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Diagnostic challenges in papillary lesions of the breast

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Summary

Papillary lesions of the breast comprise a heterogeneous group of diseases ranging from benign and atypical lesions to malignant tumours including non-invasive and invasive entities. Although diagnosis of papillary lesions featuring typical histological features is straightforward, a proportion shows overlapping features, posing diagnostic challenges. In addition to being uncommon, the excellent behaviour of papillary tumours reduces the distinguishing value of individual histological features and increases the subjectivity of interpretation of various diagnostic features. Therefore the overall categorisation, which is based on a constellation of subjective features, may vary with subsequent management implications. Concordance studies revealed that recognition of papillary carcinomas (PC) as a malignant entity by pathologists is high, but concordance of its classification into *in situ* and invasive disease can be problematic, as can assessment of prognostic and predictive factors in the invasive component. Identification of low nuclear grade atypia within benign papillary lesions and its classification into atypia or *in situ* carcinoma may also pose a diagnostic challenge. Although immunohistochemistry is helpful in evaluation of benign and atypical lesions it has a limited utility in differentiating the majority of PC as non-invasive or invasive disease. Pathologists should be aware of the various entities and the differential diagnosis of each entity, the existence of lesions with overlapping features and should follow the updated guideline recommendation for their diagnosis and management. These rare lesions usually require additional diagnostic work-up and difficult cases should trigger consensus opinion or expert referral.

Key words: Breast cancer; papillary lesions; diagnosis; challenges.

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INTRODUCTION

Papillary lesions of the breast are a heterogeneous group of diseases characterised by the presence of epithelial proliferation supported by fibrovascular cores. The presence of these fibrovascular cores is generally accepted as the hallmark of papillary lesions in the breast. Breast lesions featuring small papillary-like projections lacking fibrovascular cores are designated as micropapillary. Papillary lesions arise within the ducto-lobular system of the breast and typically show a cystic structure but solid forms occur, resulting from florid epithelial proliferation.[1–5] Although this solid pattern of growth can be seen in intraductal papilloma and encapsulated papillary carcinoma (EPC) (Fig. 1), it is the predominant growth pattern in solid papillary carcinoma (SPC).[1–6] Clinical evidence indicates that breast carcinomas featuring predominant papillary morphology are associated with better outcome compared to their non-papillary counterparts including grade matched tumours.[5–9]

Papillary lesions of the breast can broadly be classified into several types based on the following. (1) Location in the duct system. Papillary lesions can arise from large ducts or small ducts (terminal duct lobular units; TDLU). Large duct papillary lesions are typically solitary, present as a mass lesion or nipple discharge and include solitary papilloma, EPC and SPC. TDLU lesions include multiple papillomas and papillary ductal carcinoma *in situ* (DCIS) and these often present as calcification or an incidental finding associated with other lesions. (2) Nature of the proliferating epithelial cells. This can be hyperplastic in papilloma, neoplastic in papillary carcinoma (PC) or a mix of hyperplastic and neoplastic in papilloma involved by atypical proliferation. The presence of cellular differentiation such as neuroendocrine and mucinous changes can be used to differentiate EPC from SPC, while on rare occasions the degree of cytonuclear atypia in PC can also be used to differentiate *in situ* from invasive disease for management purposes[10] (see below). (3) Presence of and location of myoepithelial cells (ME). This not only helps in distinguishing benign from malignant papillary lesions but can also differentiate specific subtypes of malignant papillary lesions (Table 1). (4) Morphology of PC. PC including EPS and SPC featuring a well-circumscribed margin with or without peripheral fibrous capsule are considered as non-invasive (*in situ*) disease for management purposes. PC featuring irregular outlines with ragged edge and complex jigsaw pattern of growth in SPC, or focal areas of irregular stromal invasion beyond the capsule in EPC, are considered as diagnostic features of invasive disease.

The most common papillary lesion in the breast is benign intraductal papilloma, also called solitary/central papilloma. However, other entities, despite being rare, attract more attention due to their unique nature and behaviour, particularly EPC and SPC. Invasive papillary carcinoma (IPC) is very rare and poorly defined, making extraction of reliable data on its behaviour a challenging task. The diagnostic work-up of papillary lesions includes a spectrum of diseases with typical benign intraductal papilloma at one end and IPC at the other end of the spectrum. There are the lesions in the middle of the spectrum that comprise one of the most challenging diagnostic entities in breast pathology. These challenges often stem from one or more of the following. (1)

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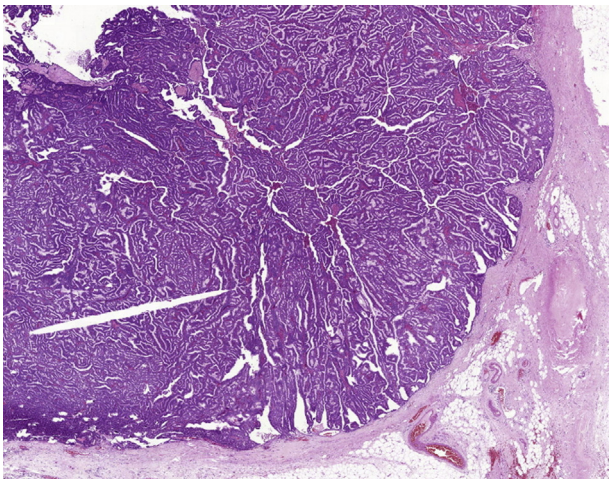

Fig. 1 Encysted/encapsulated papillary carcinoma (EPC) which shows mainly solid growth pattern and appears to lack the thick fibrous capsule mimicking solid papillary carcinoma (SPC). This tumour lacks other features of SPC including neuroendocrine differentiation, mucinous differentiation, nuclear palisading and spindling and it shows typical cystic morphology in other parts of the lesion.

Table 1 Role of myoepithelial cells in the diagnosis of papillary lesions

Papillary lesion	ME cells in papillae (epithelial/fibrous core interface)	ME cells at periphery (tumour/adjacent stroma interface)
Papilloma	Present	Present
Papilloma with atypia/DCIS	Present but absent/reduced in atypical areas	Present
Papillary DCIS	Absent	Present
Encapsulated PC	Absent	Frequently absent (>85%)
Solid PC	Absent	Usually absent (>70%)
Invasive PC	Absent	Absent

DCIS, ductal carcinoma *in situ*; ME, myoepithelial cells; PC, papillary carcinoma.

Overlapping morphological and immunohistochemical features among benign, atypical and malignant papillary lesions. (2) Lack of reliable and reproducible criteria for the diagnosis and classification of certain papillary lesions. This is more commonly experienced with cases featuring low nuclear grade atypia and more rarely in cases featuring diffuse high-grade atypia with or without triple negative phenotype or HER2 positivity.[10] Also, diagnostic features that can be reliably used to distinguish pure (pTis) from invasive (pT) EPC and SPC remain unclear, subjective and difficult to apply to individual tumours. There is a lack of clear criteria to differentiate EPC with partially solid growth pattern or focally lacking fibrous capsule from SPC, or distinguish SPC and EPC showing multinodular growth pattern from papillary DCIS (Fig. 2). Assessment of prognostic and predictive parameters in invasive disease associated with non-invasive PC is also subjective and related to interpretation of vague features defining invasion in these lesions. (3) Papillary lesions are more prone to epithelial displacement, sclerosis with epithelial entrapment and can feature florid epithelial proliferation and prominent adenotic growth pattern resulting in appearances that can mimic invasive carcinomas.[11] This can be confounded by focal lack of peripheral ME cells as seen in some cases. Benign papilloma may also show some degree of

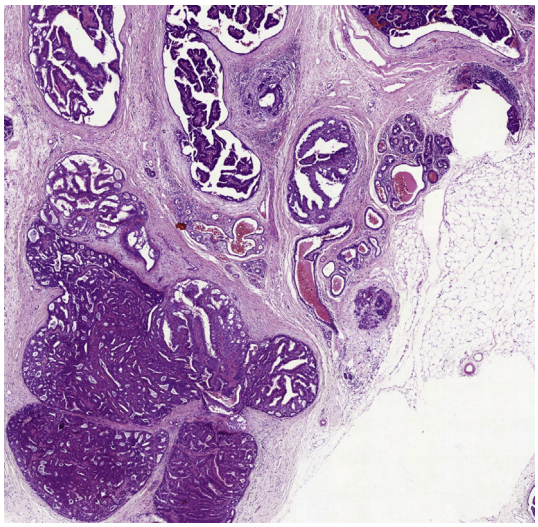

Fig. 2 Papillary carcinoma showing overlapping features between papillary ductal carcinoma *in situ* (DCIS) and multinodular encapsulated papillary carcinoma (EPC). Myoepithelial cell immunohistochemical markers may help in this differential diagnosis.

ME hyperplasia or chrondromyxoid metaplasia and these should be differentiated from adenomyoepithelioma (Fig. 3) and pleomorphic adenoma, respectively, despite the vague boundaries between these entities. (4) In addition to the difficulty and subjectivity in applying existing diagnostic criteria in the classification of papillary lesions, some pathologists may not concur or be reluctant to use certain established diagnostic features in breast pathology differently in the context of papillary lesions. For instance, designating a malignant lesion lacking peripheral ME at epithelial stromal interface, as seen in most SPC and EPC, as an *in situ* disease is not in line with the commonly used definition of invasion used in breast pathology. The concept of invasion within and beyond the fibrous capsule in EPC is confusing and not evidence based. Similarly, using tumour outlines and pattern of growth to distinguish *in situ* from invasive SPC appears subjective and not evidence based but rather descriptive and based on personal experience and opinion. Furthermore, changing the approach to the diagnosis and categorisation of SPC and EPC over time, with demonstration of loss of ME cells in PC and reported invasive events in different studies, may have resulted in reducing diagnostic concordance among reporting pathologists.[7] The recommendation of management of PC as *in situ* disease (pTis) despite the probable indolent

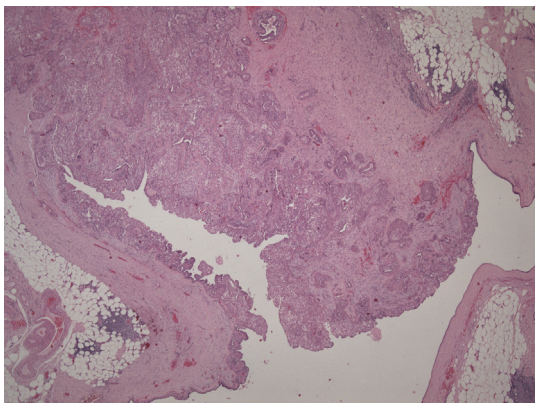

Fig. 3 Papillary lesions with prominent myoepithelial proliferation in keeping with adenomyoepithelioma.

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