]. However, these features are not unequivocal in the diagnosis of malignancy. In breast cytology presence of single cells, due to loss of cohesion of cells is considered to be a feature of malignancy [12]. In this present study, presence of single cells was found to be a feature associated with malignancy (p-value=0.022).

Malignant entities like invasive papillary carcinoma, encysted papillary carcinoma, intraductal papillary carcinoma (papillary duct carcinoma in-situ), solid papillary carcinoma requires adequate sampling along with immunostains to demonstrate loss/preservation of myoepithelial cells at the periphery of the lesion or with in lesions.This is not possible in cytology and even in needle biopsies and require excision of the entire lesion with adequate sampling and study with immunostains to demonstrate retained or absent myoepithelial cells. Some studies in

the literature have commented that papillary neoplasms are difficult to categorise even in histopathology and require immunohistochemistry with myoepithelial markers like p63, CK5/6, SMA, CK14 for demonstration of preserved or absent myoepithelial cells for an unequivocal diagnosis regarding benign/malignant nature of the lesion [13,14].

In papillary duct carcinoma in-situ, myoepithelial cells are absent or scant in papillae and present in attenuated form at the periphery of ducts. In encapsulated papillary carcinoma myoepithelial cells are usually absent throughout the lesion and at the periphery. In solid papillary carcinoma myoepithelial cells are absent within the solid papillary proliferation, may be present or absent at the outer contours of the nodules. Solid papillary carcinoma also shows neuroendocrine differentiation and are positive with synaptophysin and chromogranin [15] [Table/Fig-7a-d]. A diffuse strong positivity with oestrogen and progesterone receptor also favours malignancy [16].



[Table/Fig-7]: a: Smear showing papillaroid cluster of cells from a case of solid papillary carcinoma (PAPx200); b: Section from solid papillary carcinoma showing solid nest of cell with irregular margin (H&Ex200); c: p63 immunostain showing intralesional absence of myoepithelial cells, with preserved myoepithelial cells at the periphery of some of the nests and absence at periphery of some nests (IHCx100); d: Chromogranin positivity in a case of solid papillary carcinoma (IHCx200).

Limitation(s)

This study is limited by the small sample size.This limitation is to be expected as papillary lesions of the breast are relatively rare. Only 28 were papillary neoplasms in this series. Of the total 28 cases, histopathology follow-up was available for only 22 cases. Six cases where follow-up was not available were for equivocal cases wherein cytology could not categorise lesions into benign or malignant. Limited sampling of papillary neoplasms by aspiration, core needle biopsy or frozen section will negatively influence accurate categorisation [17].

CONCLUSION(S)

Papillary neoplasms should be taken up for excision biopsy and based on histopathology report further radical procedures, if needed should be planned. Cytological features like cellularity and atypia usually seen in malignancy in breast cytology may not hold good in the case of papillary neoplasms of breast. When a diagnosis of papillary neoplasm is made in cytology it is advisable to completely excise the lesion and give a final diagnosis after adequate sampling and judicious use of immunohistochemistry.

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