Papillary lesions comprise a diverse group of breast lesions that span the spectrum of hyperplastic and neoplastic processes. A papillary breast lesion is defined as a proliferative lesion characterized architecturally by the presence of fingerlike projections composed of a stromal core overlain by a layer of epithelial cells. The presence of a stromal core contrasts with the lack of such a component in “micropapillary” lesions, including the micropapillary pattern of ductal carcinoma in situ (DCIS) and invasive micropapillary carcinoma. Our classification of mammary papillary lesions is provided in Table 1. In contrast with the classification used by the World Health Organization (WHO), the breast tumor resembling the tall cell variant of papillary thyroid carcinoma has been included. The clinical presentation and histopathologic features of these lesions are described, and the role of immunohistochemistry in their diagnosis is highlighted. Recent molecular and genetic data on papillary breast lesions are described and recommendations for their management provided and discussed.

PAPILLARY HYPERPLASIA (PAPILLOMATOSIS)

Definition and Terminology

Papillary hyperplasia is a multifocal proliferation of the ductal epithelial cells and has a papillary architecture. Sometimes the term papillomatosis is used as a synonym for usual duct hyperplasia (UDH), but its restriction to UDH with a papillary architecture is preferred.

Clinical Aspects

Papillary hyperplasia occurs throughout the entire age range but is more common in premenopausal adult women of 20 to 55 years. Typically, patients complain of tender breasts that are thickened and have a rubbery and granular texture when palpated. Some patients have a nipple discharge that is not bloodstained.

Pathologic Features

Papillary hyperplasia is seen most often as part of the spectrum of fibrocystic changes but occasionally occurs as pure papillary hyperplasia. Frequently, it is a component of other papillary lesions of the breast, including intraductal papilloma, peripheral duct papilloma, and sclerosing papilloma, which are discussed below. As a component of fibrocystic changes, this lesion is familiar to all pathologists.
working with breast disease and does not require further discussion in this review.

**JUVENILE PAPILLOMATOSIS**

**Definition and Terminology**

Described first by Rosen and Kimmel, juvenile papillomatosis is a localized, unifocal or multifocal mass forming a florid, proliferative breast lesion occurring in young women, which has a characteristic, multicystic gross morphology.

**Clinical Aspects**

Juvenile papillomatosis most often presents in young women (younger than 30 years).

**Pathologic Features**

Juvenile papillomatosis is characterized by the presence of multiple dilated ducts and cysts, extensive UDH, extensive apocrine metaplasia, apocrine papillary hyperplasia, and intraductal and intracystic papillomas (Figure 1, a and b).

Necrosis may be seen in the areas of florid UDH, which may be associated with dystrophic calcification and an accumulation of foamy macrophages. Grossly, the necrosis has been likened to Swiss cheese because of the prominent cystic element. We think that juvenile papillomatosis is a specific clinicopathologic entity, but histologically, we regard it as a localized, accentuated form of extreme fibrocystic changes.

Recognition of juvenile papillomatosis is important because superimposed, neoplastic ductal changes, including ductal intraepithelial neoplasia and lobular intraepithelial neoplasia, are common, and there is an associated familial history of breast carcinoma in the mothers and maternal aunts in more than 50% of cases. Furthermore, more than 10% of these patients develop invasive breast carcinoma on long-term follow-up. Juvenile papillomatosis is separated from other variants of papillary hyperplasia in children and young adults by the prominent cystic changes and apocrine metaplasia that are not part of the latter spectrum of lesions.

**Molecular and Genetic Aspects**

To our knowledge, juvenile papillomatosis has been little studied using modern molecular and genetic techniques because of its rarity. Rare case reports indicate an association with neurofibromatosis type 1 and Noonan syndrome.

**Management**

The diagnosis of juvenile papillomatosis should prompt excision of mass lesions and regular follow-up of the breasts clinically and by ultrasound examination.

**NIPPLE ADENOMA—FLORID PAPILLOMATOSIS OF THE NIPPLE**

**Definition and Terminology**

The WHO defines florid papillomatosis of the nipple as a benign epithelial proliferation localized within and around the collecting ducts. We define this lesion as a localized, benign nodular lesion of the nipple, characterized by a luminal cell proliferation with a papillary architecture resembling florid UDH, located within, and surrounding, the superficial nipple ducts and in continuity with the overlying squamous epithelium of the nipple skin. Some synonyms include erosive adenomatosis and nipple adenoma.
Clinical Aspects

Patients with florid papillomatosis of the nipple usually present with a nipple discharge or small superficially located nodule in the nipple-areolar complex. 12–15 Often, there are associated inflammatory changes in the overlying skin of the nipple, which may be ulcerated and may suggest Paget disease clinically. Florid papillomatosis occurs in both sexes and over the entire age spectrum, including infancy. It is also seen in ectopic or accessory nipples. 16

Pathologic Features

Numerous small and medium-sized ducts are present, in contrast to the few large lactiferous ducts with a concertina-like outline seen in the normal nipple. There is variable cystic dilatation of ducts, and some small interspersed tubular ducts with compressed lumens are also seen (Figure 2, a and b). There is variable sclerotic fibrosis of the stroma. Under low-power examination, a prominent myoepithelial cell (MEC) layer can be seen at the periphery of the ducts. The ducts show an exuberant, intraductal epithelial proliferation, resembling florid UDH. Focally, florid papillomatosis has a papillary pattern of “papillomatosis,” but the true papillary component is often less evident than the name of the lesion suggests. Micropapillary epithelial structures and tufts resembling the proliferation in florid gynecomastia are often present. 14,16 Some ducts contain fenestrated sheets of epithelial cells, punctuated by irregular, slitlike spaces. A few mitoses are identifiable. Necrosis may occur focally and, in this context, is not a definite indicator of malignancy. Furthermore, florid papillomatosis of the nipple may have associated Toker cell hyperplasia in the epidermis, which may give a false impression of Paget disease. 17 Some examples of nipple adenoma show entrapped, compressed ducts, typical of infiltrating epitheliosis. Rare cases are associated with superimposed, premalignant or malignant neoplastic changes, including so-called atypical ductal hyperplasia (ADH), DCIS, and even superficial carcinoma. 18–20

Immunohistochemical Aspects

Immunostains for high–molecular-weight keratins (CK5/6 and CK14) may be useful to confirm the presence of UDH within the ducts and the peripheral layer of MECs around the ducts. The latter may also be stained with p63 or heavy-chain myosin. A stain for estrogen receptor (ER) shows a mosaic pattern, characteristic of UDH. 21,22

Management

Florid papillomatosis of the nipple is treated by surgical excision. 18

INTRADUCTAL PAPILLOMA

Definitions and Terminology

An intraductal papilloma is a benign, mass-forming, proliferative breast lesion with a papillary architecture confined within a duct. The number and distribution of papillomas enable them to be classified into solitary papilloma, mostly located in the large central and lactiferous ducts, and multiple papillomas, mostly located in the small- and medium-sized peripheral ducts. By convention, diffuse-ly distributed microscopic papillary proliferations in the ducts as part of the spectrum of fibrocystic changes and UDH are regarded as separate entities—that is, as papillary hyperplasia, rather than benign neoplasms. However, there are few objective data upon which to make this assumption, and in our view, despite some molecular data suggesting the contrary, most papillomas are probably localized hyperplasia, albeit sometimes associated with a superimposed, neoplastic proliferation, as a secondary event.

Clinical and Imaging Aspects

Central, large duct papillomas often present with nipple discharge, which is often bloodstained. Otherwise, papillomas may present as a mass, palpable or evident on imaging, and/or calcifications detected on mammogram. Imaging studies including ductography are often diagnostic for large, central papillomas. Ductoscopy with or without cytology-examination brushings is performed in a few centers. Fine-needle aspiration cytodiagnosis of papillomas has a significant false-positive rate. Diagnosis by frozen section is not recommended. Today, diagnosis is commonly made by core biopsy, which provides only a sample of the lesion but has been shown to be highly accurate. 23–26 Excision biopsy allows a thorough histologic assessment of the entire lesion.

Pathologic Features

Grossly, a papilloma appears as a friable nodule within a cyst formed by a dilated duct or as a solid nodule encapsulated by a sclerotic duct wall. Papillomas may extend into adjacent branches of the duct. On histology, simple papillomas have prominent sclerotic stromal cores, which is more extensive than the epithelial component. Calcifications may occur in the stroma. The papillary processes are covered by a layer of cuboidal or columnar luminal cells, with or without architectural complexity (Figure 3, a and b). 27–29 When the architecture is complex, the morphology is that of UDH (Figure 3, c and d). Importantly, an MEC layer is interposed between the stroma and luminal cell layer. There is no cytological atypia and patchy apocrine metaplasia is commonly encountered. Some papillomas show more focal MECs, which may aggregate into small nests. This feature raises the differential...
diagnosis of the papillary variant of adenomyoepithelioma. In contrast to adenomyoepithelioma, in papillomas the MECs are increased only focally, lack nuclear atypia, and lack mitoses. Furthermore, the distribution of the MECs in papilloma is restricted to the basal zone of the epithelium, maintaining their normal spatial relationship to the luminal cells.

Danger Signs in a Papillary Lesion

Kraus and Neubecker identified several features of papillomas that resulted in incorrect diagnoses of malignancy that are still relevant today and are listed in Table 2. These included marked cytologic atypia associated with apocrine metaplasia; a complex, glandular architecture simulating, cribriform DCIS; solid sheets of cells; distortion of ductal epithelium entrapped within stromal cores; and epithelium entrapped in sclerotic bands within the lesion. Apocrine metaplasia, when patchy and confined within the papilloma, is usually a sign of a benign lesion, regardless of the presence of marked nuclear atypia. Apocrine DCIS may secondarily involve a papilloma but is typically associated with extensive involvement of medium-sized and large ducts outside the papilloma. Presence of zonal necrosis and mitoses in atypical apocrine cells are features of concern and could be considered DCIS if the atypical apocrine cells extended more than 3 mm. The complex, glandular architecture simulating, cribriform DCIS within papillomas is characterized by preservation of thin, fibrous septa, usually containing MECs and separating adjacent, compressed ducts or papillary fronds. The solid sheets of cells seen in papillomas are separated from solid DCIS by the morphologic and immunohistochemical criteria established in the differential diagnosis of UDH and DCIS. Briefly, these include lack of nuclear uniformity, absence of cytoplasmic boundaries, lack of polarity, a "streaming" arrangement to the cells, irregular intercellular spaces often situated at the periphery of the duct, scanty mitoses, lack of classic cytologic atypia, and the presence of helioid bodies (Figure 3, a through d).

The problem of entrapped epithelium is overcome by experience with the entity, the well-spaced cords of cells,
the linear arrangement, the sometimes squamoid appearance, the preservation of the MEC layer, and the fact that they do not extend beyond the papillary lesion. This problem is typically encountered in sclerosing papillomas/complex sclerosing lesions (CSL). In papillary areas that have a crowded, stratified, columnar-cell morphology suggesting papillary DCIS, the presence of foci of adenosis or sclerosing adenosis within the fibrous septa argues for a benign lesion.

Practical Aspects of the Diagnosis of Papilloma in Core Biopsy

When assessing the pathology of a papillary lesion, the following questions should be asked:

- Is there a superimposed neoplastic proliferation? If in doubt, perform immunostains (see following section).
- If a neoplastic process is present, is it confined to the papilloma?
- If confined to the papilloma, what is the grade of the neoplastic proliferation?
- If cytology is low-grade, what is the size or extent of the neoplastic proliferation?

Immunostains Useful in the Diagnosis of Papillary Lesions

Immunostains are often very helpful in identifying a neoplastic process within a papillary lesion of the breast. Nevertheless, the morphology is more important than the immunostaining pattern, and a diagnosis of a neoplastic proliferation should not be made on the immunostaining pattern alone. Furthermore, the immunostains must be used in the correct context; otherwise, the implications of the staining pattern can cause an incorrect classification of the lesion. Examples of an atypical papillary lesion containing ADH and one containing DCIS are illustrated in Figures 4, a through d, and 5, a through d.

Context 1: Guidelines for Cytologically Low-Grade Lesions, With a “Flat” or Monolayered Architecture, Morphologically Suggestive of a Neoplastic Proliferation.—ER Immunostain.—A patchy staining pattern argues against a neoplastic lesion. A neoplastic process should stain all the nuclei strongly, but this pattern is not specific for neoplasia. Flat, benign hyperplastic lesions may show an identical strongly positive pattern.

CK5/6 and CK14 Immunostains.—Any positive staining argues against a neoplastic lesion. Flat, benign hyperplastic proliferations may be completely negative for CK5/6. Most MECs should stain positive in neoplastic cells and show patchy staining in hyperplastic lesions (Figures 3, d, and 4, d).

Synaptophysin and Chromogranin Immunostains.—Any positive staining is almost diagnostic of low-grade endocrine DCIS. When a distinction between low-grade ductal and lobular neoplasia is required, the loss of membranous

Figure 4. Papilloma with atypical ductal hyperplasia (ADH). a, Peripheral duct papillomas. b and c, Monomorphic epithelial cells, polarization of nuclei at right angles to the bridges, and some cells with well-defined cytoplasmic borders, characteristic of ADH. d, The immunostain for CK5/6 shows positive staining in the myoepithelial cells only (hematoxylin-eosin, original magnifications ×20 [a], ×40 [b], and ×200 [c]; original magnification ×40 [d]).
staining with E-cadherin by in situ lobular neoplasia is diagnostic.

**Context 3: Cytologically High-Grade Lesions.**—Usually high-grade lesions are readily recognizable as malignant without the need for immunostains. However, occasionally, especially in core biopsies, small foci of cells exhibiting marked nuclear atypia are seen in hyperplastic papillary lesions (this is “true” ADH). Often, the cells are apocrine, but occasionally, the cells lack definite apocrine features. The differential diagnosis is focal colonization of a papillary lesion by high-grade DCIS.

**ER Immunostain.**—This immunostain is not useful because high-grade DCIS is often only weakly positive or negative for ER staining.

**CK5/6 and CK14 Immunostains.**—These immunostains are not useful because high-grade DCIS may have a basal-type immunophenotype.

**Other Immunostains.**—Myoepithelial stains are not useful, except in helping to exclude an invasive process. An immunostain for p53 may be helpful when a mutated immunophenotype (nuclei are all either strongly positive or completely negative) indicates DCIS. Similarly, a stain for HER2 showing a 3+ positive result indicates DCIS. Finally, a stain for Ki-67 that shows a high proliferative index greater than 50% suggests DCIS.

**Context 4: Apocrine Lesions.**—Apocrine cells are usually ER negative or weak, CK5/6 and CK14 negative, and endocrine marker negative, and a low-grade apocrine DCIS has a low Ki-67 index. Therefore, none of these immunostains are useful in distinguishing between apocrine hyperplastic and neoplastic lesions. In atypical apocrine proliferations, HER2 positivity favors carcinoma, but a negative stain does not exclude that diagnosis.

**Use of Myoepithelial Stains in Papillary Lesions of the Breast**

**Myoepithelial Stains.**—Recommended stains include p40, p63, heavy-chain myosin, calponin, CD10, CK5/6, and CK14.

The presence and distribution of MECs are helpful in separating benign papillomas from papillary DCIS. However, MECs are at least focally retained in papillomas partially colonized by a neoplastic proliferation. The MECs are present both in the fronds and at the duct margins in papillomas. They are typically absent in the fronds but retained at the duct periphery in papillary DCIS. The MECs are typically completely absent throughout the lesion in encapsulated papillary carcinoma (EPC) and are often reduced or absent in most of the nodules of expansile invasion in solid papillary carcinoma (SPC).

The MECs vary in number, distribution, and immunoreactivity in different regions of the breast ducts and within both benign, hyperplastic and neoplastic lesions of the breast. Therefore, when their presence or absence is critical for interpretation, several different immunohistochemistry stains should be used. Never rely on a single stain because both false-positive and false-negative interpretations can be made. Generally, MECs are retained in hyperplastic lesions and lost in neoplastic lesions. However, even normal ducts, lobules, and apocrine cysts may lack MECs, and many cases of DCIS within papillary lesions show retention of MECs.
For purposes of clinical management and TNM classification, invasion in low-grade breast carcinomas, including papillary carcinomas, is defined as a jagged, irregular, infiltrative growth pattern, defying usual anatomic structures, and usually associated with a desmoplastic stroma. The diagnosis is based primarily on the hematoxylin-eosin-stained sections but may be confirmed by the absence of enveloping MECs, as demonstrated by immunohistochemistry. “Expansile” invasion, defined as malignant cells extending beyond the anatomic boundaries of the duct walls but with a cohesive, circumscribed, smooth margin, requires the absence of MECs at the periphery, as confirmed by immunohistochemistry. For the purposes of clinical management and TNM classification, expansile invasion is only coded and treated as invasive carcinoma in the context of a high-grade cancer (eg, medullary-like carcinoma), whereas the same pattern in low-grade cancers is regarded as in situ disease. By extension, high-grade cytology excludes the diagnosis of EPC and SPC, which are by definition low-grade cancers.

**Atypical Papillomas or Atypical Papillary Lesions**

The terms **atypical papilloma** and **atypical papillary lesion** are used by many pathologists, radiologists, and other clinicians, but there is no uniform definition of this entity. The terms have been used to encompass papillary lesions that have unusual clinical or imaging presentations, those with florid UDH, those with infiltrating epitheliosis, those with superimposed low-grade in situ mammary neoplasia, or those with low-grade malignant papillary neoplasms (see Table 3). Most pathologists use the terms to indicate the presence or possible presence of a neoplastic component in a papilloma. They are terms that are useful in the context of a core biopsy of a papillary lesion that is not clearly either a benign papilloma or diagnostic of a malignant papillary lesion.

Because the distinction between ADH (DIN1B) and low-grade DCIS (DIN1C) poses a challenge in the breast, outside of the context of papillomas, it is not surprising that this distinction when the neoplastic proliferation is within a papilloma is also controversial. Indeed, ADH and DCIS undoubtedly represent volumetric differences of the same biologic entity. Furthermore, should the criteria be different depending on whether the neoplastic proliferation is present within or outside of the papilloma? Different authors have proposed different criteria. Page et al and Lewis et al suggest that a focus of monomorphic proliferation of uniform cells less than 3 mm is considered ADH and those greater than 3 mm qualify for DCIS. Tavassoli et al used a proportion of less than 30% of the lesion involved for a diagnosis of ADH and more than 30%, for DCIS. Putti et al and Schnitt and Collins suggest that the quality is more important, and any focus of monomorphic cells that meets the criteria of DCIS should be called DCIS. A consensus statement from the WHO recommends a 3 mm cutoff. Importantly, the controversy is restricted to lesions with a low-grade cytologic morphology. In practice, when assessing core biopsies of papillary lesions, we make a diagnosis of “ADH/DIN1B suspicious for DCIS,” whenever a monomorphic, low-grade, luminal-cell proliferation larger than 3 mm is present, in the absence of necrosis and state that “excision biopsy is required for comprehensive histologic diagnosis.” This practice essentially follows the recommendations of Vandebussche et al for diagnosis of such low-grade neoplastic proliferations outside of papillary lesions and is designed to prevent overtreatment of these lesions. Any neoplastic proliferation with intermediate to high nuclear grade is diagnostic of DCIS, regardless of its size. The MECs may be retained in the stromal cores of the papillary structures involved by a superimposed neoplastic proliferation of cells, and their presence does not negate a diagnosis of DCIS. The MECs are absent in the complex cribriform areas of the proliferation.

**Molecular-Genetic Changes**

Molecular studies on papillomas show loss of heterozygosity of chromosome 16p and 16q similar to those seen in ADH and DCIS outside of papillomas. The loss of heterozygosity at the 16q23 locus is said to be specific for papillomas. Molecular-genetic studies have also shown mutations in the PIK3CA/AKT1 pathway in both simple papillomas and those with superimposed, atypical proliferations.

**Cancer Risk With Papillomas**

There is no good clinical evidence that papillomas are premalignant lesions, but there is some evidence that papillomas confer an increased risk for subsequent development of invasive carcinoma locally, elsewhere in the breast, and in the contralateral breast. Hoda et al estimated the risk to be less than 5% overall, with a 2% risk for each breast, but other studies suggest a much lower risk (around 1.3%), paralleling that of proliferative breast disease without atypia. Multiple papillomas confer more risk than single papillomas. A solitary papilloma is associated with a slightly increased risk for subsequent development of breast cancer bilaterally, but even a central, solitary papilloma has a risk of associated, premalignant, low-grade neoplastic changes and a small risk of DCIS and coexistent, adjacent invasive carcinoma. The risk is similar to that of benign proliferative breast disease without atypia. Some studies, especially in the preimmunohistochemistry era, on the association between “papilloma” and concurrent carcinoma are flawed by including “atypical” papillary lesions, some of which were neoplastic—such as encapsulated papillary carcinoma.

Neoplastic lesions rarely arise within a papilloma. Most often, they arise in the region of the terminal ductal lobular units and extend into the papilloma from adjacent ducts as a “collision” tumor. The study of Page et al showed that papillomas with superimposed ADH (DIN1B) confer an increased risk for development of invasive breast cancer that is more than 4 times that of papillomas without neoplastic atypia, which parallels that of ADH alone. The presence of

### Table 3. Pathologic Entities Encompassed by the Term Atypical Papilloma

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Intraductal papilloma with florid UDH</td>
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<tr>
<td>Intraductal papilloma with infiltrating epitheliosis</td>
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<tr>
<td>Intraductal papilloma with DIN1B/ADH</td>
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<tr>
<td>Intraductal papilloma with LIN/ALH/LCIS</td>
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<tr>
<td>Intraductal papilloma with low-grade DCIS</td>
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<tr>
<td>Intraductal papillary carcinoma</td>
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<tr>
<td>Encapsulated papillary carcinoma</td>
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<td>Solid papillary carcinoma</td>
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Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; DCIS, ductal carcinoma in situ; DIN, ductal intraepithelial neoplasia; LCIS, lobular carcinoma in situ; LIN, lobular intraepithelial neoplasia; UDH, usual duct hyperplasia.
papilloma is also associated with an increased risk of coexistent carcinoma in the adjacent breast.

**Management of Papilloma Seen in Core Biopsy**

The literature contains many conflicting studies about the risk of finding malignant lesions in an excision for papilloma. Ideally, given the differences in ethnic mixes in different communities, differences in pathology and radiology practice (subspecialty, academic, community hospital, peripheral hospital, biopsy methods, among others), the risk of upgrade should be established by a prospective population-based study in the community in which the patient lives. There is no debate concerning papillomas with superimposed neoplastic changes (atypical papillomas, DCIS in a papilloma, or papillary DCIS), which have a significant association with adjacent, concurrent carcinoma and an increased risk for development of future, invasive carcinoma. Hence, all of these papillomas require complete surgical excision given the increased risk for associated low-grade neoplastic proliferations (ADH, lobular intraepithelial neoplasia) and the bilateral increased risk for malignancy in patients with multiple peripheral duct papillomas. A partial mastectomy to assess the regional breast tissue and to remove these lesions is prudent, followed by regular mammographic screening.

The standard recommendation following a diagnosis of any papilloma by core biopsy is for complete excision of the lesion. However, solitary papillomas without atypia are associated with a low risk of concurrent and subsequent cancer. The upgrade rate after excision of a solitary papilloma without atypia diagnosed on image-guided core biopsy is approximately 5% overall, and most of the malignancies are DCIS, rather than invasive carcinoma. A few studies have reported greater upgrade rates, and for large lesions, excision by dochectomy could be warranted. Greater upgrade rates have been associated with small core biopsies, with fewer cores being taken, with whether the pathologist is a subspecialty expert in breast small core biopsies, with fewer cores being taken, with multiple peripheral duct papillomas. Hence, all of these papillomas require complete surgical excision given the increased risk for associated low-grade neoplastic proliferations (ADH, lobular intraepithelial neoplasia) and the bilateral increased risk for malignancy in patients with multiple peripheral duct papillomas. A partial mastectomy to assess the regional breast tissue and to remove these lesions is prudent, followed by regular mammographic screening.

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Molecular and Genetic Aspects

Recently, CSLs have been shown to harbor a genetic defect (mutations of the PI3K pathway genes), which suggests they may be neoplastic ab initio. However, the possibility that these changes occur because of contamination from superimposed, neoplastic proliferations needs to be excluded.

Risk of Malignancy

Although somewhat controversial because of the relatively high rate of superimposed, low-grade, neoplastic proliferations, CSLs have long been associated with an increased risk for concurrently associated carcinoma in the regional breast tissue and an increased risk for subsequent development of breast carcinoma both regionally and bilaterally. The risk is greater in large CSLs than in those found incidentally and is also somewhat age dependent. In the absence of atypia or neoplastic changes, the risk of development of clinically significant, in situ or invasive carcinoma in CSLs parallels that of florid UDH, in general. The link between CSLs and metaplastic carcinomas has been established by many authors.

Management

When seen on a core biopsy for an architectural distortion, mass lesion, or calcifications, it is prudent to ensure that the entire lesion has been removed for histologic evaluation. Typically, this means a wire-guided excision. Complete excision of CSLs by mammotome may be followed by serial imaging studies when care is taken regarding pathologic and radiologic correlation. Small, incidental CSLs lacking atypia, found on core biopsy, and completely contained within the cores can be followed by serial imaging.

ENCAPSULATED PAPILLARY CARCINOMA

Definition and Terminology

An EPC is a single, localized mass, formed by a low-grade papillary breast carcinoma, with an expansile growth pattern, a surrounding fibrous wall, and lacking a peripheral layer of MECs. Although the current WHO classification calls this tumor low-grade, cases with an EPC-like gross and histologic morphology, composed of cells with grade 3 nuclei and high Nottingham grade, have been included in this category of breast cancers by some authors. Some synonyms include intracystic papillary carcinoma and encysted papillary carcinoma.

Clinical Aspects and Imaging Features

In a nonscreened population, a palpable mass is the most common presenting symptom with an EPC. This mass is often centrally located but may be peripherally located in...
any of the quadrants of the breast. A few patients present with breast pain, and about 22% present with nipple discharge. Today, many EPCs are detected because of imaging abnormalities. Most patients are older than 60 years, but rare cases are seen in women younger than 40 years. Mammography shows a circumscribed mass with a smooth contour, similar to a fibroadenoma, sometimes containing indeterminate calcifications. Ultrasound shows a complex, semicystic appearance.

**Pathologic Features**

Fine-needle aspiration cytology shows cellular aspirates with poorly cohesive cells, often arranged in supercrowded papillary groups. Often, the cells have a columnar shape, and nuclear atypia is mild. Gross examination shows a single, yellow-brown tumor nodule, sometimes with a friable, papillary appearance present within a cystlike cavity, with a fibrous wall, and often containing bloodstained fluid. Low-power examination usually shows one cystlike cavity with a wall of fibrous tissue containing a cellular, nodular tumor with a papillary architecture (Figure 7, a through c). Rare examples involve a few adjacent cystic spaces. Carter et al\(^{94}\) required the mass to be at least 1 cm in diameter to qualify as an EPC, but Lefkowitz et al\(^{95}\) accepted nodules as small as 4 mm into this category. Adjacent ducts may show low-grade DCIS. If superimposed classic, invasive mammary carcinoma is present, it is evident at low power by irregularly infiltrating glands, nests, and cords of cells extending beyond the fibrous wall of the lesion into the adjacent breast parenchyma (Figure 7, d). Lefkowitz et al\(^{15}\) required more than a 10-mm extent beyond the capsule to qualify as a significant invasive component. Thus, 3 patterns of EPC are encountered: (1) pure EPC without DCIS or invasive carcinoma, (2) EPC with DCIS in surrounding ducts (>30% of cases), and (3) EPC with a component of invasive mammary carcinoma (>30% of cases).

In pure EPC, higher-power examination shows that the cavity is lined with a layer of luminal cells of either one cell in thickness or showing focal architectural complexity with formation of Roman arches, and cribriform structures. The peripheral border is mostly smooth but is focally interrupted by the stromal cores that extend from the capsule into the central papillary nodule.\(^{96}\) The main tumor nodule is attached to the wall by a stromal stalk and exhibits a branching, frondlike papillary architecture. The papillary structures can be lined by a single or stratified, crowded, columnar layer of luminal cells, or they can exhibit architectural complexity, forming cribriform or solid sheets of cells. Commonly, the latter 2 patterns are both present in different parts of the tumor. Other patterns include stratified spindle cells and transitional cell variants, the latter resembling noninvasive papillary transitional cell carcinoma of the bladder.\(^{95}\) The columnar variant may contain a predominant population of tall, columnar cells and a second component of polygonal cells with pale cytoplasm, which may give the false impression of a MEC layer.\(^{95}\) However, the latter cell population has the immunoprofile of luminal cells, not MECs. Sometimes the cribriform and solid sheets of cells predominate and partially mask the underlying papillary architecture, imparting a “solid” appearance.\(^{95,96}\) Importantly, the neoplasm is low grade, with grade 1 or 2 nuclei.

![Figure 7. Encapsulated papillary carcinoma (EPC).](image-url)
Superadded necrosis and squamous metaplasia may occur especially after fine-needle aspiration or core biopsy. Grade 3 nuclei and necrosis have been largely limited to EPCs with associated invasive carcinoma, and such tumors should not be included in the category of EPC, as defined by the WHO classification. There is a rare variant composed entirely of apocrine cells (Figure 8, a though d). Mitoses are typically scanty and not atypical. Apocrine EPC is a somewhat controversial entity, and some authors have interpreted lesions resembling apocrine EPC as apocrine cysts with papillomas or papillary hyperplasia. In our view, the distinction between apocrine EPC and the benign alternatives lies on demonstrating the complete absence of MECs, using multiple immunostains, and the presence of more subtle features of malignancy, including nuclear atypia and mitoses—the latter being very rare in benign apocrine lesions. After a core biopsy, neoplastic epithelium from the central nodule is often displaced and entrapped in the fibrous capsule. Usually, such entrapment is confined to the immediate vicinity of the capsule and is typically associated with deposition of erythrocytes, hemosiderin, and an inflammatory reaction (neutrophils, lymphocytes, and foamy histiocytes), which can be exuberant. Another unusual feature of EPC is that of epithelial displacement into the lymphatic system. Rarely, these displaced fragments in papillary neoplasms are seen in the axillary lymph nodes. This may follow fine-needle aspiration, core biopsy, or surgical excision and was illustrated in one of the earliest reports of EPC by Kraus and Neubecker. Distinction from “true” lymphatic invasion may be difficult (Table 4).

Approximately 50% of cases of EPC have associated DCIS in the adjacent breast ducts. This is typically low grade and of mixed cribriform and micropapillary patterns. When an invasive component is present, it has a nonspecific, invasive ductal morphology and usually lacks a papillary architecture.

**Immunohistochemistry**

The ER and high–molecular-weight keratin stains parallel those of typical low-grade neoplastic luminal cells (ER strongly positive in almost all nuclei and CK5/6 negative). The apocrine variant is usually triple negative. Stains for MECs are negative throughout the lesion—both in the papillary core and at the periphery of the cystic cavity (Figure 8, d). Multiple, different MEC immunostains

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**Figure 8.** Encapsulated papillary carcinoma, apocrine type. a. Thick, sclerotic wall, as often encountered in these lesions. b and c. The cells lining the papillary cores have the classic apocrine features. d. Absence of myoepithelial cells at the periphery of the lesion and an adjacent normal duct with an intact layer of myoepithelial cells (hematoxylin-eosin, original magnifications ×40 [a], ×20 [b], and ×100 [c]; p63, original magnification ×100 [d]).
are recommended to adequately assess these tumors. Staining for collagen IV has been shown to be positive at the periphery of EPC and less intense in the areas of invasive carcinoma, but this stain does not have any practical use in the diagnosis of this tumor.\(^\text{106}\) HER2 is typically negative, and the Ki-67 index is low (\(<15\%\)).\(^\text{97}\)

**Molecular and Genetic Features**

Fluorescence in situ hybridization analysis of papillomas and EPC have demonstrated numerical alterations in chromosomes 3, 7, 17, and X in a few carcinomas and absence of these changes in benign papillomas.\(^\text{107}\) Using array comparative genomic hybridization techniques, Khoury et al\(^\text{108}\) showed 16p gain, 16q loss, and 1q gain in a few carcinomas and EPC have demonstrated numerical alterations in array comparative genomic hybridization techniques, Khoury et al\(^\text{108}\) showed 16p gain, 16q loss, and 1q gain in many EPCs, and more complex copy number variations in some cases, suggesting a progression from an in situ to an invasive genotype. A study of EPCs using invasion-associated markers, including several matrix metalloprotei-

**Differential Diagnosis**

**Papillary DCIS.**—Papillary DCIS is essentially a diffuse multiductal, intraepithelial neoplasm involving multiple small, medium, and large ducts. Papillary DCIS features neoplastic, cuboidal, and columnar luminal cells arranged in a pseudostratified layer along branching papillary fronds of fibrovascular tissue. The presence of fibrovascular cores differentiates papillary DCIS from micropapillary DCIS. Papillary DCIS differs from EPC in that it is present within true duct walls, having an intact peripheral layer of MECs.\(^\text{94}\)

**Solid Papillary DCIS.**—Solid papillary DCIS does not present with a single, dominant, encapsulated nodule but has a multinodular architecture involving multiple ducts. The nodules are almost entirely solid, and the papillary architecture is subtle and only recognized on careful microscopic inspection.

**SPC OF THE BREAST**

**Definition and Terminology**

SPC is a low-grade breast carcinoma, characterized by the presence of a cluster of small, round, oval, and elongated, solid tumor nodules, apparently based on preexisting breast ducts. SPC has an underlying, subtle papillary architecture without associated cyst formation.\(^\text{115}\)

Solid papillary DCIS is considered synonymous with SPC by some pathologists, but in our opinion, this term is better restricted to those cases of SPC that have a demonstrable layer of MECs at the periphery of the ducts.

**Clinical Aspects**

Most cases of SPC present with abnormal calcifications (typically indeterminate) seen on screening mammogram. Others present as multiple, solid nodules, usually detected on mammogram or ultrasound, is accompanied by nipple discharge that is often bloodstained, or less commonly, as a

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**Table 4. Lymphatic Displacement Versus Lymphatic Invasion in Papillary Neoplasms**

<table>
<thead>
<tr>
<th>Features</th>
<th>True Lymphovascular Invasion</th>
<th>Lymphatic Displacement</th>
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<tr>
<td>Diagnostic malignant lesion</td>
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<tr>
<td>present</td>
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<tr>
<td>Invasive component present</td>
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<td>Dislodged tumor fragments in</td>
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<td>Intraluminal clusters are</td>
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<td>poorly cohesive and</td>
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<tr>
<td>Multiple intraluminal</td>
<td>Against</td>
<td>For</td>
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<tr>
<td>clusters in one space</td>
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<tr>
<td>Histiocytes and cell debris</td>
<td>Against</td>
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<td>in the space</td>
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<td>Attached to vessel wall</td>
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<td>&quot;Outside-in&quot; polarity</td>
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**Solitary Large Duct Papilloma.**—Solitary large duct papilloma may resemble EPC under low-power view, but the luminal cell components in papilloma show the classic morphologic and immunohistochemical features of UDH, and MECs are present in the fronds and at the periphery of the duct.

**Prognosis, Behavior, and Management**

Lymph node metastases are rare at presentation but are encountered occasionally.\(^\text{110}\) Total mastectomy has been shown to cure almost all patients with EPC. Partial mastectomy may be followed by local recurrence, which is in situ, invasive, or both.\(^\text{94–96,111,112}\) The recurrent invasive carcinoma is invasive ductal carcinoma NST and rarely papillary in type. Most patients who have recurrent disease have DCIS in the ducts adjacent to the presenting EPC. Only 3 cases of noninvasive EPC in the study by Lefkowitz et al\(^\text{95}\) developed metastases, and all those primary tumors were larger than 2 cm. In summary, when strictly defined, EPC has a behavior very similar to that of low-grade DCIS. In patients who present with EPC and superadded invasive carcinoma, the behavior depends on the size, grade, and biomarker status of the invasive component. Traditionally, recommended management was total mastectomy, but partial mastectomy is now the surgical treatment of choice. Axillary lymph node dissection is not required in the absence of an invasive component. This conservative treatment approach may not be appropriate for tumors larger than 2 cm or for those with high Nottingham grade. Sentinel lymph node biopsy should be performed in those cases of EPC that have a frankly invasive component or are larger than 2 cm, which provides the oncologist with reassurance when negative in noninvasive EPC. Most often, surgical resection is followed by radiation, but in pure EPC, this may be controversial. Endocrine therapy is recommended.\(^\text{112}\) Chemotherapy is reserved for EPC that has an invasive component of sufficient magnitude and severity to pose high systemic risk. In a large study of 917 cases of EPC from the California Cancer Registry, the 10-year survival rate was 96.8% for patients without an invasive component and 94.4% in those with an invasive component. A similar good prognosis was shown for both EPC and solid papillary carcinoma. The researchers suggested treatment be limited to local therapy.\(^\text{113,114}\)

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clinically palpable, multinodular mass. Occasionally, these neoplasms may be bilateral and may occur in men.116,117

**Pathologic Findings**

Typically, SPC is a multinodular neoplasm composed of grossly solid nodules. Low-power examination shows aggregated solid nodules with circumscribed and mostly smooth contours, sometimes abutting one another (Figure 9, a through d). Higher-power examination reveals sheets of cells punctuated by the stromal cores of underlying papillary fronds.118 These fronds are often delicate, compressed, and subtle, and the papillary nature of the lesion may be easily overlooked. The neoplastic luminal cells are arranged in sheets, have grade 1 or 2 nuclei, and are oval or spindled in shape. When spindled, the cells give the impression of a “streaming” arrangement, similar to that seen in UDHI. There may be overlapping and crowding of nuclei, and cell boundaries are often indistinct, except where the cells have a polygonal shape. Scattered mitoses are usually visible. The cells have a variable amount of eosinophilic cytoplasm, which may be granular, and is often correlated with neuroendocrine differentiation.119 In SPC with endocrine differentiation, in the areas of disruption of the cell sheets, the polygonal cells may have eccentric nuclei imparting a “plasmacytoid” appearance. This feature may be seen in aspirates from fine-needle aspiration cytology or in imprint preparations of these neoplasms.120,121 Close examination of the margins of some of the nodules reveals areas of irregularity, suggesting the absence of a residual duct wall. Foci of frankly infiltrating, invasive, classic ductal carcinoma NST are not infrequently found and are important to look for because of their impact on prognosis and management. Extracellular mucin production is quite commonly seen in both the nodules and in the frankly invasive components of the neoplasm, which may overlap with the morphology of cellular (type B) mucinous carcinoma.122 There may be similarity in the morphology of SPC and EPC, with some nodules resembling EPC and others looking like typical SPC.123,124 The infiltrating component almost never has the pattern of true invasive papillary carcinoma and, if one is being precise, the term invasive papillary carcinoma should not be used for these lesions. Cases of SPC with a frankly invasive component of ductal carcinoma NST should be termed SPC with invasive carcinoma NST, and the size of the invasive component given is the measurement of the ductal carcinoma NST component only. Very rare cases of high-grade breast carcinoma with a solid papillary architecture have been described but are, by definition, best excluded from being classified as SPC because of their more aggressive behavior.125,126

**Immunoprofile of SPC**

A heterogeneous staining pattern is typical for myoepithelial markers. Thus, some nodules have an intact layer of MECs at their periphery, and some show fewer MECs, suggesting marked attenuation of the duct wall. Most SPCs lack MECs in the stromal cores, but they are sometimes focally retained.127 Many of the solid nodules, especially those with slightly irregular margins, lack peripheral MECs,
metastatic ovarian carcinoma. Approximately 60% of tumors. Solid papillary carcinoma may show positive (hematoxylin-eosin, original magnifications x40 [a] and x100 [b]).

surprisingly, CK7 is negative in some cases (M.H., unpublished data, December 2016). The high–molecular-weight keratins will stain any residual MECs and the cells of UDH in ducts that are partially colonized by the neoplastic cells. The biomarker profile is typically strongly positive for ER and progesterone receptor and HER2.

Molecular and Genetic Features

Gene expression studies show a luminal A pattern and a close link with mucinous and endocrine breast carcinomas. The patterns of gene copy-number aberrations found in papillary carcinomas are similar to those found in luminal A breast NST cancers, which include few aberrations, losses of band 16q, and absence of p53 mutations. PIK3CA mutations, similar to luminal A breast cancers, are present in all subtypes of papillary breast carcinoma (EPC, SPC, and invasive papillary carcinoma). Approximately 60% of SPCs are positive for endocrine markers (synaptophysin and chromogranin).

Differential Diagnosis

Solid DCIS.—Solid DCIS lacks the underlying papillary architecture seen in SPC and typically has higher-grade cytologic features. Solid DCIS is often admixed with other architectural patterns of DCIS.

Florid UDH.—Florid UDH often shows a streaming architecture, variation in cell shapes, presence of spindle cells, and low-grade cytologic features similar to those encountered in some cases of SPC. In this context, immunohistochemistry for high–molecular-weight keratins, ER (Figure 9, d), and endocrine markers is very helpful.131

Encapsulated Papillary Carcinoma.—EPC typically presents as a single gross tumor mass with distinct papillary structures lying within a cystlike space, rather than the multinodular solid morphology of SPC. Nevertheless, there are cases that show an overlapping morphology between these entities.123 Both neoplasms exhibit similar molecular and genetic profiles, and their separation can be somewhat arbitrary.

Papillary DCIS NST.—Papillary DCIS NST has “open” ducts, showing a well-defined papillary architecture on low-power examination (x2 objective). In contrast, SPC forms solid nodules, within which, the underlying papillary architecture is extremely subtle and often seen on high-power examination only. Furthermore, MECs are much more prominent at the periphery of the ducts in papillary DCIS NST than they are in SPC, where there are markedly fewer or completely absent MECs.

Behavior, Prognosis, and Management

SPC is a low-grade breast carcinoma with a good prognosis.113,114,131–133 When SPC is purely multinodular, with smooth borders, and it behaves like low-grade DCIS and is staged, classified, and treated as such, from an academic and intellectual viewpoint it is likely to be an invasive carcinoma with an expansile pattern of growth. Thus, treatment is by complete excision. Usually adjuvant radiation is recommended and endocrine blockade should be considered. Clearly infiltrative foci are termed SPC with associated invasive ductal carcinoma NST. Such cases of SPC may metastasize and retain the papillary architecture in their metastases.134 These invasive tumors are staged and managed according to the size and biomarker status of the infiltrative components only and have the behavior of invasive low-grade ductal carcinoma NST. Accordingly, sentinel lymph node biopsy is recommended at the time of the wide excision. A role for chemotherapy depends on the stage and may be modified by the OncotypeDx assay (Genomic Health, Redwood City, California) result. Most of these carcinomas have low scores on that assay (M.H., unpublished data, December 2016), and response to chemotherapy is predicted to be poor.

PAPILLARY DCIS NST

Papillary DCIS NST is a multiductal, in situ, neoplastic process that involves all sizes of ducts. It is an architectural variant of DCIS, often coexisting with the more-common cribriform, micropapillary, and solid patterns; rarely poses a diagnostic problem; and has well-established management guidelines based on size, margin status, grade, age, and ER status. In contrast to SPC, the ducts are patent and the papillary architecture is readily appreciated on low-power microscopic examination (Figure 10, a and b). Importantly, the ducts present with an intact layer of MECs at their periphery. Most often, the papillary processes in the neoplastic ducts lack MECs. A subset of low-grade papillary DCIS shows neuroendocrine differentiation (Figure 11, a and b).135 The morphology of these cases can overlap with cases of SPC and may be accompanied by invasive mammary carcinoma NST, invasive spindle-cell carcinoma, or invasive mucinous carcinoma. Although the differential diagnosis includes intraductal papilloma, especially when complicated by superimposed neoplastic...
proliferations,136 such lesions are usually confined to one duct and its branches, rather than the multiductal distribution of papillary DCIS. Broad, collagenous cores favor papilloma but are not entirely specific.137 Immunohistochemistry for markers of MECs, ER, neuroendocrine markers, and high–molecular-weight keratins may be helpful in difficult cases.138,139 In contrast to papillary DCIS NST, the solid variant of papillary DCIS shows an absence of a lumen and a subtle, “occult” papillary architecture implied by the presence of delicate fibrovascular cores (Figure 11, c and d).

INVASIVE PAPILLARY CARCINOMA

Invasive papillary carcinoma is an unusual variant of mammary carcinoma with an infiltrative growth pattern composed of neoplastic ductal cells arranged around stromal papillary cores (Figures 12, a through d, and 13, a through d).140 Invasive papillary carcinoma is associated with a florid, reactive desmoplastic stroma and shares a propensity for pseudolymphatic invasion with other papillary lesions (Figure 12, d). The term invasive papillary carcinoma is most often used inappropriately to denote EPC with a component of invasive carcinoma, and these cases appear to have a slightly better outcome than matched cases of invasive ductal carcinoma NST.141,142 Most invasive carcinomas arising from EPCs are not papillary in their morphology and resemble invasive ductal carcinoma NST. Invasive papillary carcinoma also has to be distinguished from the more common invasive micropapillary carcinoma, which lacks stromal cores.143–145 Invasive papillary carcinoma is also different from the tubulopapillary carcinoma that is predominantly tubular but with some tubular structures containing intratubular papillary projections. Tubulopapillary carcinoma has a worse prognosis than does EPC with invasive carcinoma.146 Papillotubular carcinoma is one of the subgroups of invasive ductal carcinoma in the Japanese classification of breast tumors, but this term is not used widely in North America.147 Invasive papillary carcinoma has been little studied, and specific outcome data are not, to our knowledge, available in the literature. Management at the British Columbia Cancer Agency (Vancouver, Canada) is based on the size, grade, breast biomarker status, and stage, similar to that for invasive ductal carcinoma NST.

Molecular and Genetic Aspects

The molecular changes that occur in invasive papillary carcinoma of the breast are similar to those encountered in EPC and SPC (see above).129

A breast tumor resembling the tall cell variant of papillary thyroid carcinoma is a low-grade breast tumor with a complex, papillary, gyroidal, and glandular architecture, which is histologically reminiscent of the tall cell variant of papillary carcinoma of the thyroid. Some synonyms include solid papillary neoplasm with reverse polarization148 and tall cell variant of papillary breast carcinoma.

Figure 11. Special variants of papillary ductal carcinoma in situ (DCIS). a and b, Case 1: Mucinous and endocrine variant. Low- and medium-power views of papillary DCIS endocrine variant, superficially resembling an intraductal papilloma, with associated mucin in the duct lumen. c and d, Case 2: Solid papillary variant in a male breast. Low-power view showing a solid nodular pattern with compact fibrovascular cores and a p63 immunostain (d) showing continuous staining of the myoepithelial cell layer at the periphery of the involved spaces (hematoxylin-eosin, original magnifications ×40 [a] ×100 [b], and ×200 [c]; original magnification ×200 [d]).
cancer).

Although these alternative names for this tumor have been proposed, they ignore the thyroidlike characteristics of this neoplasm.

Clinical and Imaging Aspects

Most cases of a breast tumor resembling the tall cell variant of papillary thyroid carcinoma present with a mass found on routine mammographic screening or by palpation. A few cases have been detected by indeterminate calcifications detected on mammography.

Incidence

A series of 5 cases was first reported by Eusebi et al, and most of the experience with this tumor comes from his group. The tumor is rare, with fewer than 20 cases described in the literature to date. The age range is 45 to 80 years.

Pathologic Features

No special gross features are described, apart from the presence of a mass lesion. These neoplasms have a characteristic, low-power morphology, consisting of an expansile nodular aggregate of abnormal ductal structures lacking a lobular architecture (Figure 14, a). Many of the ducts contain papillary structures, some with central aggregates of foamy macrophages. Myxoid change is seen in the stroma of some of the papillae. The papillae are lined with a single layer of tall columnar cells with abundant eosinophilic, mitochondrial-rich cytoplasm (Figure 14, b and c). A concentric, whorl-like arrangement of the rows of columnar cells is striking. Many of the cells have grooved nuclei and occasional intranuclear cytoplasmic inclusions can be seen, which simulates papillary carcinoma of the thyroid (Figure 14, d). Other ducts contain fenestrated sheets of epithelium, resembling UDH, and show focal lumen formation with some follicelike structures containing dense, eosinophilic secretions reminiscent of thyroid colloid. Mitoses are scanty. Rare psammoma bodies may be seen. At the periphery of the ducts are compressed capillaries with evenly distributed endothelial nuclei, suggesting an MEC layer on hematoxylin-eosin stain. Some areas of the lesion may closely resemble a CSL, and some of these tumors are thought to possibly arise from a preexisting CSL.

Immunohistochemistry

Upon immunohistochemistry, all thyroid markers are negative (thyroglobulin, TTF1, Pax8). Immunostains for MECs (p63, calponin, heavy-chain myosin) are completely negative throughout the lesion—both at the periphery of the ducts and within the papillary structures, except in the areas showing an in situ component. The tumors are negative for HER2 and auramine-rhodamine. About 50% of cases were positive for ER and progesterone receptor. An immunostain for FLI1 highlights the endothelial cell nuclei in compressed capillaries wrapping around the ducts. The epithelial cells are positive for S100 protein, broad-spectrum keratin, GCDFP-15 (variable), EMA (variable), CK19, and CK5/6. CK14 was negative in all cases studied.

Molecular and Genetic Aspects

Studies have shown absence of the RET and BRAF mutations that are seen in papillary carcinoma of the thyroid. Molecular analysis has shown the presence of...
a missense point mutation in PIK3CA in many of these lesions, similar to the mutations encountered in invasive ductal carcinoma NST.157

Differential Diagnosis

Metastatic Papillary Thyroid Carcinoma.—Metastatic papillary thyroid carcinoma shows striking morphologic similarities to a breast tumor resembling the tall cell variant of papillary thyroid carcinoma, such that several of the original cases were thought to represent metastases to the breast. Breast involvement by metastatic thyroid carcinoma is well described but very uncommon.158,159 A simple immunohistochemical panel that includes TTF1, thyroglobulin, and PAX8 definitely excludes a thyroid neoplasm, without resorting to molecular techniques.

Papillary Breast Carcinoma of Other Types.—Papillary breast carcinoma of other types, especially EPC, may also show at least some cytoarchitectural features in common with those of papillary thyroid carcinoma in many cases. However, the gyrate, concentric, whorled pattern of a breast tumor resembling the tall cell variant of papillary thyroid carcinoma is characteristic, as is the reverse polarity of the columnar cells.148 Furthermore, the immunoprofiles of these lesions are completely different. Of note, heliod bodies (intranuclear inclusions) are a common and previously described feature of UDH and have also been reported in a case of invasive ductal carcinoma of the apocrine type.160

Papillary Hyperplasia in a CSL.—Papillary hyperplasia in a CSL may simulate a CSL because of its papillary architecture, focal “streaming” of the nuclei, variation in nuclear size and shape, and lack of uniform, round, hyperchromatic nuclei. Furthermore, both a breast tumor resembling the tall cell variant of papillary thyroid carcinoma and CSL show patchy immunostaining for CK5/6 and, often, patchy weak staining for ER. However, the characteristic reverse nuclear polarity and gyrate architecture are not features of UDH, and the complete absence of staining for CK14 and MECs further excludes a hyperplastic process.

Management

Because one patient with this tumor involving a regional lymph node has been reported,153 this neoplasm is best regarded as a low-grade carcinoma. All other cases, most of which were treated by quadrantectomy, have had uneventful follow-ups. Minimum treatment would be total surgical excision. The role for radiotherapy and chemotherapy is unknown.
References


Figure 14. Breast tumor resembling the tall cell variant of papillary thyroid carcinoma. a, Low-power showing a multinodular pattern. b and c, Papillary structures with stromal cores containing histiocytes and covered by concentric rings of columnar cell layers. d, Malignant cells containing irregular nuclei with nuclear grooves resembling those of papillary carcinoma of the thyroid; an intranuclear inclusion is also present (hematoxylin-eosin, original magnifications ×40 [a], ×100 [b and c], and ×200 [d]).