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HISTOMORPHOLOGY AND IMMUNOHISTOCHEMICAL STAINING PATTERNS IN PAPILLARY CARCINOMA BREAST: A SERIES OF 5 CASES

Ganguly S — Associate Professor, Department of Pathology, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh

Singh BP — Professor-Director & Head, Department of Pathology, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh

Thakur P* — Post Graduate Resident, Department of Pathology, Chhattisgarh Institute of Medical Sciences, Bilaspur, Chhattisgarh *Corresponding Author

ABSTRACT Papillary carcinoma breast is a rare type of breast malignancy accounting for only 0.5% of invasive breast cancers. According to the 2019 WHO Classification of Breast Tumors (5th edition), malignant papillary neoplasms comprise papillary ductal carcinoma in situ (DCIS), encapsulated papillary carcinoma (EPC), solid papillary carcinoma (SPC), and invasive papillary carcinoma (IPC). Histologic features of the tumor include cellular proliferations surrounding fibrovascular cores, with or without invasion. Conclusive differentiation between benign and malignant papillary breast lesions depends on demonstration of myoepithelial cells which may be difficult to discern on routine H & E stain. Therefore, IHC is a useful adjunct for evaluating the presence and distribution of myoepithelial cells in papillary neoplasms of the breast. Papillary carcinomas of breast are usually manifest the luminal A staining pattern (ER or PR positive; HER2 neu negative) along with negative staining for myoepithelial markers like p63 and calponin. In this case series, we report 5 cases of papillary neoplasms of breast reported at our institution, out of which one was a case of Encapsulated Papillary Carcinoma, while the other 4 were designated as Encapsulated Papillary Carcinoma with Invasion. Coexistent DCIS was seen in 3 cases, but due to the stringent criteria outlined in the latest WHO Classification, none of the tumors qualified to be designated as Invasive Papillary Carcinoma.

KEYWORDS : Papillary Carcinoma Breast, DCIS, Encapsulated Papillary Carcinoma (EPC), Solid Papillary Carcinoma (SPC), Invasive Papillary Carcinoma (IPC), IHC, ER, PR, Her2/NEU, Myoepithelial Markers, p63, Calponin

INTRODUCTION

Papillary carcinoma breast is a relatively uncommon breast malignancy and accounts for only 0.5% of invasive breast cancers.[1] These tumors typically present with bloody nipple discharge, an abnormal mass, or radiographic abnormalities.[2] Histologic features of the tumor include cellular proliferations surrounding fibrovascular cores, with or without invasion.[1,3] However, distinction of invasive papillary carcinoma from non-invasive forms is critical, as the encapsulated papillary carcinomas has much better prognosis than its invasive counterpart.[1] In general, papillary carcinoma of breast has an improved outcome compared to invasive ductal carcinoma. but comprehensive information on the clinicopathological characteristics, management, and survival is lacking due limited data in the literature.[4] In this case series, we present the clinical, histomorphological and immunohistochemical staining patterns of the 5 cases of papillary carcinoma of breast reported at our institution.

MATERIALS AND METHODS

5 cases of biopsy proven Papillary Carcinoma, Breast reported from the Department of Pathology, Chhattisgarh Institute of Medical Sciences (CIMS), Bilaspur were retrospectively analyzed. Detailed history and physical examination findings were recorded; including age, sex, side, localization, fixity and/or involvement of overlying skin, nipple discharge as well axillary/ other lymphadenopathy. Gross finding including size of lesions and presence/absence of grossly discernible intracystic component were noted. For histopathological analysis, H&E-stained slides were examined and diagnosis was confirmed by visualization of a predominantly papillary growth pattern characterized by the presence of arborescent fibrovascular stalks lined by epithelial cells.[1,3,4] Finally slides were subjected to immunohistochemical staining with ER, PR, HER2neu as well myoepithelial markers Calponin and p63.[4,5,6,12]

Observation

Table 1. Clinical Features and Gross Morphology

Case	Age/ Sex	Laterality	Side	Skin Involvement	Nipple Dis charge	Size in cm3	Intracystic Com- ponent
1.	51/F	Unilateral	Left	lymphedema (peau d' orange) change	present	6x6x3	absent
2.	45/F	Unilateral	Left	none	absent	4x4x5	absent
3.	70/F	Unilateral	Right	redness, tenderness on palpation	present	7x5x7	present
4.	46/F	Unilateral	Right	tumor fixed to overlying skin	present	7x4x6	absent
5.	56/F	Unilateral	Left	none	present	4x4x2	present

Clinical Features

All the 5 cases were reported in peri-or-post menopausal women in the age range of 45-70 yrs. All the lesions were unilateral. 4 out of 5 cases presented with nipple discharge and/or skin involvement. 2 cases showed cystic components in the lesion and 1 case showed evidence of axillary lymphadenopathy.

Gross Morphology

4 out of 5 tumors were large masses exceeding 7cm in diameter. Nipple areola complex was involved in 2 tumors. Peau d' orange change was grossly visible in 2 cases while, in 1 case (Case no. 3), the skin overlying the tumor was thickened and seemed to be infiltrated by the underlying tumor. Base was grossly involved in 2 tumors. Cut section showed 2 tumors developing inside cystic spaces. In 1 case (Case no. 5), the cystic space within which the tumor grew was well circumscribed, but in the second, (Case no. 3), the cyst contained hemorrhagic fluid along with a large exophytic intracystic tumor.

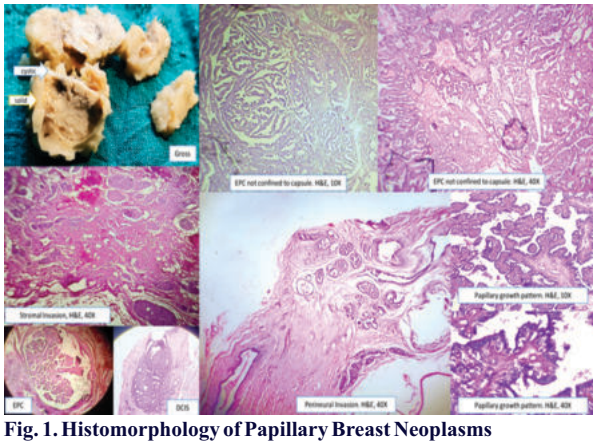

Fig. 1. Histomorphology of Papillary Breast Neoplasms

Table 2. Histomorphology

Case	Age	Sex	DCIS	Encap- sulation	Margins	Base	LVI	PNI	Calcifi- cation
1.	51	F	present	absent	involved	involved	+	-	-

2.	45	F	present	absent	not involved	not involved	-	-	-
3.	70	F	absent	present, but incomplete	involved	involved	+	-	+
4.	46	F	absent	absent	not involved	involved	-	-	-
5.	56	F	present	present	not involved	not involved	-	+	-

Histomorphology: All cases showed tumor cells arranged in papillary architecture around fibrovascular cores. Prominent intracystic tumor growth was evident in 2 cases. In 1 case (Case no. 3), the tumor grew within a well circumscribed cystic space, with no extension of tumor outside the cystic component; causing it to be diagnosed as Intracystic or Encapsulated Papillary Carcinoma (EPC).[1,7] However, in the second tumor, even though the bulk of the tumor grew within a cystic cavity, extensive infiltration into surrounding breast parenchyma, base, overlying skin as well as resection margins were visible. Except for the aforementioned case (Case no. 3), none of the other tumors showed high nuclear grade. 'Orphan Annie Eye' nuclei was seen in 1 case. None of the tumors showed Psammoma bodies, but microcalcifications were seen in 1 case (Case no. 3). This case also showed occasional areas of micropapillary, cribriform and solid patterns. Lymphovascular invasion was noted in 2 cases (including the aforementioned case), while perineural invasion was seen in 1 case (EPC). A DCIS component was found in 3 cases. Axillary lymphadenopathy found in a single case turned out to be reactive in morphology and negative for any metastatic deposits.

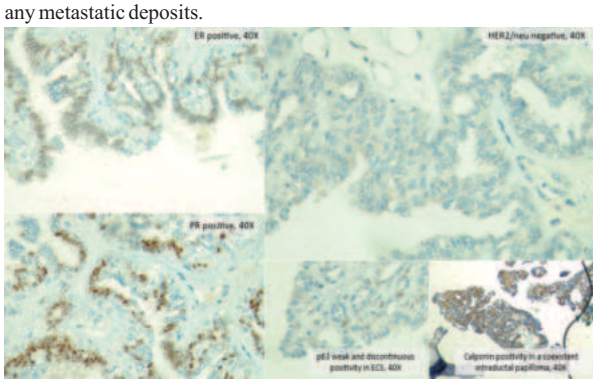

Fig. 2. IHC Staining Pattern of Papillary Breast Neoplasms

Table 3. IHC Patterns

Case	Age	Sex	ER	PR	HER2neu	p63	Calponin
1.	51	F	positive	positive	negative	negative	negative
2.	45	F	positive	positive	negative	negative	positive
3.	70	F	positive	positive	negative	negative	negative
4.	46	F	positive	positive	negative	negative	negative
5.	56	F	positive	positive	negative	weakly positive	negative

Immunohistochemistry (IHC) Staining Patterns: All 5 cases were stained positively for ER and negatively for HER2. Except for Case no. 2, all other tumors were also PR positive. Myoepithelial marker p63 stained negatively in all cases except the one diagnosed as Intracystic Papillary Carcinoma, in which a few cells showed weak and discontinuous positivity. The other myoepithelial marker Calponin also showed similar staining patterns, except for some areas of Case no. 2 surprisingly showing positive Calponin staining, in spite of well evident features of Invasive Papillary Carcinoma seen on H&E staining.

DISCUSSION

Papillary carcinoma breast is a rare form of breast cancer that is usually seen in non-Caucasian postmenopausal women in their 6-8th decade of life.[4] These tumors commonly present with bloody nipple discharge, as was observed in 4 out of 5 cases in our series.[1,2] Radiographic abnormalities like intracystic component and microcalcifications were also seen in 3 cases.[1,2,7]

According to the 2019 WHO Classification of Breast Tumors (5th edition), malignant papillary neoplasms comprise papillary ductal carcinoma in situ (DCIS), encapsulated papillary carcinoma (EPC), solid papillary carcinoma (SPC), and invasive papillary carcinoma (IPC).[1,7,8] Papillary DCIS is characterized by multifocal, peripherally distributed fibrovascular fronds lined by neoplastic epithelium but devoid of myoepithelial cells.[1,4] However, at times, a myoepithelial layer may be retained at the periphery of the involved duct, which may be evident as weak and discontinuous positivity demonstrated by myoepithelial markers.[1]

Encapsulated papillary carcinoma (EPC), also known as intracystic papillary carcinoma, is the term used to describe a solitary, cystically dilated duct surrounded by a fibrous capsule. The cyst cavity is occupied by a papillary tumor with a fibrovascular stroma covered by atypical epithelium with low or intermediate nuclear grade with no evidence of necrosis and rare mitoses.[1,7] Other architectural patterns may be seen in addition the classical papillary arrangement, including stratified spindle cell, cribriform and solid arrangements.[1] In our series purely intracystic encapsulated papillary carcinoma with no stromal, lymphovascular or perineural invasion was seen in only a single case (Case No.5). In all other cases, combinations of intracystic and invasive growth patterns were evident, which corroborates the statement of Steponavičienė et al that EPC is often associated with DCIS or invasive breast cancer[7] causing them to be labelled as EPC with Stromal Invasion. A DCIS component was seen in 3 out of 5 cases in our series.

Lymphovascular invasion (LVI) represents a major feature of biological aggressiveness among breast carcinomas and serves as an independent negative prognostic factor associated with local recurrence and distant metastasis, even in lymph node-negative patients.[9] In our series, LVI was seen in 2 out of 5 cases, including the one case with most widely invasive features (Case no. 3).

Even though perineural invasion (PNI) is a strong indicator of malignancy and is linked to adverse outcomes in malignant neoplasms; it can also be seen in many benign and non-invasive pathologic conditions, including non-invasive papillary breast lesions.[10,11] This can be the only rational explanation of our finding perineural invasion in the single case of encapsulated papillary carcinoma (EPC) which showed no other features of invasiveness.

After the revision of diagnostic criteria in the 2019 WHO Classification of Breast Tumors (5th edition), the term invasive papillary carcinoma (IPC) is reserved only for infiltrating breast carcinomas exhibiting an exclusively papillary morphology with more than 90% papillary structures in the invasive component.[1,4] With the exclusion of encapsulated papillary carcinoma with invasive features as well as solid papillary carcinomas from the diagnostic criteria, invasive papillary carcinomas have now become extremely rare.[1, 8] Consequently, none of the invasive papillary lesions qualified to be categorized as IPC in our series.

Papillary carcinomas of breast are usually manifest the luminal A staining pattern (ER or PR positive; HER2 neu negative)[12]; a fact corroborated by our study, as all 5 cases in our series showed similar IHC picture.[1,4,5,7,8] However, the conclusive differentiation between benign and malignant papillary breast lesions rests on the presence or absence of myoepithelial cells within the fibrovascular papillae.[1,7,8] Myoepithelial cells are, however, difficult to discern on routine H & E stain; therefore IHC comes forward as an useful adjunct for evaluating the presence and distribution of myoepithelial cells in papillary neoplasms of the breast.[1] Malignant papillary proliferations generally lack immunohistochemical expression of myoepithelial cell associated antigens like p63, calponin and within the papillary processes, though focal or patchy areas of immunoreactivity may be evident as partial or discontinuous staining in some cases of in cases of DCIS, encapsulated papillary carcinoma, and solid papillary carcinoma, especially if arising within a preexisting benign intraductal papilloma.[1]

Several markers, such as basal cell-type cytokeratins, smooth muscle actin, calponin, and p63, can be used to demonstrate the presence of myoepithelial cells in breast lesions,[6] out of which, p63 and calponin were employed in our study. As expected, 3 out of 5 cases showed negative staining for p63 and calponin, indicating an absence of myoepithelial cells and suggestive of malignant nature of the tumors.[1,4,5,6,7,8] However, patchy areas of weak and discontinuous p63 positivity in the encapsulated papillary carcinoma and aberrant calponin positivity in some portions of an otherwise invasive papillary neoplasm (H&E) could be suggestive of coexisting intraductal papilloma with papillary carcinoma, keeping our study in concurrence

with that Li et al who found reported that 18.36% of intraductal papillomas coexist with malignancy, of which papillary carcinomas constitute about 8.02% cases.[13]

CONCLUSION

Malignant papillary neoplasms of the breast are extremely rare and there is limited data in literature regarding their clinical presentation, histomorphology and management. Due to significant coexistence of benign and malignant papillary tumors of the breast, the crucial importance of myoepithelial stains must be particularly underscored in order to recognize their respective histological and immuno-histochemical characteristics, especially on trucut biopsy and thereby aid in appropriate risk stratification in these patients.

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