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Spectrum of papillary lesions of breast with immunohistochemistry and review of literature

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Abstract

Background: Papillary lesions of breast are very rare. They are classified as benign, borderline and malignant. Benign papillary lesions constitute less than 10% of all benign lesions of the breast and malignant papillary are less than 1% of all malignancies of breast. All papillary lesions appear similar on histopathology but they behave differently.

Objective: To differentiate the papillary lesions of breast with help of Immunohistochemisry (IHC) markers like P63, CK5/6, CD10 and SMA.

Material and Methods: This is retrospective study over a period of 5 years. We have done all above markers on histopathologically diagnosed cases of papillary lesions of breast.

Results: Out of 41, benign papillomas were 23 and invasive papillary carcinomas were 8, 5 cases were atypical papilloma and 5 were intracystic papillary carcinoma. The age group of patients was between 21 to 75 years with median age 40years. Lump in the breast was commonest presenting complaint.P63 was the most sensitive markers with minimum cross reactivity.

Conclusion: P63, CK5/6, CD10 and SMA can be used to differentiate between papillary lesions of the breast .P63 is more sensitive among all.

Introduction

Papillary lesions of the breast are a group of lesions characterized by the presence of stromal fibrovascular cores derived from the wall of the ducts within the breast. These fibrovascular cores are lined by epithelial cells. There are intervening myoepthelial cells between the epithelial cells and fibrovascular cores.Benign papillary lesions include solitary and multiple papillomas as well as florid and atypical hyperplasia within papilloma. Malignant papillary lesions include ductal carcinoma in situ arising in a papilloma, papillary carcinoma insitu, intracystic papillary carcinoma, solid papillary carcinoma as well as invasive papillary carcinoma. According to Tavassoli, the most important feature for distinguishing a papilloma from a papillary carcinoma is the presence of a relatively uniform myoepthelial layer in the proliferating intraluminal component of the lesion, and the absence of the basal myoepthelial layer in the papillary processes almost always indicates a carcinoma.[(1)]

There are many different myoepthelial markers, the most commonly used is p63. The detection rate of myoepthelial cells in benign papilloma is up to99-100%.[(2,3)] There is no cross reactivity with the epithelial cells and positive staining for stromal cells is 10%.[(2)] P63 is a good marker and antibody of choice. One more advantage for p63 is it has nuclear staining in contrast to all other myoepithelial markers which has cytoplasmic positivity. Interpretation with p63 is easy and accurate.

Smooth muscle actin (SMA) is another marker, but sensitivity is less than p63 and staining of stromal cells is much higher compared to p63. This creates an interpretation problems if stromal fibroblasts are located near the fibro vascular core.[(2)]

CD10 or CALLA antigen is also a useful marker to demonstrate myoepithelial cells. The sensitivity is 91-93% and cross reactivity is 28% which is less than SMA.

CK 5/6 will show cytoplasmic and membranous positivity in 84-100%ductal hyperplasia of papilloma in contrast to atypical hyperplasia or carcinoma insitu within papilloma where staining is negative or weak.[(4,5,6)]

Material and Method

The retrospective study comprises 41 cases of papillary lesions of breast over a period of 5 years. The exclusion criteria were unavailability of case history and paraffinblocks. Detailed clinical information was recorded from case sheets .This included age and sex of patient, duration of lump, site and quadrant of breast, associated findings like discharge from nipple, retraction of the nipple. All the cases were diagnosed on Haematoxylene & Eosin (H&E) slides. We reviewed H&E slides and performed following Immunohistochemisry (IHC) markers like P63, SMA, CK5/6, CD10, ki67. For IHC antigen retrieval was done in citrate buffer using pressure cooker. Diaminobenzidine was used as a chromogen. IHC studied was reviewed by two pathologists trained in Immunohistochemisry.

Result

This is retrospective study over a period of 5 years. We had total 41 cases of papillary lesions of the breast.

Out of 41 patients, the age group range from 21 years to 75 years. The youngest patient was 21 years who was diagnosed with intraductal papilloma. The oldest patient presented with a nipple discharge and a hard lump, later on diagnosed with invasive papillary carcinoma of breast.

The chief complaint of patients was lump in breast followed by nipple discharge. Out of 41 patients, 23 patients presented with lump in breast and 13 patients with nipple discharge as well as lump in breast. In 5 patients only nipple discharge was the presenting complaint.[Table1]

Table 1: Presenting symptoms in cases diagnosed as papillary tumors

Presenting symptoms	No of patients(n=43)
Lump in the breast	23
Lump and nipple discharge	13
Nipple discharge	5

Out of 41 cases maximum i.e. 23 were papillomas, 05 cases were papillary DCIS, 05 cases of intracystic papillary carcinoma, and 8 cases were invasive papillary carcinoma. Out of 23 papillomas 15 were single intraductal papillomas, 4 were multiple papillomatosis, and 4 papillomas were associated with florid epithelial hyperplasia. [Table 2]

Benign papillomas constitutes largest group including 23 cases. Out of 23 Cases, 15were excision biopsy and 8 were needle biopsy.

Table 2: Histopathological diagnosis of the papillary neoplasms

Diagnosis	Number of cases(n=43)
Benign papillomas (including multiple papillomatosis and florid ductal ductal hyperplasia)	23
Atypical papillomas (associated with Atypical ductal hyperplasia or DCIS)	5
Intracystic papillary carcinoma	5
Invasive papillary carcinoma	8

Immunohistochemical features of papillary neoplasm.[Table 3]

All cases of benign papillomas showed positive immunostaining with P63, SMA, CD10, and CK5/6. [Fig. 1]

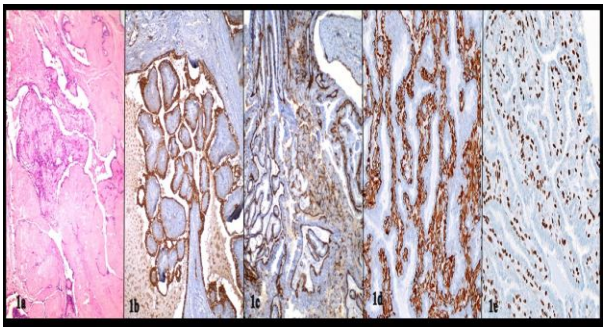

Fig. 1a: Shows benign papilloma on H&E, b: Shows CK5/6 positivity in benign papilloma, c: Shows CD 10 positivity in benign papilloma, d: Shows SMA positivity in benign papilloma, e: Shows P63 positivity in benign papilloma

P63 was positive in all benign papillomas. It showed nuclear positivity without cross reactivity.

SMA was positive in 20 cases of benign papillomas.10 cases showed stromal cross reactivity.

CD10 was positive in 21 cases with cross reactivity in 6 cases.

CK5/6 showed cytoplasmic and membranous positivity and it was positive in 20 benign papillomas.

All the markers were negative in ADH areas of atypical papillomas and focally positive in papillary DCIS and totally negative in intracystic papillary carcinoma and invasive papillary carcinoma.[Fig.3] Positive index of Ki67 was high in invasive papillary carcinoma [Fig. 3b].

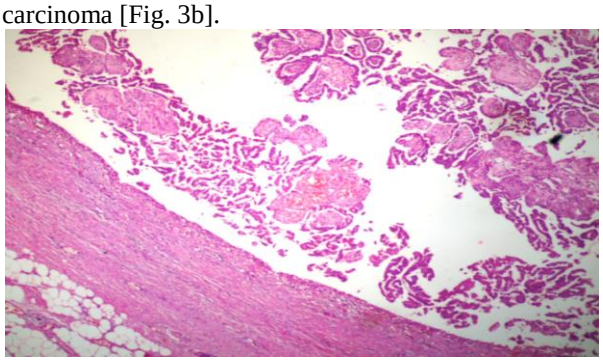

Fig. 2: Shows Intracystic papillary carcinoma of breast

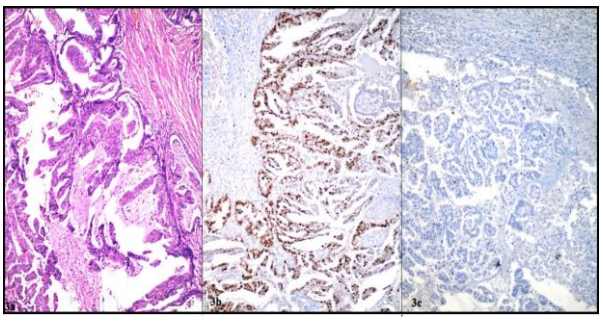

Fig. 3a: Shows invasive papillary carcinoma of breast, b: Shows Ki67 positive in invasive carcinoma of breast, c: Shows P63 negative in invasive carcinoma of breast

Table 3: Immunohistochemical features of papillary neoplasm

	CK5/6	SMA	CD10	P63
Benign papillomas	Positive	Positive	Positive	Positive
Atypical papillomas	Negative in ADH area	Negative in ADH area	Negative in ADH area	Negative in ADH area
Papillary DCIS	Focally positive	Focally Positive	Focally positive	Focally positive
Intracystic papillary carcinoma	Negative	Negative	Negative	Negative
Invasive papillary carcinoma	Negative	Negative	Negative	Negative

Discussion

Papillary lesions of the breast are very rare accounting for 10% all benign lesions and 1 to 2% of all malignancies of breast.[7] The diagnosis of papillary lesions particularly on needle biopsy is quiet challenging. The goal of this study was to evaluate myoepthelial markers like P63, SMA, CK5/6, and CD10 in differ anting a benign from malignant lesions.

There was no staining intraluminal portion in carcinoma patients while intraductal papillomas showed positive staining of myoepthelial layer.

Based on our findings, P63 was very clean marker with minimal cross reactivity with myofibrooblasts and smooth muscle cells. It has nuclear staining and it is easy to identify myoepthelial cell layer. It was positive in all benign papillomas which was correlated with study done by Lui pc et al group.[2]

SMA is another marker with less sensitivity as compared to P63.In our study 20 benign papillomas out of 23 were positive for SMA .The figure correlated with Lui pc et al group in which SMA could detect 88% of cases.[2] Also there was cross reactivity with stromal cells which created confusion in reporting.

CK5/6 shows cytoplasmic and membranous staining in myoepithelialcells. In one study done over 700 cases CK 5/6 stained myoepithelial cells in all benign, malignant and normal breast.[8] In our study it was positive in 20 benign papillomas and negative in malignant cases. CK 5/6 is used to differentiate between florid ductal hyperplasia and atypical ductal hyperplasia or carcinoma in situ. In florid ductal hyperplasia it is reported to be positive in 84-100% of cases while in atypical ductal hyperplasia or carcinoma in situ the staining is weal or negative.[9,10,11]

CD 10 is acute lymphoblastic leukemia antigen has been demonstrated to be useful myoepithelial marker. In one study done on 100 benign papillomas, sensitivity of CD 10 was 91-93% and cross reactivity to stromal cells was 28% which was less as compared to SMA.[2]

In cases of intracystic papillary carcinoma and invasive papillary carcinoma as myoepithlial layer is absent all the markers i.e. P63, CK5/6/, SMA, CD 10 were negative.

Conclusion

Differentiation of papillary lesions of breast is difficult and Immunohistochemisry markers can be very helpful. Markers used to differentiate are p63, SMA, CD10, CK5/6. P63 has highest sensitivity and lowest cross reactivity and easy to interpret nuclear positivity. SMA has more cross reactivity as compared to p63, CD10 and ck5/6. Ck 5/6, in addition to myoepthelial cells are useful in differentiating various types of hyperplasia.

Though Immunohistochemisry is useful adjuvant tool, complete removal of papillary lesions with full histological assessment is mandatory in management of this group of problematic breast lesions.

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