Clinical Importance of Histologic Grading of Lobular Carcinoma In Situ in Breast Core Needle Biopsy Specimens

Current Issues and Controversies

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Key Words: Lobular carcinoma in situ; Atypical lobular hyperplasia; Ductal carcinoma in situ; Infiltrating carcinoma; Breast core needle biopsy

Abstract

Lobular carcinoma in situ (LCIS) is considered a risk factor for development of invasive carcinoma (IC). Many variants of LCIS have been described based on pathologic features such as nuclear grade, pleomorphism, and necrosis, but little is known about the biology of these variants. The proposed 3-tier grading system for LCIS has not been validated or endorsed across laboratories. We found significant upstaging of pure pleomorphic LCIS (LCIS with nuclear grade [NG] 3), up to 25% in core needle biopsy (CNB) specimens, in an earlier study. The aim of the current study was to address the importance of pure classical LCIS (NGs 1 and 2) in CNB specimens along with clinicopathologic follow-up. In follow-up resection specimens, IC or ductal carcinoma in situ was seen in 18% (7/39), a high incidence of residual LCIS was seen in 69% (27/39), and other high-risk lesions, such as atypical ductal hyperplasia, were seen in 36% (14/39) of LCIS NG 2 cases. Our study illustrates the importance of grading LCIS; we recommend follow-up excision in LCIS NG 2 cases owing to a high incidence of residual LCIS and the likelihood of identifying other high-risk lesions.

Many historical evolutions of concepts emerged regarding lobular neoplasia since Cornil first described this entity as “intraepithelial breast carcinoma in lobules” in 1865.1 Currently, the term lobular neoplasmia encompasses atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). According to the Page criteria,2,3 ALH and LCIS differ quantitatively, although they are composed of small, round, monomorphic, dyscohesive cells with an increased nuclear/cyttoplasmic ratio; ALH is defined as fewer than 50% of the acini in the affected terminal duct lobular unit involved by the lobular proliferation, and these cells do not completely occlude the lumen or produce marked distention of the acini. LCIS is diagnosed when greater than 50% of the acini in the affected terminal duct lobular unit are completely filled and distended by the cellular proliferation.

In the current literature, several variants of LCIS are described; these include pleomorphic LCIS, pleomorphic apocrine LCIS, LCIS with comedo necrosis, and carcinoma in situ with mixed ductal carcinoma in situ (DCIS)/LCIS. The classical LCIS contains 2 types of cells: type A cells are small and relatively uniform in size, have round-to-ovoid nuclei and uniform chromatin with scant cytoplasm, and lack prominent nucleoli; type B cells are larger, with more abundant and clear cytoplasm, slightly more pleomorphic nuclei, clumped chromatin, and conspicuous nucleoli.5,6 A 3-tiered grading system has been suggested, based on the extent and degree of proliferation and/or cytologic features.7 However, this grading system requires validation by other centers and is not endorsed at this time owing to lack of long-term follow-up studies.8,9

In recent years, pleomorphic LCIS has been recognized as a distinct variant of LCIS that is composed of large, pleomorphic, dyscohesive cells with abundant eosinophilic cytoplasm,
and Nottingham grade 3 nuclei with prominent nucleoli. The emerging data also suggest that pleomorphic LCIS has been upstaged to a more significant lesion on follow-up resections in up to 25% of cases. Conversely the data on the classical LCIS are sparse, in particular the intermediate nuclear grade (NG) 2. LCIS still lacks the distinct nuclear classification of DCIS for many reasons, such as the relatively small number of patients, lack of effective clinical diagnostic methods, and insufficient evidence of how it may affect the clinical outcome. The purpose of the current study was to examine the clinical outcome of patients diagnosed with classical LCIS, principally intermediate NG 2, to provide the clinical evidence warranting grading LCIS in core needle biopsy (CNB) specimens.

Materials and Methods

Institutional review board approval was obtained for our study. All CNB specimens diagnosed as classical LCIS (including NGs 1 and 2) at our institution from January 2002 to June 2009 were retrieved from our pathology files. H&E-stained slides were reviewed, and the diagnosis was confirmed. All cases associated with DCIS or invasive carcinoma (IC; ductal or lobular) were excluded. Cases of pleomorphic LCIS were also excluded (because we reported our results in a recent study). Cases in which the only indication for excision was the presence of incidental LCIS in a CNB specimen were selected (4 cases of incidental LCIS in CNB specimens without follow-up excision were also excluded). Clinical, pathologic, and radiologic follow-up data were obtained.

The criteria for this study were adopted from the World Health Organization classification, based on the degree of proliferation and/or cytologic features. By using a similar nuclear grading system to that for DCIS, we defined LCIS categories as follows: low NG (NG 1) predominantly (>90%) monomorphic (uniform)-appearing type A cells with diffuse, finely dispersed chromatin and inconspicuous nucleoli (×20; inset, ×40); and intermediate NG (NG 2) Lobular carcinoma in situ, nuclear grade 1. Lobular units expanded with predominantly (>90%) monomorphic (uniform)-appearing type A cells with diffuse, finely dispersed chromatin and inconspicuous nucleoli (×20; inset, ×40). A, Lobular units expanded by dyscohesive, small, uniform type A cells with round to ovoid nuclei, uniform chromatin with scant cytoplasm, and lack of prominent nucleoli and type B cells with more abundant and clearer cytoplasm, slightly more pleomorphic nuclei, clumped chromatin, and conspicuous nucleoli (×20; inset, ×40). B, E-cadherin stain to show the lobular nature of the neoplasm (×20).
more than 10% and up to 90% of type B cells; cells ranging from small to slightly larger, with well-mixed type A and type B cells; slightly more pleomorphic nuclei; and clumped chromatin, frequent mitoses, and conspicuous nucleoli.

Radiology records were reviewed to ascertain the reason or method for biopsy and the presence of microcalcifications or mass lesions. The follow-up resection reports were reviewed for presence of a “significant lesion,” which in our study included DCIS, IC, or both. The presence of other risk lesions was also noted.

Statistical Analysis
The χ² test was used to compare 2 proportions.

Results
The total number of CNBs performed from 2002 to 2009 was approximately 20,000. Based on our strict criteria, 49 cases of pure classical LCIS (10 NG 1 and 39 NG 2) diagnosed in CNB specimens with follow-up excision were selected.

Radiology Results
At our institution, stereotactic- and magnetic resonance imaging–guided biopsies are performed with 9-gauge vacuum-assisted needles with a 12-mm-long trough; ultrasound-guided biopsies are routinely performed with 14-gauge non–vacuum-assisted needles. In LCIS NG 2 cases, 32 (82%) of 39 were stereotactic guided, as were 7 (70%) of 10 LCIS NG 1 cases; the remainder were guided by magnetic resonance imaging or ultrasound. Calcifications (Ca++) were seen in 1 cases; the remainder were guided by magnetic resonance imaging or ultrasound. Calcifications (Ca++) were seen in association with LCIS NG 2 cases (39/39 [100%]) and LCIS NG 1 cases (9/10 [90%]) compared with 1 (10%) of 10 LCIS NG 1 cases. The infiltrating carcinoma was morphologically ductal (tubular type) in 2 cases and lobular in 2 cases. Tumor size ranged from 1 to 3 mm. The NG was 1 or 2 and stage was T1a in 3 cases and T1b in 1 case. The foci of IC were seen in the vicinity of a prior biopsy site, and it is possible that the significant lesions were missed owing to relatively small size.

DCIS was seen in 3 (8%) of 39 LCIS NG 2 cases compared with 1 (10%) of 10 LCIS NG 1 cases. DCIS was morphologically micropapillary or cribriform with a lower NG (1-2) in all cases. E-cadherin staining was performed in all ICs and in situ carcinomas to confirm “ductal” or “lobular” morphologic features. Residual LCIS was seen in 27 (69%) of 39 LCIS NG 2 cases and 8 (80%) of 10 LCIS NG 1 cases.

Other associated high-risk lesions were also noted in the follow-up excision specimens. Atypical ductal hyperplasia or atypical ductal epithelial hyperplasia was seen in 14 (36%) of 39 LCIS NG 2 cases and 3 (30%) of 10 LCIS NG 1 cases. Intraductal papillomas and/or radial scars were seen in 15 (38%) of 39 LCIS NG 2 cases and 4 (40%) of 10 LCIS NG 1 cases. A high incidence of fibrocystic change was seen in association with LCIS NG 2 cases (39/39 [100%]) and LCIS NG 1 cases (9/10 [90%]) compared with the general population age-standardized incidence rate (89.4 per 100,000 woman-years). In 25 (64%) of 39 LCIS NG 2 and 6 (60%) of 10 LCIS NG 1 cases, columnar cell changes were found. The pathologic associations with LCIS NG 1 and NG 2 in the follow-up resection specimens are shown in Table 1.

In the 39 follow-up resections of the LCIS NG 2 cases, 14 (36%) were segmental mastectomy, 3 (8%) were total mastectomy or lumpectomy, and 22 (56%) were excisional biopsy or other type of biopsy. In the 10 LCIS NG 1 cases, 5 (50%) were segmental mastectomy, and the other 5 (50%) were excisional biopsy or other type of biopsy.

IC (ductal or lobular) was seen in 4 (10%) of 39 LCIS NG 2 cases, whereas no IC was identified in LCIS NG 1 cases (0/10). The infiltrating carcinoma was morphologically ductal (tubular type) in 2 cases and lobular in 2 cases. Tumor size ranged from 1 to 3 mm. The NG was 1 or 2 and stage was T1a in 3 cases and T1b in 1 case. The foci of IC were seen in the vicinity of a prior biopsy site, and it is possible that the significant lesions were missed owing to relatively small size.

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Table 1
Pathologic Features Associated With Follow-up Excisions*  

<table>
<thead>
<tr>
<th>Associated Diagnosis</th>
<th>LCIS NG 1 (n = 10)</th>
<th>LCIS NG 2 (n = 39)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invasive carcinoma</td>
<td>0 (0)</td>
<td>4 (10)</td>
</tr>
<tr>
<td>Ductal carcinoma in situ</td>
<td>1 (10)</td>
<td>2 (8)</td>
</tr>
<tr>
<td>ADH/Atypical DEH</td>
<td>3 (30)</td>
<td>14 (36)</td>
</tr>
<tr>
<td>Residual LCIS</td>
<td>8 (80)</td>
<td>27 (69)</td>
</tr>
<tr>
<td>Other high-risk lesions (IC, IDP)</td>
<td>4 (40)</td>
<td>15 (38)</td>
</tr>
<tr>
<td>Benign FCC with or without DEH</td>
<td>9 (90)</td>
<td>39 (100)</td>
</tr>
<tr>
<td>Benign columnar cell change</td>
<td>6 (60)</td>
<td>25 (64)</td>
</tr>
</tbody>
</table>

ADH, atypical ductal hyperplasia; DEH, ductal epithelial hyperplasia; FCC, fibrocystic change; IDP, intraductal papilloma; LCIS, lobular carcinoma in situ; NG 1, low nuclear grade; NG 2, intermediate nuclear grade; RS, radial scar.
Statistical Analysis

Upstaging to DCIS or IC was found in 7 (18%) of 39 LCIS NG 2 cases vs 1 (10%) of 10 LCIS NG 1 cases ($\chi^2 = 0.126; P > .5$). The difference was not statistically significant, which may be due to the low number of LCIS NG 1 cases in our study.

Discussion

LCIS is an established risk factor for subsequent IC, ductal and lobular. Current National Comprehensive Cancer Network guidelines recommend counseling patients concerning risk reduction with tamoxifen in premenopausal women and with raloxifene in postmenopausal women. LCIS is often multicentric and bilateral and is usually diagnosed as an incidental finding following surgical excision of another breast abnormality. There are no specific clinical findings, in particular, no palpable lump associated with these lesions, and the lesion is rarely visible on mammography as a dominant mass. When examining pathologic specimens, there are no gross macroscopic features characteristic of LCIS. Furthermore, multifocality in clinically undetectable lesions makes subsequent management planning difficult when LCIS may be the most significant finding of a CNB, and there is no standard of care for treatment.

With regard to the management of LCIS, some investigators recommend routine surgical excision as a follow-up procedure for all CNB specimens with LCIS, whereas others have taken a more conservative approach. Based on published studies, a follow-up excisional biopsy seems prudent in all cases of LCIS diagnosed by CNB. In a meta-analysis of 9 separate studies of 228 patients with newly diagnosed LCIS, 15% of 172 patients who did not undergo unilateral mastectomy as primary treatment had IC in the ipsilateral breast, and 9.3% of 204 patients had IC in the contralateral breast in the follow-up study. Therefore, the risk for developing breast cancer is bilateral, and the development of contralateral breast cancer is 3 times more likely in patients with LCIS than in patients without LCIS. A more aggressive approach may be more beneficial because studies have also shown that carcinoma is 3 times more likely to develop in the ipsilateral compared with the contralateral breast.

So, is subsequent resection really necessary in all cases of LCIS or can the indication be more selective based on histologic classification? The classification of lobular intraepithelial neoplasia 1 through 3 introduced by Brathauer and Tavassoli was not universally endorsed by pathologists owing to sparse outcome data. Recent studies, however, have recognized pleomorphic LCIS as a distinct variant that is composed exclusively of lobular cells with grade 3 nuclei. The studies proposed that this entity needs to be separated from classical LCIS owing to its more aggressive biology, and the accepted treatment is similar to that for DCIS.

The prognostic value of grading of invasive lobular carcinomas (ILC) was addressed by few studies. In a large study by Rakha et al., a multivariate analysis showed that histologic grade is an independent predictor for shorter survival and for disease-free survival. In the same study, the ILC of intermediate NG (2) showed higher local/regional recurrence (44% vs 37%) and distant metastasis than the low NG (1) IC. The results of this study provide strong evidence for routine assessment and reporting of histologic grading for ILC, and, in fact, the authors recommended routine reporting of the Nottingham grade for ILC.

In contrast, the significance of routine histologic grading of LCIS has not been addressed by many studies, although it is used by many pathologists in practice. In our current study, we assessed the clinical importance of histologic grade in LCIS with available long-term follow-up. To date, no other similar studies could be found in the literature. Our study, for the first time, exemplifies the increased upstaging of NG 2 LCIS in a significant number of cases compared with NG 1 LCIS, although our study results are not statistically significant. We also found that pleomorphic LCIS, like its invasive correlate, is a distinct entity with a high risk of upstaging (25% in our earlier study). A great majority of classical LCIS, including NGs 1 and 2, cases in our study were associated with microcalcifications, although in the majority of the cases, microcalcifications were associated with fibrocystic change rather than LCIS. The upstaging to a more significant lesion in comparison with pleomorphic LCIS was lower (25% vs 18%) for NG 2. Only 1 case of NG 1 cores was upstaged to DCIS rather than an IC. We believe that a risk of 18% upstaging is clinically significant, and, therefore, we propose that a 3-tiered nuclear grading system should be adopted for LCIS.

Although our study has not addressed the long-term prognostic significance of grading LCIS, we reveal data that indicate the association of NG 2 LCIS with other lesions of known prognostic significance such as DCIS and IC. As the recent literature integrates LCIS as an important component of low-grade carcinoma based on molecular data, we, as pathologists, need to understand more about LCIS and its other high-risk associations such as flat epithelial atypia. It is important that we are all on the same page and use a universal system of reporting.

We believe there is clinical justification for adopting a 3-tiered grading system for LCIS. We also recommend follow-up excision for patients with LCIS NG 2 owing to residual LCIS that may be NG 1, 2, or even 3 and the 18% likelihood of identifying additional significant lesions, resulting in upstaging.
Anatomic Pathology / Original Article

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Presented in part as poster presentations at the 98th annual meeting of the United States and Canadian Academy of Pathology; March 7-13, 2009; Boston, MA.

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