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Papillary Lesions in Breast Pathology Practice: Diagnostic Challenges and Practical Approach. A Six-Year Experience from a Tertiary Care Hospital

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Abstract:

Aims and Objectives: *1. Retrospective study of papillary lesions of the breast diagnosed on core needle biopsies (CNB); 2. Correlation of CNB diagnosis with diagnosis on excision biopsy, using immunohistochemistry (IHC) for myoepithelial markers where appropriate.*

Methods: *One hundred six cases of papillary lesions of the breast diagnosed on CNB over a six year period (from Jan 2010 to Dec 2016) were studied and correlated with their diagnosis on excision biopsy.*

Results: *The pathologic diagnosis for the 106 papillary lesions obtained at core biopsy was benign in 89 cases, atypical in 11, and malignant in 6. Four of the 89 benign lesions were 'upgraded'. The total upgrade rate for papillary lesions without atypia and with atypia was 4.49% (4/89 cases) and 45.4% (5/11 cases) respectively. The overall positive predictive value for malignancy (including DCIS) with core needle biopsy was 85.7% while the negative predictive value was 94.9%. All cases classified as malignant on CNB turned out to be malignant on excision biopsy.*

Conclusion: *Papillary lesions of the breast are heterogeneous and CNB diagnosis can be diagnostically challenging due to limited sampling, difficulty in accurately characterizing atypia and conclusively ruling out in-situ or invasive components; potentially leading to an erroneous diagnosis. Therefore all such lesions must be excised and subjected to carefully selected IHC markers. This study identifies the most common breast lesions sent to our consultation practice, reiterates salient diagnostic features, differential diagnoses and common pitfalls as well as provides a practical approach that can solve most of these diagnostic dilemmas.*

Keywords: ***Benign Intraductal Papiloma, Juvenile papillomatosis, Atypical papilloma, Papilloma with ductal carcinoma in situ (DCIS), Papillary DCIS, Encapsulated papillary carcinoma, Solid papillary carcinoma.***

Introduction

Papillary lesions of the breast are a heterogeneous group of neoplasms, and include benign intraductal papilloma (IDP), Juvenile papillomatosis, Atypical papilloma (or IDP with atypia), Papilloma with DCIS, Papillary ductal carcinoma in situ (papillary DCIS), and variants of papillary carcinoma (encapsulated/intracystic and solid papillary carcinoma). These neoplasms are unified by 'papillary' morphology, i.e. arborizing fronds with fibrovascular cores of various thicknesses and lining epithelium.[1] While identification of papillary architecture is often straightforward, subclassification can often prove diagnostically challenging on needle core biopsies (CNB) due to limited material. Their distinction requires due consideration of clinicoradiographic features, understanding of the various terminologies, astute histologic evaluation and judicious use of IHC.

Papillary lesions of the breast are currently classified as equivocal lesions on CNB and equivalent to a diagnosis of B3/uncertain malignant potential according to UK and European guidelines.[2] Thus a diagnostic excision is recommended for all of these lesions. In our centre, a diagnosis of a papillary lesion on core needle biopsy (CNB) following clinical or mammographic detection, leads to an excision biopsy, regardless of the annotation of presence or absence of atypia, in situ or invasive neoplasia. Proceeding to subsequent excision is based on two assumptions: first that papillary lesions are heterogeneous and that sampling error may occur on CNB, potentially missing a malignant component, and secondly, atypia and neoplasia can be difficult to accurately characterize in a papillary lesion, potentially leading to an erroneous diagnosis on CNB. Herein we present the clinicopathological experience and correlation between CNB and excision biopsy diagnoses of

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papillary lesions of the breast at our centre over a six-year period.

Materials and Methods

A review of the hospital data base was performed to identify all diagnoses of papillary lesions made on standard CNB (14 gauge) from 2010 until 2016 (i.e. a six year period). Papillary lesions were excluded from the study if additional findings were present on the CNB which would have led to a recommendation of subsequent excision, regardless of the concomitant diagnosis of a papillary lesion (e.g. invasive neoplasia). However, cases were retained in the study whether or not 'atypia' was used to describe the papillary lesion, in the absence of any other significant diagnosis. All papillary lesions, regardless of atypia, had been recommended for excisional surgery as standard practice and thus excision biopsies were available in all cases. The clinicoradiological features which had prompted the CNB were noted in each case. The study was approved by the institutional Ethics and Research Committee.

Results

A total of 106 cases were identified with a CNB diagnosis of a papillary lesion and with no other significant finding. The age range of the cases was 25 to 68 years, with the largest number of cases in the age group of 41-50 years (Table 1). All cases had had mammographic abnormality in the form of microcalcifications or lesion other than microcalcification (LOTM) that had prompted the needle biopsy. Seventy six patients had been symptomatic with subareolar lump, nipple discharge or both (Table 2). Excision biopsy was recommended and available in each case.

Table 1: Age distribution of the cases

Age group (years)	Frequency (n = 106)	Percent (%)
< 30	2	1.8
30 - 40	14	13.2
41 - 50	74	67.9
51 - 60	10	9.4
61 - 70	6	5.6

All CNB diagnoses were compared with the final diagnoses on excision biopsy in order to assess the accuracy of prediction of malignancy. The pathologic diagnosis for the 106 papillary lesions obtained at core biopsy was benign in 89 cases, atypical in 11, and malignant in 6. Surgical open biopsy correlations were available for all the lesions (Table 3). 89 of 106 cases were diagnosed as benign papillary lesions on CNB and the histologic diagnosis on excision was in agreement in all but 4 cases (i.e. four cases were 'upgraded'). Two of these turned out to be papillary DCIS while the other two were Encapsulated papillary carcinoma (two) on IHC. The mean age of these patients was 50 years and the mean tumor size was 2.7 cm. The total upgrade rate for papillary lesions without and with atypia was 4.49% (4/89 cases) and 45.4% (5/11 cases) respectively. In our series, the overall positive predictive value for malignancy (including DCIS) with core needle biopsy was 85.7% while the negative predictive value was 94.9%. On the other hand, all cases classified as malignant on CNB turned out to be malignant on excision biopsy.

Table 2: Clinico-radiological features of the cases

Clinicoradiological features	Number of cases	Percentage of cases
Abnormal mammography	**n= 106**	
Microcalcifications	79	74.5%
Lesion Other than microcalcifications (LOTM)	27	25.5%
Symptomatic patients	**n=76**	
Nipple discharge only	57	75%
Subareolar lump only	4	5.3%
Both discharge and subareolar lump	15	19.7%

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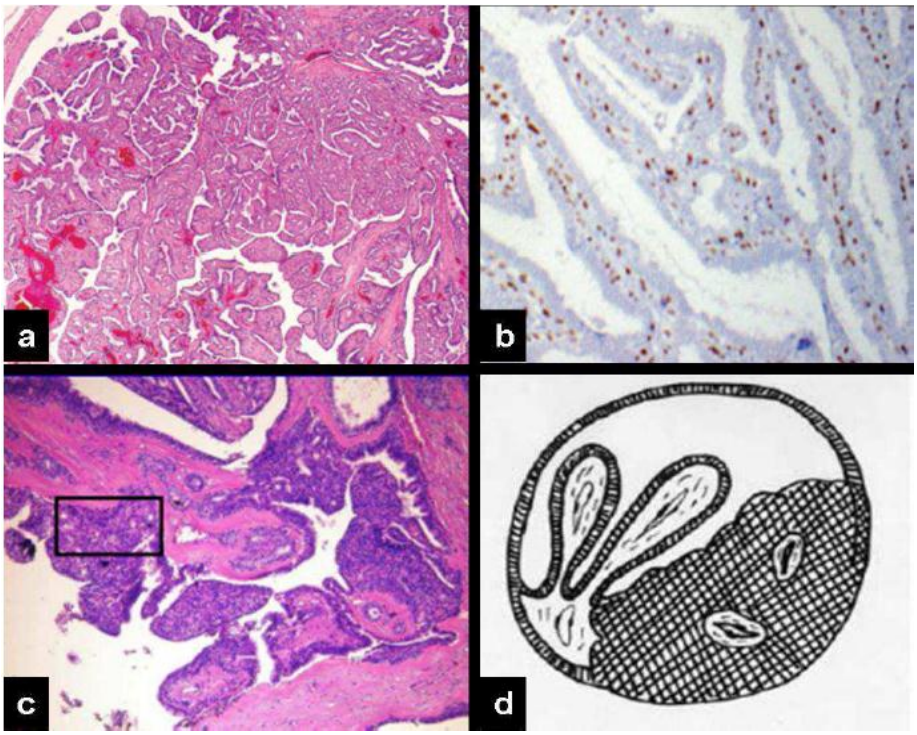

Fig 1 (a) Intraductal papilloma: The fibrovascular stalks are typically broad with variable degree of stromal fibrosis (H&E, x40); **(b)** The presence of the intervening myoepithelial cell layer in the papillae is highlighted by p63 immunostaining (x100); ***(c) Intraductal papilloma with usual epithelial hyperplasia*** (H&E, x40); **(d)** Schematic representation of the same showing a solid sheet of epithelial cells almost obscuring the lumen of a large duct *(Adapted from Moritani S et al. Virchows Arch 2007; 450: 539-47).*

Table 3. Histologic findings at CNB and surgical excision

Histologic findings on CNB	**n = 106**	**Histologic findings at surgical excision (n = 106)**	
Benign Papillary Lesion	n = 89	Intraductal papilloma [Fig 1(a) & (b)]	56
		Papilloma with Hyperplasia of Usual Type (Papillary Hyperplasia) [Fig 1(c) & (d)]	14
		Papillary Apocrine Metaplasia [Fig 2(b)]	6
		Nipple adenoma (Florid papillomatosis of the nipple)	4
		Sclerosing papilloma/Complex Sclerosing Lesion	3
		Juvenile Papillomatosis	2
		Papillary DCIS NST (Low nuclear grade) [Fig 2 (d)]	*2*
		Encapsulated Papillary Carcinoma [Fig 3(a) & (b)]	*2*
Papillary Lesion with Atypia / Atypical Papillary Hyperplasia	n = 11	Papilloma with Hyperplasia of Usual Type (Papillary Hyperplasia)	6
		Papillary DCIS NST (Low nuclear grade)	*3*
		Solid papillary carcinoma with invasive ductal carcinoma NST [Fig 4(a)]	*2*
Neoplastic Papillary Lesion - Malignant	n = 6	*Papillary DCIS NST (High nuclear grade)*	*2*
		Encapsulated Papillary Carcinoma	*2*
		Solid papillary carcinoma [Fig 3(c) & (d)]	*1*
		Solid papillary carcinoma with coexisting Invasive carcinoma	*1*

DCIS ductal carcinoma in situ; NST No special type
Malignant diagnoses on excision biopsy are in italics

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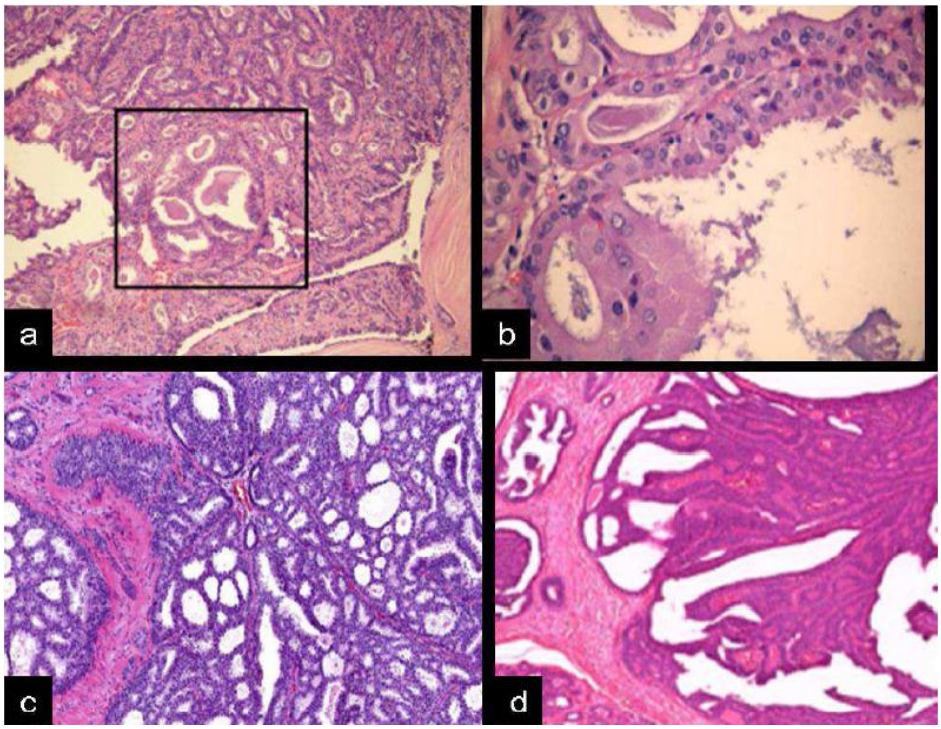

Fig 2 (a) ***Atypical Papilloma*** with focal atypical epithelial proliferation and low grade nuclei (H&E, x40), ***(b) Atypical Apocrine metaplasia*** showing apocrine cells with a three-fold variation in nuclear size (H&E, x100), ***(c) Papilloma with ductal carcinoma in-situ (DCIS)*** showing monomorphic epithelial cells with a polarized, cribriform pattern (H&E, x40), ***(d) Papillary ductal carcinoma in situ (DCIS)*** of no special type. Higher-power view illustrating tufts of proliferating cells projecting into the lumen of the ductal spaces (H&E, x40).

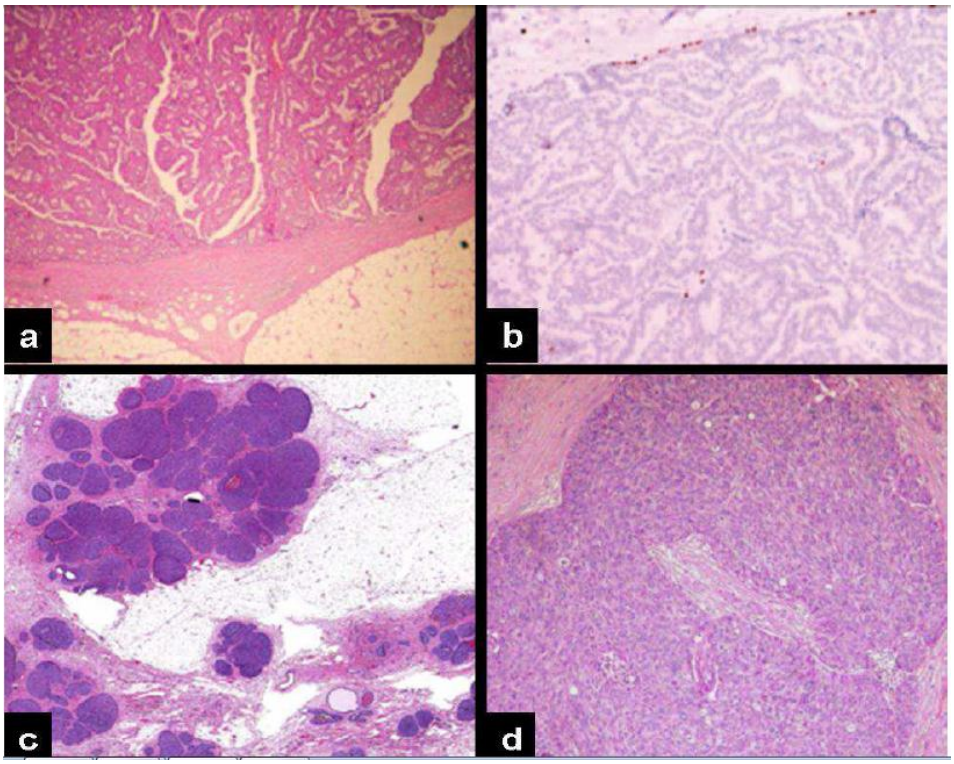

Fig 3 (a) ***Encapsulated papillary carcinoma (EPC),*** Low-power view illustrating a solitary tumor with thin, complex arborizing papillary fronds, surrounded by a fibrotic rim **(b)** ***EPC***, IHC for p63 shows a patchy myoepithelial cell layer around the duct and almost complete absence of myoepithelial cells within the papillary fronds (x40), **(c)** ***Solid papillary carcinoma (SPC)***, Low-power view, showing multiple solid nodules with delicate fibrovascular stroma. **(d)** ***SPC***, The tumor cells are low grade, have amphophilic granular cytoplasm and lack myoepithelial cells at their periphery. Focal rosette formations are seen.

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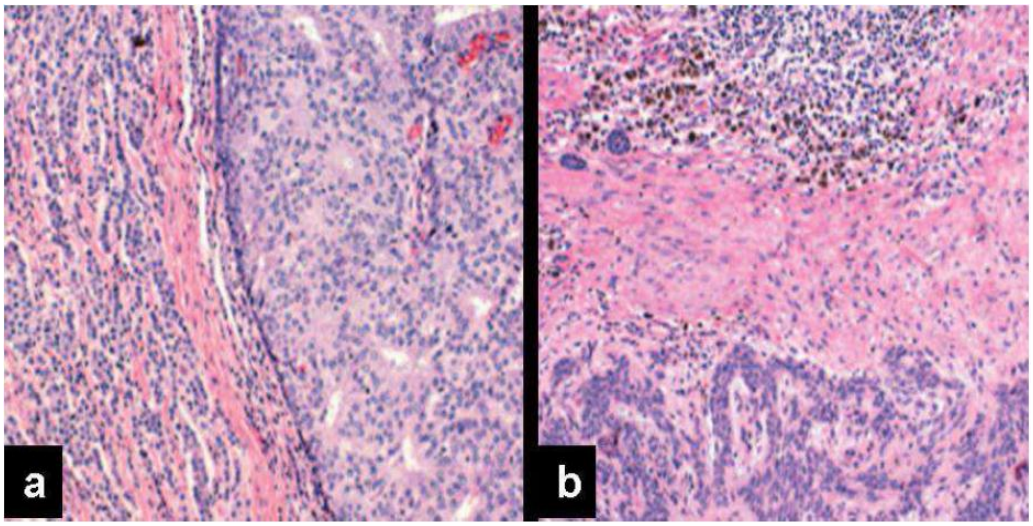

Fig 4 (a) ***Solid papillary carcinoma with invasive ductal carcinoma NST***, A relatively circumscribed papillary lesion (right) with adjacent infiltrating duct carcinoma (on the left) (H & E, x 40); **(b)** ***Epithelial displacement,*** Displaced clusters of epithelial cells in the background of biopsy-site changes (abundant hemosiderophages, macrophages and lymphoplasmacytic infiltrate) adjacent to the distorted edge of an intraductal papilloma (H & E, x 40).

Discussion

Papillary lesions comprise a diverse group of breast lesions that span the spectrum of hyperplastic and neoplastic processes and thus have different biological behavior.[3] Correct diagnosis of this group of superficially similar but biologically distinct lesions is important because of the differences in management and outcome.[4] Breast screening programs aim to reduce morbidity and mortality related to breast cancer by detecting microcalcifications or LOTM that prompt a CNB, the advantages of which have been well documented in literature. It is less invasive, does not deform the breast and can be performed quickly. Large core biopsy is now suggested at most centers because of its better characterization of benign and malignant lesions and lower frequency of insufficient samples.[5] According to the report by Wu et al 14-gauge core biopsy can provide a definitive diagnosis in 99% of solid tumors excluding papillary lesions.[6]

Despite different patterns of involvement and staining, intraductal papillomas (IDP) with extensive DCIS, papillary DCIS, and papillary carcinoma may be difficult to distinguish and interpret, especially if there is limited or fragmented tissue as in a core biopsy. To confound matters, these lesions may coexist. In these cases, the pathologist cannot always provide definitive diagnoses and instead, usually designate the lesion as papillary carcinoma, at least in situ and defer definitive Fig 4 (a) Solid papillary carcinoma with invasive ductal carcinoma NST, A relatively circumscribed papillary lesion (right) with adjacent infiltrating duct carcinoma (on the left) (H & E, x 40); (b) Epithelial displacement, Displaced clusters of epithelial cells in the background of biopsy-site changes (abundant hemosiderophages, macrophages and lymphoplasmacytic infiltrate) adjacent to the distorted edge of an intraductal papilloma (H & E, x 40). classification till excision biopsy is available.[1] The presence or absence of myoepithelial cell layers in the papillary component of the lesion is the most important feature to differentiate a benign papilloma from a papillary carcinoma. The role of assessing myoepithelial cells in papillary lesions of the breast is twofold. The first is to identify the presence of myoepithelial cells that are interposed between the stromal fibrovascular cores and the overlying epithelial cells, and this is useful in the differentiation of papillary ductal carcinoma in situ and papilloma. The second role is to assess the presence or absence of a complete myoepithelial cell layer around the papillary lesion, particularly important in encapsulated papillary carcinoma. Table 4 shows salient HPE and IHC features that can help in distinction of these papillary lesions.

Bianchi et al[7] included a comprehensive literature review on the outcome of 3032 lesions from 54 series diagnosed as papillary lesions without atypia on CNB. The mean upgrade rate to malignancy was 7.6%, although the upgrade rate varied widely between series (0–29%). The current series had an almost identical upgrade rate to the published mean, i.e., 4.5% (4/89 cases), giving a negative predictive value of 94.4% when a papillary lesion without atypia was diagnosed on CNB.

Atypia associated with papillary lesions or focal atypical epithelial proliferation can be recognized on CNB and must be commented upon. Wen et al[8] described a meta-analysis of 34 studies in which a papillary lesion with atypia was diagnosed on CNB and found an upgrade rate to malignancy of 36.9%. Similarly, a recent review of published literature

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by Bianchi et al [7] indicated a mean upgrade rate to malignancy of 34%. Therefore, there is an overall consensus in the literature that this diagnosis should lead to excisional biopsy.[9] In the current series, the overall upgrade rate to malignancy (including DCIS) was 45.4% (5/11) when a papillary lesion with atypia was diagnosed (Table 3). Therefore, the results of this study and those previously published indicate that it is mandatory to comment on the presence or absence of atypia when a papillary lesion is diagnosed on CNB and that 'atypia' should definitely lead to excision.

The WHO definition of papillary carcinoma in situ (Papillary DCIS) requires that 90% or more of the papillary processes are totally devoid of myoepithelial cell layer regardless of the presence of epithelial proliferation, and/or that any of the recognized patterns of DCIS occupies 90% or more of the lesion. These lesions are fundamentally distinct from papillomas with DCIS. In papillary DCIS, the papillary proliferation is itself neoplastic and there is no evidence of a pre-existing benign papilloma, whereas in a papilloma with DCIS [Fig 2 (b) & (c)], foci of DCIS are engrafted upon the scaffolding of a pre-existing benign papilloma. However there are no universally accepted criteria for distinguishing atypical papilloma and papilloma with DCIS from each other.[10]

Intracystic or encapsulated papillary carcinomas of the breast are circumscribed nodules of papillary carcinoma surrounded by a fibrous capsule in which a peripheral layer of myoepithelial cells is not identifiable. They may occur alone but more often the surrounding breast tissue contains foci of low or intermediate grade DCIS, usually with a cribriform or micropapillary pattern.[11] In our series, there was a discordant rate of 50% for encapsulated papillary carcinoma as two of four cases were under-reported as benign. This underscores the difficulty in diagnosing this lesion on limited tissue and without use of IHC. Another diagnostic pitfall to be kept in mind is pseudoinvasion or displaced epithelium within the core needle biopsy site. In such cases however, the epithelial fragments or clusters are confined to the organizing hemorrhage, granulation tissue or scar of the needle biopsy site and the epithelium or stroma may show varying degrees of degenerative changes [Fig 4 (b)]. Only foci of unequivocal invasive carcinoma present beyond the fibrotic rim of the main nodule must be taken as evidence of invasive papillary carcinoma and in such a situation, only the size of the frankly invasive component must be reported for staging purposes in order to avoid overtreatment.[12] There is an excellent prognosis for patients diagnosed with IPC regardless of whether the tumor is diagnosed as in-situ or invasive.

Immunohistochemistry (IHC) has been shown to clarify the issue of myoepithelial cells in many cases. The histological characteristics of various papillary lesions of the breast alongwith their staining patterns for basal cytokeratins (CK 5/6) and myoepithelial markers (p63) have been summarized in table 4.[13] Of all the commonly used markers, p63 shows the best results with highest sensitivity and lowest cross reactivity, and the nuclear staining is easy to interpret. Basal CKs are useful to differentiate between the different types of epithelial hyperplasia (usual, atypical or ductal carcinoma in situ), with usual hyperplasia being usually positive and the atypical to malignant proliferations being negative. The staining is strong and is present in the majority of the cells, facilitating interpretation even in small samples, as in core biopsy. CK5/6 appears to have a better sensitivity and specificity than other markers and also highlights myoepithelial cells. However, as highlighted in table 4, caution must be exercised when interpreting CK 5/6 reactivity in areas of apocrine metaplasia and squamous differentiation. Neuroendocrine markers are useful in differentiating solid papillary carcinoma (spindle cell type, neuroendocrine type) from papilloma with extensive florid epithelial hyperplasia. When coupled with basal CKs, a very high specificity can be achieved.[11]

Encapsulated papillary carcinomas (IPC) of the breast have traditionally been considered to be variants of ductal carcinoma in situ (DCIS). However, it is not clear if all lesions categorized histologically as IPC are truly in situ carcinomas, or if some such lesions might represent circumscribed, early or encapsulated nodules of invasive papillary carcinoma. Assessment of the presence or absence of a MEC layer at the periphery of the nodules is of utmost significance for this distinction.[14] In our study, IHC for myoepithelial markers (calponin, p63) and cytokeratin 5/6 was done in all cases for and resolved the issue. All benign intraductal papillomas, showed a MEC layer around virtually the entire periphery of the lesion with all MEC markers, while all cases of IPC lacked such a layer. One possible explanation for this observation is that these are in situ lesions in which the delimiting MEC layer has become markedly attenuated or altered with regard to expression of these antigens, perhaps due to their compression by the expansile growth of these lesions within a cystically dilated duct. Alternatively, it may be that at least some lesions that have been categorized as IPC using conventional histologic criteria actually represent circumscribed, encapsulated nodules of invasive papillary carcinoma.[15] Regardless of whether these lesions are in situ or invasive carcinomas, available outcome data indicate that they seem to have an excellent prognosis with adequate local therapy alone. Therefore, most authors believe that it is most prudent to continue to manage patients with these lesions as they are currently managed (ie, similar to patients with DCIS) and to avoid categorization of such lesions as frankly invasive papillary carcinomas.[16]

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Conclusion

Kraus and Neubecker[12] in 1962 identified several features of papillomas that resulted in incorrect diagnoses of malignancy that are still relevant today. Diagnosis of papillary lesions of the breast is difficult, and requires clinical, histological and immunological evaluation. Cytokeratin 5/6, p63 and neuroendocrine markers can be used as an initial panel for investigation of papillary lesions. Classifying papillary lesions definitively only on needle biopsies is challenging, even with IHC, and excision should still be considered the standard of care. An algorithm using appearance of the lesion on HPE alongwith a cocktail of IHC markers (cytokeratins, myoepithelial markers and neuroendocrine markers) can almost always reveal the right identity of papillary lesions (Fig 5).

In summary, the results of the current study, together with those reported in the literature, indicate that the presence or absence of atypia is a necessary descriptor for papillary lesions reported on CNB and that the presence of atypia mandates definite excision. The majority of papillary lesions without atypia remain benign lesions on excision. Though CNB is useful in the diagnosis and characterization of papillary lesions of the breast, it has its limitations and cannot always predict malignancy. Since the clinicopathologic features and risk factors of papillary lesions developing into invasive carcinomas are not well established, we recommend all papillary lesions of the breast diagnosed by core needle biopsy be excised due to the considerable upgrade rate.

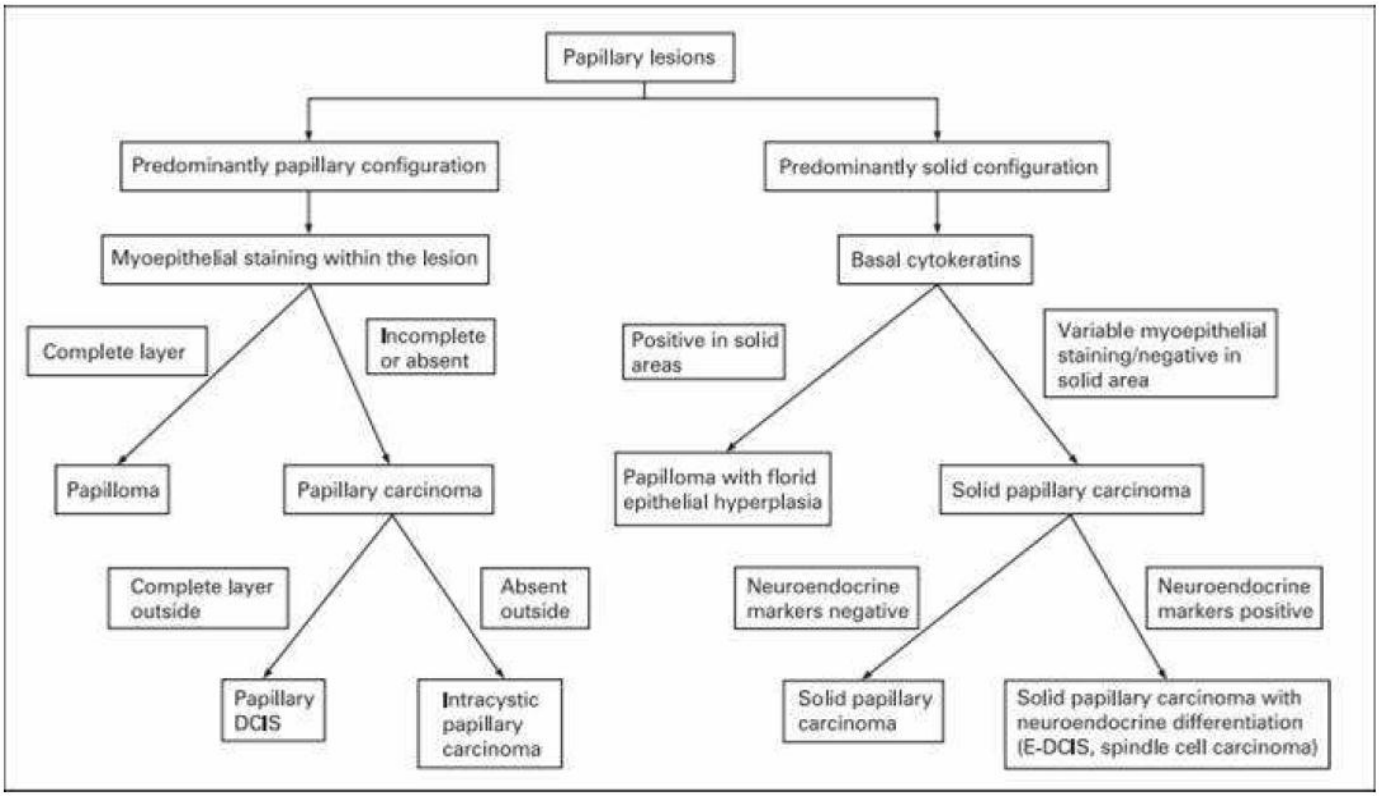

Fig 5 Practical approach to papillary lesions using a panel of immunohistochemical stains *[Collins LC et al. Intracystic papillary carcinomas of the breast: a re-evaluation using a panel of myoepithelial cell markers. Am J Surg Pathol 2006; 30: 1002-7]*

Reference

[1] Jorns JM. Papillary Lesions of the Breast - A Practical Approach to Diagnosis. Arch Pathol Lab Med 2016; 140: 1052-59.

[2] Lavoue V, Fritel X, Antoine M, et al. Clinical practice guidelines from the French College of Gynecologists and Obstetricians (CNGOF): benign breast tumours. Eu J Obstet Gynecol Reprod Biol 2016; 200: 16–23.

[3] Hoda SA, Brogi E, Koerner FC, Rosen PP. Rosen's Breast Pathology. 4th ed. New York, NY: Lippincott, Williams, and Wilkins; 2014: 95–151, 489–52.

[4] Agoumi M, Giambattista J, Hayes MM. Practical Considerations in Breast Papillary Lesions. A Review of the Literature. Arch Pathol Lab Med. 2016; 140: 770–90.

[5] Pisano ED, Fajardo LL, Tsimikas J, Sneige N, Frable WJ, Gatsonic CA, et al. Rate of insufficient samples for fine-needle aspiration for nonpalpable breast lesions in a multicenter clinical trial: the radiologic diagnostic oncology group 5 study. Cancer 1998; 82: 678–88.

DOI: 10.23958/ijirms/vol02-i05/12

[6] Wu Yao-Chung, Chen Dar-Ren, Kuo Shou-Jen. Personal experience of ultrasound-guided 14 gauge core biopsy of breast tumor. Eur J Surg Oncol 2006; 32(7): 715–8.
[7] Bianchi S, Bendinelli B, Saladino V, et al. Non-malignant breast papillarylesions-B3 diagnosed on ultrasound-guided 14-gauge needle core biopsy: analysis of 114 cases from a single institution and review of the literature. Path Oncol Res 2015; 21: 535–46.
[8] Wen X, Cheng W. Nonmalignant breast papillary lesions at core-needle biopsy: A meta-analysis of underestimation and influencing factors. Ann Surg Oncol 2013; 20: 94–101.
[9] Wyss P, Varga Z, Rossle M, et al. Papillary lesions of the breast: outcomes of 156 patients managed without excisional biopsy. Breast J 2014; 20: 394–401.
[10] Collins LC, Schnitt SJ. Papillary lesions of the breast: selected diagnostic and management issues. Histopathology 2008; 52: 20-29.
[11] Collins LC et al. Intracystic papillary carcinomas of the breast: a re-evaluation using a panel of myoepithelial cell markers. Am J Surg Pathol 2006; 30: 1002-7.
[12] Putti TC, Pinder SE, Elston CW, Lee AH, Ellis IO. Breast pathology practice: most common problems in a consultation service. Histopathology. 2005; 47(5): 445-57.
[13] Wei S. Papillary lesions of the breast – An update. Arch Pathol Lab Med. 2016; 140: 628-43.
[14] O'Malley F, Visscher D, MacGrogan G, et al. Intraduct papillary lesions. In: Lakhani SR, Ellis IO, Schnitt SJ, et al., editors. WHO Classification of Tumours of the Breast. 4th ed. Lyon: IARC, 2012; 99–110.
[15] G M Tse, P H Tan, T Moriya. The role of immunohistochemistry in the differential diagnosis of papillary lesions of the breast. J Clin Pathol 2009; 62; 407-13.
[16] Collins LC, Carlo VP, Hwang H, Barry TS, Gown AM, Schnitt SJ. Intracystic papillary carcinomas of the breast: a reevaluation using a panel of myoepithelial cell markers. Am J Surg Pathol. 2006; 30(8): 1002-7.
[17] Kraus FT, Neubecker RD. The differential diagnosis of papillary tumors of the breast. Cancer. 1962; 15: 444–55.

DOI: 10.23958/ijirms/vol02-i05/12