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Original Research Article

Papillary Lesions of the Breast: Experience from a Tertiary Care Center

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Abstract

Introduction: Papillary breast lesions are a group of lesions that are characterized by presence of papillae supported by fibrovascular cores lined by epithelial cells with or without myoepithelial cell layer.

Aims: This study was conducted to analyse the clinicopathological characteristics of papillary lesions of the breast.

Materials and Methods*:* A retrospective and prospective analysis of 12 cases of papillary lesions of breast received over a period of 2 years was done. The patient's clinical details were collected from medical archives and the histopathological findings were reviewed. The lesions were classified into benign, atypical and malignant categories.

Results: During the study period, 12 cases of papillary lesions of breast were reviewed. The mean age was 43 years. The central quadrant was the most common location (66.6%). The most common presenting complaint was lump (75% cases), more commonly as solitary lump (83.3%) rather than multifocal disease (16.7%). Benign papillary lesions (58.3%) were more common than the malignant lesions (41.7%). The most common papillary lesion was intraductal papilloma (50% of the cases), followed by invasive micropapillary carcinoma and intracystic papillary carcinoma constituting 25% and 16.7% cases respectively.

Conclusion*:* Diagnosis of papillary lesions is challenging and its classification includes different entities that have specific diagnostic criteria. Due to their heterozygosity in morphology with benign, atypical and malignant subtypes, morphological features such as type of fibrovascular core and continuity of myoepithelial layer along with immunohistochemical stains for myoepithelial cells should be considered for accurate diagnosis and proper management.

Keywords: Fibro Vascular Core; Myoepithelial; Papillary Lesions.

Introduction

Papillary lesions comprise of a distinct spectrum of breast lesions and their diagnosis continues to be a challenge due to their heterozygosity in morphology, with benign, atypical and malignant subtypes, the differentiation of which may sometimes be difficult even for an experienced pathologist. They are rare and constitute less than 10% of benign breast lesions and less than 1% of malignant breast neoplasms [1–3]. There is

limited data in the literature that discusses their clinical presentation, detailed histopathological features including the presence of atypia or associated ductal carcinoma in situ and prognosis [4]. On the other hand, high frequency of coexistence of several lesions in presence of a papillary lesion and different terminologies used for the same papillary lesion sometimes make clinicians confused on decision making.

This study aimed at discussing the diagnostic difficulties of papillary lesions along with presence and absence of few critical histopathological findings. The objectives of the study were to analyze the different histopathological findings, both epithelial and stromal, in various papillary lesions and to identify those histopathological findings that can differentiate between benign, atypical and malignant papillary lesions. Immunohistochemical analysis was also conducted for myoepithelial cells, which aided in identifying benign, atypical and malignant papillary lesions and in analysis of hormonal status in all malignant cases.

Materials and Methods

A retrospective and prospective study of 12 papillary lesions of breast was conducted over a period of 2 years in the Department of Pathology of a tertiary health care hospital. Breast core biopsy specimens were excluded from the study and those cases, which fulfilled the definition of papillary lesions, were included.

The clinical history and radiological findings were retrieved from medical archives. Macroscopic findings were noted and microscopic findings were reviewed. While reviewing, importance was given to histopathological findings such as type of lesion whether infiltrating or non-infiltrating, presence of papillary pattern, architectural complexity, presence of fibrovascular core, whether broad and sclerotic or thin and arborizing fibrovascular cores, associated benign changes in the adjacent breast tissue. The lesions were classified according to WHO classification of papillary lesions (2012) [5,6].

Further, Immunohistochemical (IHC) staining was performed for myoepithelial cells, which aided in identifying benign, atypical and malignant papillary lesions and also to know the hormonal status in all malignant cases.

Various histopathological features were analysed for their frequency and were compared with the final diagnosis using cross tabs and Chi-square value (Ç2) with one-degree freedom, wherever appropriate. A p-value of <0.05 was considered significant for all the performed tests. All tabulations and statistical analysis was done using IBM SPSS 20.0 data software.

Results

A total of 12 cases of papillary lesions were seen during the study period. The mean age of the patients was 43 years (age range: 18-70 years). The central quadrant was the most common location (66.6%). The right side breast was most commonly involved (66.6%), followed by left side (16.7%) and bilateral breast (16.7%). The most common presenting complaint was lump (75% cases), followed by nipple discharge (16.7% cases), mastalgia and heaviness in the breast (8.3% cases). Ten cases (83.3%) presented as solitary lesion while two were multifocal. Further, these lesions were categorized into benign, atypical and malignant [Table 1].

Papillary lesions were categorized on the basis of fibrovascular cores as broad sclerotic type or the thin arborizing type. In 71.4% cases of benign lesions, broad sclerotic fibroepithelial cores were observed [Figure 1 (A-C)] and the remaining 28.6% of cases had a thin arborizing fibrovascular core [Figure 1(D-F)]. In comparison, 100% of malignant lesions predominantly showed thin, arborizing fibrovascular cores.

We observed a higher degree of association of epithelial proliferation and architectural complexity in malignant lesions (60-100% cases) compared to benign tumours (0-40% cases). The histopathological findings associated with papillary lesions are tabulated in [Table 2].

Table 1: Distribution of papillary lesions of the breast

Type of Papillary lesions	No.	%	Clinical Diagnosis	No.
Benign	7	58.3		
Intraductal papilloma- Solitary	6	50	Fibroadenoma	3
			Fibrocystic disease	2
			Duct ectasia	1
IntraductalPapillomatosis	1	8.3	Fibrocystic disease	1
Malignant	5	41		
Invasive micropapillary carcinoma	3	25	Carcinoma of breast	2
			Benign adnexal tumour	1
Intracystic papillary carcinoma	2	16.7	Carcinoma of breast	2

Table 2: Histopathological findings of papillary lesions of the breast

Histopathological findings		Benign	%	Malignant	%
Fibrovascular cores	Broad	5	71.4	0	
	Thin	2	28.6	5	100
Location	Central	6		2	
	Peripheral	1		3	
Number	Solitary	6		4	
	Multifocal	1		1	
Epithelial changes:					
Epitheliosis		2	28.6	5	100
Epithelial hyperplasia, usual type		2	28.6	4	80
Sclerosingadenosis		2	28.6	3	60
Comedo necrosis		0	0	3	60
Stromal changes:					
Fibrosis		3	42.8	3	60
Hyalinization		3	42.8	3	60
Sclerosis		3	42.8	3	60
Osteoclast giant cell		0	0	3	60
Calcification		1	14.3	3	60
Haemorrhagic/hemosiderin		1	14.3	4	80
Lymphocytic infiltration		2	28.6	3	60
Blood vessel proliferation		2	28.6	4	80

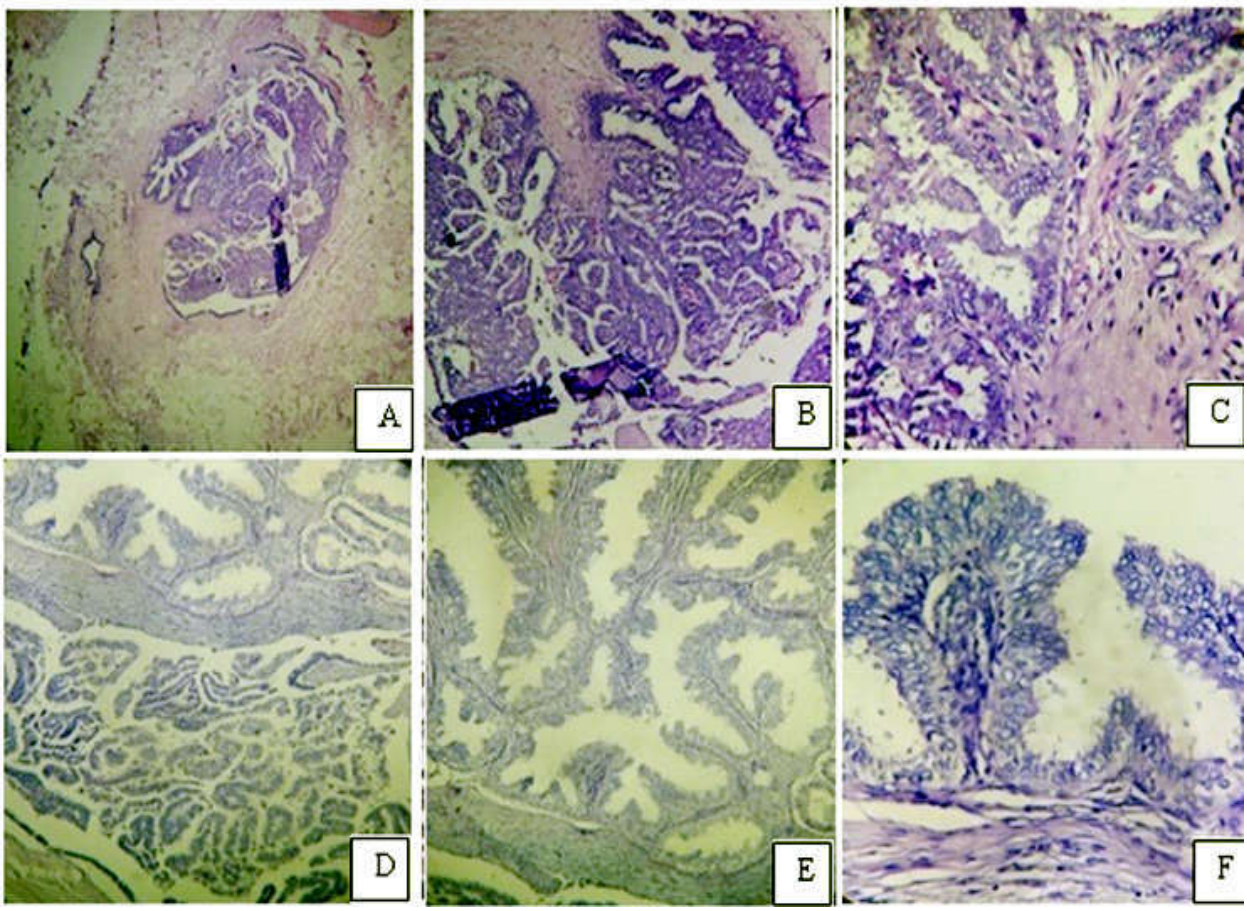

Figure 1: A-F: Intraductal benign papilloma (H&E): [A, B]: Papilloma with surrounding sclerotic stroma. (4x, 10x) [C]: Papilloma exhibiting broad sclerotic fibrovascular core. (40x) [D-F]: Papilloma with arborising papillary fronds and thin fibrovascular cores. (D, E: 10x; F: 40x)

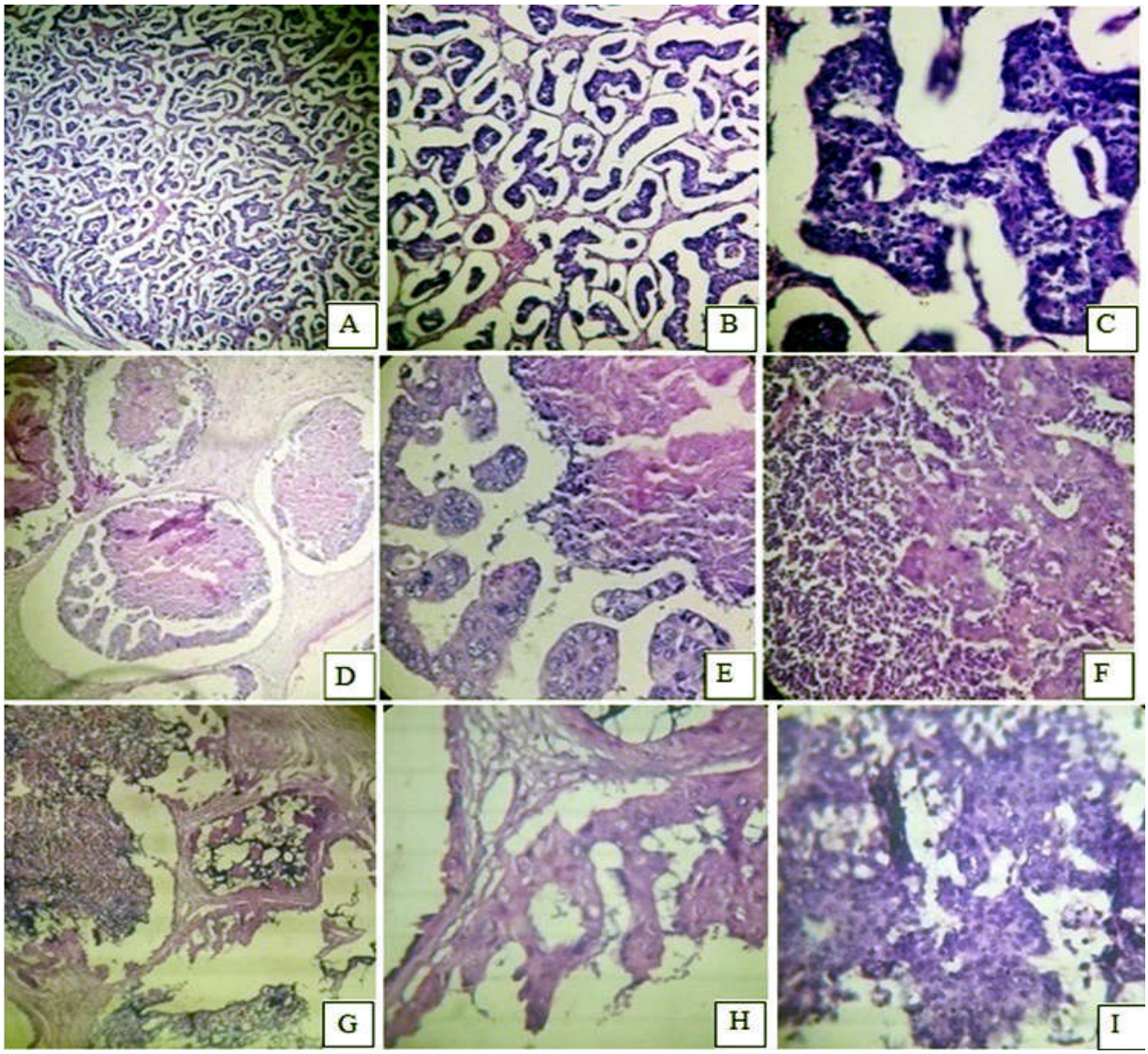

Fig. 2: A-C: Invasive Micropapillary Carcinoma (H&E): Tumour cells in micropapillary pattern lying in empty stromal lacunae and lacking true fibrovascular cores. (A, B, C: 4x, 10x, 40x respectively), D-E: Invasive Micropapillary papillary carcinoma (H&E): D, E: Micropapillary lesion lacking true fibrovascular cores with comedo neecrosis (D: 10x, E: 40x) F: lymph node with metastasis from micropapillary carcinoma. (40x), G-I: Intracystic Papillary carcinoma (H&E): Tumour composed of papillary fronds projecting into the lumen with absence of myoepithelial cells. (G: 4x; H, I: 40x)

The most common papillary lesion accounting for 50% of the cases was intraductal papilloma, seen in 6 cases with age of presentation ranging from 18-50 years. This benign tumour was usually solitary and was mostly well-circumscribed, nodular lesion that was located more commonly in the subareolar region. Intraductal papillomas exhibited various types of metaplasias most common being apocrine (57%) followed by mucinous (28.8%) and clear cell (14.2%) types.

A single case of papillomatosis was encountered in an 18-year-old female. Histopathological findings were similar to intraductal papilloma, but the attachment to the duct wall was discerned only focally.

Three cases of invasive micropapillary carcinoma with age of presentation 35, 58, 65 years respectively, were seen. [Figure 2 (A-C), Figure 2 (A-C)] Apocrine metaplasia was noted along with associated lesions like microcalcification, hyalinization, osteoclast like giant cells haemorraghe and hemosiderin pigment.

An interesting case of a 65-year-old female presented with mass in upper outer quadrant of right breast since 1 year, with exophytic growth above skin level, blackish, 9x8

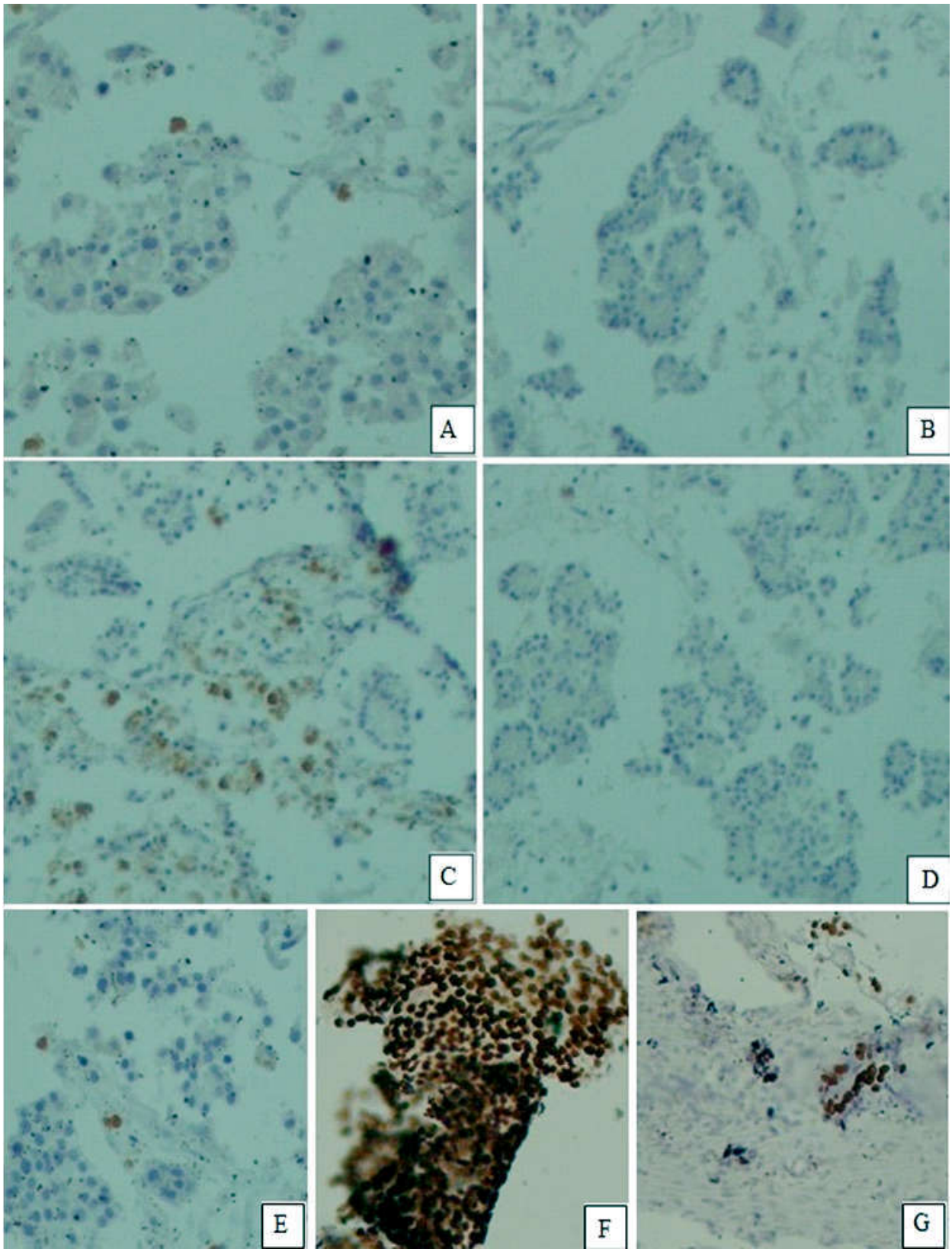

Fig. 3: A-D: Invasive Micropapillary carcinoma with absent myoepithelial cells (IHC): A: negative for p63 (40x) B: negative for CK6 (40x) C: negative for synaptophysin (40x) D: negative for chromogranin (40x), E-G: Intracystic Papillary carcinoma with absent myoepithelial cells (IHC): E: negative for p63 (40x) F: Positivite for ER (40x), G: focal Positivite for PR (40x)

cm, and firm, fixed. Cilinical diagnosis and FNAC was suggestive of benign adnexal tumor. A histological diagnosis of Invasive micropapillary carcinoma of breast was given and Immunohistochemical (IHC) staining was done to rule out neuroendocrine tumour. It was negative for p63, CK- 6, synaptophsin and chromoganin, thus confirming our diagnosis [Figure 3 (A-D)].

Intracystic papillary carcinoma also called, as encapsulated papillary carcinoma is a variant of intraductal papillary carcinoma. These lesions exhibit cystic spaces that surround papillary proliferation and lie within a dilated duct. They accounted for 16.6% of total number of cases [Figure 2(G-I)]. The age of presentation of these lesions were 50 and 62 years respectively. Apocrine metaplasia was noted along with associated lesions like microcalcification, hyalinization, comedo necrosis haemorraghe and hemosiderin pigment.

On statistical analysis the variables such as age, location, laterality, focality, epithelial change, stromal change, nuclear pleomorphism and presence or absence of broad sclerotic fibrovascular cores, only nuclear pleomorphism and presence or absence of broad sclerotic fibrovascular cores were found to be statistically significant with a p-value of <0.05. These two variables were also considered the reliable parameters on histopathology review of the slides.

Discussion

Papillary lesions of the breast include different entities based on clinical and morphological evaluation. They are characterized by the presence of papillary, arborizing epithelial proliferation, which is supported by fibrovascular stalks with or without an intervening myoepithelial layer [4]. Its diagnosis continues to be one of the most challenging aspects. Identification of whether the lesion is benign or malignant has a great impact on therapy [4]. In this study, the diagnostic issues in various types of papillary lesions encountered in our hospital are discussed.

Papillary lesions of the breast include benign forms comprising of intraductal papilloma (central, peripheral, or atypical- intraductal papilloma with ADH/DCIS/LCIS); juvenile papillomatosis and malignant lesions comprising of intraductal papillary carcinoma, encapsulated papillary carcinoma (without/with invasion); solid papillary carcinoma (in situ/invasive), invasive papillary carcinoma and invasive micropapillary carcinoma [5].

Intraductal papillomas are the most common type of papillary lesions and presents as solitary lesions in the subareloar region in most of the cases [7,8]. The most common clinical finding is the presence of palpable mass followed by presence of nipple discharge that can be either bloody, serous or serosanguinous in nature [9]. The diagnosis is usually straightforward with lesion characterized by arborizing papillae exhibiting fibrovascular stalks that are covered by myoepithelial cells [10]. In cases with florid epithelial hyperplasia or atypical ductal hyperplasia the diagnosis is difficult as these findings obscure the papillary nature of the lesion [4]. But, generally these changes are focal. Stromal changes such as diffuse sclerosis can also create confusion mimicking invasion. These papillomas are usually subjected to various morphological changes such as torsion with secondary haemorrhagic infarction of the papillae [7]. We encountered various epithelial and stromal changes like sclerosing adenosis, epitheliosis, fibrosis, hyalinization and haemorrhagic infarction. In difficult cases, immuno-histochemistry for identifying the myoepithelial cells proves the benign nature of these lesions [4].

Multiple papillomas or papillomatosis is a disease of younger age group. They most commonly affect the peripheral terminal duct-lobular units or distal portions of the terminal ducts unlike their solitary counterpart that affects almost always-central ducts [9-10]. The morphology of papillomatosis is similar to that seen in intraductal papillomas. Ueng et al., describes that papillomatosis generally have focal attachment to the duct wall [4]. However, there is enough evidence of multiple points of attachment of several papillae in papillomatosis [4-10]. WHO states the term papillomatosis is confusing and should be avoided as this term has also been used for usual ductal hyperplasia and multiple papillomas [1].

Most of the benign papillary lesions pose less diagnostic problems. Atypical epithelial proliferations (ADH and DCIS) may occur in papillomas, and are usually of low grade. Diagnosis of these low-grade papillary lesions such as intraductal papilloma with atypical ductal hyperplasia (ADH) or papillomas with Ductal Carcinoma Insitu (DCIS) also termed as atypical papillomas requires expertise [8]. Atypical ductal papillomas are defined as presence of a focal proliferation of atypical epithelial cells with low nuclear grade (WHO). Ueng et al. termed such lesions as low grade Ductal Intraepithelial Neoplasia (DIN) and described that these changes are seen only focally [4]. Different authors use different terminologies and criterias to identify these lesions [4,11,12]. Page et al. termed a lesion as papilloma with low-grade DCIS when it had morphology similar to non-comedo DCIS with a size greater than 3mm and intraductal papilloma with ADH when the atypical epithelial proliferation is < 3 mm [11]. However, the same authors term those papillomas that are more than 3mm in size with epithelial proliferation as papillomas with atypia. This definition replaces alternative terminologies that were focused on the proportion of atypical cells (30 or 90%) within a papilloma. In contrast, Collins et al. stated that the extent or the size of atypical epithelial proliferation in the lesion is not required for diagnosis of atypical

papillomas [13]. An intermediate- or high-grade DCIS within a papilloma can be diagnosed regardless of the extent of atypia. However, the diagnosis is made when there is morphological evidence such as architectural and cytological features of atypical proliferation in these lesions [13,14].

Atypical papillomas exhibit decreased number of myoepithelial cells that can be proved by immunohistochemistry. The management of both intraductal papillomas with ADH/DCIS is by complete excision and a stringent follow-up.

Papillary carcinoma constitutes less than 1-2% of breast carcinomas. They are generally non-invasive. However, some papillary carcinomas can have stromal invasion that displays morphological features of infiltrating ductal carcinoma [4]. The invasive nests can be either micro-invasive or grossly evident [17].

Intraductal papillary carcinomas are rare and accounts for 2% of all breast cancers. They affect women in their fifth and sixth decade of life [15]. It is distinguished by other types of intraductal carcinoma by the presence of a true fibrovascular stalk of the lesion [16]. Morphologically, these lesions are similar to DIN and show near complete or complete absence of myoepithelial cells in the papillae [4].

The diagnostic term for larger intracystic papillary carcinomas has changed to encapsulated papillary carcinoma because the fibrous capsule that surrounds these lesions usually lacks a myoepithelial cell layer [4]. 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, the diagnosis of frankly invasive carcinoma can only be made if invasion is present outside the fibrous capsule. If not, encapsulated papillary carcinoma should be staged as papillary carcinoma in situ, and has an excellent prognosis. Regional lymph-node metastases occur only rarely without evidence of invasion. These occur in elderly patients (average age of 65 years). The tumor often presents as a solitary, retroareolar well-defined mass on mammography, and a cystic lesion with solid components on ultrasound.

On gross examination, it commonly appears as a circumscribed friable mass within a cystic cavity, and hence is also termed intracystic papillary carcinoma. Histologically, one or more well-circumscribed nodular masses within a cystically dilated duct surrounded by a thick fibrous capsule are typically evident. The duct spaces are filled by slender fibro vascular stalks, which are devoid of myoepithelial cells. They behave indolently and are best regarded as intraductal papillary carcinomas for management purposes, particularly if persistence of a basement membrane around the duct can be ascertained with collagen IV or laminin immunostains [4].

Another form of sharply circumscribed, a variant of intraductal papillary carcinoma and frequently non-invasive papillary carcinoma is solid papillary carcinoma, but, in contrast to encapsulated papillary carcinoma, this tumor is usually composed of multiple adjacent nodules, and the papillary nature may not be readily apparent because of its predominantly solid growth patterns. Diagnostic criteria include the presence of small, monotonous cells with hyper-chromatic nuclei with significant mitotic activity with often at least focal granular eosinophilic cytoplasm that may show neuroendocrine or mucinous differentiation [5]. Generally, the prognosis is good, and when a surrounding myoepithelial cell layer is present, the tumor is classified as an in situ carcinoma.

Invasive Micropapillary Carcinoma (IMPC) is an aggressive yet rare form of breast cancer with a propensity for lymphovascular invasion and regional lymph node metastasis. It is characterized by micropapillary clusters of neoplastic cells, lacking true, central, fibrovascular cores and lying within fairly prominent clear empty stromal lacunae [4]. These tumours are of higher grade and exhibit higher nuclear pleomorphism. Often they show lymphocytic infiltration along with inverse polarity of tumour cell clusters with exposed basal layer. Foci of intraductal carcinoma are seen almost in all cases of micropapillary carcinoma [18]. This should not be confused with micropapillary DCIS; wherein the ducts are dilated and lined by very small tumour cells. Micropapillary DCIS is often multifocal and multicentric in contrast to IPMC, which often presents as palpable mass.

Invasive papillary carcinoma of the breast is regarded as a specially differentiated adenocarcinoma of the breast with papillary morphology, but otherwise no distinguishing clinical, genetic, or prognostic features [4].

Myoepithelial cell continuity was noted in all the benign papillary lesions, while there was complete absence of the myoepithelial cells. Morphology of the papillae differed in benign and malignant lesions. The papillae had broad and sclerotic fibrovascular cores in benign 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 [19].

Limitations

An important gap in the literature related to papillary lesions of the breast is the lack of universality in classifying the various lesions. This is due to use of various terminologies and criteria to categorize them. To the best of our knowledge, we have incorporated WHO classification to define these lesions, however, the classification is limited by certain overlapping features. The limitations of the present study were the small size of

population and lack of follow up. Larger studies and a stringent follow up especially in those cases where only lesional excisions were performed may throw a better insight into the various prognostic factors of papillary lesions.

Conclusion

To conclude, diagnosis of papillary lesions of the breast is challenging due to its varied clinical, radiological and pathological features that has direct impact on management. The continuity of myoepithelial layer and presence of broad and sclerotic fibrovascular cores are consistent features in benign papillary lesions. In this review, we have provided guidelines to distinguish and accurately diagnose the various papillary lesions based on H&E morphology. The diagnostic dilemma in papillary lesions of the also occurs in core biopsies where under-sampling can be a problem. Immunohistochemical work-up to identify myoepithelial cells is useful in distinguishing papillary carcinoma from atypical papilloma. Distinguishing papillary carcinoma from other papillary lesions of the breast is extremely important; therefore excision biopsy of the entire lesion is necessary in all suspected papillary lesions.

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