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Original Article

Pathology Section

Gray Zone Papillary Breast Lesions as a Diagnostic Dilemma: An Institutional Experience

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ABSTRACT

Introduction: Papillary lesions of breast presents as both diagnostic and therapeutic challenge in clinical practice. Papillary lesions arise within the ducto-lobular system and are classified into benign, borderline and malignant. Benign and malignant papillary lesions comprise less than 10% and 1% of all breast lesions cases respectively. Many papillary lesions share overlapping morphologic features and pose diagnostic dilemma. The rarity of the lesions and limited data available in the literature has prompted us to take up this study.

Aim: To categorise gray zone papillary lesions of the breast with the help of immunohistochemical markers.

Materials and Methods: Nineteen papillary lesions of breast were reviewed in the Department of Pathology in a tertiary health care hospital, Bengaluru, Karnataka, India from January 2016 to June 2019. Immunohistochemistry with the help of available myoepithelial markers was done in all challenging cases. Results were analysed by consensus opinion by two senior pathologists.

Results: Pathological diagnosis for 19 cases of papillary lesions included 12 Intraductal papilloma, three cases of Atypical papilloma, two cases of Encapsulated papillary carcinoma and one case each of Papillary Ductal Carcinoma In Situ (DCIS) and Invasive Papillary Carcinoma (IPC). Immunoprofile for both luminal and myoepithelial cells was employed in difficult cases.

Conclusion: A thorough knowledge of the clinical presentation with sonomammographic findings, histopathology and judicious use of immunoprofile will help the pathologist and clinician for the optimal management of these gray zone papillary breast lesions.

Keywords: Atypical papilloma, Encapsulated papillary carcinoma, Intraductal papilloma, Invasive papillary carcinoma

INTRODUCTION

Breast lumps are one of the commonly excised specimens in the surgical department. The 2012 WHO blue book classifies papillary lesions of the breast into Intraductal Papilloma and its variants-intraductal papilloma with atypical hyperplasia, intraductal papilloma with DCIS, intraductal papilloma with lobular carcinoma insitu. The rest include intraductal papillary carcinoma (papillary ductal carcinoma in situ), encapsulated papillary carcinoma, solid papillary carcinoma and IPC [1].

Many of these lesions co-exist and categorising papillary lesions is confounded by variable terminologies and lack of definitive criteria for a given entity. Immunohistochemistry is a valuable adjunct in highlighting the myoepithelial cells which are not apparent morphologically [2]. The most commonly used immunomarkers in diagnosis of papillary lesions are those of myoepithelial cells, basement membrane, basal cytokeratins (CK5/6), oestrogen receptor for clonality and neuroendocrine differentiation. P63 is a very good marker with highest sensitivity and specificity. Both SMA and CD10 are less sensitive markers than p63 and are known to cross react with myofibroblasts and vascular endothelium [3]. These myoepithelial cell markers are routinely used in categorising the papillary lesions [4,5].

This study outlines the spectrum of papillary lesions with key morphological features and Immunohistochemical (IHC) markers which were a valuable tool for the complete diagnosis.

The scarcity of data and improved outcome for papillary carcinoma has prompted us to take up this study in our set up [6]. Herein authors present a clinicopathological experience and review practical approach to diagnostically challenging cases of 19 papillary lesions of the breast over a 3.5 year period.

MATERIALS AND METHODS

This was a retrospective, descriptive study conducted from January 2016 to June 2019 in the Department of Pathology of a tertiary health care hospital, Bengaluru , Karnataka, India. Out of 300 breast lumps excised, 19 papillary lesions of the breast were retrieved from the histopathology consultation files for the above study period of 3.5 years.

Cases coded as intraductal papilloma, intraductal papilloma with atypia, papilloma with DCIS, papillary DCIS and all the malignant papillary carcinoma were included. Clinical data, radiological findings were noted from case files. Lesions not fulfilling the criteria of papillary lesions and core biopsy samples are excluded from the study. Institutional ethical clearance was obtained (IEC/010/2018-19) for this study.

The paraffin embedded hematoxylin and eosin stained, histopathology slides were reviewed and histomorphological findings were noted. A minimum of 2 hotspots were selected from screened histopathology slides. IHC work up using the markers p63, CD10, SMA, CK5/6 along with ER, PR, HER2 and ki67 were employed in all doubtful cases. Antigen retrieval was done in citrate buffer using pressure cooker. Antibodies from BioGenex with the following catalog number AM418-5M, AM451-5M, AM128-5M, AN892-5M, AN710-5M, AN711-5M, AN726-5M and AM297-5M were respectively used for the above antigenic markers of interest. Qualitative estimation for the presence or absence of myoepithelial cells from IHC markers were reviewed by trained pathologist and interpreted. Allred score system for immunohistochemical evaluation of hormonal status ER and PR with score ≤2 is negative and with >2 score was considered positive. HER2 status was interpreted using ASCO 2013 guidelines.

STATISTICAL ANALYSIS

A descriptive statistical analysis was employed using Microsoft excel worksheet. All the data were expressed in percentages (%).

RESULTS

A total of 19 (6.3%) papillary lesions of the breast were encountered during the study period [Table/Fig-1]. The mean age of the patient was 53 years. Twelve cases occurred in the right breast and 7 cases were seen on the left breast. The clinical and radiological presentations of these papillary lesions are detailed in [Table/Fig-2]. Clinical suspicion of malignancy was encountered in only one case.

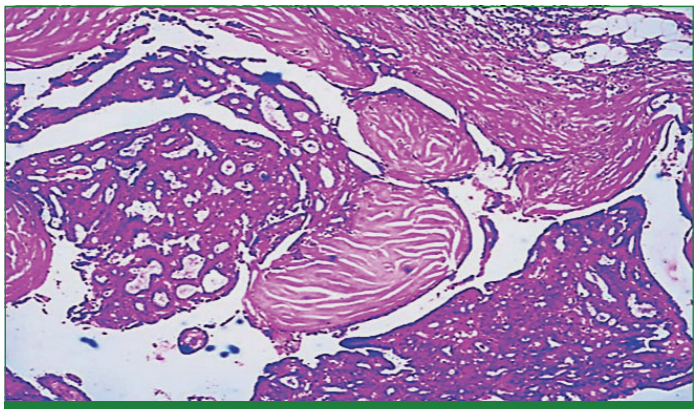
	Number	Percentage
Intraductal papilloma	7	36.87%
Intraductal papilloma with florid ductal hyperplasia	5	26.31%
Intraductal papilloma with atypical ductal hyperplasia	1	5.26%
Intraductal papilloma with DCIS	2	10.52%
Papillary DCIS	1	5.26%
Encapsulated papillary carcinoma	2	10.52%
Invasive Papillary carcinoma	1	5.26%

[Table/Fig-1]: Distribution of Papillary lesions.

Ultrasonographic features	Percentage of cases
Microcalcifications	34.5%
Lesions other than microcalcifications (LOTM)	65.5%
Symptoms	
Nipple discharge only	31.57%
Subareolar lump only	42.13%
Both discharge and subareolar lump	26.3%

[Table/Fig-2]: Clinico-radiological features of papillary lesions.

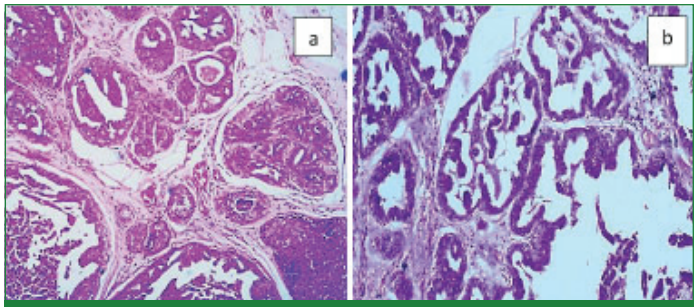
Intraductal papilloma was the commonest lesion accounting for 36.87% (7) cases. Age group ranged from 38-53 years. Morphologically papillomas were characterised by papillae lined by epithelial cells in a broad sclerotic core [Table/Fig-3]. Five cases were associated with usual ductal hyperplasia (26.31%), 2 cases of which were associated with DCIS (10.52%) [Table/Fig-4a].



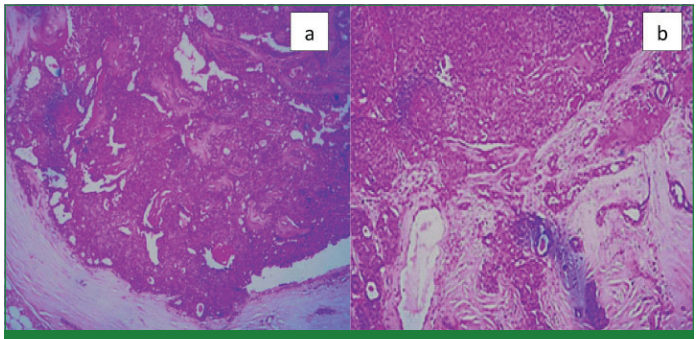
[Table/Fig-3]: Microphotograph of Intraductal papilloma with broad sclerotic band associated with florid ductal hyperplasia (H&E,10X).

An isolated case of solitary intraductal papilloma with atypical ductal hyperplasia (5.26%) was seen in a 45-year-old female that showed focal proliferation of a mildly atypical uniform cell population. One case of papillary DCIS (5.26%) was encountered in a 47-year-old female with a lump in the breast showing papillary fronds covered by neoplastic cells with low grade nuclei [Table/Fig-4b].

Two cases of encapsulated papillary carcinoma presented with a grey white solid cystic mass in a 45-year-old and 63-year-old female respectively. High degree of architectural complexity with foci of invasion was seen in one of the case studied [Table/Fig-5].

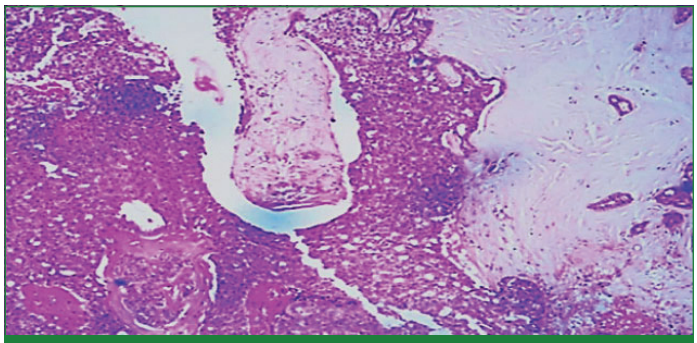


[Table/Fig-4]: Microphotographs of a) Intraductal papilloma with focal areas of DCIS and b) Papillary DCIS. (H&E,10X).



[Table/Fig-5]: Encapsulated papillary carcinoma with monotonous proliferation of neoplastic cells and absence of myoepithelial cells in the periphery (a) with foci of invasion (b) (H&E,10X).

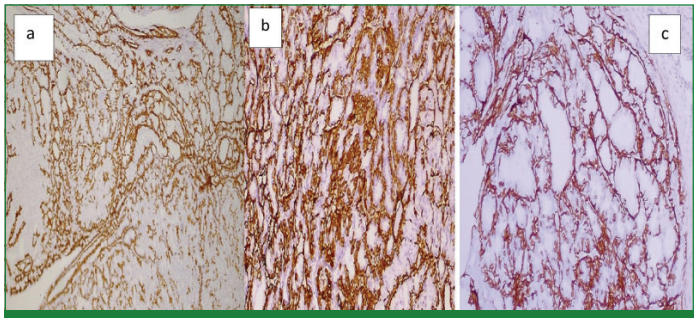
A case of IPC was seen in a 62-year-old female that showed invasive front of tumour cells in a dense sclerotic stroma along with papillomatosis [Table/Fig-6].



[Table/Fig-6]: Microphotograph of Invasive papillary carcinoma (H&E,10X).

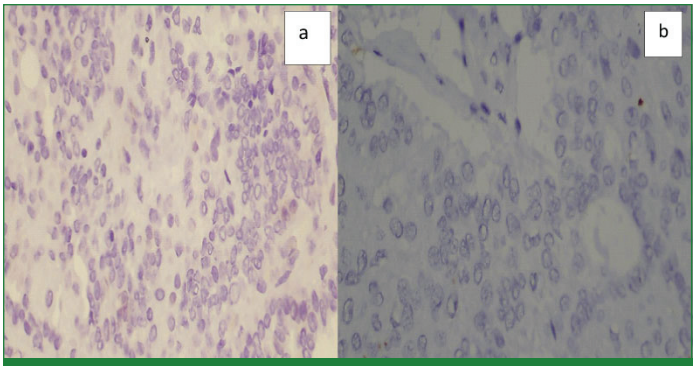
Size of the lump varied from the smallest 4×3×2 cm to largest lump of 9×6×1cm dimension. Bilateral lump was seen in a case, in which contralateral breast showed features of fibrocystic disease with Usual Ductal Hyperplasia (UDH) and foci of adenomyoepithelioma.

All the myoepithelial markers (p63, SMA and CD10) were positive in intraductal papilloma with florid ductal hyperplasia [Table/Fig-7] and negative in ADH areas of atypical papillomas. p63 is a nuclear localiser, easy to interpret with best results. SMA localises in the cytoplasm and CD10 has a membrane staining pattern.



[Table/Fig-7]: Microphotograph shows p63 (a), SMA (b) and CD10 (c) positivity in Intraductal Papilloma (IHC-10X).

CD10 and CK5/6 were totally negative in encapsulated papillary carcinoma [Table/Fig-8] and IPC. Proliferative ki67 index was high in IPC.



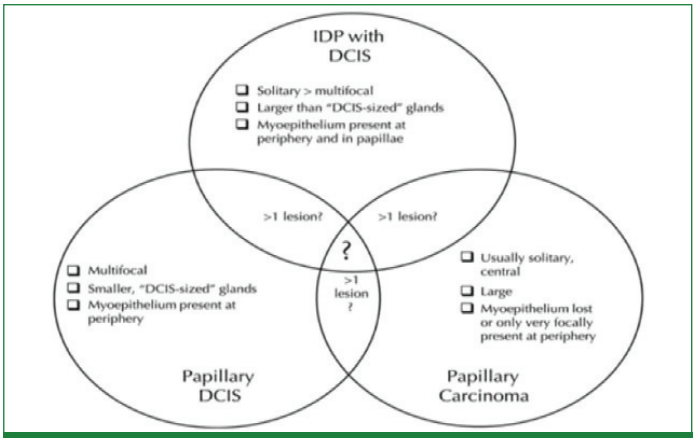
[Table/Fig-8]: Microphotograph shows a) CD10 and b) CK5/6 negativity in Encapsulated papillary carcinoma (IHC-10X).

DISCUSSION

Papillary lesions of the breast constitute around 10% of all benign breast lesions and less than 1% of all malignancies of the breast [3]. Morpholologic evaluation of papillary lesions of breast is characterised by the identification of papillary architecture lined by proliferative epithelial cells. Loss of myoepithelial cells within the fibrovascular papillae is an important feature to diagnose malignant papillary proliferations and separate it from benign intraductal papillomas [3]. The precise diagnosis of these papillary lesions continues to be a challenge in day to day practice. These papillary lesions demonstrate spectrum of biologic behaviour. Prognosis based reclassification of papillary breast lesions is pivotal in evaluating the gray zone papillary lesions. Collins and Schnitt modified the base of WHO classification (2012) by separating papillary lesions into benign and malignant and encapsulated from solid papillary carcinomas of the breast [7]. In this study, the diagnostic issues of gray zone papillary lesions are discussed and categorised based on the WHO Classification system with the help of immunohistochemistry.

Diagnostic evaluation was carried out by cytological examination of the nipple discharge or fine needle aspiration or core biopsy if a mass lesion was identified [8]. Further classification can be challenging for the practising pathologists even more when a limited sample of core biopsy is available for the study.

Role of IHC in core biopsy samples is of great value in evaluating the benign and malignant process [4]. There are two fold role of assessing myoepithelial cells in papillary lesions of breast. First is to identify myoepithelial cells within the papillary frond which is helpful in differentiation of papillary DCIS and papilloma. Secondly to identify the presence or absence of myoepithelial cells around the papillary lesion for confirmation of encapsulated papillary carcinoma. Pictorical representation in differentiating intraductal papilloma with DCIS, Papillary DCIS and papillary carcinoma is depicted in [Table/Fig-9] as described by Jorns JM [9]. The role of myoepithelial cells and IHC in the diagnosis of breast papillary lesions is described in [Table/Fig-10] [10,11].



[Table/Fig-9]: Representation of key morphological and immunohistochemical features in differentiating Intraductal papilloma with Ductal carcinoma insitu, Papillary DCIS and Papillary carcinoma.

Histomorphology is a primary guide in evaluating the papillary lesions of the breast. Myoepithelial cells which are difficult to discern on haematoxylin and eosin stained slides are visualised with the help of immunomarkers for myoepithelial cells. Individual myoepithelial markers vary in their sensitivity and specificity and exhibit different degrees of cross reactivity with other native cells like pericytes, stromal myofibroblasts, and vascular smooth muscle cells to elicit false positive reactions. Thus combination of atleast 2 or more myoepithelial markers are employed in distinguishing papillary lesions in most of the laboratories. In addition, CK5/6 and CK14 basal markers are particularly useful in identifying a neoplastic process within a papillary lesion. Heterogenous / mosaic expression of basal CKs is characteristic of benign lesions and negative in papillary carcinomas [2,12].

Intraductal papillomas are the commonest type of papillary lesions and presents as solitary retro-areolar mass of benign appearance on mammography. Diagnosis of these lesions are always straight forward and pose difficulty when accompanied by florid epithelial hyperplasia or atypical ductal hyperplasia as these may obscure the true papillary nature of the lesion. Stromal changes with diffuse sclerosis mimic that of invasion. Secondary changes like haemorrhage or infarction are due to needling procedures or torsion of fibrovascular core. We encountered various epithelial and stromal changes like adenosis, epitheliosis, fibrocystic disease, fibrosis and sclerosis and haemorrrhagic infarction. Similar changes were seen in the study by Rakha EA et al., Wei S et al., Basavaiah SH et al., [12-14]. A case of morphologically diagnosed encapsulated papillary carcinoma with entrapped cells and lacking myoepithelial cells at epithelial stromal interface was proven by IHC as intraductal papilloma with extensive florid ductal hyperplasia. Histopathologically, many of these lesions are alarming on low magnification. Careful attention for recognising

	p63 stain in papillary fronds	p63 in periphery of lesion	CK5/6, CK14	ER & PR
Intraductal papilloma	Positive	Positive	Positive -ME Cells -UDH (heterogenous positivity)	Positive (patchy) -Luminal cells -UDH (heterogenous positivity)
Papilloma with ADH or DCIS	Positive in papilloma. Scant in ADH/DCIS component.	Positive	Positive -ME Cells -UDH (heterogenous positivity) Negative -ADH/DCIS	Positive (patchy) -Luminal cells -UDH (heterogenous positivity) Positive strong and diffuse in ADH/ DCIS.
Papillary DCIS	Negative	Positive	Negative in neoplastic cell population.	Positive strong and diffuse in neoplastic cell population.
Encapsulated papillary carcinoma	Negative	Usually negative	Negative in neoplastic cell population	Positive strong and diffuse in neoplastic cell population
Solid papillary carcinoma	Negative	Negative/positive	Negative	Positive strong and diffuse in neoplastic cell population.
Invasive papillary carcinoma	Negative	Negative	Negative	Negative

[Table/Fig-10]: Immunohistochemical features of papillary lesions of the breast.

the hyperplastic changes and variability in the lining epithelium will guide for the accurate diagnosis of papilloma with florid hyperplasia. Streaming of cells in UDH should be differentiated from spindling of cells in solid papillary carcinoma. Bland apocrine metaplasia favours benignity [12]. In ambivalent situations, IHC for myoepithelial cell markers resolves the complex nature of the benign papillary lesion.

Diagnosis of atypical papillomas needs expertise. It is defined as presence of focal proliferation of atypical epithelial cells with low nuclear grade within the papilloma. Page and colleagues proposed an extent criterion of 3 mm in size and the proportion of the lesion (<33%) to differentiate atypical hyperplasia from DCIS. However diagnosis is made by architectural and cytological features of atypical proliferation without a quantity requirement. Papilloma with florid hyperplasia has patchy ER positivity with high expression of CK5 (>20%) on IHC. In contrast, reverse is true for papilloma with atypical ductal hyperplasia [2,12,15,16]. Present study showed 2 cases of DCIS along with papilloma with solid, papillary and trabeculated variants and a case of papilloma with atypical ductal hyperplasia similar to the study reported by Basavaish SH et al., [14].

Papillary DCIS lesions are frequently multifocal, peripheral in location and exist with other variants of DCIS. Thin and delicate papillae with scant or absent myopithelial cells within the papillae and retention of myoepithelial cells at periphery of involved ducts differentiates from other DCIS lesion [10,13]. IHC for myoepithelial cells and basal markers will help in categorising the lesion.

Absence of myoepithelial cells at the periphery of the nodule is the hallmark feature of Encapsulsated Papillary Carcinoma (EPC) which helps in distinguishing from other benign papillary lesions. The absence of myoepithelial cells in the periphery of the lesion is interpreted as an insitu lesion or a minimally invasive carcinoma with expansile growth [3,7,15]. Currently, WHO working group categorises EPC entity as Tis disease (in situ) in the absence of conventional invasive carcinoma [7,17,18]. Entrapment of epithelial cells in the fibrous capsule and their displacement into a previous biopsy tract is always a challenge to classify as an insitu lesion or an early invasion. The size of the invasive component from the fibrous wall is measured rather than incorporating the entire encapsulated papilloma [2,15,18]. Moderate to intense staining pattern to collagen type IV at the periphery have been reported in EPC. The neoplastic cells are also positive for ER, PR and negative for CK5/6 and CK14 [11,13,18].

Solid Papillary Carcinoma (SPC) are characterised by multiple, solid circumscribed expansile nodules of monomorphic oval to spindle shaped epithelial cells embedded in a dense fibrous stroma. The neoplastic cells exhibit neuroendocrine and mucinous diffferentiation. Nuclear palisading is diffuse and obvious when compared to EPC. The majority of SPC lack peripheral myoepithelial cells. They are negative for CK5/6 and are diffusely positive for ER, synaptophysin and chromogranin. SPC are more frequently associated with co-existing invasive carcinoma of mixed mucinous, neuroendocrine-like or invasive ductal No Special Type [6,9,12,13,17,18].

IPC is an extremely rare invasive carcinoma exhibiting an exclusively papillary morphology in >90% of the invasive tumour. Invasion beyond the fibrotic capsule must be present to diagnose definitive invasion. Myoepithelial stains are absent in both papillary carcinoma and invasive carcinoma component and are not beneficial to differentiate these lesions. IPC must be differentiated from invasive micropapillary carcinoma (without fibrovascular core), as latter is considered aggressive and associated with lymphovascular invasion and axillary lymph node metastases [2,6,9,12,13]. Selective use of myoepithelial cell markers to mark the absence of myoepithelial cell staining at the periphery of large expanded duct to categorise an invasive carcinoma should always be done in the background of routine morphological evaluation of hematoxylin and eosin stained slides.

LIMITATION AND FUTURE RECOMMENDATIONS

Literature study has shown different terminology and similar sounding nomenclature in the classification for papillary lesions of the breast thereby causing confusion among pathologist and clinician. However, the recent WHO classification of papillary lesions of the breast in 2012 is able to connect the terminology and classification to incorporate clinical and biological behaviour, the lack of precision in differentiating papilloma with atypical ductal hyperplasia and papilloma with DCIS still exists.

IPC is a controversial entity as many of the studies include the incidence, clinical features, outcome of papillary carcinoma to include heterogenous papillary lesions, ranging from intraductal papilloma to insitu and invasive papillary tumours. Invasive carcinomas arising from insitu papillary carcinomas often lack papillary architecture. Stringent follow-up of all benign lesions with mammogram and malignant lesions to higher oncocentre and further studies in these excision specimens throw much insight into various prognostic factors.

CONCLUSION

Papillary lesions of the breast are a diverse group of tumours sharing many morphologic similarities. Many overlapping morphological and clinicoradiological findings are common. A conglomerate of morphological evaluation along with judicious use of immunohistochemistry for luminal and myoepithelial markers helps in diagnosing challenging cases of papillary lesions. Diverse biological behaviour has mandated to study and further reclassify the disease process.

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