Papillary Lesions of the Breast

A Practical Approach to Diagnosis

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Papillary lesions of the breast are a heterogeneous group of neoplasms, which includes benign intraductal papilloma (IDP) as well as papilloma with atypia (atypical papilloma) and ductal carcinoma in situ (DCIS), papillary DCIS, and variants of papillary carcinoma. These neoplasms are unified by “papillary” morphology, consisting of arborizing fronds with fibrovascular cores of various thicknesses and lining epithelium. Identification of papillary architecture is often straightforward. However, subclassification can often prove diagnostically challenging, especially when there is limited lesional tissue present, such as with suboptimal core biopsy sampling. Key areas of diagnostic challenge include differentiation of (1) benign IDP with florid hyperplasia and atypical papilloma; (2) atypical papilloma and IDP with DCIS; (3) IDP with widespread DCIS, papillary DCIS, and papillary carcinoma variants; and (4) pseudoinvasion and associated frank invasive carcinoma.

INTRADUCTAL PAPILLOMA

Intraductal papilloma is a benign, circumscribed, intraductal proliferation comprising fibrovascular cores covered by benign inner myoepithelial and outer epithelial layers. Intraductal papilloma can be broadly divided into central, which involve large, central lactiferous ducts, and peripheral, which involve the terminal duct lobular units. Central IDPs tend to be solitary, and peripheral IDPs are usually multiple. Multiple peripheral IDPs are usually multiple. Multiple peripheral IDPs are usually multiple. Multiple peripheral IDPs are usually multiple. Multiple peripheral IDPs are usually multiple. IDPs can be large enough to be appreciated via palpation. Peripheral IDPs are most frequently identified as small masses or densities on radiographic studies. Both may have microcalcifications because these lesions may infarct and/or become sclerotic with time.

On histologic examination, IDPs may have variable amounts of epithelium, from one to multiple layers. The epithelium is often of columnar morphology and/or displays usual ductal hyperplasia (UDH) and/or apocrine metaplasia. Less frequently, there may be squamous, chondroid, or osseous metaplasia, findings more often identified in the setting of abundant sclerosis. Depending on the degree of epithelial present, the myoepithelium may be variably prominent but is uniformly present, both at the periphery and within the papillae. Uncommonly, myoepithelial hyperplasia may be seen. Sclerosis is variably prominent and is more pronounced with prior infarction, which may be spontaneous because of limited space for growth within the involved duct or torsion of fibrovascular cores, or it may be a result from biopsy or other trauma. Examples of benign IDPs are shown in Figure 1, A through F.

PAPILLOMA WITH ATYPIA (ATYPICAL PAPILLOMA)

There is variability in criteria used for the diagnosis of IDP with atypia, both in practice and in the literature. However, we refer to IDPs with foci of architectural and cytologic atypia that quantitatively and qualitatively fail to fulfill criteria for the diagnosis of DCIS as papilloma with atypia or atypical papilloma; this diagnosis is equivalent to that of atypical ductal hyperplasia elsewhere in the breast. Typically, the IDP exhibits focal solid or cribriform epithelial expansion of small (<0.3 cm) size and composed of small, monotonous epithelial cells. Foci of atypia are negative for high–molecular-weight cytokeratin (CK) 5/6 and diffusely positive for estrogen receptor (ER) via immunohistochemical (IHC) staining. An example of IDP with atypia and corresponding CK5/6 IHC is shown in Figure 2, A through C.

PAPILLOMA WITH DCIS

Intraductal papillomas that exhibit foci of architectural and cytologic atypia, which would be deemed DCIS elsewhere in the breast, are designated as IDP with DCIS. These lesions
are usually larger than 0.3 cm and have a solid or cribriform growth pattern with cytologic enlargement, monotony, and readily identifiable cell borders. Ductal carcinoma in situ involving an IDP is usually of low or intermediate nuclear grade and, thus, shares the IHC staining pattern of atypia, with the involved foci being CK5/6− and ER being diffusely positive. An example of IDP with DCIS is shown in Figure 3, A and B.

Figure 1. Two examples of benign intraductal papilloma. Benign intraductal papilloma with sclerotic capsule, prominent fibrovascular cores and benign epithelial, and myoepithelial lining at low-power magnification (A) and high-power magnification (B). C through F, Branching benign intraductal papilloma (C) with foci of usual ductal hyperplasia (D), apocrine metaplasia (E), and columnar cell morphology (F) (hematoxylin-eosin, original magnifications ×40 [A and C], ×200 [B], and ×400 [D through F]).
PAPILLARY DCIS

Papillary DCIS is a variant of DCIS with prominent papillary architecture (i.e., delicate papillae with fibrovascular cores). However, the epithelium is neoplastic, and there is complete involvement of involved ducts with no discernable benign IDP. Papillary DCIS often exhibits involvement of multiple ducts, as seen in all types of DCIS, and is frequently seen alongside other patterns of DCIS. Papillary DCIS is most commonly of low or intermediate nuclear grade and thus is CK5/6⁺ and ER is diffusely positive. Myoepithelium is present at the periphery of the duct and is sparse to absent within the papillae. Microcalcifications are variable, and necrosis is uncommon. An example of papillary DCIS is shown in Figure 4, A and B.

PAPILLARY CARCINOMA

Papillary carcinoma is an uncommon variant of breast cancer representing just 1% to 2% of breast carcinomas. Papillary carcinoma is more often seen in older women, with a mean age in the seventh decade, as compared with other breast cancer subtypes. Nearly one-half of cases are present as a central breast mass, which are usually circumscribed on imaging studies. Nearly one-third of patients also report bloody nipple discharge. Papillary carcinoma variants include encapsulated and solid types.

Encapsulated Papillary Carcinoma

Encapsulated papillary carcinoma was previously referred to as intracystic or encysted papillary carcinoma and was thought to be a variant of DCIS. The World Health Organization classifies these as tumors in situ, and they are managed accordingly. However, recent publications have shown that most either completely lack myoepithelium, both within papillae and at the periphery or, less frequently, have very sparse myoepithelium at the periphery only. Because of this, authors have suggested that they likely represent a good-prognosis subtype of invasive carcinoma or may, at least, be a lesion in transition.

Encapsulated papillary carcinoma usually presents as a solid mass with surrounding cystic space and a thick, encircling fibrotic capsule. The microscopic features are identical to that of DCIS within an IDP or papillary DCIS; however, DCIS morphology is present throughout the lesion, and the lesion is typically larger and expansile. Like atypia and DCIS, the carcinomatous epithelium in encapsulated papillary carcinoma is negative for CK5/6. These carcinomas are usually low to intermediate grade and, accordingly, are ER diffusely positive, although high-grade tumors with less-consistent ER staining are occasionally encountered. Encapsulated papillary carcinoma may have associated, frankly invasive components, which are usually of the ductal type and, when present, should be staged according to the greatest dimension of invasive ductal carcinoma.

Solid Papillary Carcinoma

Solid papillary carcinoma is a variant of papillary carcinoma with distinctive morphology characterized by closely apposed cellular nodules of carcinomatous epithelium. The solid nests are typically arranged in a multinodular or jigsawlike pattern within a background of dense fibrosis but lack an encircling fibrotic capsule. The cells are usually low to intermediate grade and often have a neuroendocrine appearance. Unlike the previously described papillary lesions fibrovascular cores may be more delicate and thus more difficult to identify. Like the encapsulated variant, these tumors are considered in situ but lack myoepithelium.
Figure 3. A. Intraductal papilloma with ductal carcinoma in situ (DCIS) with solid growth (circles), moderate cytologic atypia, and prominent cell borders (inset). B. Corresponding cytokeratin 5/6 immunohistochemical staining showing loss of staining within the foci of DCIS (hematoxylin-eosin, original magnifications ×40 [A] and ×400 [inset], original magnification ×40 [B]).

Figure 4. A. Multiple ducts involved by papillary ductal carcinoma in situ, with (B) diffuse, strong positivity for estrogen receptor via immunohistochemical staining (hematoxylin-eosin, original magnification ×20 [A]; original magnification ×20 [B]).

Figure 5. A. Encapsulated papilloma carcinoma with thick, fibrous capsule, and (B) corresponding p63 immunohistochemical stain showing complete lack of myoepithelium at the periphery and within papillae (hematoxylin-eosin, original magnification ×10 [A]; original magnification ×10 [B]).
and thus may be better classified as a good-prognosis subtype of invasive carcinoma. Additionally, solid papillary carcinomas are negative for CK5/6 and are often positive for neuroendocrine markers, such as synaptophysin and chromogranin. Solid papillary carcinomas may also exhibit intracellular and extracellular mucin production and may be associated with a frank, invasive component with mucinous or other histology. An example of a case of solid papillary carcinoma is shown in Figure 6.

**DIAGNOSTIC CHALLENGES**

**Differentiating IDP With UDH and Atypia**

Atypical papilloma may be difficult to distinguish from IDP with florid UDH. Histologic features establishing atypia are identical to those required for diagnosis elsewhere in the breast and may include focal, solid or cribriform architecture and cytologic monotony. However, florid UDH within an IDP may exhibit increased cell size and reactive changes that can be worrisome for atypia. In this setting, IHC may be helpful in establishing the diagnosis of atypia because these lesions have negative staining for CK5/6 and have strong, diffuse positive staining for ER. In contrast, UDH stains strongly positive with CK5/6 and, typically, is less strongly

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*Figure 6. Solid papillary carcinoma comprising irregular nests within dense, fibrotic stroma. Fibrovascular cores (inset) are uniformly present but are more subtle than in other papillary lesions of the breast (hematoxylin-eosin, original magnifications ×40 and ×400 [inset]).*

*Figure 7. Case with both benign intraductal papilloma and usual ductal hyperplasia (UDH) (A), with corresponding cytokeratin 5/6 immunohistochemical (IHC) stain highlighting UDH (B), and focus of atypia (C), with corresponding cytokeratin 5/6 IHC stain showing loss of staining in atypical epithelium (D) (hematoxylin-eosin; original magnification ×200 [A and C]; original magnification ×200 [B and D]).*
ER positive. However, it is important to note that columnar cell alteration (columnar cell change/hyperplasia) and apocrine metaplasia, which are commonly seen in IDPs, are also negative for CK5/6 and thus may be a pitfall in stain interpretation.22,23 Figure 7, A through D, shows a case with areas of IDP with both UDH and atypia and the corresponding CK5/6 staining.

**Differentiating IDP With Atypia From IDP With DCIS**

Differentiation of atypia from low-grade DCIS is best made morphologically, while accounting for the size of the abnormal area, because it shares the staining pattern seen in atypia. Thus, staining for CK5/6 and ER do not allow for distinction.23,24 However, these stains may be helpful in highlighting the area of interest to help determine the extent of involvement of an area that appears morphologically abnormal.

**Differentiating IDP With Extensive DCIS, Papillary DCIS, and Papillary Carcinoma**

An IDP with DCIS is often larger than ducts involved by papillary DCIS and may be as large as papillary carcinoma. Of importance, IDP with DCIS should still exhibit areas recognizable as benign IDP, whereas carcinomaous epithelium appears throughout in papillary DCIS and papillary carcinoma. Additionally, papillary DCIS is typically multifocal, whereas IDP with DCIS and papillary carcinoma most often have larger, solitary lesions. Fortunately, these lesions with morphologic overlap can usually be distinguished with the help of IHC because an IDP with DCIS should have myoepithelial staining both at the periphery and within papillae of the papillary lesion. This differs from papillary DCIS, which typically has peripheral staining only, and papillary carcinoma, which typically lacks myoepithelium altogether or has just very focal peripheral staining.

Despite different patterns of involvement and staining, IDP with extensive DCIS, papillary DCIS, and papillary carcinoma may be difficult to distinguish, especially if there is limited lesional tissue present on core biopsy. Fragmentation can also make it difficult to determine whether there is a solitary lesion or a multifocal process and can also cause difficulty in stain interpretation. Confounding matters, these lesions may coexist. For example, papillary DCIS may be present elsewhere in a patient with an IDP involved by DCIS or in a patient with papillary carcinoma. Therefore, different staining patterns may be present within different areas of the core biopsy. In these cases, we cannot always provide definitive diagnoses and, instead, usually designate the lesion as papillary carcinoma, at least in situ and defer definitive classification to the excision.

Figure 8 shows a schematic of key features most helpful in differentiating IDP with DCIS, papillary DCIS, and papillary carcinoma, taking into account that there may be overlaps of features as well as cases with more than one lesion.

**Differentiating Pseudoinvasion From Invasive Carcinoma**

Benign IDPs with abundant sclerosis represent an area of significant diagnostic challenge because benign glands entrapped within sclerosis can appear infiltrative and may also exhibit reactive atypia, mimicking an invasive carcinoma. A key feature that helps to establish the diagnosis of benign, entrapped glands is background benign histology (ie, there is no indication of a neoplastic process in the IDP or elsewhere). Other features of benignity are confinement within investing sclerosis and, if previously biopsied, association with hemorrhage and/or fibrotic biopsy tract. Myoepithelium is usually retained in sclerotic foci with entrapped benign glands, at least in a patchy distribution, further supporting a benign process (Figure 9, A and B). Thus, myoepithelial IHC stains may be helpful to differentiate difficult cases from a low-grade invasive carcinoma.
However, epithelial displacement may occur because of prior biopsy, and in this setting, myoepithelium may be scarce or absent. Therefore, other features (i.e., hemorrhage, fibrous tract) are most helpful ruling out an invasive process. Papillary DCIS or papillary carcinoma may also have pseudoinvasion within surrounding sclerosis or may have associated frankly invasive carcinoma. In the case of DCIS, myoepithelial markers are extremely helpful because they highlight the periphery or DCIS-involved glands and are absent in the invasive component (Figure 10, A and B). Conversely, in the setting of papillary carcinoma, pseudoinfiltration in dense sclerosis may be difficult to differentiate from true invasion. Unfortunately, in this case, myoepithelial stains are not helpful because they typically show loss in both papillary carcinoma and invasive carcinoma components. Therefore, invasion beyond the sclerotic capsule and/or hemorrhagic/fibrotic biopsy tract must be present to diagnose definitive invasion (Figure 11). As noted previously, staging should be assessed based on the frankly invasive component alone, if present.
DISCUSSION

Papillary lesions of the breast are a heterogeneous group that can usually be distinguished via careful histologic evaluation, with the use of IHC when helpful, and consideration of clinicoradiographic features. Immunohistochemistry using CK5/6 is most helpful in supporting a morphologic impression of atypia. Myoepithelial markers are useful in distinguishing IDP with DCIS, papillary DCIS, and papillary carcinoma, as well as in supporting frank invasion in the setting of DCIS. However, myoepithelial markers are not helpful in establishing invasion in the setting of papillary carcinoma. Diagnostically challenging cases may represent more than a case of papillary neoplasm, and in some cases, definitive classification may need to be deferred to complete evaluation of the excision specimen.

References

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