Papillary Neoplasms of the Breast

A Review

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Context.—Interpretation of papillary lesions of the breast remains a challenging task because of the wide morphologic spectrum encountered in the benign, atypical, and malignant subtypes. Data on clinical significance and outcome of papillary lesions, with superimposed atypia or areas similar to ductal carcinoma in situ partially replacing the benign elements, are sparse. Furthermore, complete excision of even a fully developed papillary carcinoma confined to a dilated or cystic duct is associated with an excellent prognosis, whereas a complex papilloma extending into multiple branches of a duct may ultimately recur as a carcinoma because of incomplete excision of microscopic foci. This makes an outcome-based classification difficult.

Objective.—An arbitrary yet practical approach to classification is outlined, with discussion of methods to circumvent the various diagnostic difficulties. The limitations in precise diagnosis of papillary lesions in aspirates are addressed, and the implications of finding papillary lesions in core biopsies are discussed. Although the focus is on intraductal lesions, associated invasive carcinomas and invasive micropapillary carcinoma are also presented.

Data Sources.—The literature on papillary lesions and invasive micropapillary carcinoma is reviewed.

Conclusions.—It would be prudent to completely excise any papillary lesion that has not been entirely removed by the initial core biopsy. The optimal management of localized papillary lesions is complete excision with a small rim of uninvolved breast tissue without any prior needle instrumentation if and when the papillary nature can be determined by imaging. Thus managed, most of these lesions behave indolently, and outcome is usually excellent.

The common feature characterizing papillary lesions is a papillary, arborescent epithelial proliferation supported by fibrovascular stalks with or without an intervening myoepithelial (ME) cell layer. Papillary lesions of the breast include intraductal papilloma, papillomatosis, atypical papilloma (or papillomatosis), carcinoma arising in a papilloma, and intraductal papillary carcinoma (with or without invasion). Distinction of these subtypes is not always an easy task. Adding to the difficulties, there are, currently, different terminologies and criteria used to categorize the variety of papillary lesions; some of these are not necessarily outcome based. When a papillary lesion is encountered in the breast, the most important question to answer is whether it is benign or malignant. The complete absence of an ME cell layer in the fibrovascular fronds of a papillary lesion indicates a carcinoma; however, the presence of ME cells does not invariably exclude the diagnosis of intraductal papillary carcinoma. Therefore, the role of ME markers and immunohistochemistry in the assessment of papillary lesions will be addressed. It is important to note that the significance of the complete absence of an ME cell layer for papillary lesions composed purely of uniform apocrine cells is not well established.

Furthermore, depending on their location in the mammary duct system, papillary lesions may be solitary, centrally (subareolar) located or multifocal, and peripherally located within terminal duct-lobular units. These are associated with different risks for associated carcinoma or subsequent carcinoma. Whether the lesion is located simply in the distal portions of the duct system, but not necessarily in the terminal duct-lobular unit, is not always clear cut. Therefore, the designations of papillomatosis and multifocal intraductal papillary carcinoma are often arbitrarily applied for multiple microscopic lesions generally separated by uninvolved mammary tissue; the terms papilloma and papillary intraductal carcinoma have been used for the centrally located lesions. Three dimensional studies, however, can reliably determine the precise location within the duct system and accurately distinguish the two categories.

This review will address the morphologic spectrum and the diagnostic problems associated with papillary lesions as well as incorporating the concept of ductal intraepithelial neoplasia (DIN) into the terminology.

ASPIRATION CYTOLOGY

Precise classification of papillary lesions of the breast on fine-needle aspiration remains a challenging area in cytology. Of particular significance is the difficulty in distinguishing between benign and malignant papillary lesions on the basis of cytology, although a few authors have...
reported some useful discriminating features to aid in the differential diagnosis between the two.4-6 Most studies, however, report low concordance between cytologic and histologic diagnoses of papillary lesions.7-9

Papillomas usually yield highly cellular smears containing clusters of ductal cells, often with a papillary configuration, and readily identifiable bipolar cells that represent ME cells. Sheets of apocrine cells and a proteinaceous background with histiocytes and siderophages may also be present. The cytology of fibrocystic changes, radial scars, fibroadenoma, low-grade ductal carcinoma, or apocrine carcinoma often appear similar, however, to that of papillary lesions.10,11

With the excellent samples obtained by needle-core biopsies, there is no need, in our opinion, to perform aspiration biopsies. Furthermore, if imaging studies were able to clearly identify a papillary lesion in women of all ages, including those 45 years or younger, when the likelihood of carcinomas is less, complete excision of the lesion with a rim of uninvolved breast tissue would be the optimal approach. Any needling procedure by either aspiration or core biopsy can introduce artifacts with significant impact on the ultimate diagnosis.

**PAPILLARY LESIONS DIAGNOSED ON CORE BIOPSIES**

Whether or not all papillary lesions identified on core biopsies should be surgically excised remains a controversial issue. In all cases in which a papillary lesion is identified on a core biopsy, correlation with clinical, mammographic, and sonographic findings is crucial. Some investigators12-16 have suggested that papillary lesions can be diagnosed accurately on core needle biopsies and that papillomas without atypia can be followed up without surgical excision. Based on available data, we cannot endorse leaving behind a papillary lesion based on evaluation of a small portion of the lesion by a core biopsy. Rizzo et al17 advocated surgical excision of all intraductal papillomas identified on core needle biopsies because of an upgrade of almost a fourth of these lesions caused by the presence of either atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS) on subsequent surgical excision. Another study18 also found a malignancy in the subsequent excisional biopsy in a quarter of patients with papillary lesions classified as probably benign on a core biopsy. Valdes et al19 similarly found that 23% of papillary lesions without atypia on fine-needle aspiration biopsy, core needle biopsy, or mammotome were malignant at surgical excision. The authors17 concluded that no distinct clinical, radiologic, or cytologic signs could distinguish between a papilloma and a papillary carcinoma; they recommended, therefore, surgical excision of all papillary lesions diagnosed on percutaneous needle biopsies.

Clearly, with 3 to 4 cores (obtained with a 14-gauge needle) of a 2.5-cm papillary lesion showing completely benign features, it is impossible to predict what may be present in the residual lesion; complete excision should be performed on such a case. On the other hand, a 0.5- to 1-cm lesion, sampled with 3 to 4 cores by an 8- to 9-gauge needle, which shows a benign lesion, was probably excised nearly in its entirety given the 4- to 6-mm width of cores obtained by 8- to 9-gauge needles. When atypia is present in a papillary lesion on core biopsy, a designation of ‘an at least atypical papillary lesion’ would be appropriate until a definite classification can be made based on the subsequent excisional biopsy. Because of potential histologic variability within a papillary lesion, complete excision is prudent in most cases, regardless of the findings on an initial core biopsy that has not removed the lesion in its entirety.

**INTRA DUCTAL PAPILLOMA**

**Clinical Presentation**

Intraductal papillomas are generally solitary and located in the subareolar region in the major and lactiferous ducts, hence the derivation of the term central/solitary papilloma. They occur most frequently in women older than 50 years and are often present with serous or serous-hemorrhagic nipple discharge.20-22 A circumscribed mass or a solitary dilated retroareolar duct may be seen on mammography or ultrasonography in the case of larger lesions; smaller lesions are usually occult.23-25 Calcifications are rarely detected in papillomas but do occur in both large and small papillary lesions.26-28 Galactography may demonstrate a smooth filling defect or a complete obstruction to retrograde flow of contrast material.29 Magnetic resonance imaging may show a well-defined enhancing lesion within a fluid-filled duct.26

**Morphology**

Papillomas are characterized by an arborescent proliferation with epithelial and ME cells overlying fibrovascular stalks protruding into ductal lumens. Epithelial cells line the luminal aspect of the papillae, and an ME cell layer is present between the epithelial cells and the basement membrane (Figure 1, A through D). Epithelial proliferations of the low-risk DIN (intraductal hyperplasia) type without cytologic atypia are frequently observed either focally or diffusely in papillomas. When prominent and forming solid sheets, the proliferating epithelial cells often obscure the papillary nature of the lesion. At higher magnification, however, delicate fibrovascular cores with intervening ME cells are often apparent (Figure 2, A through C). In some planes of the section, the fibrovascular stalk may not be apparent at all, resulting in an interpretation of pure low-risk DIN (intraductal hyperplasia). These areas of diffuse or florid hyperplasia show streaming or whorling of the proliferating cells; have irregularly distributed and often overlapping, bland nuclei; and have inconspicuous cytoplasmic margins and slitlike secondary lumens; all these features are clues indicating a benign process.

When there is sclerosis in the papillary processes, the lesion qualifies as a sclerosing papilloma; the amount of sclerosis is highly variable, ranging from focal to diffuse. Distorted tubules entrapped in the sclerotic areas may create a pseudoinvasive pattern (Figures 3, A through D, and 4, A and B); the identification of persistent ME cells around these entrapped ducts confirms their benign nature.

Aside from apocrine metaplasia, which is rather common in papillomas, squamous, mucinous, clear cell, and sebaceous metaplasia may also occur at much lower frequency. As a rule, microcalcifications are not a common feature of either solitary/central or peripheral/multifocal papillary lesions, whether benign or malignant. When microcalcification is encountered, it is most frequently in the setting of a sclerosing papilloma.

Hemorrhagic infarction because of torsion of the papillary stalk may hinder accurate interpretation of the lesion. In cases of extensive infarction, diagnoses should be based
on any remaining viable tissue; if there is no viable tissue remaining, then the lesion is designated as an infarcted papillary lesion.

**PAPILLOMATOSIS**

**Clinical Presentation**

Classic papillomatosis, also referred to as peripheral/multiple papillomas, is characterized by papillary proliferations within multiple terminal duct-lobular units or in the distal branches (terminal ducts) of the duct system. Patients with papillomatosis are generally younger than those with either solitary/central papilloma or papillary carcinoma. Papillomatosis may occasionally present with nipple discharge or a mass lesion when extensive; however, it is most often an incidental microscopic finding. When present in abundance, nodular masses or, rarely, microcalcifications may be seen on mammography.

**Morphology**

The morphologic appearance is similar to intraductal papillomas. However, although the attachment to the duct wall is seen only focally or, at most, in a few foci in solitary papillomas, it is more common to find simultaneous protrusion and proliferation of several papillae with multiple points of attachment in papillomatosis.

**ATYPICAL PAPILLOMA AND CARCINOMA ARISING IN A PAPILLOMA**

Papillomas can display focal proliferations of a mildly atypical, monotonous cell population identical to low-grade DIN (DIN 1/ADH/DCIS, grade 1; Figures 5, A through F, and 6, A through C). When DIN 1 occupies less than a third of the papillary lesion, the term atypical papilloma has been used. If at least a third, but less than 90% of the lesion displays such changes, the designation of carcinoma arising in a papilloma has been used. When completely excised, these 2 groups do not seem to differ in clinical behavior, as observed in a retrospective study that used this quantitative approach. It is noteworthy that although 90% was used as the cut-off point, none of the lesions had atypical areas that occupied more than 65% to 70% of the papillary lesion. Currently, to avoid the term carcinoma, we designate all such lesions as papillomas with DIN 1/atypical papilloma (Table 1). Rarely, papillomas may display focal areas similar to grade 2 or grade 3 DIN (DCIS, grades 2–3). Again, our preference is to designate...

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Figure 1. Intraductal papilloma. A, Focal minimal areas of sclerosis are present within the fibrovascular cores (hematoxylin-eosin [H&E], original magnification ×40). B, Myoepithelial and epithelial cells overlying the fibrovascular cores can be appreciated (H&E, original magnification ×100). C, On higher magnification, the 2 cell layers are clearly evident (H&E, original magnification ×400). D, Immunostain for p63 highlights the myoepithelial cells in the intraductal papilloma and the duct wall (original magnification ×200).
Figure 2. Intraductal papilloma with low-risk ductal intraepithelial neoplasia (DIN; intraductal hyperplasia). A, The core biopsy of an intraductal papillary lesion shows sheetlike epithelial proliferation on low magnification. B, The papillary processes are fused and hard to discern; however, fibrovascular cores are appreciable and some slitlike, secondary lumens are present. C, On higher magnification, the proliferating epithelial cells appear heterogeneous with overlapping nuclei, and there are a few slitlike fenestrations, indicating low-risk DIN (intraductal hyperplasia) in this papillary lesion (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], and ×200 [C]).

these lesions as papillomas with focal DIN 2 to DIN 3/DCIS, grade 2 to grade 3, or DIN 2 to DIN 3/DCIS, grade 2 to grade 3 arising in a papilloma. The main reason we prefer to designate these as DINs and specify the grade and extent is that even a fully developed intraductal or intracystic papillary carcinoma is known to have an excellent prognosis with nearly 100% survival at 10 years.29

Variable criteria have been used for diagnosing an atypical papilloma.30,31 Page and colleagues30 categorize a lesion as a papilloma with DCIS, when the papilloma shows any area of uniform histology and cytology consistent with noncomedo DCIS that is greater than 3 mm in size, whereas papillomas that contain a histologically identical epithelial proliferation that is greater or equal to 3 mm in size are classified as papillomas with atypia.30 Although outcome data of atypical papillomas diagnosed based on the Page et al30 criteria have been reported, the number of cases, to our knowledge, has been limited; there were 8 patients with atypical hyperplasia within the papillomas and there were no papillomas with DCIS in the study.30 Others, such as Collins et al,32 do not rely on the extent/size of the atypical proliferation and render a diagnosis of atypical papilloma when the atypical proliferation in the papilloma demonstrates some, but not all, of the combined architectural and cytologic features that have been proposed for low-grade DCIS. These criteria have been adopted or analogized from conventional criteria for differentiating ADH and DCIS in mammary ducts without papilloma. Given the significant interobserver variability in the application of these criteria in the setting of pure epithelial proliferation, its superimposition on papillary lesions is unlikely to have much utility.

The possible outcome of applying only qualitative criteria or nonproportional quantitative criteria would be that many localized larger papillomas with only a small proportion of low-grade, atypical proliferation would be categorized as carcinomas. Such lesions require only localized excision with a complete rim of uninvolved breast tissue and have an excellent prognosis;28 designating them as carcinoma might prompt unwarranted treatment and cause undue alarm simply for finding a 3-mm focus of low-grade DIN (DCIS, grade 1) in a 3-cm, otherwise benign papilloma.

IMMUNOHISTOCHEMICAL FEATURES OF PAPILLARY LESIONS

The distinction of benign and malignant papillary lesions based on hematoxylin-eosin (H&E) morphology can be very challenging, especially in cases where there is limited and/or fragmented material, as in core biopsies. In recent years, there has been a considerable increase in the number of different antibodies available for use in the diagnosis of breast lesions. A summary of immunohistochemical features for the differential diagnosis of papillary lesions is provided in Table 2.

In our experience, high molecular weight cytokeratins, ME cell markers, and basement membrane markers are most helpful in distinguishing papillary lesions suspicious for having atypia, carcinoma, or invasion. The absence of an ME cell layer throughout an intraductal papillary lesion generally confirms a diagnosis of papillary DIN (papillary DCIS). The significance of the total absence of ME cells in apocrine papillary lesions lacking atypia is not well established and requires further evaluation. The identification of ME cells by markers, such as p63, calponin, and CD10...
Figure 3. Sclerosing papilloma. A, On core biopsy, focal areas of sclerosis are identifiable (hematoxylin-eosin [H&E], original magnification ×40). B, Calcification is present in the sclerotic area of this papilloma (H&E, original magnification ×100). C, Distorted tubules within a sclerotic stroma mimic an infiltrative process (H&E, original magnification ×200). D, p63 immunostain demonstrates persistence of myoepithelial cells around the tubules identifying them as benign (original magnification ×200).

Figure 4. Sclerosing papilloma. A, On low magnification, the sclerosis is seen to involve almost the entire papilloma with an admixed adenosis pattern. B, The sclerosis and adenosis within the papilloma creates an occlusive growth pattern almost simulating nodular sclerosing adenosis; the designation of intraductal adenoma has also been used for this lesion (hematoxylin-eosin, original magnifications ×10 [A] and ×100 [B]).
Figure 5. Atypical papilloma (papilloma with ductal intraepithelial neoplasia 1 [DIN 1]). A, Papillary proliferation is present within confluent, dilated ducts. B, Most of the lesion is a classical intraductal papilloma (seen on the left), whereas a minor portion (seen on the right), comprising almost 30% of the entire lesion, shows proliferation of a uniform cell population, similar to cribriform-type DIN 1 (ductal carcinoma in situ, grade 1). C and D, The proliferation of relatively uniform cells with distinct cell margins, rounded nuclei, and formation of rigid cribriform spaces reflects atypia (hematoxylin-eosin, original magnifications ×10 [A], ×40 [B], and ×200 [C and D]). E, Immunostain for calponin demonstrates the presence of residual myoepithelial cells overlying the fibrovascular cores and beneath some of the atypical proliferating cells. F, Calponin immunostain shows the absence of myoepithelial cells within the areas of atypical epithelial proliferation (original magnifications ×100 [E] and ×200 [F]).
is very helpful in supporting a diagnosis of papilloma when processing artifacts blur the morphologic differences between the epithelial and ME cell layers on H&E section.

High molecular weight cytokeratins (CK) are typically found in ductal epithelial lining and squamous epithelium. The antibody 34βE12 identifies a cocktail of acidic and basic CK, including CK1, CK5, CK10, and CK14.33–35 In the normal breast, CK5/6 and 34βE12 stain the ME cells and mammary duct epithelial cells. Several studies have demonstrated the diminished to absent immunoreactivity to CK5/6 and 34βE12 in 80% to 100% of low-grade to high-grade DIN (ADH/DCIS) lesions, whereas 88% to 100% of benign intraductal proliferations (low-risk DIN/intraductal hyperplasia) display strong mosaic distribution of immunoreactivity throughout the lesions.36–40

The atypical neoplastic cell population within a papilloma with DIN (an atypical papilloma and carcinoma arising in a papilloma) is also frequently negative for CK5/6 and 34βE12 (Figure 4). A combination of ME cell markers and antibodies to high molecular weight cytokeratins, such as CK5/6 and 34βE12, may be more useful in the differentiation of papillomas and papillary carcinomas.41–43 Cyto-keratin 34βE12 has the advantage of simultaneous decor- ration of the ME cells while identifying the proliferating cells as low-risk DIN or DIN 1 to DIN 3.

CLINICAL SIGNIFICANCE OF PAPILLOMAS AND PAPILLOMATOSIS WITH OR WITHOUT ATYPIA

In the distant past, papillomas were regarded as malignancies or as precancerous lesions and were treated by simple or radical mastectomy.44,45 Studies demonstrating the benign nature of papillomas led to acceptance of local excision as the treatment of choice.3,22,46–48 Subsequently, however, an increased risk for breast cancer was reported in patients with papillomas,49,50 and a higher incidence rate was noted in association with multiple papillomas.22,48,51 The risk of developing cancer after a biopsy with papil-lomatous lesions was reported to be 7.4 times that of the normal population of comparable age.51 However, the influence of atypia was not a feature evaluated in these early studies. Furthermore, the risk of subsequent cancer is also affected by the presence of other coexisting proliferative lesions, which are frequently evident in the proximity of many papillary lesions22,51; the extent of surgical excision (complete versus incomplete, ie, with or without a rim of uninvolved mammary tissue) is another feature not assessed and/or noted in many earlier studies. It is impor-tant to note that these earlier studies did not have the extensive tissue sampling employed today. A thorough review of the “Materials and Methods” sections of the older studies confirms the limited or absent information available on the number of slides per lesion and/or specimen size.

Compared with solitary papillomas, papillomatosis is more likely to be associated with atypia or DIN. In a retrospec-tive study of multiple papillomas52 most patients with multiple papillomas (44 of 61; 72%) had coexisting atypical or malignant epithelial lesions. In another study of 25 papillary lesions,53 6 of 16 patients (38%) with peripheral papillomas had associated carcinomas compared with none of 9 patients (0%) with central papillomas.

With the growing awareness of the presence of atypical proliferations in papillary lesions, a few studies attempted to determine the impact of such finding on the relative
risk of subsequent breast cancer. Page et al\(^7\) reported the risk of subsequent invasive breast carcinoma for papillomas containing atypical hyperplasia to be greater than 4 times that of patients with papillomas lacking atypical hyperplasia, whereas the risk for papillomas lacking atypical hyperplasia closely approximated the risk of proliferative disease without atypia.

In a retrospective study of 119 central papillomas, MacCrogan et al\(^6\) found no statistical difference in recurrence among several categories of papilloma with epithelial proliferation: papillomas with florid hyperplasia (22 patients; 18%), papillomas with focal atypia (40 patients; 34%), atypical papillomas (24 patients; 20%), and carcinomas arising in a papilloma (33 patients; 28%). The uneventful outcomes for these patients could be explained by the complete excision of the atypical cell population localized to a lesion confined to a dilated segment of a duct. Recurrences appeared to be related to the presence of proliferative lesions in the surrounding breast tissue.\(^6\)

A more recent, larger study\(^5\) addresses the impact of multiplicity as well as atypia on subsequent breast cancer risk. The study\(^5\) included 372 solitary papillomas, of which 54 had atypical hyperplasia (15%), and it included 41 multiple papillomas, of which 13 had atypical hyperplasia (32%). The atypical hyperplasia (ADH and/or atypical lobular hyperplasia) was identified either within the papilloma or in the nearby terminal duct-lobular units (ADH was defined as an architecturally complex, cribriform-like proliferation of monotonous cells that lacked malignant cytologic features and was confined to an area measuring <3 mm at the greatest dimension and only partially involving a “basement membrane-bound space,” with a second nonatypical population of cells composing the remainder of the papilloma). After a mean follow-up of 16 years, patients with a single papilloma lacking atypia had a 2-fold risk of developing breast cancer, similar to the relative risk of 1.9 for patients with proliferative disease without atypia. The relative risk associated with single papillomas with atypia was elevated (relative risk, 5.1) and was even slightly higher than the relative risk of 4.1 associated with nonpapillary ADH. Patients with multiple papillomas had a higher relative risk (3.0) than patients with single papillomas or proliferative disease without atypia; multiple papillomas with atypia had an even higher relative risk (7.0). This study evaluated cases collected at Mayo Clinic (Rochester, Minnesota), between 1967 and 1991, and there is no mention of lesion size or sampling method; furthermore, the inclusion of cases that had simultaneous nonpapillary proliferative lesions detracts from the validity of extrapolating the risk to pure papillary lesions.

### Table 1. Morphologic Features of Papillary Lesions

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<td><strong>ME cells within the duct</strong></td>
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**Abbreviations:** DIN, ductal intraepithelial neoplasia; DCIS, ductal carcinoma in situ; ME, myoepithelial cells.

* See the second paragraph of the section on noninvasive papillary carcinoma.

### Table 2. Immunohistochemical Features of Papillary Lesions

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**Abbreviations:** CK, cytokeratin; DCIS, ductal carcinoma in situ; DIN, ductal intraepithelial neoplasia; ME, myoepithelial cells.
INTRAEPITHELIAL NEOPLASIA CONCEPT AND PAPILLARY LESIONS

Our current preference is to use the term ductal intraepithelial neoplasia (1, 2, or 3, as the case may be) for pure epithelial lesions rather than atypical intraductal hyperplasia or DCIS. We prefer to use these latter terms in the setting of papillary lesions as well to avoid the designation of carcinoma. A papillary DCIS would become DIN 1 (or rarely, DIN 2 or DIN 3), papillary type. Atypical papilloma would be designated as papilloma with DIN 1; the proportion of the lesion involved by the DIN 1 should be specified. In rare cases when a higher-grade DIN (DCIS, grades 2 or 3) focally involves a papilloma, it would be designated as a papilloma with DIN 2 or DIN 3.

INTRADUCTAL PAPILLARY CARCINOMA (DIN 1–3, PAPILLARY TYPE)

Definition and Clinical Presentation

Intraductal papillary carcinomas account for 2% of all breast cancers. Most occur during the fifth and sixth decades of life. It is important to distinguish solitary, central papillary carcinomas from the multifocal, peripheral type, as the latter may require a wider excision because of the more extensive distribution of the process. Multifocal peripheral intraductal papillary carcinoma is basically a variant of the classic DIN 1 to DIN 3 (intraductal carcinoma) because it originates in the terminal duct-lobular unit and is distributed in the same manner and, therefore, requires similar management.

Morphologic Features

The complete or nearly complete (90%) absence of ME cells within the intraluminal papillary fronds is one of the most important distinguishing features of papillary intraductal carcinoma. The presence of ME cells, even extensively, does not necessarily exclude the possibility of a papillary intraductal carcinoma, however. Furthermore, even in the setting where there is a near absence of ME cells in the papillary processes, the ME cell may be present in the surrounding duct wall. The epithelial cells supported by the fibrovascular stalks can display a variety of proliferative patterns, including cribriform, solid, micropapillary, or stratified spindle-cell patterns (Figure 7, A through D). The neoplastic cells often appear deceptively bland and are categorized as low grade. High-grade intraductal papillary carcinomas do occur, albeit with lower frequency. Features useful for differentiating intraductal papillomas, atypical papillomas, and papillary intraductal carcinomas are summarized in Table 1. Localized apocrine metaplasia is generally not a feature of papillary intraductal carcinomas, although rarely, complete apocrine differentiation may be present, called apocrine papillary intraductal carcinoma. These apocrine papillary carcinomas often display abundant epithelial proliferation in solid or cribriform pattern, often with at least focal atypia overlying the fibrovascular stalks. Whether or not an apocrine lesion with an absent ME cell layer but only one layer or minimally stratified epithelial cell layer qualifies as DIN 1, papillary type (papillary DCIS, grade 1) has not been well established.

Immunostain for ME markers (calponin, p63, CD10, etc) are useful in unmasking the presence and extent of distribution of ME cells in papillary lesions and can be helpful in arriving at an accurate diagnosis. One of the problems in interpretation of these lesions is how to manage a lesion in which there is complete absence of an ME cell layer, even around the cystically distended duct in which the papillary lesion is proliferating. Does the absence of an ME cell layer around a duct constitute or reflect invasion? This problem is often compounded when needle instrumentation results in partial spillage of the duct content into the surrounding stroma. This issue is discussed below.

Variants of Intraductal Papillary Carcinoma.—Intracystic (Encapsulated) Papillary Carcinoma.—Intraductal papillary carcinomas that are solitary, and frequently, centrally located, have also been designated intracystic (encysted) papillary carcinomas by some authors. The term intracystic may be appropriate for lesions that grossly exhibit a cystic space around the papillary proliferation; however, it serves no distinctive purpose because, morphologically, all intraductal papillary carcinomas are located within a variably dilated cystic duct.

The term encapsulated papillary carcinoma has been coined for papillary carcinomas that appear circumscribed and encapsulated but which lack demonstrable ME cells around the cystically dilated duct. The possibility that a subset of circumscribed papillary carcinomas lacking a demonstrable peripheral ME cell layer may actually represent invasive papillary carcinomas has been raised by some authors. In our opinion, however, these tumors are well delineated and behave indolently and are best regarded as intraductal papillary carcinomas for management purposes, particularly if persistence of a basement membrane around the duct can be ascertained with collagen IV or laminin immunostains.

Microglandular adenosis is a notable example of a benign lesion with complete absence of an ME cell layer; in this setting, the basement membrane is actually multilayered and thickened, possibly to compensate for the loss of the ME cell layer. Nevertheless, although the absence of detectable ME cells in a duct wall may not necessarily indicate stromal invasion, this finding should prompt a careful evaluation for possible invasion. In case of larger lesions (>3 cm), it would be prudent to assess sentinel nodes, just as many prefer to assess sentinel nodes for extensive DIN 1 to DIN 3 (DCIS, grades 1–3).

Nassar et al described 19 circumscribed solid papillary carcinomas that appeared noninvasive on H&E morphology alone. No immunohistochemical stains were performed to assess the ME cell layer. No metastatic disease was found in the lymph node dissections performed for 12 of the patients (63%). The 12 patients were alive with no evidence of disease at a mean follow-up of 5.7 years, and 6 were dead (32%) of unrelated causes at a mean of 11.5 years, indicating that most papillary carcinomas that appear to be in situ by H&E morphology are clinically indolent and behave like noninvasive carcinomas.

Rare cases of similar tumors with axillary lymph node metastasis have been reported in the literature. It is possible that these cases may have had occult foci of invasion undetected by the sampling, that a separate occult primary tumor had existed, or that the lymph node tumor could actually have represented a carcinoma arising from a glan- dular inclusion (although this would be, admittedly, quite rare). Another possibility is that many of these lesions re-
Figure 7. Intraductal papillary carcinoma (ductal intraepithelial neoplasia I, papillary type). A, A well-demarcated lesion composed of thin, complex, and branching papillary processes (hematoxylin-eosin [H&E], original magnification ×40). B, Immunostain for p63 shows a patchy myoepithelial cell layer around the duct and almost complete absence of myoepithelial cells within the papillary fronds (original magnification ×40). C, The thin papillary processes are lined by atypical elongated epithelial cells that appear stratified, monomorphic, and hyperchromatic; no discernable myoepithelial cells are identified beneath the epithelial cells, and there is focal microcalcification (H&E, original magnification ×200). D, Immunostain for p63 demonstrates the presence of a myoepithelial cell layer around the duct; only rare myoepithelial cells are noted within the lesion (original magnification ×200).

receive a needle core or aspiration biopsy before excision. Most of these lesions are also located in the nipple/subareolar region, where a rich lymphatic network exists. It is conceivable that manipulation and instrumentation of these often large and friable lesions may dislodge tumor cell fragments into the lymphatic channels from where they can be easily transported to the axillary nodes; the nodal involvement may reflect benign transport in, at least, some cases.

Solid Papillary Carcinoma.—The term solid papillary carcinoma (SPC) was first proposed by Maluf and Koerner to describe a variant of intraductal papillary carcinoma, which is characterized by a compact cellular proliferation within multiple nodules that represent dilated ducts (Figure 8, A through C). The neoplastic tumor cells are low to intermediate grade and appear to be streaming, so that the lesion resembles florid intraductal hyperplasia at low magnification. However, the homogeneity (monotony) of the neoplastic cells, as well as the presence of significant mitotic activity in some cases, are clues to the diagnosis of SPC. Many of these cases display neuroendocrine differentiation, often have at least focal granular eosinophilic cytoplasm, and are immunoreactive with neuroendocrine markers. Solid papillary carcinoma is thought to be one possible precursor of colloid (mucinous) carcinoma of the breast because of its frequent association with the latter, but other types of invasive carcinoma can also be seen in association with SPCs.

Like intracystic (encapsulated) papillary carcinomas, the possibility that many of these SPCs actually represent “pushing-border” or “expansile” variants of invasive carcinoma has been raised by some authors; however, the behavior of these tumors is also generally indolent, and even for SPCs with associated invasive carcinomas, the prognosis is relatively favorable compared with invasive ductal carcinomas of comparable size. In the series reported by Nassar et al, only 17.8% (5 of 28) of patients who had SPC with invasive carcinoma died of the disease after a mean of 6.6 years (1–19 years). The size of the invasive component in the 28 cases varied from 0.1 cm to 4 cm; the invasive component was less than 0.5 cm in 9 cases (26.6%), 0.5 cm to 1 cm in 3 cases (8.8%), 1 cm to 2 cm in 6 cases (21.4%), 2 cm to 3 cm in 6 cases (21.4%), and more than 3 cm in 6 cases (21.4%).
cm in 12 cases (35.2%), and greater than 2 cm in 3 cases (8.8%); the size could not be determined in 7 cases (20.6%); the invasion was multifocal in 13 cases (38%). Axillary lymph node metastases were present in 6 cases (20%), and the invasive tumors in all 6 cases were less than 1.5 cm. Among the 5 patients who died of the disease (17.8%), the size of the invasive component measured less than 0.5 cm in 3 cases (60%) and 1 cm to 2 cm in 2 cases (40%); 1 patient (20%) had positive axillary nodes, and all 5 patients (100%) developed distant metastases. Although this could suggest that some small but aggressive clones do exist, it should be kept in mind that, even when an entire sample is submitted for pathologic evaluation, only a single slide of each block is evaluated: Our sampling is not exhaustive and could easily miss areas of invasive carcinoma hidden deeper in the blocks.

Invasive Carcinoma Associated With Papillary Carcinoma

Most papillary carcinomas are noninvasive; however, a small proportion of papillary carcinomas have unequivocal associated stromal invasion. The invasive foci generally display the morphology of an infiltrating duct carcinoma lacking papillary features (Figure 9, A and B). Morphologic variants include tubular carcinoma and infiltrating duct carcinoma not otherwise specified (NOS). The size of the invasive focus may range from microinvasive to substantial and grossly visible. Some authors reserve the term invasive papillary carcinoma to invasive carcinomas with an exclusively papillary pattern; these have been reported to account for less than 2% of all breast carcinomas with a higher frequency of occurrence in postmenopausal and nonwhite women. It is reasonable to speculate, however, that many invasive papillary carcinomas described in older studies may have included intraductal papillary carcinomas that appeared invasive in an expansile fashion, intraductal papillary carcinomas with associated invasive ductal carcinoma, and possibly even invasive micropapillary carcinomas.

Epithelial Displacement After Needle Instrumentation Procedures

Epithelium displaced by a needle core or aspiration biopsy has been described in intraductal papillomas as well as in intraepithelial (in situ) and invasive neoplasms. The epithelium can be dislodged and displaced into the surrounding stroma, often in the needle tract, and even into adjacent lymphatic channels. Displaced epithelium can even be transported to axillary lymph nodes. It is important to be aware of the possibility of displacement after needle aspiration or core biopsy to distinguish displaced epithelium from true stromal or lymphovascular invasion.

Papillary lesions, because of their inherent friability, are particularly prone to epithelial displacement after needle instrumentation procedures. The diagnosis of microinvasive or early invasive carcinoma associated with intraductal papillary carcinomas is frequently challenging, and the presence of displaced epithelium can cause much confusion in this setting. The history of a recent needling procedure, presence of prior biopsy site changes, degenerative changes in the “invasive” cell clusters, and absence of reactive, altered stroma surrounding the fragments of epithelium are clues indicating epithelial displacement (Figure 10, A and B).
INVASIVE MICROPAPILLARY CARCINOMA

Definition and Clinical Features

The term invasive micropapillary carcinoma (IMPC) of the breast was coined in 1993 to describe a distinct variant of breast cancer characterized by small micropapillary clusters of tumor cells that lack true, central, fibrovascular cores and that lie within empty stromal lacunae. It is possible that the empty lacunae are, at some point, filled with fluid that is washed out by processing. Invasive micropapillary carcinoma is now a recognized subtype of infiltrating duct carcinoma. It can occur in pure form or, more often, as a partial component admixed with infiltrating duct carcinoma NOS. Rare association with variants, including tubular, mucinous, or papillary carcinoma, and even infiltrating lobular carcinoma, has also been reported. The incidence of IMPC is 0.9% to 1.7% of invasive breast carcinomas when occurring in pure form and up to 7.6% when admixed with other types of mammary carcinoma. The mean age at presentation is similar to that of patients with infiltrating duct carcinoma NOS. Most of these patients present with a palpable mass; an abnormal density or microcalcifications may also be detected on mammography.

Morphology

Most IMPCs are moderately or poorly differentiated with an intermediate to high nuclear grade. Expression of MUC1 in the stroma-facing surface of the tumor cells in IMPC has been demonstrated, consistent with its distinctive inside-out pattern. An associated intraductal carcinoma of micropapillary, cribriform, or papillary type is frequently present, which is a helpful clue when excluding the rare possibility of metastatic ovarian/peritoneal serous papillary carcinoma or metastatic micropapillary carcinoma from other organs, such as the lung or urinary bladder. On occasion, true lymphovascular invasion may be difficult to distin-
Figure 11. Invasive micropapillary carcinoma. A, Clusters of tumor cells lacking true fibrovascular cores reside within empty-appearing stromal spaces; ductal intraepithelial neoplasia 2 (ductal carcinoma in situ, grade 2) with microcalcification is also barely evident in the upper part of the field. B, The tumor cells have intermediate-grade nuclear atypia with their apical surfaces facing toward the empty spaces in some clusters. C, Invasive micropapillary carcinoma metastatic to a lymph node; the typical morphology is often retained, at least focally, when the tumor metastasizes (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B], and ×100 [C]).

Clinical Significance

The propensity of IMPC, whether in pure or mixed form, for lymphovascular invasion and lymph node metastasis is well known and documented in several reports.72,74–78,80,81,84,85 Studies that categorized the tumors into groups according to the percentage of micropapillary component have found no correlation between the proportion of micropapillary carcinoma and the percentage of lymph node metastasis or lymphovascular invasion; tumors with any amount of micropapillary pattern showed higher propensity for lymphovascular invasion and lymph node metastasis compared with infiltrating duct carcinoma NOS.74–78,81 Therefore, when an invasive micropapillary pattern is seen as a focal/partial component of a tumor, it is important to note the presence of this micropapillary element in the diagnosis. An estimate of the percentage of the micropapillary component would also be desirable. As increasing numbers of cases are described, a better understanding of this lesion may evolve if it was noted that the proportion of IMPC within an infiltrating duct carcinoma NOS has impact on outcome. A few studies have reported that a relatively higher percentage of IMPCs are positive for estrogen receptor (61%–91%), progesterone receptor (50%–70%), and Her2/neu (54%–78%) compared with infiltrating duct carcinoma NOS; however, other studies have not found a statistically significant difference in the expression of these proteins.74,80,84 A higher frequency of p53 protein overexpression (38.9%–75%) has been noted among IMPC compared with infiltrating duct carcinoma NOS.51,84–86 Thor et al.87 demonstrated chromosomal loss of the short arm of chromosome 8 in all of the 16 IMPCs studied. According to follow-up results of most series, a poor outcome (higher rate of recurrence, metastasis, and death from disease) is expected for patients with IMPC75–77,81,84; however, the prognosis of IMPC does not differ from that of invasive ductal carcinoma NOS of similar stage, and therefore, the micropapillary pattern may not have any independent prognostic significance.75,80 The more aggressive behavior appears to be related to the higher frequency of lymphovascular invasion and lymph node metastases.

SUMMARY

The assessment of papillary lesions continues to be one of the most challenging areas in breast pathology. In this review, we have provided guidelines to distinguish and accurately diagnose the various papillary lesions based on H&E morphology with the adjunctive use of immunohistochemistry when needed. The incorporation of the concept of DIN into the terminology of papillary lesions not only provides an alternative way to categorize these lesions but also, and more important, avoids the use of the term carcinoma, preventing overtreatment as well as diminishing the psychological and social impact of a diagnosis of cancer on the patient.

The limitations of cytology in the diagnosis of papillary lesions have also been addressed. The management of papillary lesions found on core biopsy remains an issue of much debate, however. It would be prudent, in our opinion, to completely excise any papillary lesion where the initial core biopsy has not removed the lesion in its en-
tirety. Some small papillary lesions are excised completely with the 8-gauge and 9-gauge needles, obviating reexcision. Epithelial displacement by needleling procedures is not infrequently encountered because of the increasing popularity of these procedures, and the pathologist should be aware of this possibility. We are particularly concerned about the possibility that areas interpreted as invasion in association with the solid, encapsulated papillary carcinomas may, in fact, reflect dislodged tumor cells; because there are no ME cells around cells dislodged from a papillary PIN (DCIS) into the surrounding stroma, it is impossible to exclude true invasion. A rather long follow-up is necessary to confirm the true nature of such areas.

Variants of intraductal papillary carcinoma (DNA–3, papillary type), such as solid papillary carcinoma and encapsulated papillary carcinoma, have recently been implicated as possible low-grade invasive carcinomas based on the absence of ME cells around the circumscribed nodules; however, the fact that the majority of such lesions behave indolently should always be kept in mind to avoid the overtreatment of such patients.

Optimally, in our opinion, localized papillary lesions should be excised completely with a small rim of uninvolved breast tissue without any prior needle instrumenta- tion if and when the papillary nature can be determined by imaging.

References


