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Original Research Article

Papillary Lesions of Breast: An Experience in a Tertiary Care Centre

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Abstract

Introduction: Papillary lesions are a group of lesions characterized by presence of papillae supported by fibrovascular cores lined by epithelial cells with or without myoepithelial cells. This group of lesions span spectrum of hyperplastic to neoplastic processes. Diagnosis of papillary lesions is challenging for pathologists. Distinction between various lesions as benign, atypical and malignant papillary lesions aid in patient management. *Materials and methods:* This is a five years study from January 2013 - December 2017. All the cases diagnosed as papillary lesions were considered for the study. Total of 21 cases were reviewed. All the patient details were archived from patient's records. Paraffin blocks were also archived and IHC for p63, CK5/6, ER, PR and Her2/Neu were performed. Histopathology slides were reviewed by pathologists who were blinded about the original diagnosis. *Aims:* This study was conducted to analyse the clinico-pathological and immunohistochemical characteristics of papillary lesions of the breast. *Results:* Age ranged from 29-61 years. Only 2 cases presented with bloody nipple discharge. Male – female ratio was 1:8.5. Majority of the specimen were lumpectomy, followed by modified radical mastectomy and biopsies. Diagnosis of papilloma was made in 6 cases, while remaining 13 cases were diagnosed as papillary carcinoma. Adjacent breast showed changes like inflammation, fibrocystic change, atypical ductal hyperplasia, carcinoma in situ and invasive carcinoma. IHC showed positivity for ER in 10 cases, PR in 9 cases and Her2/neu in 1 case. P63 showed continuous positivity in papillomas but negative in carcinomas. *Conclusion:* Papillary lesions of breast can range from hyperplastic to neoplastic lesions. Accurate diagnosis will aid in patient management. Immunohistochemistry will help in delineating the lesions.

Keywords: Papillary lesions; Papilloma; Papillary carcinoma; IHC.

Introduction

Papillary neoplasms are a group of lesions which are characterized by, presence of papillae, supported by fibrovascular cores, lined by epithelial cells with or without myoepithelial cell layer [1].

Whenever a papillary lesion is diagnosed in the breast, it is equally important to categorize it either as benign or malignant. The complete absence or under representation of a myoepithelial (ME) cell layer in the fibrovascular fronds of a papillary lesion indicates a carcinoma, [2] however the presence of ME cells does not invariably exclude the diagnosis of intraductal papillary carcinoma [1].

The papillary carcinoma is characterized by complete absence of myoepithelial cell layer lining the fibrovascular core, however intraductal papillary carcinoma can show presence of myoepithelial cells. Hence both presence and absence of myoepithelial cells is important in the diagnosis of papillary lesions. Immunohistochemistry for myoepithelial cells like p63, CK5/6, SMA, CK14 help in assessment of papillary lesions.

Treatment decision for carcinoma breast are highly dependent of expression of various IHC markers such as hormone receptors, proliferation markers. These IHC markers also help to classify breast carcinoma in to various molecular subtypes which behave differently and are distinct biologically.

Furthermore, depending on their location in the mammary duct system, papillary lesions may be solitary, centrally (subareolar) located or multifocal, and peripherally located within terminal duct-lobular units. These are associated with different risks for associated carcinoma or subsequent carcinoma [4].

Therefore, the immunohistochemistry for ME markers aid in the assessment of papillary lesions [4]. Immunohistochemical markers such as steroid hormone receptors, markers of tumour proliferation, and factors involved in angiogenesis and apoptosis are often used to guide treatment decisions, to classify breast cancer into subtypes that are biologically distinct and behave differently, and both as prognostic and predictive factors [6].

This study was undertaken to analyse spectrum of papillary lesions with different histopathological findings. Immunohistochemical analysis was also conducted for myoepithelial cells, and in analysis of hormonal and Her2neu status in all the papillary lesions.

Materials and methods

A cross sectional study of a total of 21 papillary lesions of breast was conducted from January 2013 to December 2017 (5 years) in the Department of Pathology of a tertiary health care hospital. Breast core biopsy, lumpectomy and modified radical mastectomy specimens which were diagnosed as papillary lesions on histopathology were considered for the study.

All the patient details were archived from patient's records.

Paraffin blocks were also archived and IHC for p63, CK5/6, ER, PR and Her2/Neu were performed using peroxidase-antiperoxidase method (Biogenex) using,

Primary antibody: Monoclonal mouse antihuman Cytokeratin 5/6 clone D5/16 B4, ER, PR, Her2/ Neu, Ki67.

Pressure cooker was used for target antigen retrieval.

Histopathology slides were reviewed by two pathologists who were blinded about the original diagnosis. They were asked to evaluate for the following features while reviewing the slides.

1. Presence of papillary pattern
2. Architectural complexity
3. Presence of fibrovascular core whether broad and sclerotic or thin and arborizing fibrovascular cores
4. Infiltrating or non-infiltrating
5. Associated benign changes in the adjacent breast tissue such as, inflammation (Mastitis), Fibrocystic changes, UDH (Usual Ductal Hyperplasia), ADH (Atypical Ductal Hyperplasia), DCIS (Ductal Carcinoma in-situ), Carcinoma.

Results

Out of 21 cases of papillary lesions of breast 19 were females and 2 were males. Age of the patients ranged from 25 years to 74 years. Mean age being 47 years.

Most of the patients presented with lump (57%). Lumpectomy (58%) were most commonly received surgical specimens. Out of 21 cases 7 were benign including papilloma and atypical papilloma, 14 were malignant papillary lesions whereas 2 cases had papilloma and papillary carcinoma adjacent to each other (Table 1).

A total of 09 papillomas identified. 05 were central while 04 were peripheral.

Adjacent breast tissue showed different lesions as shown in (Table 2).

Immunohistochemistry was done for ER, PR, Her2-neu, P63 and CK 5/6. The results are tabulated in table 3.

The morphology and immunohistochemistry of papilloma, papillary carcinoma and adjacent breast lesions like atypical ductal hyperplasia and Duct carcinoma in situ (DCIS) are shown in Figures 1,2,3,4 respectively.

Table 1: Distribution of various papillary lesions of breast

Diagnosis	Number	Percentage
Papilloma	4	19
Atypical papilloma	3	14
Papillary carcinoma	7	24
		09
Invasive papillary carcinoma	5	24
Papilloma with papillary carcinoma	2	05
		05
Total	21	100

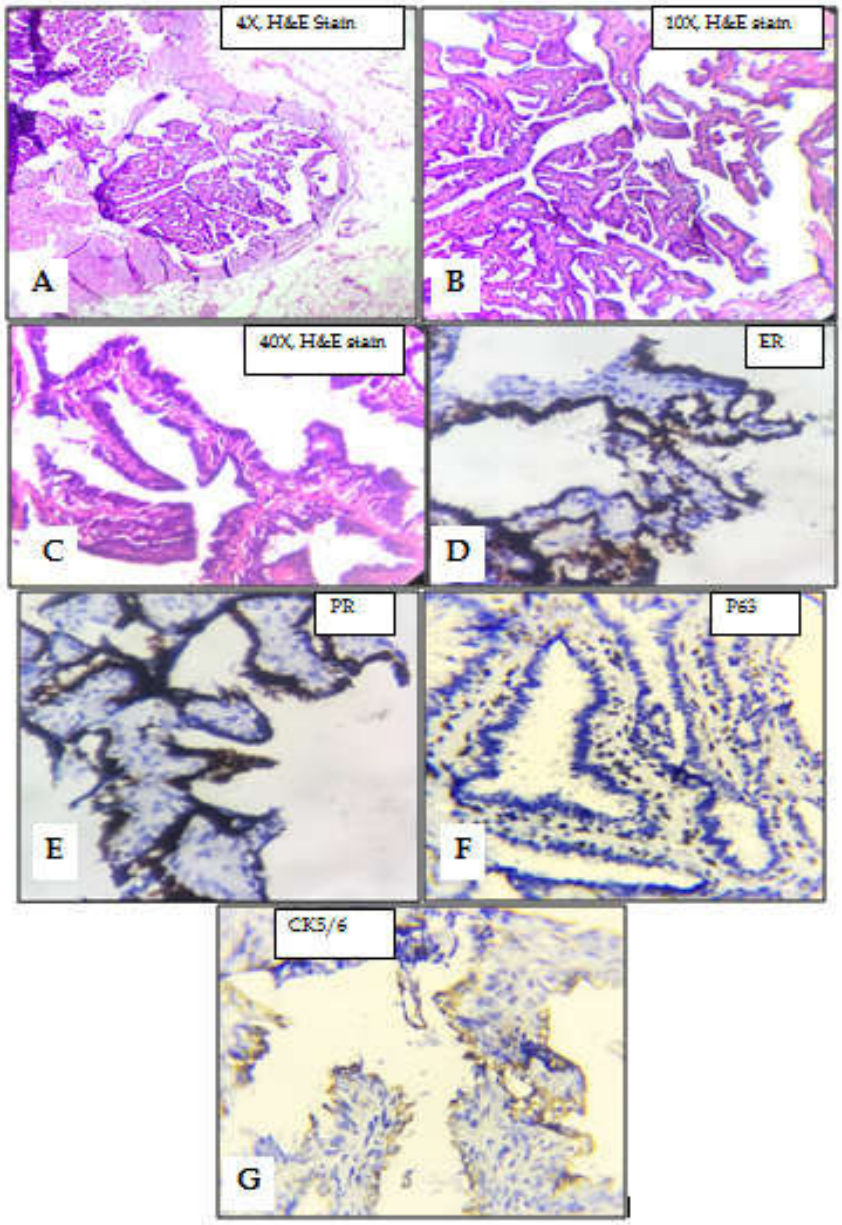

Fig 1 (A-G): Papilloma on hematoxylin and eosin stain (A,B,C) and immunonohistochemistry of papilloma- ER (D), PR (E), P63 (F) and CK5/6 (G).

Table 2: Distribution of various lesions in adjacent breast tissue

Parameter	Number	Percentage
Mastitis	3	16
FCD/UDH	8	42
ADH	3	15
DCIS	6	32
Ductal Carcinoma	2	10

Table 3: Results of Immonohistochemistry in papillary lesions of breast

IHC Marker	Papilloma (6)	Atypical papilloma (3)	Intracystic and Intraductal papillary Ca (9)	Invasive papillary Ca(5)
ER	100	100	100	100
PR	100	100	100	88
Her2neu	--		25	0
P63	100	66	-	Negative
CK5/6	100	66	-	Negative

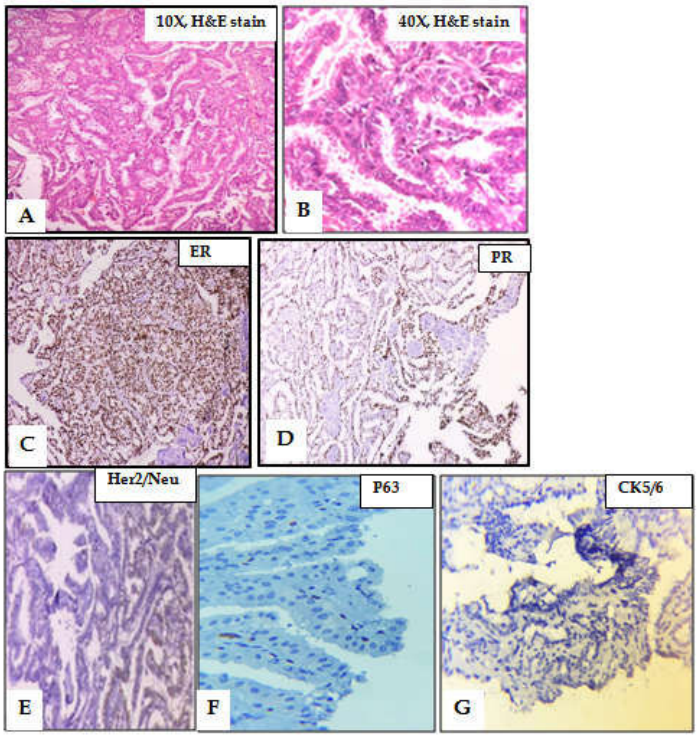

Fig 2: Papillary carcinoma hematoxylin and eosin stain (A,B) and immunohistochemistry of papillary carcinoma, ER (C), PR (D)positive, and Her-2 Neu(E) P63 (F), CK 5/6 (G) are Negative

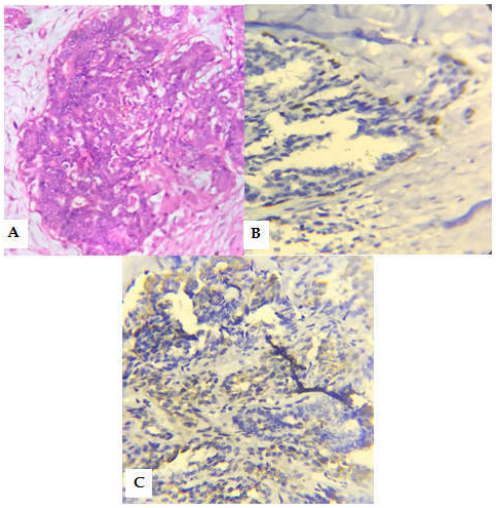

Fig 3: Atypical ductal hyperplasia in H&E stain (40X) (A), P63 (B) and CK 5/6 (C) incomplete positive

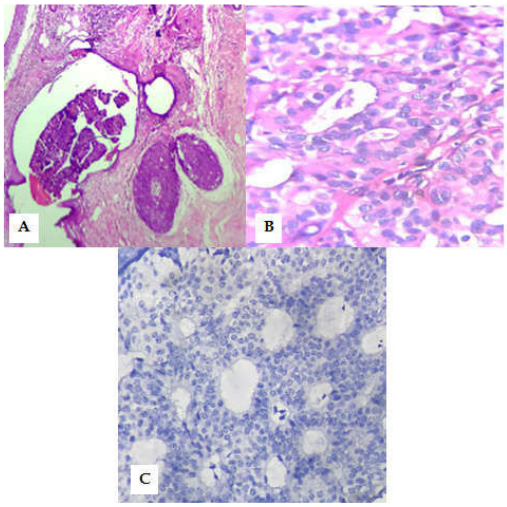

Fig 4: Ductal carcinoma in situ (DCIS) in H&E stain (40X) solid (A) AND Cribriform (B) pattern, P63 negative (C)

Discussion

Papillary lesions comprise a wide spectrum of breast lesions ranging from benign papilloma to papillary carcinoma. There common feature of these papillary lesions are true fibrovascular core supporting arbosent epithelial proliferation with or without intervening myoepithelial layer.

WHO classifies Papillary lesions as,

1. Intraductal papilloma
- Intraductal papilloma with atypical hyperplasia
- Intraductal papilloma with ductal carcinoma in situ
- Intraductal papilloma with lobular carcinoma in situ
2. Intraductal papillary carcinoma
3. Encapsulated papillary carcinoma
- Encapsulated papillary carcinoma with invasion
4. Solid papillary carcinoma
- In situ
- Invasive

Distinction between these subcatagories is not an easy task always, as pathologists differ in their terminologies and criteria to catagorize these lesions. Hence, distinction between thee is important as the management and outcome are totally differet different for each category of lesion [4].

Diagnosis of benign, pre malignant and malignant papillary breast lesions, especially in core biopsies, is challenging for most pathologists, and these lesions pose problems for patient management [3].

Intraductal papillomas are generally solitary and located in the subareolar region in the major and lactiferous ducts, hence the derivation of the term central/solitary papilloma whereas, peripheral/ multiple papillomas, are characterized by papillary proliferations within multiple terminal duct-lobular units or in the distal branches (terminal ducts) of the duct system [4].

Some intraductal papillomas may have areas of atypical ductal epithelial proliferation that would fulfill the criteria for ADH or DCIS if observed outside of the context of a papillary lesion, more often in peripheral papillomas than those in the central location. These lesions are designated as papilloma with ADH and papilloma with DCIS, respectively. The atypical features include the presence of evenly spaced, small, regular cells with round, monotonous nuclei characteristic of those in ADH and low-grade DCIS, and complex architecture patterns (ie, solid, cribriform, or micropapillary [7].

Intraductal papillary carcinoma and intracysticpapillary carcinoma are almost used interchangebly.

Intraductal papillary carcinoma, also known as papillary DCIS and noninvasive papillary carcinoma, is distinguished by the complete or near-complete absence of myoepithelial cells in the papillary fronds of the intraductal neoplastic proliferation [7].

Encapsulated papillary carcinoma is morphologically similar to intraductal papillary carcinoma with the exception that the myoepithelial cells are absent at the surrounding thick fibrous capsule [4]. Traditionally considered to be a variant of DCIS and termed 'intracystic' or 'encysted' papillary carcinoma characterized by the presence of papillary carcinoma within an apparent cystically dilated duct [9].

Solid papillary carcinoma grows in a solid papillary pattern, displays low-grade cytologic features, and often has neuroendocrine differentiation as well as intracellular or extracellular mucin production.

The term invasive papillary carcinoma should be reserved for invasive adenocarcinomas with an exclusively (.90%) papillary histomorphology [7].

Hence morphological features along with presence or absence of myoepithelial cell layer are important in differentiating various subcategories of papillary lesions. Myoepithelial morphology can be more accurate with use of IHC. p63 is one of the p53 homologues and related genes, and it seems to play a crucial part in the regulation of epithelial proliferation and differentiation. p63 is expressed in the myoepithelial cells in the breast [15,16] and as a marker of ''undifferentiation,'' [29] and may be useful as a myoepithelial marker in assessing breast lesions [7].

Cytokeratin (CK), an intermediate filament protein, reflects the epithelial cell type, state of tissue growth, differentiation, functional status and is used for the fingerprinting of various carcinomas [1]. The normal resting breast tissue is composed of luminal cells which express CK 8/18, CK 7, CK 19. The basal/myoepithelial cells express CK 5/6, CK 14, CK 17 and smooth muscle actin. A small subset of cells, comprising less than 5% of entire cell population, express CK 5. These cells are dispersed in the inner layer of ductal system and differentiate into myoepithelial or glandular cells

via intermediary cells [5].

The combination of broad, sclerotic fibrovascular cores, and epithelial staining for CK5/6 was identified as a characteristic that could clearly distinguish benign and malignant papillary lesions, although benign and atypical cases were not separated using this approach. Not with standing this limitation, combined assessment of fibrovascular cores and CK5/6 staining features could form a useful addition to clinicopathologic assessment [8].

Myoepithelial cell continuity by histomorphology and immunohistochemistry, almost continuous presence of ME lining was noted in all the benign papillary lesions. In atypical papillomas and intraductal carcinoma with DCIS cases, there was a definite reduction in the myoepithelial cells, whereas in malignant lesions, there was complete absence of the myoepithelial cells. Morphology of the papillae differed in benign, atypical and malignant lesions. The papillae had broad and sclerotic fibrovascular cores in benign lesions, thin and arborizing fibrovascular cores in most of the atypical lesions and all malignant cases had typical thin, arborizing fibrovascular cores. This morphological difference was of great help in most of the difficult cases to arrive at the diagnosis and was found statistically significant (p-value <0.05). Similar findings were also described by Pathmanathan et al and Basavaiah et al.

P63 was positive in all the papillomas, 75% of atypical papillomas and negative in papillary carcinomas. Bavikar et al. and Ichihara S et al. studies showed the similar features [10,11].

CK 5/6 was positive in all papilloma, 66% of atypical papillomas and 12% papillary carcinomas. Similar findings were observed in a study done by Pathamanathan et al. (92% benign and 4% malignant cases positive for ck5/6) [8].

Apart from studying the spectrum of papillary lesions, this study was also aimed to examine the changes in adjacent breast tissue. Adjacent breast tissue showed a wide range of lesions from mastitis to DCIS (duct carcinoma in situ). One case of papilloma was associated with Atypical ductal hyperplasia (ADH), and 04 cases of papillomas (1-central, 3- peripheral) were associated with DCIS. Most common pattern of DCIS was cribriform, followed by solid, comedo, micropapillary and clinging type. The benign changes included fibrocystic change, mastitis, focal calcifications and metaplastic changes.

As cases of papilloma were associated with either ADH or DCIS, it becomes imperative to examine the adjacent breast tissue carefully, especially in biopsy specimens. A note of caution can be included in cases of biopsy specimens of papillomas.

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