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Original Research Article

Diagnostic Evaluation of the Papillary Lesions of the Breast

Dr. Hemrajani Deepika[1], Dr. Nehra Pritika[2*], Dr. Choudhary Nikita[2], Dr. Harsh Anita[3]

[1]M. D, Professor, Department of Pathology, Sawai Man Singh Medical College, Jaipur, India
[2]M. D., Resident, Department of Pathology, Sawai Man Singh Medical College, Jaipur, India
[3]M.D, Professor, Department of Pathology, Sawai Man Singh Medical College, Jaipur, India

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***Corresponding author:** Dr. Nehra Pritika

Abstract

Papillary Lesions of Breast, defined histologically by presence of fibrovascular cores with varying epithelial proliferation, encompass a wide spectrum of benign intraductal papilloma, atypical papilloma with ADH/DCIS, papillary DCIS, encapsulated papillary carcinoma, solid papillary carcinoma and invasive papillary carcinoma. Due to tumor heterogeneity, sub-classification is diagnostically challenging on histopathology alone thus requiring help of immunohistochemistry (IHC). The aims & objectives of this study was to assess papillary lesions of breast and to determine the histopathological features which can categorize various papillary lesions along with IHC.A retrospective analysis of 39 cases of papillary breast lesions retrieved over a period of 8 years (July 2011 to July 2019) was done. The histopathology was reviewed independently by two pathologists using a standard review form which included 10 parameters. IHC was applied on all the cases to confirm or refute the histopathological diagnosis. Statistical analysis were performed using PRIMER software. Out of 39 cases, the most common papillary breast lesion was benign intraductal papilloma with 28 cases (72%), followed by one case of atypical papilloma with DCIS (2%) and 10(26%) malignant papillary lesions. The statistically significant histopathological features which aided in differentiating benign lesions from malignant lesions were presence of apocrine metaplasia, bland nuclear features and absence of atypia. IHC was necessary in diagnosing all the malignant papillary lesions and 2 benign papillary lesions. Papillary lesions of breast are difficult to interpret on microscopy alone due to intrinsic heterogeneity. The combination of histopathological features along with IHC helps in distinguishing benign, atypical and malignant papillary lesions.

Keywords: Papillary, Papilloma, Breast, Duct carcinoma insitu, Papillary carcinoma, IHC.

INTRODUCTION

Papillary lesions of breast occur in women of all ages with the majority of papillary carcinomas found in fifth and sixth decades. Intraductal papillomas account for 5-6% of the benign breast lesions and less than 2% of breast carcinomas are papillary carcinomas [1].

Papillary lesions of the breast encompass spectrum of lesions ranging from benign intraductal papilloma (IDP) and atypical papilloma with ductal carcinoma insitu or atypical ductal hyperplasia (DCIS/ADH) to malignant lesions, comprising of papillary carcinoma in-situ, encysted papillary carcinoma, solid papillary carcinoma and invasive papillary carcinoma. The one feature uniting them is the presence of papillae, i.e., proliferation of epithelium supported by fibrovascular stalk with or without a layer of myoepithelial cells occurring anywhere in ductal system.

In India, limited studies have been done in the area of these diagnostically challenging papillary lesions in terms of discussing their clinical manifestations, overlapping histological features and their biological potential.

In contrast to ductal carcinomas of breast, papillary lesions, although rare, behave very differently. Benign lesions and papillary carcinomas arising from and restricted to a cystically dilated duct are best managed by local excision while benign multiple papillomatosis with high rate of recurrence, have an increased risk of malignant transformation when excised incompletely. Carcinoma with lymph node metastasis and invasive component are staged and managed similar to ductal carcinoma [2].

Histologically, the main feature distinguishing a papilloma from a papillary carcinoma is the presence of a relatively uniform myoepithelial layer in the

papillary processes, while absent basal myoepithelial layer almost always indicates a carcinoma, but this distinction is not always straight forward. Due to their overlapping features, it is difficult to subclassify them based on histology alone.

To reveal distribution of both epithelial and myoepithelial cells and to define properties of an epithelial proliferation, Immunohistochemistry (IHC) helps pathologists to reach a proper diagnosis. p63, calponin, SMA and CD10 are the markers used for myoepithelial cells with p63 being the most common and most sensitive marker. CK5/6 shows heterogeneous positivity in ductal hyperplasia of papilloma as opposed to weak or negative staining in atypical hyperplasia or carcinoma insitu within papilloma. Papillary carcinomas stain positively for ER, PR and negatively for HER2neu [3].

The present study aims to discuss the diagnostic evaluation of papillary lesions by identifying those histopathological findings that can differentiate between benign, atypical and malignant papillary lesions along with IHC study for confirmation. Hormonal receptor profile may be applied subsequently on all malignant lesions to decide the further management.

MATERIALS AND METHODS

The present study is a retrospective hospital based cross sectional study of 39 papillary lesions of breast retrieved over a period of 8 years (July 2011 to July 2019).

Core biopsies, trucut biopsies, microdochectomy, lumpectomy and mastectomy specimens which fulfilled the criteria for papillary lesions were included. Cases whose paraffin blocks could not be retrieved and with incomplete history and follow up were excluded from the study.

Histopathology Review and Diagnostic Classification

The histopathology was reviewed on haematoxylin and eosin (H&E) stained sections independently by two pathologists using a standard review form which included broadly 10 epithelial and stromal parameters.

Consensus observations were used in analysis. Based on the histopathological review of architectural features and IHC visualization of myoepithelial cell layer, cases were labelled as benign, atypical, or malignant. The lesions were classified according to World Health Organization (WHO) classification of tumours of the breast, 2012. Atypical and malignant lesions were grouped under one category because of presence of only one case of atypical lesion in our study.

Immunohistochemical Staining and Evaluation

IHC was applied on all the cases. In benign lesions, for confirmation of myoepithelial cell layer, p63 marker was used. Calponin was used as a second marker in doubtful cases.

ER, PR and HER2neu were applied in all the malignant cases for the hormonal status, evaluated using Allred scoring system.

Statistical Analysis

All the ten epithelial and stromal histopathological features were analyzed for their frequency. Chi square test with one degree freedom, wherever applicable, was used to test for associations between histopathological features and categories. P-value of <0.05 was considered significant. Statistical analysis were performed using PRIMER software.

RESULTS

A total of 39 cases were studied over the duration of 8 years. The mean age of patients was 44 years (range 20-80 years). 71% of benign papillomas were in 30-50 yrs age group (Table 1).

Table 1: Age Distribution among different categories of papillary lesions

Categories	<30 years	30-50 years	>50 years
Benign(28 cases)	4	20	4
Atypical (1 case)	0	0	1
Malignant(10 cases)	0	5	5

Histopathological Features

Histopathological features of these 39 lesions were assessed systematically based on the review form and on IHC by two pathologists (Table 2).

Table 2: Histopathology Review Form

Sr. No	Histopathological Features	Benign (28 cases)	Malignant (11 cases)	p value
1	**Architectural Features**			0.177
	Papillary-Single layer	21 (75%)	6(55%)	
	Papillary-Stratified	7 (25%)	3(27%)	
	Atypical architectural patterns in ADH	0(0)	1(9%)	
	Solid	0(0)	1(9%)	
2	**Extent Of Atypia**			**<0.001**
	None	22(79%)	1(9%)	
	Focal <30% of lesion	6(21%)	7(64%)	
	Focal < 60% OF LESION	0(0)	2(18%)	
	Uniformly atypical	0(0)	1(9%)	
3	**Myoepithelial Cell Layer**			**<0.001**
	Uniformly present	25(89%)	0(0)	
	Focally absent	1(4%)	0(0)	
	Can not comment	2(7%)	7(64%)	
	Completely absent	0(0)	4(36%)	
4	**Nuclear Features (of normal epithelial cells)**			**<0.007**
	Small uniform chromatin	24(86%)	4 (36%)	
	Larger, chromatin margination, small nucleoli	4(14%)	7 (64%)	
5	**Cell Borders**			0.108
	Distinct	27(96%)	8(73%)	
	Indistinct	1(4%)	3(27%)	
6	**Metaplasia**			**0.017**
	None	7(25%)	8(73%)	
	Apocrine	21(75%)	3(27%)	
7	**Fibrovascular Cores**			0.058
	Thin and arborizing	5(18%)	6(55%)	
	Broad and sclerotic (or both)	23(82%)	5(45%)	
8	**Epithelial Entrapment In Capsule (n = 37)**			0.333
	Present	6(23%)	5(45%)	
	Absent	20(77%)	6(55%)	
9	**Perilesional Sclerosis (n=37)**			0.419
	Minimal	22 (85%)	8(73%)	
	Moderate	3(11%)	3(27%)	
	Prominent	1(4%)	0(0)	
10	**Surrounding Breast Changes (n= 36)**			0.069
	Normal	11(44%)	7 (64%)	
	Usual ductal hyperplasia	13(52%)	2 (18%)	
	Atypical Ductal hyperplasia	1(4%)	0(0)	
	DCIS	0(0)	2 (18%)	

Out of 39 cases, 28 (72%) were benign, one (2%) was atypical and 10 (26%) were malignant.

The characteristics that favored a benign lesion were broad and sclerotic fibrovascular cores in 23 (82%) cases, presence of apocrine metaplasia in 21 (75%) cases and no atypia in 22 (79%) cases. Myoepithelial layer lining the papillary cores in all the benign lesions was confirmed histologically, except in two cases where IHC was needed for confirmation.

Among 28 benign intraductal papillomas, 24 (86%) were central papillomas and four (14%) cases were of multiple peripheral papillomatosis. eight (29%) cases were associated with changes of usual ductal hyperplasia within the papilloma (Papilloma with UDH).

In our study, we encountered only one case of atypical papillary lesion, diagnosed as Papilloma with DCIS. Histologically, there was presence of thin and delicate fibrovascular cores with no apocrine metaplasia and focal atypia in less than 60% of the lesion. Presence of DCIS component within the papilloma as well as in the surrounding breast was confirmed on IHC.

For proper statistical analysis, this case was included along with malignant category.

Malignant lesions were defined with the help of absence of myoepithelial cell layer histologicaly

which was subsequently confirmed on IHC. The presence of atypia in nine out of ten(90%) cases and absent apocrine metaplasia in seven(70%) cases was also noted. We found equal distribution (55% each) of thin arborizing fibrovascular cores and broad sclerotic fibrovascular cores.

Immunohistochemistry

IHC was applied on all the 39 cases which changed the histopathological diagnosis in 13(33%) cases including two benign, one atypical and 10 malignant cases (Table 3).

Table 3: IHC in challenging papillary lesions

SN	Histopathological Diagnosis	IHC Results	Final Diagnosis
1	Suspicious of papillary lesion	+ve : p63 uniformly present	Intraductal Papilloma
2	Papillary lesion with hyperplasia	+ve : p63 uniformly present	Papilloma with UDH
3	? Duct Papilloma ? DCIS	+ve: p63 in periphery & few papilla	Papilloma with DCIS
4	Intracystic papillary Ca	-ve :p63 in papilla but +ve in periphery *Presence of globoid cells on HPE Review	Papillary DCIS
5	Intraductal papilloma with fibrocystic disease		
6	Duct Papilloma		
7	Intermediate grade DCIS		
8	Invasive Papillary Ca	-ve : p63 in papilla as well as in periphery	Encysted Papillary Ca
9	Intracystic papillary lesion		
10	Encysted Papillary Ca		
11	Invasive Papillary Ca	-ve : p63 in papilla as well as in periphery	Encysted Papillary Ca with invasion
12	Neuroendocrine Ca	-ve : p63 in solid areas +ve : ER,synaptophysin,CD56	Solid Papillary Ca with neuroendocrine differentiation
13	Papillary Adenocarcinoma	-ve :p63,CK5/6,ER,PR,Her2neu, PAX8,GATA3 Mib- 15-20%,Incomplete panel	Invasive Papillary Ca - Undifferentiated

+ve : Positive , -ve : Negative , Ca : Carcinoma

P63 nuclear staining for myoepithelial cell layer helped in confirming the benign cases (Figure 1B). In atypical papilloma with DCIS (Figure 1B), p63 was seen along the papillary cores while negative in areas of DCIS (Figure 1F).

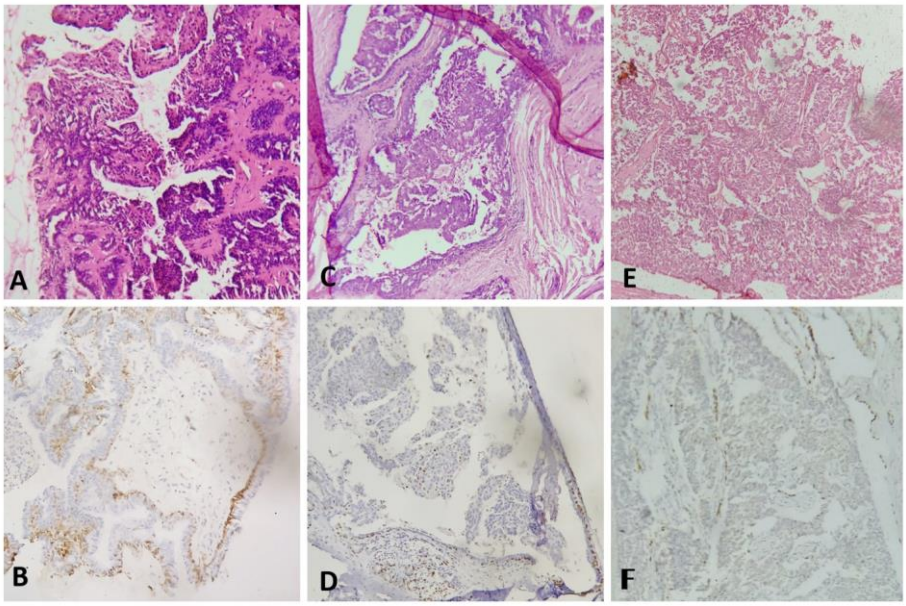

Figure 1: (A) Benign Intraductal Papilloma - H&E stained, 100x magnified microphotographs showing complex papillae with broad fibrotic core and double layer of epithelium with (B) positive cytoplasmic staining for calponin (brown) in myoepithelial cell (MEC) layer (IHC, 100x). (C) Papilloma with UDH (H&E, 100x) – Benign intraductal papilloma showing areas of usual ductal hyperplasia with (D) heterogeneous p63 staining among UDH region and positive nuclear staining along the MEC layer (IHC, 100x). (E) Papilloma with DCIS (H&E, 100x) - Benign papilloma with changes of DCIS with (F) negative p63 staining of areas showing DCIS and positive staining in MEC layer (IHC, 100x)

In malignant lesions, p63 helped in confirming the absence of myoepithelial cell layer as well as in subcategorization of malignant lesions.

Among 10 malignant cases, four (40%) cases were of papillary DCIS. Consistent with the insitu nature of this lesion, p63 was absent within the papilla but present peripherally around the papillary lesion (Figure 2A & B).

Four (40%) cases of encapsulated papillary carcinoma were diagnosed based on the absence of myoepithelial cell layer inside as well as outside the papillary lesion by p63 staining. All the four cases were ER, PR positive and HER2 negative. In our study, there were two males and both were diagnosed with encapsulated carcinoma. One of them showed invasion in the adipose tissue (Figure 2C & D).

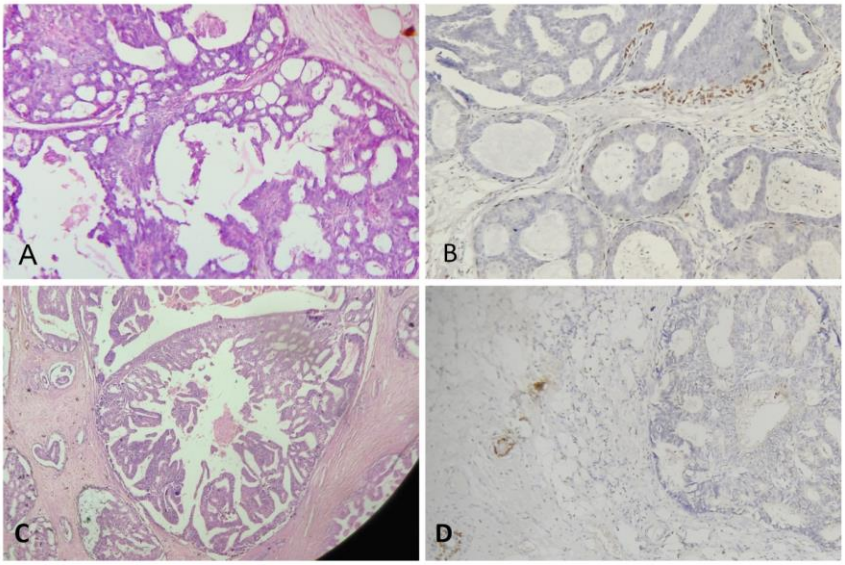

Figure 2: (A) Papillary DCIS (H&E, 100x) with (B) absent p63 within the papilla and positive in the periphery (IHC, 100x). (C) Encysted Papillary Carcinoma (H&E, 100x) showing (D) negative p63 staining for MEC layer both inside and outside the papillary lesion (in left area showing positive control) (IHC, 100x)

One (10%) case of solid papillary carcinoma had absent p63 staining inside the solid areas of lesion. Neuroendocrine differentiation was present which was confirmed by diffuse positivity of synaptophysin and CD56 (Figure 3).

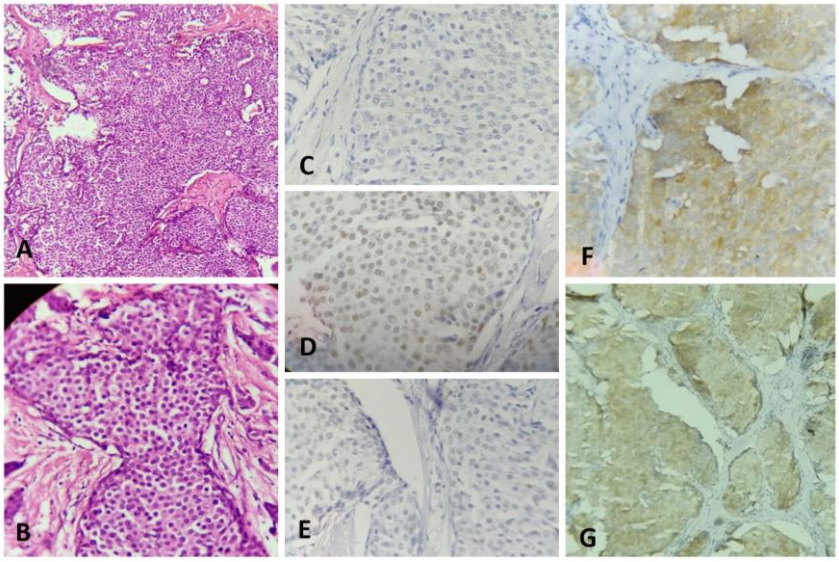

Figure 3: (A) Solid Papillary Carcinoma (H&E, 100x) microphotograph shows thin fibrovascular papillary cores with monotonous population of neoplastic cells; (B) on 400x showing neuroendocrine differentiation; on IHC, 400x magnified microphotographs showing (C) negative p63 staining, (D) – positive ER, (E) negative staining for Her2neu, (F) positive staining for Synaptophysin and (G) positive staining for CD56

There was a single (10%) case of invasive papillary carcinoma which was negative for p63, ER, PR, Her2neu, GATA 3, PAX-8, along with Mib labelling index of 15-20%.Further panel could not be applied because of exhaustion of tissue (Figure 4).

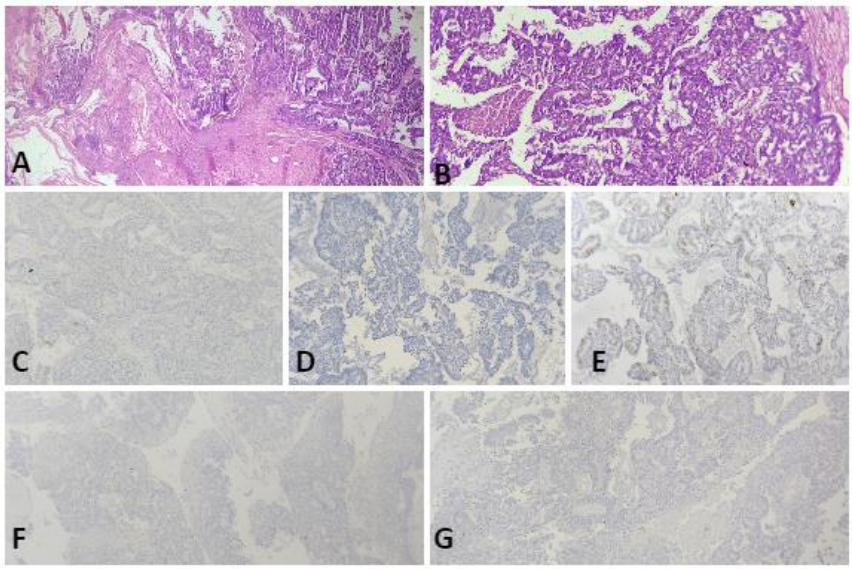

Figure 4: (A) Invasive papillary carcinoma (H&E, 100x) showing (B) stromal invasion (H&E , 400x) and on IHC, 100x shows (E) Mib index of 15-20% and negative staining for (C,D,F,G) p63, ER, GATA3 and PAX-8 respectively

Predictive Assessment of Benign and Malignant Papillary Lesions

For distinction between benign and malignant lesions, three out of 10 histopathological parameters were found to be statistically significant- extent of atypia (P value <0.001), nuclear features of normal epithelial cells (P value <0.007) and apocrine metaplasia (P value < 0.017). However, none of these individual features were helpful in the differentiation of papillary lesions (Figure 5).

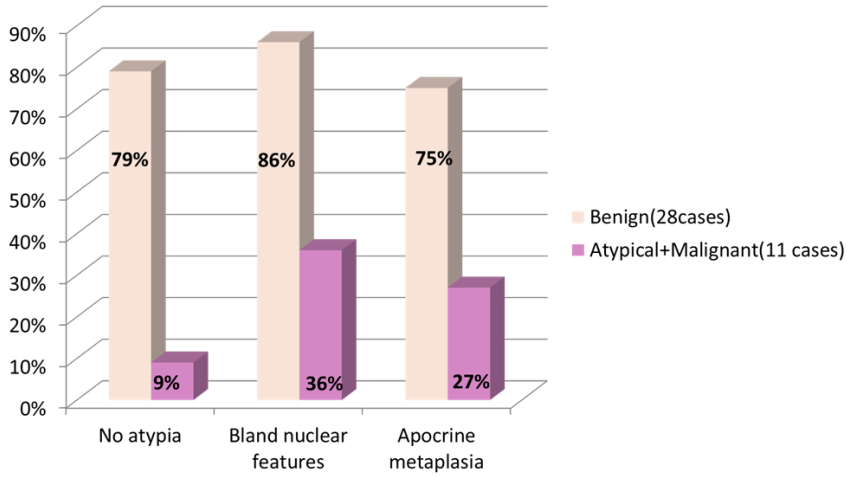

Figure 5: Significant Histological Parameters differentiating benign and malignant papillary lesions

Combining IHC staining along with the histological presence of myoepithelial cell layer proved to be statistically significant (P value < 0.001) for separating benign lesions from the malignant ones.

Broad and sclerotic fibrovascular cores, although seen in 82% of the benign lesions, was not statistically significant (P value – 0.058) because of its presence in significant number of (55%) malignant lesions also.

DISCUSSION

Papillary lesions of the breast are heterogeneous group and have varied morphologic characteristics that carry differing prognostic impact for the affected patients. Clinically, such cases may present

as a nipple discharge or a palpable breast lump or both. Radiologically, even though identified as multiple lesions with or without calcifications, or a intracystic lesion or solid complex lesion, the detection is not sensitive enough to distinguish papillary lesions [4].

Cytologically, diagnosing papillary lesions comes under a gray zone area due to complications in differentiating papillary lesions from other non papillary benign mimics as well as differentiating the benign and malignant papillary lesions. Such lesions are categorized as "indeterminate" due to nonspecific defining criteria according to the National Cancer Institute (NCI)-sponsored conference for formulating guidelines for breast FNA [5].

Few studies done in this area like that of Pratibha *et al.,* in 2010, Deepti Aggarwal *et al* in 2014 and Suvradeep Mitra *et al* in 2015 concluded the diagnosis of papillary breast lesions lesions as being almost unclassifiable, unidentifiable, or undiagnosable by cytology [6-8].

The categorization of this diagnostically challenging group continues to be a dilemma, more so on core biopsies due to under sampling. Excision biopsy of the whole lesion is required in all complex papillary lesions to accurately identify the papillary carcinoma from other papillary breast lesions. In our study, we have included all the cases from core biopsies to excision specimens, and we agree with Lam *et al*., who suggested that a core biopsy is unreliable and excisional biopsy should be performed for definitive diagnosis [4].

In 2010, Pathmanathan *et al* categorized papillary lesions by combined assessment of presence of broad, sclerotic fibrovascular cores and CK5/6 staining in epithelial cells. In her study, broad and sclerotic fibrovascular cores was seen in 45% of benign lesions versus in 13% of malignant lesions only [9].

Similarly, in 2016 study by Basavaiah *et al*., broad and sclerotic fibroepithelial cores were observed in 92.9% cases of benign lesions in comparison to 83.3% of atypical and 100% of malignant lesions predominantly showing thin, arborizing fibrovascular cores [10].

However in our study the presence of broad and sclerotic fibrovascular cores was insignificant as it was seen in both benign (82%) and malignant lesions (45%), hence it was not statistically significant.

In accordance with the study of Pathmanathan *et al*, which also reviewed papillary lesions on the comprehensive list of histopathological features, none of the ten parameters individually helped in conclusive diagnosis of benign over malignant lesion [9].

However, in our study, statistically significant features like presence of apocrine metaplasia, bland nuclear features and absence of atypia can be used in combination to categorize benign lesion histopathologically.

The precise differentiation of papillary lesions into benign, atypical and malignant group is difficult on histopathology alone, therefore immunohistochemistry is used to help differentiate them. In this study the important histopathological parameter that helped distinguish the lesions was the presence of myoepithelial cell layer and its confirmation on IHC with p63.

Myoepithelial markers like p63 along with confirmation of benign papillary lesions are also useful in distinguishing IDP with DCIS, papillary DCIS and encysted papillary carcinoma.

Bavikar *et al.,* (2017) in a retrospective study of 5 years reviewed 41 cases of papillary breast lesions along with IHC (p63, CK5/6, CD10 and SMA) and found p63 to be the most sensitive myoepithelial marker with minimum cross reactivity to differentiate benign from malignant lesion [11].

According to GM Tse *et al* study in 2009, CK5/6, p63 and neuroendocrine markers can be used as an initial panel of investigation while dealing with problematic papillary lesions of the breast [12].

The prognosis of papillary group of breast lesions is broadly better than other breast lesions. Benign papillomas without surrounding breast changes are managed on excision alone. Encapsulated papillary carcinoma and solid papillary carcinomas, although categorized as malignant, have indolent clinical course and are managed as insitu lesions when present without invasion. However, rarely, when present with invasion or lymph node metastasis, they are staged and treated same as ductal carcinoma breast [1].

CONCLUSION

Papillary lesions of breast with a wide spectrum of benign and atypical to malignant lesions are needed to be diagnosed and categorized accurately due to their varied prognosis and treatment. Along with the consideration of clinico-radiological features, histopathology with the immunohistochemistry proves to be a very important diagnostic tool in identification of such lesions.

Currently, for the accurate diagnosis, excision specimens are necessary but future studies and researches are being done in this area, to categorize these lesions on minimum sampled tissue, to provide the patients with better results and prevent unnecessary extensive surgery and follow up.

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