Small Glandular Proliferations of the Breast With Absent or Attenuated Myoepithelial Reactivity by Immunohistochemistry

A Review Focusing on the Differential Diagnosis and Interpretative Pitfalls

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Context.—Small glandular proliferations of the breast encompass a variety of benign, atypical, and malignant lesions that show some degree of morphologic overlap. Myoepithelial stains are frequently used in the workup of these lesions in order to rule out or establish a diagnosis of invasive carcinoma. Some benign lesions show absent or diminished myoepithelial staining, and may represent an interpretative pitfall, particularly in small core biopsy samples.

Objective.—To review small glandular proliferations of the breast that show absent or diminished staining with myoepithelial immunohistochemical markers.

Data Sources.—The study comprised a review of published literature and clinical case material.

Conclusions.—The interpretation of myoepithelial stains in small glandular proliferations of the breast can, on some occasions, represent a challenge in diagnosing these lesions. Recognition of the key histopathologic features and immunohistochemical staining patterns of the entities in the differential diagnosis is crucial in their workup.

Small glandular proliferations of the breast encompass a variety of benign, atypical, and malignant lesions. These proliferations show some degree of morphologic overlap and making the distinction among them may be difficult, particularly in limited core biopsy samples. Pathologists frequently employ myoepithelial immunohistochemical stains when a small glandular proliferation is seen, in order to rule out or establish a diagnosis of invasive ductal carcinoma. Both benign and malignant small glandular proliferations can show complete loss of myoepithelial expression, whereas others show attenuated or focal loss of immunohistochemical expression with these markers, either of which can be a diagnostic pitfall.

In this review, we present two examples of small glandular proliferations seen in core biopsies that show loss or attenuation of staining with myoepithelial markers and therefore can be mistaken for invasive ductal carcinoma. A brief review of small glandular proliferations with these patterns of immunoreactivity will follow, and it will focus on the histologic and immunohistochemical staining characteristics that help with the differential diagnosis. Key histopathologic features of small glandular proliferations discussed in this review are summarized in Table 1. Selected immunohistochemical markers, including myoepithelial stains, useful in the differential diagnosis of these lesions are summarized in Table 2.

EXAMPLE 1

Ultrasound revealed an ill-defined hypoechoic mass, measuring 2.5 cm in its greatest dimension, in a 51-year-old woman with no prior history of breast disease who presented with a palpable mass in the upper outer quadrant of the left breast.

Core biopsy was performed and showed a proliferation of small glands growing within fibrous and adipose tissue (Figure 1, A and B). The glands grew in an infiltrative manner without a stromal reaction. The glands were round to oval, with open lumina (Figure 1, C), and some had an angulated, teardrop shape (Figure 1, C, inset). The glands were lined by a single layer of cuboidal cells with eosinophilic to clear cytoplasm and uniform round nuclei. Luminal secretions were not identified. The differential diagnosis included tubular carcinoma, sclerosing adenosis, and microglandular adenosis (MGA). Immunohistochemical staining revealed a lack of myoepithelial reactivity in lesional glands with calponin and p63 (Figure 1, D), and showed no expression of estrogen receptor (ER). A reticulin histochemical stain highlighted basement mem-
branes surrounding the glands (Figure 1, E). S100 protein immunostain showed diffuse staining in the lesion (Figure 1, E, inset). A diagnosis of MGA was rendered.

In the excisional biopsy, morphologically similar MGA was present. Additionally, MGA merged with foci that were more complex in shape, characterized by irregular interconnected glands and solid nests (Figure 1, F). These foci showed moderate cytologic atypia and infrequent mitoses. These foci represented atypical MGA, which was seen merging with usual MGA.

<p>| Table 1. Histopathologic Features of Small Glandular Proliferations With Absent or Attenuated Myoepithelial Staining |
|---------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>Growth Pattern</strong></th>
<th><strong>Gland shape</strong></th>
<th><strong>Luminal Secretion</strong></th>
<th><strong>Luminal Cytoplasmic Snouts</strong></th>
<th><strong>Stroma</strong></th>
<th><strong>Squamous Differentiation</strong></th>
<th><strong>Chronic Inflammation; Lymphoid Aggregates</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular carcinoma</td>
<td>Haphazard, infiltrative</td>
<td>Angulated, open, teardrop shaped</td>
<td>May be present; basophilic</td>
<td>Present</td>
<td>Desmoplastic, elastic</td>
<td>Not present</td>
</tr>
<tr>
<td>MGA</td>
<td>Haphazard, infiltrative</td>
<td>Round, uniform</td>
<td>Dense, eosinophilic, PAS positive, diastase resistant</td>
<td>Not present</td>
<td>Hypocellular fibrous tissue or adipose tissue, no stromal reaction</td>
<td>Not present</td>
</tr>
<tr>
<td>Radial scar</td>
<td>Stellate, infiltrative, radial</td>
<td>Compressed, angulated, tubular</td>
<td>Not present</td>
<td>Not present</td>
<td>Elastotic, fibrotic (old lesion) or cellular (early lesion)</td>
<td>Occasional</td>
</tr>
<tr>
<td>LGASC</td>
<td>Infiltrative, may be stellate</td>
<td>Angulated, branching</td>
<td>May be present; eosinophilic, keratinous</td>
<td>Not present</td>
<td>Fibrous, circumferential cellularity around glands</td>
<td>Present, extent varies</td>
</tr>
<tr>
<td>Displaced epithelium</td>
<td>Clustered, haphazard, infiltrative</td>
<td>Variable, round</td>
<td>Not present</td>
<td>Not present</td>
<td>Reactive, granulation tissue or fibrosis, no desmoplasia</td>
<td>Occasional</td>
</tr>
<tr>
<td>Syringomatous adenoma</td>
<td>Infiltrative</td>
<td>Tadpole shaped, comma shaped</td>
<td>Occasionally present, eosinophilic, PAS positive</td>
<td>Not present</td>
<td>Sclerotic or cellular and myxoid</td>
<td>Present, keratin cysts</td>
</tr>
</tbody>
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Abbreviations: LGASC, low-grade adenosquamous carcinoma; MGA, microglandular adenosis; PAS, periodic acid–Schiff.

<p>| Table 2. Immunohistochemical Staining Properties of Small Glandular Proliferations With Absent or Attenuated Myoepithelial Staining |
|---------------------------------------------------------------|---------------------------------------------------------------------------------|</p>
<table>
<thead>
<tr>
<th><strong>ER/PR</strong></th>
<th><strong>Smooth Muscle Myosin Heavy Chain</strong></th>
<th><strong>Basement Membrane—Laminin, Collagen IV</strong></th>
<th><strong>S100 Protein</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Tubular carcinoma</td>
<td>Strong, diffuse positivity</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>MGA</td>
<td>Focal, heterogeneous positivity (similar to surrounding breast tissue)</td>
<td>Negative, Variable, may be attenuated or focally absent circumferentially in the central nidus</td>
<td>Variable in glands and cellular stroma (&quot;lamellar pattern&quot;)</td>
</tr>
<tr>
<td>Radial scar</td>
<td>Absent or variable circumferential staining, glands with squamous differentiation may show</td>
<td>Absent or variable circumferential staining, glands with squamous differentiation may show</td>
<td>Variable, may be attenuated or focally absent circumferentially staining</td>
</tr>
<tr>
<td>LGASC</td>
<td>Absent or variable</td>
<td>Luminal positivity</td>
<td>Luminal positivity</td>
</tr>
<tr>
<td>Displaced glands</td>
<td>Variable (depending on lesional tissue displaced)</td>
<td>Variable, may be attenuated or focally absent</td>
<td>Variable, may be attenuated or focally absent</td>
</tr>
<tr>
<td>Syringomatous adenoma</td>
<td>Negative</td>
<td>Absent or variable circumferential staining</td>
<td>Absent or variable circumferential staining</td>
</tr>
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</table>

Abbreviations: ER, estrogen receptor; LGASC, low-grade adenosquamous carcinoma; MGA, microglandular adenosis; PR, progesterone receptor.
Figure 1. Example 1: microglandular adenosis (MGA). A and B, Small glands infiltrate breast tissue in a haphazard manner without a stromal reaction. C, Glands are round to oval and focally angulated (inset) and contain uniform bland nuclei. D, A p63 immunostain shows no reactivity in lesional glands. E, A reticulin stain highlights basement membrane investing the glands. S100 protein shows diffuse nuclear staining (inset). F, Excisional biopsy shows MGA (top left) merging with atypical MGA (bottom right), characterized by glands with more architectural complexity and cytologic atypia (hematoxylin-eosin, original magnifications ×40 [A], ×100 [B], ×200 [C and F], and ×400 [C, inset]; original magnifications ×200 [D; and E, inset] and ×400 [E]).
Invasive carcinoma, which most often has a triple-negative phenotype, has been reported to arise in association with MGA and atypical MGA in 23% to 64% of cases. The actual frequency is likely much lower because most reported cases are seen in consultation, and thus referral bias is likely a factor. When invasive carcinoma is present, there is usually a morphologic transition from MGA to carcinoma, with atypical MGA and in situ carcinoma present in transitional areas. In situ carcinoma retains the infiltrative growth pattern of MGA and is characterized by solid nests of cells with significant cytologic atypia and increased mitoses. Basement membrane is retained in glands containing in situ carcinoma, and a stromal reaction is not seen. Invasive carcinomas arising in MGA are usually poorly differentiated ductal carcinomas with solid or nested growth. Invasive carcinomas show loss of basement membrane and are accompanied by a desmoplastic response. A variety of morphologies or types of carcinoma arising in MGA have been reported and include clear cell, basaloid, metaplastic, and adenoid cystic, among others. In general, the immunohistochemical staining patterns of MGA are similar to those seen in atypical MGA and carcinoma arising in association with MGA, with a few considerations. The expression of S100 protein may be decreased in atypical MGA and carcinoma, which may be a pitfall in relying on the expression of this marker to make a diagnosis. Increasing Ki-67 and p53 labeling has been observed in the progression from MGA to carcinoma.

Molecular data provide evidence that MGA and atypical MGA are clonal lesions and support the morphologic and immunohistochemical observations that they are direct precursors of some invasive triple-negative breast carcinomas. Comparative genomic hybridization studies have demonstrated that a subset of MGA cases show molecular progression from MGA and atypical MGA to carcinoma, with alterations more similar between distinct morphologic components of the same tumor versus morphologically similar lesions from different patient samples. In a recent study in which distinct components of MGA, atypical MGA, and carcinoma were subjected to next-generation sequencing, identical mutations in TP53 and other cancer genes were identified in MGA/atypical MGA and matched triple-negative breast carcinomas.

Excisional biopsy should be performed when conventional MGA is diagnosed in a needle core biopsy, in order to rule out coexisting carcinoma. Microglandular adenosis may recur in rare cases if not completely excised, and atypical MGA should be excised with wide margins. Carcinoma arising within MGA is managed similarly to other carcinomas of similar grade, hormone receptor status, and stage.

**Tubular Carcinoma**

The most important differential diagnosis of MGA is tubular carcinoma, a special type of well-differentiated invasive ductal carcinoma in which virtually the entire tumor is composed of tubular glands. The frequency of tubular carcinoma among invasive breast cancers is 1% to 4%. The clinical presentation of tubular carcinoma is not different from that of conventional invasive ductal carcinoma, with the exception that tubular carcinoma is more likely to be detected on screening imaging than as a palpable abnormality and is more often multifocal. Compared with conventional invasive ductal carcinomas, tubular carcinomas are typically smaller in size, with most tumors measuring 1 cm or less.
Figure 2. Microglandular adenosis (MGA), atypical MGA, and invasive carcinoma arising within MGA. A, Uniform round glands with open lumina infiltrate breast tissue. B, Glands are lined by a single layer of cuboidal cells. Eosinophilic secretion is present in lumina, which is periodic acid–Schiff positive and diastase resistant (inset). C, MGA with apocrine eosinophilic granules. D, Glands lack myoepithelial staining (calponin in this case). A laminin immunostain highlights basement membrane surrounding the glands (inset). E, Atypical MGA shows solid nests of cytologically atypical cells with a growth pattern similar to that of MGA. Luminal secretion is diminished. F, MGA and atypical MGA (top left) merge with invasive carcinoma (bottom right), which shows invasive growth, a stromal reaction, and a greater degree of atypia (hematoxylin-eosin, original magnifications ×100 [A and F], ×400 [B], and ×200 [C and E]; original magnifications ×400 [B, inset] and ×200 [D; and D, inset]).
a spiculated mass or architectural distortion, which may contain a central area of lucency.33–36 Mammographic calcifications often are the reason for biopsy and represent calcifications present within the tubular carcinoma. Tubular carcinoma can also be an incidental finding in a biopsy performed for calcifications that are present in an adjacent benign proliferation, such as columnar cell change.34–36 Similar to other invasive carcinomas, ultrasound shows an ill-defined hypoechoic mass with shadowing.36

On microscopic examination, tubular carcinoma is characterized by small, open tubules arranged in a haphazard manner and showing infiltrative growth (Figure 3, A through E). The World Health Organization suggests that 90% of the tumor forming tubules is a practical cutoff point for classifying an invasive carcinoma as tubular carcinoma.20 Tumors with a proportion of tubules that is significant but constitutes less than 90% of the tumor may be designated as a “mixed” tubular carcinoma or a well-differentiated carcinoma with tubular features. The stroma of tubular carcinoma is desmoplastic and often contains elastosis. Neoplastic glands contain one cell layer and are oval, angulated, or teardrop shaped. Apical cyttoplasmic snouts, similar to those seen in columnar cell change, are frequently present (Figure 3, F). Nuclei are small, uniform, and low grade. Mitotic figures are usually absent. Calcifications may be present within tubular carcinoma glands or in the tumor stroma. Ductal carcinoma in situ is associated with tubular carcinoma in approximately 50% to 70% of cases and is usually micropapillary, with low to intermediate nuclear grade.20,21,26,28–30,37,38 Tubular carcinoma is frequently associated with atypical lobular hyperplasia/lobular carcinoma in situ and columnar cell alterations.23,30,32,37,39 Columnar cell lesions were seen in association with tubular carcinoma in 93% of cases in one study.25 Lobular carcinoma in situ and/ or atypical lobular hyperplasia is associated with tubular carcinoma in approximately half of cases.23,37,39 Virtually all tubular carcinomas express ER and PR and lack HER2/neu overexpression by immunohistochemistry.20,23,26,40,41

Certain features are helpful in distinguishing tubular carcinoma from MGA. The stroma of tubular carcinoma is desmoplastic and often elastic, whereas MGA infiltrates adipose tissue and hypocellular fibrous tissue without a stromal reaction. The glands of tubular carcinoma are angulated and teardrop-shaped, and some show luminal cyttoplasmic snouts, similar to the luminal cyttoplasmic snouts seen in columnar cell change. Glands of MGA, in contrast, are more uniform, are round, and lack cyttoplasmic snouts. Tubular carcinoma, like MGA, may contain luminal secretions; however, the secretions present in tubular carcinoma are basophilic when present,7 and they are neither dense nor brightly eosinophilic, like those seen in MGA. Immunostains can be particularly helpful in distinguishing these entities. A myoepithelial layer is absent in both tubular carcinoma and MGA; however, MGA is invested by a basement membrane, which can be identified with the use of immunohistochemical stains (and special stains). Important, virtually all tubular carcinomas and well-differentiated ductal carcinomas show diffuse and strong reactivity for ER and PR,21,23 whereas MGA is ER and PR negative.

EXAMPLE 2

Ultrasound showed a 0.8-cm ovoid dense mass with partially obscured margins in the right lower central breast.

The core biopsy showed an infiltrative proliferation of small glands in sclerotic stroma. Lymphoid aggregates were present at the periphery of the lesion (Figure 4, B). The round to angulated glands had a squamoid appearance, and some contained eosinophilic luminal secretions (Figure 4, C, inset). The differential diagnosis included radial scar (RS), low-grade adenosquamous carcinoma (LGASC), or benign entrapped glands at the edge of a sclerosing papillary lesion. Immunohistochemical staining with p63 and smooth muscle myosin revealed attenuation of staining with some glands, whereas other glands showed complete loss of myoepithelial reactivity (Figure 4, D). A diagnosis of “atypical small glandular proliferation with squamous features” was made, with a note indicating the differential diagnosis included LGASC and RS.

Excisional biopsy showed duct ectasia with rupture, and resulting luminal cholesterol debris (“cholesteroloma”) and reactive inflammatory changes (Figure 4, E). Entrapped glands with squamous metaplasia were present in the fibrotic wall of the involved duct, similar to those seen in the core biopsy (Figure 4, F).

SMALL GLANDULAR PROLIFERATIONS THAT CAN SHOW ATTENUATED MYOEPITHELIAL STAINING—EPITHELIAL DISPLACEMENT, RS, LGASC, AND SYRINGOMATOUS ADENOMA

Example 2 showed an uncommon example of how entrapped ductal epithelium in a ruptured duct led to the worrisome appearance of infiltrative small glands in a biopsy of a suspicious breast mass. Entrapped glands are most often seen within sclerosing and papillary proliferations. As seen in example 2, entrapped glands may show attenuated and focal loss of myoepithelial staining, despite being part of benign lesions that have myoepithelial cells. Other small glandular proliferations that may show this attenuated pattern of myoepithelial staining include displaced glands from a needle biopsy procedure, RS, and LGASC.

Epithelial Displacement

The phenomenon of epithelial displacement, or mechanical transport of epithelium, following needle biopsy procedures is not equivalent to the process of entrapped glands seen in example 2. Some similarities between the two processes include the infiltrative growth of glands, the loss of myoepithelial staining, and the frequent association with papillary lesions. Although it is most commonly encountered in excisional biopsy specimens following needleling procedures, epithelial displacement can also be observed in rare cases in needle core biopsy samples from patients without a history of a prior needle procedure (Figure 5, A and B).24–44

Because most core biopsies result in benign diagnoses, the incidence of epithelial displacement in excisional biopsies is difficult to assess; however, rates of 28%44 and 32%45 have been reported in excisional biopsies performed for carcinoma. Papillary lesions are particularly prone to epithelial displacement (Figure 5, C) because of the friability of the papillae and cystic nature of papillary lesions.46,47 Nagi et al47 found that 50 of 53 cases (94.3%) with epithelial displacement were associated with some form of underlying benign or malignant papillary lesion.
Displaced epithelium may be observed in needle biopsy tracts, lymphovascular channels (Figure 5, D), and axillary lymph nodes. In excisional biopsy specimens, displaced epithelium is most commonly found within the biopsy site (Figure 6, A and B). It can be recognized by the presence of isolated epithelial clusters in reactive granulation tissue–like stroma associated with hemorrhage, fat necrosis, inflammation, hemosiderin-laden...
**Figure 4.** Example 2: Ruptured duct ectasia presenting as a small glandular proliferation on needle core biopsy. A, Ultrasound shows a circumscribed hypoechoic mass with posterior shadowing. B, Low-power view of the core biopsy shows a sclerotic stroma with peripheral lymphoid aggregates. C, Glands within the stroma are angulated with squamous features (high power, inset). D, Immunohistochemical staining with p63 shows loss of myoepithelial reactivity in some glands. E, Excisional biopsy shows a ruptured duct with entrapped small glands associated with a luminal “cholesteroloma.” F, Entrapped glands within the fibrotic duct are similar to those seen in the core biopsy (hematoxylin-eosin, original magnifications ×100 [B and E], ×200 [C and F], and ×400 [C, inset]; original magnification ×200 [D]).
macrophages, and foreign-body giant cell reaction. In contrast to invasive carcinoma, which is often intimately associated with the adjacent stroma, displaced glands or cell clusters often appear “out of place” from the surrounding stroma. Furthermore, the needle tract can be identified by its linear appearance. Immunohistochemical stains can be employed in an attempt to highlight the presence of myoepithelial cells around

Figure 5. Examples of displaced epithelium. A, Epithelial displacement in a case of micropapillary ductal carcinoma in situ (inset) arising in a cyst. B, Displaced epithelium appears to be “pushed” into the surrounding tissue without a stromal reaction. C, Encapsulated papillary carcinoma with evidence of prior disruption (lower right). D, This case showed displacement of epithelium into a lymphatic channel, as well as multiple other foci of displaced epithelium in the needle tract (not shown) (hematoxylin-eosin, original magnifications ×40 [A and C], ×400 [A, inset; and B], and ×200 [D]).

Figure 6. Displaced epithelium in needle tract seen in an excisional biopsy specimen. A, Displaced epithelium within a biopsy tract is associated with lymphohistiocytic inflammation. The surrounding breast tissue showed ductal hyperplasia (not shown). B, Displaced epithelium demonstrating reactive atypia. C, Smooth muscle myosin heavy chain shows a lack of myoepithelial cells surrounding the displaced glands (arrows) (hematoxylin-eosin, original magnifications ×100 [A] and ×400 [B]; original magnification ×400 [C]).
displaced glands; however, these stains are typically only helpful when a myoepithelial cell layer is present, because staining may be attenuated or even absent in epithelial fragments that have undergone displacement (Figure 6, C). Failure to detect myoepithelial cells in this scenario should not be overinterpreted as a definitive sign of invasive carcinoma.

Radial Scar

Radial scar is a benign sclerosing lesion that radiographically, grossly, and microscopically resembles invasive mammary carcinoma. For those lesions that are greater than 1 cm in size or harbor more proliferative change with greater architectural complexity, the term complex sclerosing lesion is used.52–58 Microscopically, RSs are composed of a central elastotic and fibrotic nidus with entrapped and distorted glands that radiate out in a stellate configuration (Figure 7, A through C). The radiating ducts often demonstrate a spectrum of nonproliferative and proliferative change, including columnar cell change, adenosis, apocrine metaplasia, ductal hyperplasia, and papillomata (Figure 7, D).52,56,57 Peripherally, RSs often contain a ring or corona of dilated ducts and cysts.53 Calcifications are often encountered in RS and in the stroma as well as in lesional glands.58 Squamous metaplasia may also be seen in RSs, particularly in small glands in the nidus.59–62 In core biopsy specimens, it may be difficult to appreciate the radial configuration of the lesion in the absence of the central nidus. Features that are helpful in suggesting RS include the centrifugal growth of the lesional glands as well as the presence of proliferative breast disease within and at the periphery of the lesion.

In the vast majority of cases, detecting the presence of myoepithelial cells with immunohistochemical stains may be helpful in distinguishing RS from invasive carcinoma. A potential pitfall, however, is the occasional attenuation or loss of myoepithelial staining in glands in the center of RSs (Figure 8), which may lead to the false impression of invasive carcinoma. Very rarely, tubular carcinomas have been known to arise within preexisting RSs.

Figure 7. Radial scar. A, Radial scar with stellate configuration seen on low-power magnification of a core biopsy sample. B, Squamous metaplasia is present in the cellular nidus of the lesion. C, Radial scar with a fibrosclerotic nidus as well as ductal hyperplasia and a papilloma present at the periphery of the lesion. D, Radial scar associated with cystic columnar cell change and calcifications (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B], and ×100 [C and D]).
Low-Grade Adenosquamous Carcinoma

Low-grade adenosquamous carcinoma is a rare variant of metaplastic carcinoma that is composed of infiltrative small glands with variable degrees of squamous differentiation (Figure 9, A through D). The angulated, compressed, or ovoid-shaped glands dissect through lobules and around native ducts. Cytologically, the lesional epithelial cells are bland and mitoses are infrequent. Luminal keratin debris, which occasionally calcifies, may be present. The accompanying stroma may either be fibrotic or cellular. When cellular, the bland spindled cells are embedded in a fibromyxoid stroma and tend to demonstrate circumferential growth around neoplastic glands. Lymphoid aggregates are often present within or at the periphery of the tumor and are a helpful diagnostic clue. Low-grade adenosquamous carcinoma has been reported to arise in association with a number of preexisting lesions, including papillomata, adenomyoepitheliomata, RS/complex sclerosing lesions, and fibroepithelial tumors. This association has led some authors to suggest that such lesions represent precursors to LGASC; however, further studies are necessary to support such a theory.

Kawaguchi and Shin studied the immunohistochemical staining patterns of 30 cases of LGASC. They found variable degrees of circumferential expression of myoepithelial markers in the basal location of the lesional glands (Figure 9, D, and E, inset). Variable expression of myoepithelial markers was also noted in the cellular stroma with a distinctive “lamellar” staining pattern that was most commonly highlighted with smooth muscle myosin heavy chain and calponin. Additionally, the luminal cells demonstrated p63 immunoreactivity, highlighting the proportion of squamous differentiation within any given case. Cytokeratin stains often showed greater intensity of staining in the luminal cells within glands in comparison with the basal cells, a pattern described as “core” staining (Figure 9, F). In this study, stromal cells were negative for CK markers, with only 1 case demonstrating focal CK7 positivity in the absence of any other CK positivity. Other studies have reported variable CK positivity in stromal cells. Despite the inconsistent staining with myoepithelial and keratin markers, LGASC is typically negative for ER, PR, and HER2. Additionally, one study showed predominately epithelial immunoreactivity and focal stromal reactivity for basal markers (CK5/6, CK17, and CK14) in 4 cases of LGASC, as well as epidermal growth factor receptor (EGFR) epithelial overexpression in half of the cases (2 of 4). In practice, although the combination of morphology and immunohistochemical staining may be of utility in suggesting the diagnosis of LGASC, often it is difficult to for pathologists to render an unequivocal diagnosis of such in a limited core biopsy sample.

Syringomatous Adenoma

Finally, syringomatous adenoma is a rare small glandular lesion that arises in the nipple/areolar region that can be difficult to distinguish from LGASC because of the similarities in morphology. Syringomatous adenoma is characterized by nests, cords, and glands that infiltrate around lactiferous ducts (Figure 10, A). The nests of cells exhibit “tadpole” and “comma” shapes, similar to those seen in syringoma of the skin. Glands can be compressed or narrowed and are composed of either a flattened single or double cell layer of squamoid or cuboidal epithelium. Keratin cysts with luminal keratinous debris are common. Lesional epithelial structures can be seen invading the smooth muscle of the nipple and show perineural involvement. The stroma appears fibrotic, or loose and cellular and may show “cuffs” surrounding epithelial nests, cords, and glands. Location of the lesion is of particular importance in the differential diagnosis because syringomatous adenoma more commonly arises in the nipple or superficial subareolar region, whereas LGASC arises in deeper and more peripheral aspects of the breast. The presence of lymphoid aggregates favors LGASC because syringomatous adenoma typically is not associated with inflammation, except in the vicinity of ruptured squamous cysts, in which foreign-body giant cells may also be seen. Immunohistochemistry is of limited utility in distinguishing LGASC from syringomatous adenoma because both demonstrate variable staining with myoepithelial markers (Figure 10, B) and are ER/PR negative. A recent study showed that both entities demonstrate similar CK staining profiles, with evidence of both squamous and glandular differentiation.

CONCLUSIONS

The two illustrative examples are of small glandular proliferations in the breast that show complete loss of expression in one, and focal loss in the other, of
Figure 9. Low-grade adenosquamous carcinoma (LGASC). A, Low-power examination shows a proliferation of glands with squamous differentiation growing within a cellular stroma. A lymphoid aggregate is seen at the periphery of the biopsy. B, Squamous microcysts with luminal keratin are seen in this case. The stroma is cellular with a fibromyxoid appearance. C, Another example of LGASC in a core biopsy shows more glandular differentiation. D, Higher-power magnification shows areas with subtle squamous differentiation, highlighted by p63 (inset). E, Smooth muscle myosin shows a lamellar pattern of staining in the stroma surrounding neoplastic glands. F, Cytokeratin 7 shows stronger staining in luminal ductal cells of LGASC, a pattern that has been described as “core” staining (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B and D], and ×100 [C]; original magnification ×200 [D, inset; E; and F]).
myoepithelial cell markers. An understanding of the patterns of myoepithelial staining (or lack thereof) in these lesions is critical in their diagnostic workup. Further, recognition of the pitfalls in the use and interpretation of myoepithelial stains in small glandular proliferations, particularly when encountered in small core biopsy samples, is essential.

References

Figure 10. Syringomatous adenoma. A, Cords, nests, and glands grow in an infiltrative pattern within the smooth muscle of the nipple. Keratin cysts are also present. B, Smooth muscle myosin shows variable staining in neoplastic glands, with most showing no staining in this example (hematoxylin-eosin, original magnification ×100 [A]; original magnification ×100 [B]).


