Original Article

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Papillary Lesions of Breast - Limitations of H&E and Pivotal Role of IHC: Single Cancer Centre Study

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ABSTRACT

Background: Papillary breast lesions constitute wide spectrum of heterogeneous pathological group. Diagnosis becomes challenging in case of overlapping histomorphological features.

Material & Methods: Retrospectively 69 papillary lesion were taken into consideration from January 2017 to March 2021.

Results: Routine H&E & CK5/6, P63 is used for further differentiation. Cases were divided into three main divisions 1) benign –intraductal papilloma 2) atypical – intraductal papilloma with ADH/ DCIS 3) malignant - Intra ductal papillary carcinoma, encapsulated papillary carcinoma, solid papillary carcinoma & invasive papillary carcinoma. Papilloma comprised of 28 patients between 25-60 years of age & varies in size from 0.6 to 2.8 cm. Papilloma with ADH/DCIS accounted for 8 patients between 34-65 years age group with size of lesion between 0.5 to 3.0 cm. Intraductal papillary carcinoma comprised of 12 patients with size range 1.6 to 4.0 cm in age group of 42 to 65 years. Encapsulated papillary carcinoma comprised of 4 patients with age between 60 to 73 years and lesion size 0.8 to 14 cm. Solid Papillary carcinoma comprised of 10 patients between 39-81 years of age & lesion varies in size from 1.0 to 8.5 cm. Invasive papillary carcinoma comprised of 7 patients between age of 65 to 80 year and size varies between 2.0 to 6.5 cm.

Conclusion: Diagnosis of papillary carcinoma is challenging and its classification includes different entities that have specific diagnostic criteria. Due to heterozygosity in morphology of benign, atypical and malignant subtypes, morphological features should be supplemented by IHC for accurate diagnosis.

Keywords: *Papillary Breast Lesions, Myoepithelial Cells, Immunomarkers, P63, CK5/6*

Introduction

Papillary breast lesions consist of a diverse group of lesions that span the wide spectrum from benign and atypical lesions to malignant tumor including non-invasive and invasive entities.[1]They are rare and constitute less than 10% of benign breast lesion and 1% of malignant breast neoplasms. [2-5]The presence of these fibrovascular stalks is accepted as the hallmark of papillary lesions of breast[6]. However, once identified as papillary lesion further subcategorization is problematic many times even for an experienced pathologists into as benign, atypical or malignant category. [5]

Identification of myoepithelial cell layers became essential key feature in differentiate various papillary breast lesion from benign to malignant and in situ to invasive. There is a continuous myoepithelial cell layer noted in all the benign papillary lesions, definite reduction in the myoepithelial cells seen in atypical papilloma and intraductal papillary carcinoma cases, whereas complete absence of the myoepithelial cells in malignant lesion[6,7]. Immunohistochemistry has a crucial role in differentiation of various papillary breast lesions. P63 is the Commonly used myoepithelial marker, which shows best results due to highest sensitivity and lowest cross reactivity, and easy interpretation of nuclear staining. Different types of epithelial hyperplasia (usual, atypical or ductal carcinoma in situ) are differentiating by use of Basal cytokeratin (CKs). Usual hyperplasia is positive for CK5/6 and the atypical to malignant proliferations are negative. Neuroendocrine markers (chromogranin A and synaptophysin) may be positive in solid papillary carcinoma.

Therefore a panel of CK5/6 and p63 markers can be a used as an initial panel of investigation when one is dealing with problematic papillary lesions of the breast. Our objective was to analyses the clinical presentation, the histopathological characteristics and immunohistochemistry from patients of papillary breast lesions.

Materials and Methods

Design: Retrospective observational–descriptive study.

Patients: An observation was made from the database of patients with definite histopathological diagnosis of breast

papillary lesions that were diagnosed from January 2017 till March 2021.

Inclusion Criteria : All Cases of Breast Lesion diagnosed as "papillary lesion" registered in the department during study period.

Exclusion Criteria : all registered breast lesion except papillary lesion were excluded from this study.

Statistical analysis: For the statistical analysis the Statistical Package of Social Sciences (SPSS) 20.0 program was used. To compare tests, parametric and non-parametric hypothesetic trials were run according to the normality determination. Significant confidence level of 95% with a p-value <0.05 was considered statistically. These are considered to be normal values.

Variables: The following were considered: Age, Sex, Size, Location, clinical presentation, Microscopy and IHC findings.

Results

A total of 69 (2.7%) cases of papillary lesions were seen among 2550 new registered breast lesion during the study period. The mean age of the patients was 54 years (age range: 31-81 years) (Table-1). Among all cases female were predominant except three were male (Table-2). Size varies 0.5 to 14 cm (Table-3). These cases were equipropotional in laterality with two cases presented with bilateral lesion (Table-4). The most common presenting complaint was breast lump (89.85 % cases), followed by nipple discharge (31.88 % cases) and pain (14.49 % cases) (Table-1). The central quadrant was the most common location (35/69 cases) (Table- 5).

Modified radical mastectomy, lumpectomy and microdochectomy specimens were received for examination (Table-6). Among them node evaluation done for 30 cases (Table-7)

The most common papillary lesion was intraductal papilloma (40.57 %), with an age range of 25-60 years. In two cases, there was a suspicion of invasion and hence IHC (CK5/6 & P63) was used. First case was encountered in a 50-year old female with 3 cm lump in left breast. Histopathological findings were similar to papilloma except an area with suspicion of intraductal papillary carcinoma focally, on IHC CK5/6 shows positivity in epithelial cells and P63 shows continuous positivity in myoepithelial cells inside the fronds and around the ducts so diagnosed as papilloma with atypical ductal hyperplasia was made. Second case were of 35 year old female with 2.5 cm lump in left breast diagnosed primarily as intraductal papillary neoplasm due to difficulty in identifying myoepithelial cells focally, but on IHC , CK5/6 in these area shows discontinuous positivity in papillary fronds with p63 was positive in periphery of duct diagnosed as papilloma with duct carcinoma in situ (DCIS). Intraductal papilloma with ductal carcinoma in situ /ADH constituted for 11.59% of cases. Myoepithelial cell may be scant or absent from this foci shows lack of staining for HMWK. (Figure -1, Table-8, 9, 10 and 11)

Intraductal papillary carcinoma constituted for 17.39% of cases. Age ranges between 42-65 years. Among them one is male patient with age of 52 year presented with 2.5 cm of left breast lump. On histopathology, there are no or scant myoepithelial cells interposed between the papillae and the epithelial proliferation. At the periphery of the ducts, the myoepithelial cell layer present which was highlighted by IHC. (Figure-2, Table-8, 9, 10 and 11)

Encapsulated papillary carcinoma presented with circumscribed round mass with age range between 60-73 years constitutes 5.79% of cases. These lesion formed by a thick fibrous capsule surrounds a nodule composed of delicate fibrovascular stalks and neoplastic epithelial cells arranged in solid and cribriform pattern. There is absence of myoepithelial cells along fibrovascular core and also in periphery of duct which differentiate this entity from DCIS. (Figure-3, Table-8, 9, 10 and 11)

Solid papillary carcinoma constituted 14.49% of cases with age ranges between 49-80 years of age. The lesion comprised of multiple circumscribed masses embedded in fibrous stroma. Cellular masses appear non invasive because of their circumscription, but they lack peripheral myoepithelial cells as demonstrated with IHC stains. (Figure-4, Table-8, 9, 10 and 11)

Seven cases were of invasive papillary carcinoma. The age of presentation ranged from 50-81 years with the average tumor size of 2-6.5 cm. Two of them were male with presented as right sided centrally located lump in 57 and 71 years of age. All of them were found strongly positive for hormonal receptors and negative for Her2neu marker on immunostaining. (Table-8, 9, 10 and 11)

Discussion

The diagnostic work-up of papillary lesions includes a spectrum of diseases varying from typical benign intraductal papilloma at one end and invasive papillary carcinoma at the other end of the spectrum. There are several other lesions in the middle of the spectrum which are most challenging to diagnose due to overlapping morphological features.

Table: 1 Characteristics of patients with histopathological diagnosis of breast papillary lesion (*n* = 69). Among them 20 cases had both nipple discharge, palpable mass and 9 cases had all three symptoms.

Variable	No. of patients	Percentage
Age		
< 50 years	17	24.63%
≥50 years	52	75.36%
Diagnostic Symptoms		
Nipple discharge	22	31.88%
Palpable mass	62	89.85%
Pain	09	13.04%

Table: 2 Distribution of papillary lesion based on sex (n=69).

	Total cases	percentage
FEMALE	66	95.65%
MALE	3	4.34%
TOTAL	**69**	**100%**

Table: 3Distribution of papillary lesion based on size (n=69), More than half of the cases, (58%) presented with tumor size more than 2cm and less than 5cm.

Tumor size	No. of cases
<2 cm	19 (27.59%)
2-5 cm	40 (57.97%)
>5 cm	10 (14.49%)

Table: 4 Distribution of papillary lesion based on site (n=69). One case among 69 was show bilateral lesion having intraductal papilloma right side and solid papillary carcinoma at left side of breast.

Tumor site	No. of cases
Right sided	34
Left sided	34
Bilateral lesion	1

Table: 5 Distribution of papillary lesion based on location (n=69). Out of 69 cases, 35 cases had lesion in central quadrant, 23 in upper quadrant and 9 in lower quadrant. Two case were presented with lesion covered whole of the breast.

Quadrant involved	No. of cases
Central	35 (50.72%)
UOQ	18 (26.08%)
UIQ	05 (7.24%)
LOQ	04 (5.79%)
LIQ	05 (7.24%)
Overlapping	02 (2.89%)

Table: 6 Distribution of papillary lesion based on procedure done (n=69). In 1 case Microdochectomy was followed by lumpectomy. In 7 cases lumpectomy was followed by MRM.

Procedure done	
Microdochectomy	6
Lumpectomy	41
MRM	22

Table: 7 Distribution of papillary lesion based on node status done (n=30). There were 30 cases presented with nodal dissection. Among them four cases show node positivity. Two of them belong to invasive papillary carcinoma and two among solid papillary carcinoma

cases	
Node negative	26
Node positive	4
Total	**30**

Table: 8 Distribution of papillary lesion of breast on HPR.

Types of papillary lesion	No. of cases
BENIGN	
Intra ductal papilloma	28 (40.57%)
ATYPICAL	
Papilloma with ADH/DCIS	8 (11.59%)
MALIGNANT	
Intra ductal papillary carcinoma	12 (17.39%)
Encapsulated papillary carcinoma	04 (5.79%)
Solid papillary carcinoma	10 (14.49%)
Invasive papillary carcinoma	7 (10.14%)
TOTAL	**69 (100%)**

Table: 9 Histopathological findings (n=69). Out of 69 cases, 25 cases were presented with broad sclerotic fibrovascular core and 37 cases presented with thin arborizing fibrovascular core. Also there were 7 cases with both broad & thin fibrovascular core.

FIBROVASCULAR CORE	BENIGN	ATYPICAL	MALIGNANT
BROAD	25 (34.21%)	0	0
THIN	0	4 (10.52 %)	33 (42.10%)
BROAD+THIN	3 (2.63%)	4 (10.52 %)	0

Table: 10 Comparison of subcategories papillary breast lesion-(N-69).

	Papilloma	Papilloma with ADH/ DCIS	Papillary DCIS	Encapsulated papillary carcinoma	Solid Papillary carcinoma	Invasive papillary carcinoma
Case no.	28 cases	8 cases	12 cases	4 cases	10 cases	7 cases
size	0.6 to 2.8 cm	0.5 to 3.0	1.6 to 4.0 cm	0.8 to 14 cm	1.0 to 8.5 cm	2.0 to 6.5 cm
Age range	25-60 years	34-65	42-65 years	60 -73 years	49-80 years	50-81 years
gender	28/28 female	8/8 female	11/12 female 1/12 male	4/4 female	10/10 female	5/7 female 2/7 male

Table: 11 Immunophenotypic features of papillary lesion of breast.

Entity	CK5/6, P63			ER	PR	HER2	Synapto/chromo positive
	Continuous	Discontinuous	Absent				
Intraductal papilloma	28	0	0	patchy +ve	patchy +ve	-ve	0
Papilloma with ADH/ DCIS	0	8	0	diffuse +ve	diffuse +ve	-ve	0

Entity	CK5/6, P63			ER	PR	HER2	Synapto/chromo positive
	Continuous	Discontinuous	Absent				
Intraductal papillary CA	0	12	0	diffuse +ve	diffuse +ve	-ve	0
Encapsulated papillary CA	0	0	4	strong +ve	strong +ve	-ve	0
Solid papillary CA	0	0	10	strong +ve	strong +ve	-ve	4
Invasive papillary CA	0	0	7	diffuse strong +ve	strong +ve	-ve	0

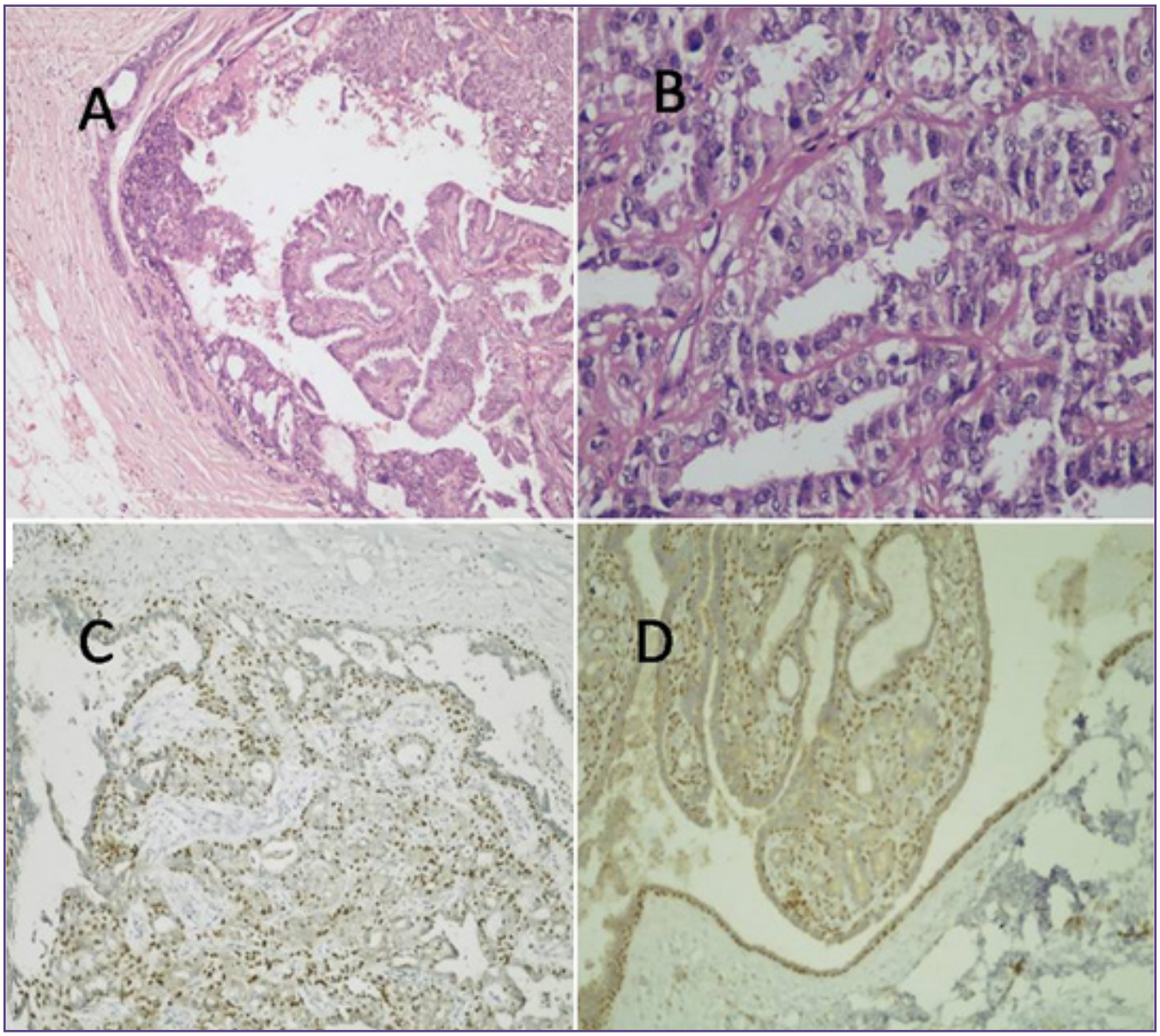

Fig. 1 (A, B) Benign intraductal papilloma with sclerotic capsule, Benign epithelial and myoepithelial cells with prominent fibrovascular cores. (C, D) P63 immunostain highlights the myoepithelial cells in the papilloma and the duct wall.

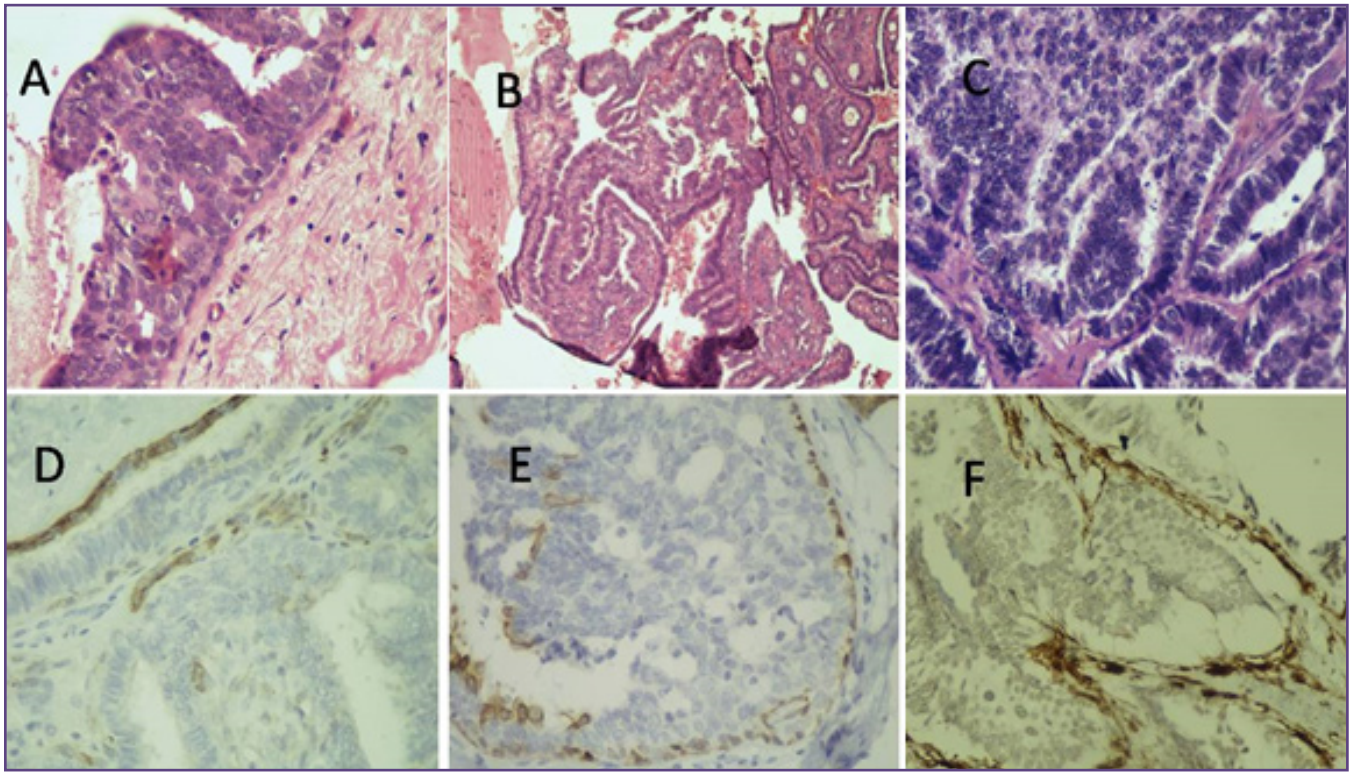

Fig. 2 (A, B, C) Intraductal papillary carcinoma- a well circumscribed lesion composed of thin, branching complex papillae lined by atypical epithelial cells. (D, E, F)- P63 immunomarker show myoepithelial cells in the duct wall and complete absence within the papillary fronds.

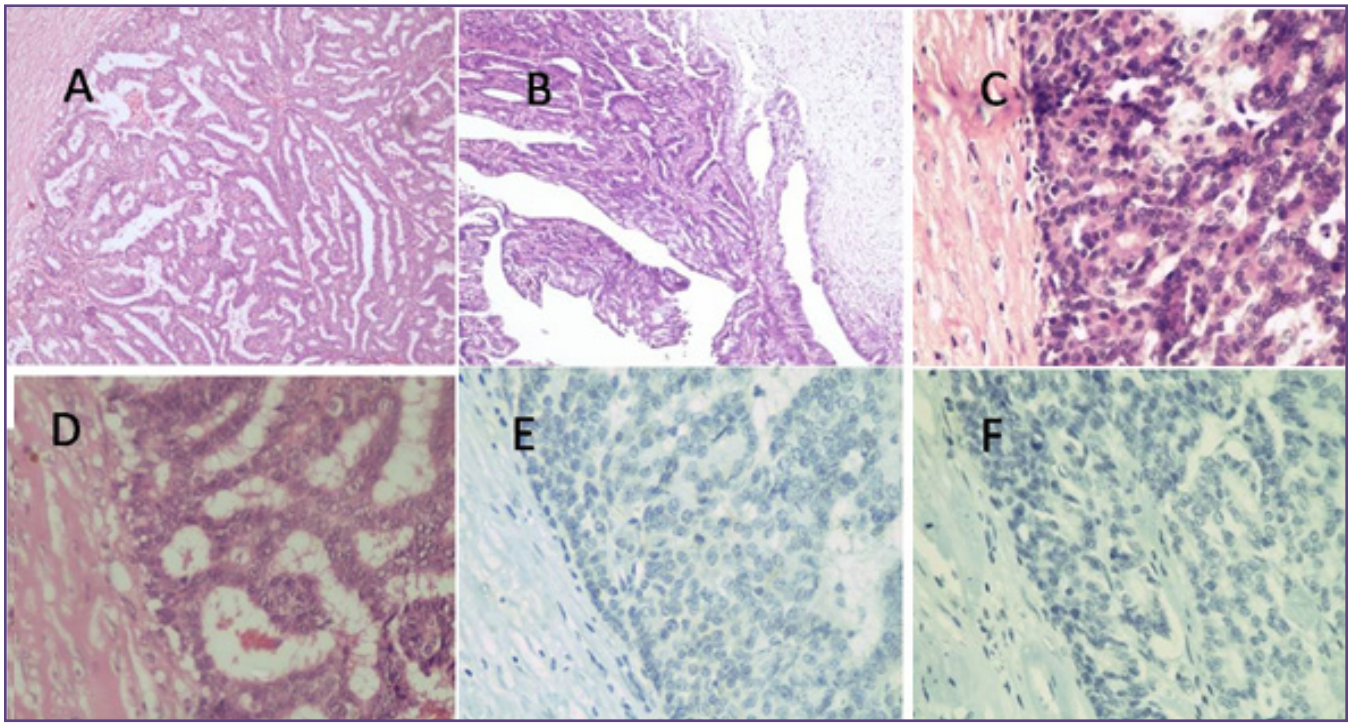

Figure-3 (A, B, C) -Encapsulated papillary carcinoma- A nodule surrounded by fibrous capsule with papillary configuration. (D, E, F)- Absence P63 and ck5/6 immunomarker staining at the periphery and with the lesion.

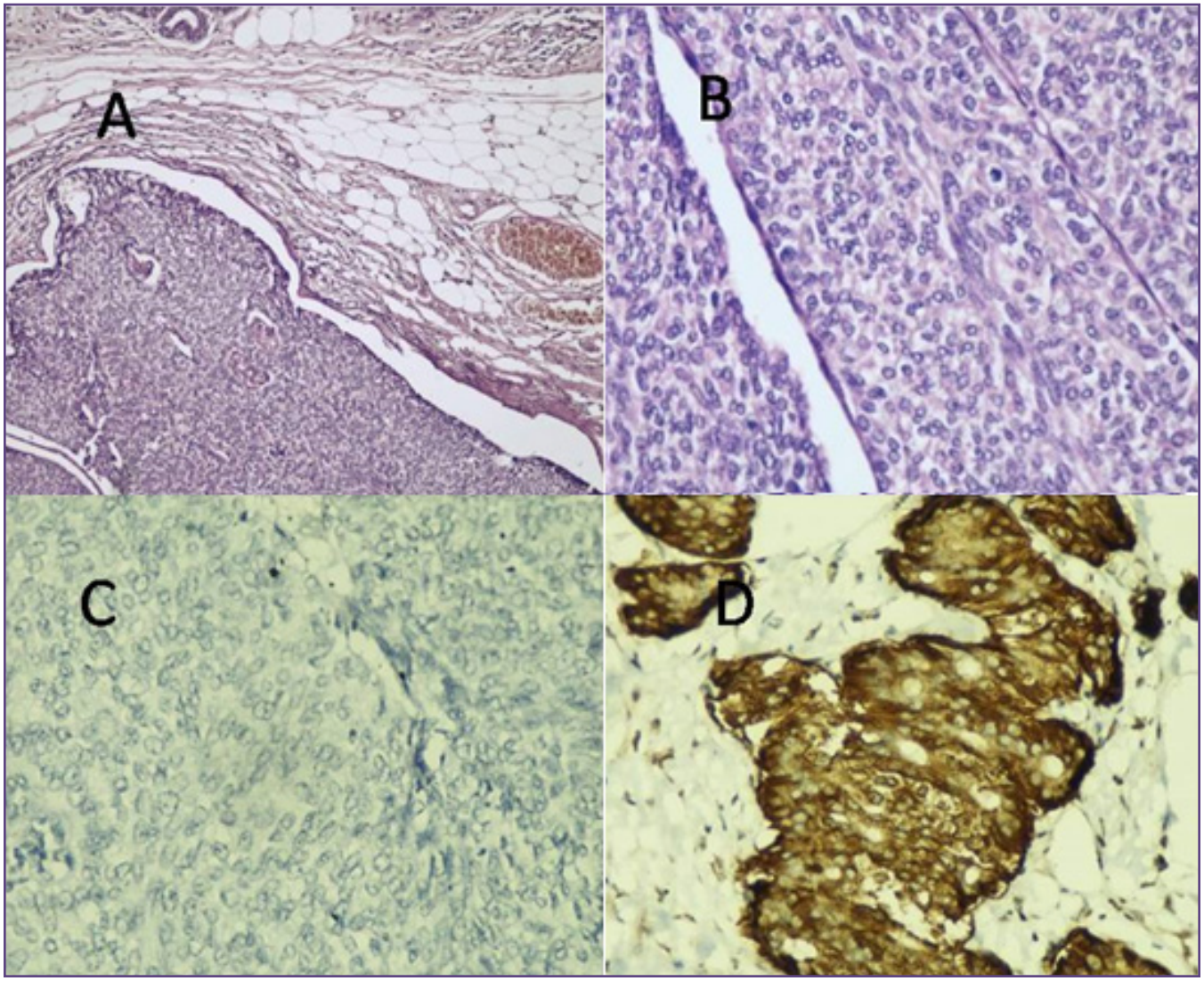

Fig. 4 (A, B)-Solid papillary carcinoma comprising irregular nests within dense, fibrotic stroma. Fibrovascular cores are present uniformly but subtle than other papillary lesions of the breast, (C, D) P63 immunomarker show absence of myoepithelial cells and strong positivity for synaptophysin immunostain.

WHO classification of Papillary lesions of breast

- Intraductal Papilloma
  - Intraductal papilloma (8503/0)
  - Intraductal papilloma with atypical hyperplasia (8503/0)
  - Intraductal papilloma with ductal carcinoma in situ (8503/2)
  - Intraductal papilloma with lobular carcinoma in situ (8520/2)
- Intraductal papillary carcinoma (8503/2)
- Encapsulated papillary carcinoma (8504/2)
- Encapsulated papillary carcinoma with invasion (8504/3)
- Solid papillary carcinoma In situ (8509/2)
- Solid papillary carcinoma Invasive (8509/3)

Intraductal papillomas are the most common type of papillary lesions and presents as solitary lesions (90%) in the sub areolar region in most of the cases. Cases are seen between the ages of 30-50 years. The most common clinical finding is the presence of palpable mass followed by presence of nipple discharge that can be either bloody or serous in nature[8-10]. The diagnosis is usually uncomplicated as lesion characterized by presence of

arborizing papillae having fibrovascular stalks which are covered by myoepithelial cells[10]. Features favouring benignity in a papillary breast lesion are a hyalinised stroma in broad papillary fibrovascular cores, presence of two cell types (epithelial and myoepithelial), normochromatic nuclei, scant mitotic activity, foci of apocrine metaplasia and lack of cribriform pattern[11]. In cases with florid epithelial hyperplasia or atypical ductal hyperplasia the diagnosis become difficult as these findings obscure the papillary nature of the lesion[6]. But, generally these are focal changes. Presence of diffuse sclerosis in stroma can also create confusion and mimicking as invasion. Immunohistochemistry for identifying the myoepithelial cells in difficult cases helps in diagnosis of these lesions [6].

Most of the benign papillary lesions showed less diagnostic problems. Low grade papillary lesions require special attention such as intraductal papilloma with atypical hyperplasia or papilloma with DCIS which collectively grouped under term atypical papillomas[10]. Atypical ductal papilloma showed low nuclear grade features with presence of a focal proliferation of atypical epithelial cells. Page et al. termed a lesion as papilloma with DCIS when it had morphology similar to non-comedo DCIS with a size greater than 3mm[11-13]. However, the same authors term lesions less than 3mm in size with epithelial proliferation as papilloma with atypia. In contrast, Collins et al. stated that diagnosis of atypical papilloma doesnot required the size and extent of the atypical epithelial proliferation in the lesion[11]. However, the diagnosis is made when there is morphological evidence such as architectural and cytological features of atypical proliferation in these lesions. Immunohistochemistry proved the decreased number of myoepithelial cells in aypical papilloma and help in diagnosis[14]. Myoepithelial cell may be scant or absent from this foci shows lack of staining for HMWK and expressed estrogen receptor. In problematic cases, HMWK is a useful adjunct to distinguish between ADH or DCIS and usual duct hyperplasia in a papilloma. The management of both intraductal papilloma with atypical hyperplasia and papilloma with DCIS is by complete excision and follow-up.

Intraductal papillary carcinomas is a rare entity comprises of only for 2% of all breast cancers and affect women in their fifth and sixth decade of life[15]. Presence of fibrovascular stalk in intraductal papillary carcinoma distinguished it by other types of intraductal carcinoma. [16]Morphologically, these lesions show near complete or complete absence of myoepithelial cells in the papillae with uniform population of atypical epithelial cells. Many of times tumor cells arrange in various patterns including micropapillary, cribriform or solid structures which obscuring the spaces between the papillary fronds. A potential diagnostic trap is the occasional presence of globoid cells which are scattered large pale eosinophilic cells, arranged along the basal layer, can be mistaken for myoepithelial cells. [11]

Encapsulated papillary carcinoma (Intracystic papillary carcinoma) is a well circumscribed papillary tumor surrounded by a thick fibrous capsule , centrally located and often presents as a breast mass with or without bloody nipple discharge. The fibrovascular cores are delicate and are surrounded by monotonous proliferation of atypical epithelial cells. As with intraductal papillary carcinoma , there is complete lack of myoepithelial cells along the fibrovascular cores, but in contradistinction to this , there is also an absence of myoepithelial cells at the periphery .[17] The question of whether an encapsulated papillary carcinoma represents an in situ lesion or an indolent form of invasive papillary carcinoma has not been resolved. However, diagnosis of invasive carcinoma made only when there is frank fibrous capsular invasion seen, otherwise it should be staged as papillary carcinoma in situ with excellent prognosis. Metastases of the regional lymph node in these cases very rarely occur without any evidence of invasion. Regardless of invasive nature they are associated with an excellent prognosis with adequate local therapy alone. [18-20]

Solid papillary carcinoma presents in older women with breast mass. Microscopically the tumor is composed of multiple, solid nests of neoplastic epithelial cells with a fine fibrovascular network conferring the papillary architecture. Production of mucin is common finding in solid papillary carcinoma. There is also complete absence of myoepithelial cell within the neoplastic nodule with some of nests lacks myoepithelial cell at the periphery. [21,22] Sometimes there is presence of myoepithelial cell layer in surrounding and classified as an in situ carcinoma. The major differential diagnosis is usual ductal hyperplasia. Recognition of fine fibrovascular core with monotonous appearance of epithelial cells, cellular polarization around fibrovascular cores, mucin production and mitotic activity favors solid papillary carcinoma over UDH. ER is strong and diffuse positive and CK5/6 is negative in solid papillary carcinoma. Solid papillary carcinoma (spindle cell type, neuroendocrine type) distinguished from papilloma with extensive florid epithelial hyperplasia by use of neuroendocrine markers (synaptophysin and chromogranin.

Invasive papillary carcinoma accounts for less than 2% of all the breast cancers. [23] In papilloma there is presence

of continous myoepithelial lining, whereas it absent in the papillae or at the periphery of the invasive papillary carcinoma with areas of stromal invasion, higher nuclear grade and necrosis. [1, 5]

Presence and distribution of myoepithelial cells is one of the most useful features as from the foregoing discussion in differentiating various papillary breast lesions. Since myoepithelial cells may be difficult to appreciate on routine H&E sections, Immunohistochemistry is extremely helpful and plays a pivotal role in differentiation of papillary breast lesions. Among all CK5/6 and P63 can be used as an initial panel of investigation when one is dealing with problematic papillary lesions of the breast, the results (and management protocol) should be interpreted with great attention as study groups using these marker was not enough large and for the individual marker, the sensitivity and specificity are not absolute. [23] For current scenario immunomarker plays most important role in diagnosis, however complete removal of papillary lesions with thorough histological examination still remains standard practice in problematic group of papillary breast lesions.

In the conclusion, assessment of papillary lesions continues to be one of the most problematic areas in breast pathology. Accurate diagnosis of papillary lesions remains challenging only by standard H&E staining due to overlapping features and wide spectrum ranging from benign to invasive carcinomas and their differential diagnosis are extremely demanding. Awareness of such differential diagnosis and adoption of specific diagnostic criteria of histomorphological approach and generous use of IHC are likely to improve consistency of diagnosis of these lesions. IHC is extremely useful in the diagnosis of papillary lesions and attention should be paid to the choice of biomarkers and the interpretation of the results.

Smaller study group and lack of follow up is important limitation of this study. To know the frequency of subtypes a similar study with larger no. of cases, over a longer duration, with stringent follow up should be attempted for better insight into the various prognostic factors of papillary lesions.

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Nil

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