Lobular Breast Cancer: Common Problems in Diagnosing LCIS in Core Needle Biopsies

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Introduction:
Lobular breast cancer can present an array of pathologic diagnostic challenges and pitfalls that are distinct from those encountered in tumors of ductal differentiation. Recognition of lobular carcinoma in situ (LCIS) and distinction from DCIS is particularly important because of unique management implications and problems in differential diagnosis. These issues are most significant in core needle biopsy evaluation and in non-invasive tumors (LCIS). Therefore this lecture emphasizes practical issues in LCIS encountered in core biopsies.

Outline of Lecture:
- Definition of lobular differentiation
  - Morphology
  - Immunohistochemistry
- Features of LCIS in core biopsies associated with higher risk for unsampled invasive cancer
  - LCIS with necrosis
  - Pleomorphic LCIS
- Variants of LCIS that mimic DCIS
  - Florid LCIS
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- Variants of LCIS that mimic invasive cancer
  - LCIS in sclerosing adenosis
- Variants of LCIS that may go undetected
  - LCIS in papilloma
  - LCIS in fibroadenoma
  - LCIS in atrophic breast
- Clinical significance of LCIS in core needle biopsies

Definition of Lobular Differentiation
There are several ways to define lobular differentiation of breast cancer: morphology (the traditional method); immunohistochemical (loss of E-cadherin immunoexpression and mislocalization of p120); or molecular (mutation in E-cadherin gene 16q22.1). Since the latter is not practical in daily cases, the first two options remain. Most pathologists have probably encountered cases in which there is discrepancy between the morphology and immunohistochemistry. Recent studies suggest that the definition of E-cadherin immunophenotype probably is not as simple as “lack of staining”; instead, occasional cases with morphologic and molecular criteria for lobular differentiation have been found to show variable degrees/patterns of E-cadherin expression (discussed below). In short, while it may be valid to equate “loss of E-cadherin staining” with lobular differentiation, it is not necessarily valid to exclude lobular differentiation in morphologically “lobular” tumors just because of positive E-cadherin staining. Thus, morphology is essential in defining lobular breast tumors. There are several morphologic variations of lobular breast cancer, particularly with respect to in situ tumors.
Morphologic variations of LCIS:
Classic LCIS
- classic lobulocentric pattern
- florid pattern
- ductocentric pattern
- with necrosis
- with Pagetoid spread
- involving collagenous spherulosis

Pleomorphic LCIS

Key morphologic features of classic LCIS:

Architecture:

Low magnification:
- Lobulocentric (acinar) growth = clusters of distended acini (grape cluster-like)
- Ductocentric florid growth = solid expansion of larger ducts
- Ductocentric minimal growth = bulbous outpouchings from duct (clover leaf-like)

Higher magnification:
- Loss of cell-cell cohesion
- Loss of polarity at the periphery
- Lack of glandular/acinar formation

Cytology:
- Round/polygonal cells
- Round nuclei
- Intracytoplasmic vacuoles / signet ring formation (mucicarmine positive*)
  +/- targetoid dot-like material in vacuole

*normal ductal epithelium should not contain mucicarmine positive cytoplasm

Note: Two variations of non-pleomorphic LCIS were described by Haagensen, Cancer 1978:
  Type A (classic type) = smaller cells, scant cytoplasm, round nuclei, tiny or absent nuclei.
  Type B (large cell type) = more cytoplasm, larger nuclei, more variable size/shape, nucleoli.

Currently, we do not report the Haagensen sub-type of LCIS but it is important to recognize that the nuclear changes of Type B LCIS should not be classified as pleomorphic LCIS (see below)

Key morphologic features of pleomorphic LCIS:

Architecture:
- Same as for classic LCIS; common to have central necrosis
- Mimics high grade DCIS

Cytology:
- Large polygonal cells
- May have apocrine cytoplasm
- Nuclear size 4X lymphocyte nuclei
- Moderate to severe nuclear atypia

Potential Pitfall: Pleomorphic LCIS has more severe nuclear atypia and nuclear size increase than Type B LCIS. The latter should not be overdiagnosed as pleomorphic LCIS.

Distinction of ALH from LCIS: There is evidence of different risks for developing cancer between ALH (relative risk of about 4) and LCIS (relative risk ranging from 4 to 12) and therefore, when possible, the diagnostic distinction should be made (based on literature summarized by Rosen PP. "LCIS and ALH" in Breast Pathology, 3rd ed; LWW, 2009). However, there are no universally accepted criteria. Criteria by Page and Simpson and criteria by Rosen focus on the proportion of acini in a terminal duct lobular unit (TDLU) that are expanded (distended) by the tumor cells. Page and Simpson define full distention of a single acinus as 8 or more cells across the diameter, though this criteria may not be fulfilled in many cases that most pathologists would otherwise call LCIS. Pagetoid extension into the terminal ducts can be seen in either ALH or LCIS.
LCIS: Half or more of the acini are fully distended by tumor cells only.

ALH: Less than half of the acini are distended by tumor cells.

In some cases the findings fall at the border between the two and the classification is up to the pathologist’s judgment. Clearly this will result in some observer variation in such borderline cases. In reaction to this, some authors have proposed lumping any non-invasive atypical lobular entity into a category of “lobular neoplasia”. Rosen strongly advises avoiding this approach because 1.) it does not allow for recognition of clear cut cases with clinical significance, such as LCIS with necrosis or pleomorphic LCIS, that is much different from minimal ALH and because 2.) most cases can be separated into conventional categories whereas only rare cases sit at the border.

**Immunophenotype of LCIS:**

**E-cadherin:** Most cases of lobular carcinoma (in situ or invasive) lack E-cadherin immunoexpression, which is otherwise present in a membranous pattern in luminal epithelium (regardless of benign or malignant) and in myoepithelium. This immunophenotype results from E-cadherin gene mutation (16q22.1), found in most lobular cancers (Berx et al. EMBO J 1995; 14: 6107 and Berx et al. Oncogene 1996; 13: 1919). The E-cadherin protein is normally located at the cell membrane and has an extracellular domain, an intramembranous domain and an intracytoplasmic domain. The function is to maintain cell to cell adhesion. The E-cadherin complex also involves catenins (alpha, beta, gamma and p120 catenins). Loss of the E-cadherin protein via gene mutation leads to loss of cell to cell cohesion, resulting in the morphology of lobular cancer.

Interpretation of E-cadherin is straightforward in most cases: there is complete loss of expression in ALH/LCIS/invasive lobular carcinoma. However, recently it has been demonstrated that some cases with true molecular defects in the E-cadherin gene may still express E-cadherin in one of several aberrant patterns, though the protein may not be functional in terms of achieving cell to cell adhesion (Da Silva et al. Am J Surg Pathol 2008; 32: 773), including granular cytoplasmic pattern, dot-like or patchy discontinuous membranous pattern or even continuous membranous pattern; these patterns have been referred to as “aberrant E-cadherin reactivity” (Choi et al. Mod Pathol 2008; 21: 1224) and should not automatically exclude a diagnosis of lobular differentiation (Da Silva et al. Am J Surg Pathol 2008). Thus, caution is advised in interpretation of E-cadherin; the presence of membranous E-cadherin should not be automatically equated with ductal differentiation:

*Complete lack of E-cadherin:* Supports a diagnosis of lobular differentiation.

*Presence of E-cadherin:* Does not exclude lobular differentiation. Revert to morphology and/or p120.

**Pitfall:** Entrapped normal ductal epithelium in LCIS and myoepithelium will express E-cadherin. These cells should be recognized as distinct from LCIS cells and not overcalled as “positive” tumor.

**p120 catenin (a.k.a. p120):** This inner membrane bound protein is associated with E-cadherin. In ductal epithelium (benign or malignant), p120 immunohistochemistry shows membranous expression. In lobular cancer, loss of E-cadherin is associated with loss of the anchoring of p120 to the membrane and instead p120 shows cytoplasmic expression (Dabbs et al. Am J Surg Pathol 2007; 31: 427. Sarrio et al. Oncogene 2004; 23: 3272). This marker is a helpful adjunct to E-cadherin, particularly in the setting of aberrant E-cadherin reactivity. Interpretation is as follows:

*Membranous p120:* Ductal differentiation.

*Cytoplasmic p120:* Lobular differentiation.

**ER/PR/HER2:** Classic LCIS is usually ER/PR positive and HER2 negative. Pleomorphic LCIS can often be ER/PR negative and may be HER2 positive.
Features of LCIS in core biopsies associated with higher risk for unsampled invasive cancer

Identification of either of the following two variants in a core needle biopsy should prompt for excision due to association with invasive cancer.

Classic LCIS with necrosis: This pattern may mimic DCIS with necrosis. In one of the larger studies of this variant, 12 of 18 cases were associated with invasive carcinoma.

Pleomorphic LCIS: This pattern also may mimic DCIS (and may present with necrosis, as well). It is also associated invasive carcinoma and therefore excision is warranted.

Variants of LCIS that mimic DCIS

Classic LCIS is managed differently than DCIS. LCIS, viewed as a marker or non-obligate precursor of invasive cancer, usually has a multifocal, multicentric distribution and is treated by observation, with consideration of hormonal therapy (Tamoxifen); margins are not evaluated. In contrast, DCIS is a direct precursor of invasive cancer, usually presents in a continuous segmental distribution and is treated by complete excision, with attention to margin status (+/-radiation). Therefore classic LCIS should not be over-diagnosed as DCIS.

Florid LCIS or LCIS with necrosis that involve ducts may mimic DCIS. Key features in a lower grade in situ carcinoma that should raise concern for lobular differentiation are: loss of polarity; loss of cell-cell cohesion; intracytoplasmic vacuoles and absence of micro-acini.

**Possible pitfall:** Micro-acini may be formed by residual normal ductal epithelium entrapped within LCIS. Thus, attention should be paid to the cytology of micro-acini since they may not necessarily represent the in situ carcinoma cells. E-cadherin will mark these residual normal ductal cells.

**Possible pitfall:** Co-existence of DCIS and LCIS in the same slide or even in the same duct may occur. Typically there will be a distinct morphologic appearance to each type of in situ cancer. In such settings, recognition of LCIS should not automatically lead to an overall diagnosis of LCIS since the second morphologic pattern could represent co-existing DCIS. E-cadherin is worthwhile in this setting.

Solid LCIS within lobules may mimic lobular extension of DCIS (so-called cancerization of lobules). If the tumor cells are packed tightly within solid LCIS, it may be difficult to appreciate loss of cell-cell cohesion. In this setting, clues to lobular differentiation are loss of polarity, intracytoplasmic vacuoles, and absence of micro-acini. Some cases of solid in situ carcinoma in a TDLU with a low magnification appearance of a cluster of grapes may be impossible to diagnose without E-cadherin immunostaining; in such cases, we have a low threshold for obtaining such staining.

Pleomorphic LCIS, particularly with comedonecrosis, may mimic DCIS. Loss of cell-cell cohesion is a key finding to suggest this variant when evaluating what otherwise looks like DCIS.

**Possible pitfall:** Co-existence of DCIS and pleomorphic LCIS in the same slide or even in the same duct may occur. Again, if two morphologic patterns of in situ carcinoma are present and one appears to be pleomorphic LCIS, E-cadherin is advised to rule out the possibility that the other pattern is DCIS.

LCIS involving collagenous spherulosis may mimic cribriform DCIS. The key thing is to recognize the features of collagenous spherulosis (pink collagenous or blue mucinous spherules surrounded by the thin waxy pink myoepithelial cell cytoplasm and nucleus); this will allow for excluding consideration of DCIS. The second task to recognize single LCIS tumor cells percolating within the epithelial layers of the collagenous spherulosis. Its helpful to simply remember to exclude LCIS whenever collagenous spherulosis is identified.

Variants of LCIS that mimic invasive carcinoma

When LCIS involves sclerosing adenosis, it can mimic invasive cancer. This may occur in two settings: First, if the sclerosing adenosis is extensive and already on its own resembles infiltrative growth, the superimposed LCIS may contribute further to the mimicry of invasive cancer. Second, if the LCIS is florid within the sclerosing adenosis, the LCIS- expanded acini/ducts may appear to coalesce and give the appearance of a solid sheet of invasive carcinoma. Recognition of sclerosing adenosis in the periphery of such lesions should be a clue to exercise caution and consider myoepithelial immunostaining before diagnosing invasion. Both scenarios are even more problematic in core biopsies because the periphery of the sclerosing adenosis may not be sampled in the core, making it difficult to see clues of that background lesion.
Variants of LCIS that may go undetected:
Because LCIS may colonize underlying benign abnormalities and may do so in a minimal manner, there are a few settings in which superimposed LCIS may go undetected in either a core biopsy or excision.

**LCIS within fibroadenoma:** Normally, a mild degree of usual ductal hyperplasia may be found within fibroadenomas. Sometimes, the distorted ducts within a fibroadenoma may slightly dilate or appear to be clefted due to expansion of the mass overall once removed from the breast. The epithelium lining these ducts may appear to fall apart slightly, something that most pathologists are used to observing without causing alarm. However, if LCIS is colonizing such a fibroadenoma, the appearance of epithelium falling apart may not be artifactual but may be due to true lack of cohesion of LCIS cells. Thus, attention should be directed to any epithelium within a fibroadenoma that appears to be discohesive.

**LCIS within papilloma:** There are 3 types of cells that may appear underlying the luminal epithelium lining a papilloma: prominent myoepithelium; prominent second layer of epithelium (so-called dimorphic pattern of epithelium); in situ carcinoma (either LCIS or DCIS). Each of these may resemble the other and it may easy to misinterpret LCIS as one of the other two, thus allowing the diagnosis of LCIS to go undetected. Besides standard morphologic criteria, immunohistochemistry may be helpful in separating these entities.

**LCIS within atrophic lobules/ducts:** By definition, post-menopausal atrophy of the terminal duct lobular unit means that the number of epithelial cells, their size, and the size of the acini are markedly diminished. Never the less, atrophic TDLU’s may still be colonized by LCIS or ALH. Key findings to suspect ALH/LCIS are prominent nuclei in lobules that should otherwise contain shrunken, atrophic nuclei and loss of cell-cell cohesion. In some cases, abundant eosinophilic cytoplasm is also a clue, since cytoplasm in benign atrophic epithelium should be scanty.

Management of ALH/LCIS in core needle biopsies: The evidence to guide which forms of ALH or LCIS should be excised when found in core needle biopsies is complicated to interpret because of non-uniform design of outcome studies and varying results. Study design variables that influence the incidence of finding a worse lesion on excision of a biopsy containing ALH/LCIS include the patient age, clinical findings, radiologic findings, size of biopsy needle, number of cores, associated pathology in biopsy, and possible bias in defining which patients underwent surgical excision in the study. Nevertheless, a recent review of the literature found that 26% of patients with LCIS on core biopsy had DCIS or invasive cancer on surgical excision (Arpino et al. Cancer 2004; 101: 242). Whether all forms of ALH/LCIS (in the absence of worse pathology in the core biopsy) require excision is controversial. At one end of the spectrum, both classic LCIS with necrosis and pleomorphic LCIS can be associated with adjacent invasive cancer. Thus, either lesion found in a core biopsy should be followed by excision to exclude invasive cancer. At the other end of the spectrum, it is uncertain whether a core biopsy containing minimal ALH should be excised.

Regardless of the morphologic pattern, any case of ALH/LCIS in a core biopsy in which there is suspicious clinical or radiologic findings, discordant radiologic-pathologic findings, or concurrent higher risk lesion (atypical ductal hyperplasia, flat epithelial atypia, radial scar, DCIS, etc) should prompt consideration of excision. Ultimately, the management of core biopsy findings of ALH/LCIS requires careful clinical, radiologic and pathologic correlation.

Margin management in excisions with LCIS: This depends on the type of LCIS:
**Classic LCIS:** margins are not reported because, in cases with invasive cancer, the presence of LCIS at margins does not affect local recurrence (Ben-David et al. Cancer 2006; 106:28. Sasson et al. Cancer 2001; 91: 1862). Life-long clinical follow-up, however, is advised even if the worst finding is LCIS only.
**Pleomorphic LCIS:** margins are reported, just as the case with DCIS.

References: Additional references for LCIS topics are provided in the accompanying review article: Chen YY and Rabban JT. Patterns of Lobular Carcinoma In Situ and Their Diagnostic Mimics in Core Needle Biopsies. Pathology Case Reviews 2009; 14: 141
Patterns of Lobular Carcinoma In Situ and Their Diagnostic Mimics in Core Needle Biopsies

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Abstract: Lobular carcinoma in situ (LCIS) of the breast may exhibit a spectrum of morphologic growth patterns and may also colonize underlying benign breast lesions. This diversity in appearance can create diagnostic challenges, especially in core needle biopsy specimens. Some LCIS variants may mimic ductal carcinoma in situ or invasive breast carcinoma. Furthermore, some LCIS variants are frequently associated with adjacent invasive lobular carcinoma. Therefore, familiarity with this morphologic spectrum is essential when evaluating LCIS in core needle biopsies. This review focuses on histologic and immunohistochemical features that help to distinguish unusual patterns of LCIS from the lesions they mimic.

Key Words: lobular carcinoma in situ, breast, pleomorphic carcinoma

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CASE REPORT

A 60-year-old woman underwent breast core needle biopsy for mammographic calcifications. The core contained a well-circumscribed proliferation of monotonous round cells with mild nuclear atypia growing in a cribriform pattern (Fig. 1A). Calcifications were present in adjacent benign terminal duct-lobular units. An initial diagnosis of low grade cribriform type ductal carcinoma in situ (DCIS) was considered. On review, however, many of the proliferating cells showed loss of cell-cell adhesion and did not demonstrate immunexpression of E-cadherin (Fig. 1B). In addition, the cribriform spaces were noted to be lined by a thin rim of glassy eosinophilic material that contained 1 or 2 inconspicuous nuclei and the center of the spaces contained pale eosinophilic acellular material. Myoepithelial immunostains highlighted the cells lining the spaces (not shown). Based on these findings, a diagnosis of lobular carcinoma in situ (LCIS) involving collagenous spherulosis was made. A wire-guided excision of the remaining calcifications contained no residual material in situ carcinoma.

LCIS and atypical lobular hyperplasia (ALH) are usually incidental findings in breast excisions and on occasion they may appear in core needle breast biopsies. Whereas the diagnosis of LCIS or ALH is typically straightforward in excisional material, the diagnosis can be challenging in a core needle biopsy, especially if LCIS is superimposed on an underlying benign alteration. The histologic distinction between ALH and LCIS is quantitative, based on the extent and degree of lobular involvement. Some experts question whether this distinction can be evaluated reliably in core needle biopsies and therefore some have proposed the broader diagnostic term "lobular neoplasia" in core biopsies. For the purpose of this review, the term LCIS will be used. Though the medical application of Ockham's razor is that a single diagnostic solution should be sought to explain complicated alterations, LCIS proves an exception since it can present admixed with a second pathologic abnormality, such as sclerosing adenosis, fibroadenoma, or collagenous spherulosis. The spectrum of morphologic patterns and variants of LCIS may make its recognition difficult or may pose challenges in differential diagnosis with DCIS, invasive carcinoma, or benign proliferations (Table I). This review will address selected potential pitfalls in diagnosis and the morphologic and immunohistochemical tools that may help resolve such problems. Detailed discussion of the clinical and epidemiologic significance of LCIS, and its management, is beyond the scope of this review but is the topic of several excellent current reviews.

CLASSIC LCIS

Classic LCIS is a distortion of lobules and/or ducts by a monomorphic proliferation of discohesive epithelium exhibiting round shape, centrally placed nuclei and mild nuclear atypia and enlargement (Fig. 2A). Cellular discohesion refers to the loss of normal adherence between cells. This is manifested as a rim of space in between individual LCIS tumor cells. This is a major feature of lobular differentiation (Fig. 3A). In normal ductal epithelium and many ductal proliferations, the columnar cell shape and basal location of the nucleus confers polarity to the cell. Because of the round or polygonal cell shape and central nucleus, LCIS cells have lost their polarity (Fig. 3A). Intracytoplasmic vacuoles or a signet ring appearance may be present (Fig. 4). There may be a distinct thin pink rim that outlines the intracytoplasmic vacuoles; and the vacuoles may contain a dot-like material, producing a targetoid appearance. Vacuoles and signet ring formation can be helpful clues of lobular differentiation since these are not usual features of ductal lesions. LCIS is frequently a lobulocentric process but it can extend into ducts or, as discussed later, it can be a purely ductocentric process. At low magnification, lobulocentric LCIS presents as a cluster of enlarged acini filled and expanded by tumor cells, much like a cluster of grapes (Fig. 2A). Ductocentric LCIS may present in a number of different growth patterns. In longitudinal section, minimal involvement of a duct may present with a pagetoid pattern; alternatively, florid involvement may fill and expand the duct (Figs. 2B, C). In cross-section, minimal involvement of a duct may produce bulbous outpouchings of the duct that resemble a cloverleaf (Fig. 2D).

Loss of the cell surface adhesion molecule E-cadherin explains the morphologic appearance of discohesive cells and this can be demonstrated by immunohistochemical loss of E-cadherin (Fig. 3B). Normal luminal epithelium and lesions of ductal differentiation demonstrate crisp membranous E-cadherin expression and such tissue serves as internal control for the immunostain. Complete loss of immunexpression is not always observed. Rare LCIS cases may show an aberrant expression consisting of a dot-like cytoplasmic or patchy granular membrane pattern (Fig. 3C). Thus, complete absence of expression is not required to diagnose lobular differentiation. Recently, immunexpression of p120 has been reported as a useful adjunct to E-cadherin immunostaining. This protein is part of the E-cadherin–catenin complex and is normally located at the inner aspect of the cell membrane.
FIGURE 1. LCIS within collagenous spherulosis resembles low grade DCIS, however, cellular discohesion indicates lobular differentiation (A); this impression is supported by absence of E-cadherin immunoeexpression (B).

TABLE 1. Patterns of LCIS and Potential Diagnostic Problems

<table>
<thead>
<tr>
<th>LCIS Pattern</th>
<th>Potential Problem</th>
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<tr>
<td>Florid (solid) LCIS</td>
<td>Mimics low grade DCIS</td>
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<tr>
<td>LCIS with necrosis</td>
<td>Mimics comedo-type DCIS</td>
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<tr>
<td>Pleomorphic LCIS</td>
<td>Mimics high-grade DCIS</td>
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<tr>
<td>LCIS in collagenous spherulosis</td>
<td>Mimics cribriform-type DCIS</td>
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<tr>
<td>LCIS in sclerosing adenosis</td>
<td>Mimics invasive lobular carcinoma</td>
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<tr>
<td>LCIS in fibroadenoma</td>
<td>Mimics usual ductal hyperplasia</td>
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<tr>
<td>LCIS in papilloma</td>
<td>Mimics prominent myoepithelial dimorphic papillary carcinoma or DCIS in papilloma</td>
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<tr>
<td>Pagetoid growth of LCIS</td>
<td>Mimics histiocytes or myoepithelium</td>
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<tr>
<td>LCIS in atrophic lobules</td>
<td>Mimics normal myoepithelium</td>
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<tr>
<td>LCIS coexisting with DCIS</td>
<td>May not be recognized</td>
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</table>

FIGURE 2. LCIS is typically lobulocentric (A). Pure ductocentric LCIS may resemble DCIS especially when florid (B). LCIS may spread into ducts in a pagetoid fashion (C). Bulbous outpouchings from a duct should prompt evaluation for pagetoid involvement by LCIS (D).

When E-cadherin is lost, p120 redistributes to the cytoplasm. Thus, in contrast to the membranous expression pattern in ductal epithelium, p120 shows diffuse cytoplasmic expression in LCIS.

FIGURE 3. Individual LCIS tumor cells are surrounded by empty spaces, indicating loss of cell to cell cohesion (A). In contrast to membranous E-cadherin immunoeexpression in normal ductal epithelium (B, lower left), E-cadherin is absent in tumor cells with lobular differentiation (B). Rare cases of LCIS may show a focal dot-like cytoplasmic or granular membranous E-cadherin expression (C). In contrast to normal membranous p120 expression in ductal epithelium, diffuse cytoplasmic expression occurs in lobular lesions (D).

FIGURE 4. Lobular differentiation is strongly suggested by intracytoplasmic vacuoles (A) and signet ring morphology (B). A central dot-like deposit in the vacuoles produces a targetoid appearance (A).

FIGURE 5. Florid LCIS involving lobules (A) or ducts (B) may resemble DCIS if cellular discohesion cannot be appreciated. (Fig. 3D). p120 may be of value when the E-cadherin results are not easily interpreted.

SOLID PATTERN (FLORID) LCIS

Cellular discohesion is a key feature of LCIS. In florid LCIS, the tumor cells have proliferated to maximally fill each lobule or duct and there may not be any residual empty space between the cellular components.
crowded tumor cells. When the cells are packed tightly against each other in such solid, florid lesions, discohesion may not be appreciated (Figs. 5A, B). If the cell membranes are well defined, a mosaic-like appearance may result. This pattern may resemble solid pattern low grade DCIS. Central necrosis may be seen (discussed later). Lobulocentric growth is a low magnification clue that the lesion may be LCIS, though carcinomatization of lobules by low grade DCIS can mimic this pattern and should be excluded. Intracytoplasmic vacuoles or signet ring morphology should trigger further evaluation for LCIS, including E-cadherin immunohistochemistry. Columnar tumor cell shape, polarization of the tumor cells, and glandular or acinar architecture favor DCIS but it should be noted that LCIS may rarely show gland-like structures within the proliferating solid mass of cells. Pure ductocentric florid LCIS may be even more difficult to separate from solid low grade DCIS using routine morphology, especially in a core needle biopsy (Fig. 5B). Again, vacuoles, signet rings, and loss of cell polarity should trigger further work up for lobular differentiation.

**LCIS WITH NECROSIS**

Florid ductocentric LCIS may cause marked expansion and filling of the duct accompanied by central necrosis (Fig. 6A). The degree of central necrosis may range from focal to extensive. Calcification may also be found within necrosis. At low magnification, the pattern may resemble comedo-type DCIS. The diagnosis of LCIS might not be considered if the characteristic pattern of lobulocentric LCIS is not present in the core biopsy. One clue to lobular differentiation is discordance between the degree of nuclear atypia and presence of necrosis. Most comedo-type DCIS exhibit moderate or severe nuclear atypia and pleomorphism, whereas LCIS with necrosis exhibits monomorphic nuclei with mild atypia, unless it is the pleomorphic variant (Fig. 6B). LCIS with necrosis is uncommon. The 2 main reasons to be aware of this variant are to distinguish it from DCIS and to exclude adjacent invasive cancer. In one of the larger studies of LCIS with necrosis, 12 of 18 cases were associated with invasive carcinoma. Thus, detection of necrosis in LCIS in a core needle biopsy should prompt surgical excision to exclude adjacent invasive cancer.

**PLEOMORPHIC LCIS**

In classic LCIS, the nuclei are monotonous and round; atypia is mild; and nuclear size is only slightly larger than normal ductal epithelium. A minority of cases deemed pleomorphic LCIS exhibit significant nuclear atypia, pleomorphism, enlargement, nuclei, and eosinophilic or apocrine cytoplasm (Figs. 6B, 7A, B). The degree of atypia mimics high grade DCIS and the presence of necrosis in pleomorphic LCIS further accentuates this mimicry. Key to the diagnosis of lobular differentiation in this setting is cellular discohesion. If clear space is seen around individual tumor cells of a high grade in situ carcinoma, the possibility of pleomorphic LCIS should be considered and could be confirmed by immunohistochemical absence of E-cadherin. Pleomorphic LCIS is often associated with invasive lobular carcinoma, therefore distinguishing it from classic LCIS in a core needle biopsy is important in order to prompt surgical excision and to exclude invasive cancer. Distinguishing pleomorphic LCIS from classic LCIS is based primarily on the degree of nuclear atypia, though the presence of macronucleoli and abundant apocrine cytoplasm also typify pleomorphic LCIS. Evaluation of nuclear atypia is subjective. The upper end of atypia of classic LCIS approaches the lower end of atypia of pleomorphic LCIS. A threshold to distinguish pleomorphic from classic LCIS nuclei has been suggested by some authors: the size of pleomorphic LCIS nuclei is typically 4 times or greater than that of lymphocytes. Thus, attention to nuclear size is needed to prevent underdiagnosing pleomorphic LCIS as the classic type.

**LCIS IN COLLAGENOUS SPHERULOSIS**

LCIS may colonize collagenous spherulosis, resulting in a pattern that mimics low grade cribriform DCIS. Collagenous spherulosis is a benign alteration of lobules in which spherical deposits of eosinophilic hyalinized or basophilic mucinous matrix are enveloped by stretched out myoepithelial cells. These deposits are surrounded by normal ductal epithelium. The result sometimes mimics cribiform DCIS, especially when LCIS is superimposed on this lesion. Clues to the correct diagnosis are discohesion of the proliferating cells and the presence of the stretched out, thin, eosinophilic myoepithelial cytoplasm lining the circumference of the spherules. Often a myoepithelial nucleus can be appreciated within the thin circumferential rim of cytoplasm. P63 immunostaining will highlight these nuclei and calponin or smooth muscle myosin heavy chain will highlight the myoepithelial cytoplasm (Fig. 1). In contrast, the spaces of cribriform DCIS are empty and are not lined by myoepithelial cytoplasm.

**LCIS IN SCLerosing ADENOSIS**

Sclerosing adenosis may be colonized by LCIS. This may produce 2 patterns that resemble invasive lobular carcinoma. First, if the LCIS is florid, marked expansion of the underlying sclerosing adenosis may cause fusion of the lobules, obscuring the surrounding myoepithelium, intervening stroma, and acinar architecture, thereby producing a low magnification appearance of a near-solid sheet of invasive tumor cells (Fig. 8A). A second pattern that may mimic stromal invasion at high magnification is the appearance of narrow cords and compressed tubules involved by LCIS within stroma (Figs. 8B, C). Without appreciating the low magnification architecture of underlying sclerosing adenosis, this pseudo-infiltrating pattern could be mistaken for invasive lobular carcinoma. To distinguish LCIS in sclerosing adenosis from invasive cancer, the same...
fibroadenoma, if inspection at higher magnification is not
Chen and Rabban
adenosis is another clue. These features may not be easi­
approach is advised as for distinguishing sclerosing adenosis from
can be subtle (B), mimicking prominent myoepithelium.
the proliferation; swirling, streaming distribution of acini; recogni­
tion of myoepithelium, either on
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panetary forms including dimorphic papillary carci­
oma, low grade DCIS within a papilloma, or prominent myoepi­
plasia and this can be accompan ied by epithe lioid cytologic changes.
Unlike LCIS tumor cells, such cells will exhibit cell to cell cohesion.
Myoepithelial immunostains can help make this distinction.

LCIS IN PAPILLOMA

LCIS may colonize a papilloma, creating diagnostic confu­sion with a variety of entities including dimorphic papillary carci­
oma, the tumor cells exhibit 2 morphologic appearances: a
luminal layer of columnar cells and a basal layer of round or
cellular discohesion and by nuclear atypia that matches the atypia of the overlying columnar
epithelial tumor cells. Similarly, myoepithelial hyperplasia in a papil­
oma can resemble pagetoid spread of LCIS. Such myoepithelial cells
often can be distinguished from LCIS by lack of discohesion and by
lack of uniform, monotonous nuclei but myoepithelial immunostains
can be of value for confirmation. Distinction of DCIS colonizing a
papilloma from LCIS colonizing a papilloma is possible using the same
approach as in nonpapillary settings.

PAGETOID SPREAD OF LCIS

Involvement of extralobular ducts by LCIS may produce a
variety of growth patterns depending on the extent of proliferation.
As mentioned earlier, florid proliferation of LCIS may fill and
expand the duct. Alternatively, minimal duct involvement without
distortion of the duct architecture may occur when LCIS tumor cells
grow beneath the ductal epithelium in a pagetoid fashion. In a
longitudinally oriented duct, a layer of tumor cells is interposed
between the overlying native ductal epithelium and the underlying
basement membrane. Occasionally, cross-sections of involved ducts
may show an outpouching pattern resembling a clover-leaf or
sawtooth pattern at low magnification. Recognition of cellular dis­
cohesion helps differentiate pagetoid LCIS from its main mimics:
intraluminal histiocytes and epithelioid myoepithelium. Pigmented
foamy histiocytes may sometimes accumulate with ductal epithe­
lium in the setting of hemorrhage, duct obstruction, inflammation,
necrosis, or sloughing of lesions such as papilloma or DCIS in other
parts of the ductal tree. Foamy cytoplasm, cytoplasmic pigment, and
bland, variable shaped nuclei distinguish such histiocytes from
LCIS. Myoepithelial cells can exhibit a variable degree of hyper­
plasia and this can be accompanied by epithelioid cytologic changes.
Unlike LCIS tumor cells, such cells will exhibit cell to cell cohesion.
Myoepithelial immunostains can help make this distinction.

LCIS IN ATROPHIC LOBULES

In postmenopausal women, atrophic lobules may contain LCIS.
This may go unnoticed because the extent of proliferation may be
minimal in the atrophic setting (Fig. 10A). Furthermore, the tumor cells
may exhibit myoepithelial morphology, referred to by some authors as
the myoid form of LCIS.24 This is a cytologic change in postmeno­
pausal women in which the cytoplasm appears darkly eosinophilic or
basophilic and the nuclei also appear deeply basophilic (Fig. 10B).
These changes are thought to be a result of atrophy and cytoplasmic
condensation. Because the entire acinus or duct may undergo shrinkage,
the number of tumor cells colonizing the acini may be few and this may
not result in its expansion. At low magnification, the involved atrophic
lobule may be interpreted as unremarkable if the tumor cells resemble
myoepithelium. Discohesion is a clue that these are not myoepithelial
cells; myoepithelial immunostains, along with E-cadherin, will resolve
this differential diagnosis.

FIGURE 8. Florid LCIS in sclerosing adenosis may raise con­
cern for stromal invasion (A). At high magnification, tubules
at the periphery of sclerosing adenosis mimic infiltrating lobu­
lar carcinoma (B, C). Myoepithelial immunostaining (calponin)
confirms an intact myoepithelium and confirms the under­
lying diagnosis of sclerosing adenosis (D).

FIGURE 9. LCIS may go undetected at low magnification if
involving a fibroadenoma (A). The proliferation may be pre­
sumed to be usual ductal hyperplasia, a common finding in
fibroadenoma, if inspection at higher magnification is not
performed. Similarly, pagetoid growth of LCIS in a papilloma
can be subtle (B), mimicking prominent myoepithelium.
approach is advised as for distinguishing sclerosing adenosis from
invasive cancer: recognition of overall smooth lobular contours of the
proliferation; swirling, streaming distribution of acini; recogni­
tion of myoepithelium, either on H & E stain or myoepithelial
immunostaining (Fig. 8D). Often the basement membrane around
each acini still can be seen even if the myoepithelium is compressed
beyond recognition. Presence of adjacent uninvolved sclerosing
adenosis is another clue. These features may not be easily appreci­
ated in a core needle biopsy and so myoepithelial immunostaining is
prudent before diagnosing invasive lobular carcinoma if there is any
hint of sclerosing adenosis in the biopsy.

LCIS IN FIBROADENOMA

LCIS may occur within a fibroadenoma.21,22 It may go unno­ticed at low magnification if the degree of proliferation is minimal,
particularly since a variable degree of ductal hyperplasia is not uncom­
mon within typical fibroadenomas (Fig. 9A). When ductal hyperplasia
is present within the distorted ducts, there often are detached small
clusters of proliferating epithelium floating within the dilated clefs of a
fibroadenoma. This combination of mild hyperplasia and clefing may
mask the cells of LCIS when they are present. Cellular discohesion and
loss of cell polarity are the key clues raising concern for LCIS in a
fibroadenoma. DCIS may also colonize fibroadenoma and its distinc­
tion from LCIS should be made.

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studies at one end of the spectrum do report that upstaging of LCIS are found in a core biopsy. Similarly, LCIS presenting with a function of the clinical setting (eg, type and extent of calcifications or radio logic mass) and of the morphologic type of LCIS. Since coexisting of DCIS. makes this a setting, E-cadherin immunohistochemistry may be helpful to exclude coexisting of DCIS.

**LCIS COEXISTING WITH DCIS**

Classic LCIS may coexist in the same duct with DCIS. In rare instances, if LCIS is the more prominent pattern, an associated minor component of solid low grade DCIS may go undetected. Generally pure LCIS exhibits a uniform, monotonous pattern. A clue that an additional component of DCIS could be present is heterogeneity of the in situ proliferation at low magnification. This includes the presence of a solid or cribriform pattern without cellular discohesion; the presence of cells with well-developed polarity; or the presence of a second component with higher nuclear grade. Before making a diagnosis of pure LCIS in this setting, E-cadherin immunohistochemistry may be helpful to exclude coexisting of DCIS.

**CLINICAL SIGNIFICANCE OF LCIS IN A CORE BIOPSY**

The rarity of finding pure LCIS or ALH in a core biopsy without another lesion that would mandate excision on its own merit (eg, atypical ductal hyperplasia, DCIS, or invasive carcinoma) makes this a difficult issue to study in a prospective manner. Less than 2% of all core needle biopsies contain pure LCIS/ALH. Existing studies in the literature are limited by small case numbers, heterogeneous indications for the core biopsy, and/or by selection bias in determining which patients undergo follow up excision. Thus, it is challenging to compare these reports. Nevertheless, studies at one end of the spectrum do report that upstaging of LCIS in the core biopsy to invasive carcinoma or DCIS in the excisional specimen occurs in up to 35% of patients.20-22 Other studies do not report such upstaging.23-33 The true risk of upstaging is likely a source of confusion with invasive carcinoma.

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