Papillary lesions of the breast

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Abstract

Papillary lesions include benign and malignant lesions. As this array of papillary lesions cannot be differentiated by clinical and imaging means, the diagnosis relies on pathologic examination. Intraductal papillomas are benign, and often complicated by superimposed epithelial metaplasia or hyperplasia. When they are involved by atypical duct hyperplasia, the prevailing practice is to upgrade the diagnosis to ductal carcinoma in situ when the extent of involvement is ≥3 mm. Intraductal papillary carcinomas has low grade malignant epithelial changes, retaining an outer myoepithelial layer but lost the myoepithelial cells within the lesion around fibrovascular cores. Encapsulated papillary carcinomas and solid papillary carcinomas have distinctive morphology, but both are characterized by frequent loss of myoepithelial cells surrounding the lesion, although the current classification still consider these to be in situ lesions. Invasion is used for irregular groups, tongues and nests of tumor cells extending into the stroma beyond the rounded boundary. Immunohistochemistry is useful in differentiating papillary lesions, with positivity of myoepithelial markers, high molecular weight cytokeratins and heterogeneous staining of ER denoting benignity and vice versa. Core needle biopsy is frequently used in diagnosing papillary lesions: both under- and over-diagnoses may occur, the former being more frequent. Genetically papillary carcinomas are grouped mostly into luminal cancers, further attesting to the generally low grade nature of all subtypes of papillary carcinomas.

Keywords core needle biopsy; encapsulated papillary carcinoma; immunohistochemistry; intraductal papillary carcinoma; intraductal papilloma; solid papillary carcinoma

General overview

Papillary lesions of the breast include a wide range of lesions with variable biologic behavior, ranging from benign, atypical to malignant. In the malignant category, most of the lesions are of low nuclear grade, and most are also considered to behave in an in situ manner. Nevertheless, this group of malignant papillary lesions is still outnumbered by benign papillary lesions; accurate identification and differentiation between the benign and malignant groups is crucial. For the management of papillary lesions, most agree complete excision for malignant papillary lesions. However, there are no universally adopted criteria for benign papillary lesions.

Triple assessment approach (clinical, radiological and pathological) is not useful in papillary lesions. Clinically papillary lesions may present with nipple discharge, either blood stained or serosanguinous, originating from the same lactiferous duct opening. There are few, if any differentiating clinical features between benign and malignant papillary lesions. Radiologically papillary lesions also defy accurate classification. The mammographic appearance of papillary lesions is usually a soft-tissue mass, and uncommonly (less than half of the cases) calcification of varying morphology may be present, and sometimes the calcification pattern is pleomorphic and suggests infiltrating mammary carcinoma. Ultrasonography of papillary lesions typically shows a solid, oval, intraductal mass with heterogeneous internal echoes, often associated with duct dilatation. A cystic component may be seen, particularly in the larger, central lesions, may be hypervascular on color Doppler. Magnetic resonance imaging (MRI) for papillary lesions has a high sensitivity, but low specificity, and is useful in establishing the extent and distribution of multiple lesions.[1] The radiological differentiation between benign and malignant papillary lesions is unreliable, with overlapping radiological features. Even in MRI, the most sensitive imaging modality, all papillary lesions will show contrast enhancement to similar extent.

Pathologically all papillary lesions are characterized by intraductal epithelial proliferation around fibrovascular cores arising from the ductal wall. Recapitulating normal mammary anatomy, there is a retained layer of myoepithelial cells interposed between the epithelial cell layer and the fibrovascular cores. As papillary lesions are derived from the ducts, a layer of myoepithelial cells is also present around the papillary lesions, separating them from the adjacent breast stroma. In benign papillary lesions, myoepithelial cells within these two compartments are retained, but they may be lost to various extents in atypical to malignant papillary lesions. Thus assessment of the myoepithelial cells in a papillary lesion provides important clue to the correct diagnosis. The term micropapillary should not be confused with papillary, and the latter is defined by the presence of fibrovascular cores, whereas in the former, the epithelial proliferation forms bulbous structures without encasing true fibrovascular cores.

Classification and different subtypes

In the WHO classification of breast tumours, papillary lesions are classified into intraductal papilloma, intraductal papillary carcinoma, encapsulated papillary carcinoma and solid papillary carcinoma. Invasive papillary carcinoma is now grouped under rare tumors but not under papillary lesions.[2–6]

Intraductal papilloma

Based on the anatomical location, intraductal papillomas can be divided into central (solitary) and peripheral (multiple). Intraductal papillomas show fibrovascular cores covered by myoepithelial cells and epithelial cells. The former can be attenuated, and the latter may show different degree of hyperplasia, particularly florid epithelial hyperplasia or metaplasia (apocrine, squamous). As the lesion is intraductal in origin, there is also an intact layer of myoepithelial cells around the surrounding ductal wall. Identification of myoepithelial cells in both compartments helps to confirm the diagnosis. Other changes that can occur in intraductal papillomas include hemorrhage, infarction, stromal

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fibrosis (in extreme examples, the papillary architecture may be obscured, and the terms sclerosed papillomas or ductal adenomas are coined), mucinous, clear cell and sebaceous metaplasia.[7] The fibrovascular cores are generally considered to be broad and fibrous (compared to papillary carcinomas, which possess long and slender fibrovascular cores). Rarely papillary carcinomas may possess broad fibrovascular cores.[8] Benign glandular entrapment may occur and this may create a false impression of invasion, nevertheless, the identification of myoepithelial cells (albeit attenuated), the bland morphology of the 'infiltrative' epithelial cells, and hyalinized/altered stroma and the general directional alignment between the epithelium and the fibrosis of the stroma confirm the benign nature.[9]

More problematic situations may arise when there are atypical duct hyperplasia (ADH) or ductal carcinoma in situ (DCIS) involving the intraductal papilloma, both being characterized by atypical epithelial proliferation, usually in typically solid or cribriform patterns commonly seen in ADH/DCIS rather than true papillary patterns. (Figure 1a–c). In these areas, myoepithelial cells may be scanty or absent. The definitions between these two entities have been a matter of debate. A cutoff of 3 mm for the extent of atypical focus initially proposed by Page[10] was most widely adopted to define the two (<3 mm for ADH involving papilloma and ≥3 mm for DCIS involving papilloma). Nevertheless this guideline is pragmatic, and seems to lack solid scientific evidence.[11] It is important to note that this extent criterion is only applicable to atypical epithelial proliferation with low grade features. When intermediate to high nuclear grade is detected, the lesion should be diagnosed as DCIS irrespective of the size of the atypical focus.[12]

The risk of intraductal papillomas for subsequent carcinoma depends on the superimposed epithelial changes within or around the lesion. When there are benign proliferative changes, the incurred risk is two times; the risk is higher in multiple papillomas; and for papillomas with atypia, the risk is 5–7.5 times.[10,13,14]

Intraductal papillary carcinoma

Intraductal papillary carcinoma, compared to intraductal papillomas, is frequently more peripherally located, and may be multiple. It possesses slender, branching fibrovascular stalks, covered by a single population of neoplastic cells. The neoplastic cells are usually columnar, of low to intermediate grade nuclei, and are arranged into characteristic atypical architecture, typically geometric, solid, cribriform or micropapillary patterns. Myoepithelial cells are also typically absent in both the periductal and peri-fibrovascular cores compartments.

Encapsulated papillary carcinoma

Encapsulated papillary carcinoma is characterized by a rounded tumor contour and a thick encapsulating fibrous capsule. The tumor is mostly solitary and rounded, and similar to intraductal papillary carcinoma, there can be a loss of myoepithelial cells in both periductal and peri-fibrovascular cores compartments. In fact the presence of myoepithelial cells is not considered a determining factor in its diagnosis.[15,16] (Figure 2a and b). The exact nature of encapsulated papillary carcinoma is still uncertain. The lack of myoepithelial cells was suggested to be evidence of as invasion,[15,16] but an intact basement membrane detected by collagen type IV staining demonstrated an in situ nature.[17]

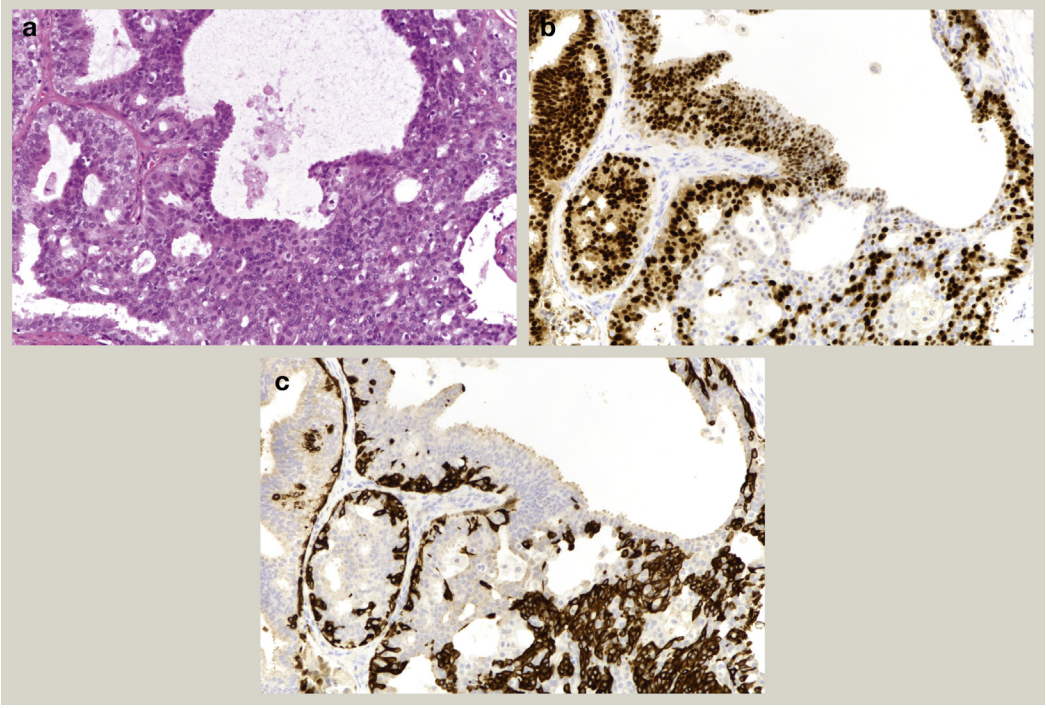

Figure 1 (**a**) Extensive epithelial hyperplasia involving a papilloma. The central lower part exemplifies florid hyperplasia, whereas atypical duct hyperplasia is seen on the left side. (H&E, 20×). (**b**) ER staining, showing heterogeneous staining in the central lower part, and uniform staining on the left side. (ER, 20×). (**c**) CK5/6 staining, showing positive staining in the central lower part and negative staining on the left side. (CK5/6, 20×).