Lobular Neoplasia of the Breast
An Update

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• Context.—Lobular neoplasias (LNs) of the breast include atypical lobular neoplasia and lobular carcinoma in situ. Recent evidence suggests that LN is not only a risk factor for invasive lobular carcinoma, but is also a nonobligate precursor. Pleomorphic lobular carcinoma in situ (PLCIS) is a subtype of LN that has high-grade nuclei and other features that may mimic high-grade ductal carcinoma in situ. The management and follow-up of patients diagnosed with LN on core biopsy is a current issue of debate. However, recent genomic and molecular studies have identified candidate genes that may be important in understanding the pathogenesis of atypical lobular neoplasia and lobular carcinoma in situ, and thus may lead to other therapeutic interventions.

Objective.—To review the literature on LN of the breast and discuss current issues in the diagnosis and management of this entity, with particular attention to the relatively newly recognized lesion PLCIS. Because the management of PLCIS varies from the other LN lesions, the recognition of PLCIS by the pathologist is necessary. Current issues in the molecular pathogenesis of LN are also presented.

Data Sources.—Extensive review of the literature. Hematoxylin-eosin–stained and immunohistochemical-stained tissue from the author’s personal collection.

Conclusions.—Although morphology and immunohistochemical stains, such as E-cadherin, are important in the diagnosis and understanding of LN, genomic and molecular studies may guide the way these lesions are handled in the future. Recognizing PLCIS is important both for patient management and for our future understanding of LN pathogenesis.

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In situ lobular neoplasia (LN) of the breast was first documented by Ewing1 in 1919 in 2 photomicrographs with the captions “atypical proliferation of acinar cells” and “precancerous changes . . . atypical proliferation in a segment of a duct.” Decades later, Foote and Stewart2 characterized LN as a monomorphic population of cells that arise from and expand the terminal duct lobular unit and spread through the ductal system in a pagetoid manner. They noted that such lesions were not appreciated on clinical or gross examination and were often multicentric and bilateral. Although Foote and Stewart2 recognized a spectrum of LN, they felt that even the slightest degree of this process constituted “an extreme hazard.” Hence, any extent of LN was considered malignant and warranted complete mastectomy.

Our understanding of LN remained unchanged for almost 40 years, until Haagensen et al3 published a report on a series of 211 patients with lobular carcinoma in situ (LCIS) without associated invasive carcinoma. They reiterated many of the features originally described by Foote and Stewart2 and expanded on the clinical features, noting an overall incidence of 3.8%, with most of these cases occurring in premenopausal women. In stark contrast to Foote and Stewart, however, Haagensen et al3 suggested that LN was a benign proliferation that portended increased risk for subsequent carcinoma in either breast, and hence required monitoring with close follow-up.1 Central to their argument were follow-up data that showed an increased risk for development of invasive carcinoma (overall 17%) spread across a long interval of time (up to 25 years). More importantly, this risk applied with relatively equal frequency to both the ipsilateral and contralateral breast. As a result, they suggested that such lesions be termed lobular neoplasia rather than carcinoma in situ. This study was widely accepted and resulted in a major shift in our understanding of the biologic potential of LN. Lobular neoplasia quickly became viewed as a risk factor for subsequent breast carcinoma in either breast instead of a nonobligate precursor for invasive disease. Shortly thereafter, sentinel work by Page et al4 documented the relative risk of these lesions and correlated this risk to the extent of LN.

RESHIFTING PARADIGM

The argument that LN was not a precursor to invasive disease was based on several important observations. The first was the relatively low frequency of development of invasive carcinoma, along with the long lag time in those who ultimately developed invasive disease. The second was the development of disease in either breast with relatively equal frequency. If LN was a precursor to invasive disease, then how could its presence in one breast result in a cancer in the opposite breast? The third was the observation that the invasive carcinoma following LN was equally likely to be ductal or lobular. If it was truly a precursor, then one would expect LN to develop solely into invasive lobular carcinoma.
Figure 1. Lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH). Both LCIS and ALH are characterized by a monomorphic population of discohesive cells in the terminal duct lobular unit. A and B, In LCIS, greater than 50% of the acini are filled and distended (hematoxylin-eosin, original magnifications \( \times 100 \) [A] and \( \times 200 \) [B]). Distention has been defined as 8 or more cells across the diameter of an acinus.\(^6\) C and D, In ALH, less than 50% of the spaces are filled, and the acini are partially to completely filled with cells, but minimal distention is present (hematoxylin-eosin, original magnifications \( \times 100 \) [C] and \( \times 200 \) [D]).

More recent work by Page et al, along with molecular evidence, has raised doubts about these initial observations, once again shifting our understanding of the biologic nature of this peculiar lesion. Page et al\(^6\) reviewed follow-up data on 261 benign breast biopsies with atypical lobular hyperplasia (ALH) taken from 252 women between 1950 and 1985. Their findings showed that invasive carcinoma arising after a diagnosis of ALH was 3 times more likely to arise in the breast diagnosed with ALH than in the opposite breast, and that this invasive carcinoma was much more likely to be lobular than ductal. In addition, molecular studies have shown that the genetic profiles of LCIS and synchronous invasive lobular carcinoma are often similar to each other.\(^7,8\) These findings suggest that some LN lesions are indeed nonobligate precursors to invasive lobular carcinoma.

**HISTOLOGIC FEATURES**

Lobular neoplasia exhibits a spectrum of acinar involvement that can be subdivided into LCIS and ALH. Criteria for the diagnosis of LCIS include characteristic nuclear, cytologic, and architectural features. More specifically, LCIS is classified as a monotonous, discohesive proliferation of round, slightly hyperchromatic cells that are evenly spaced and distend and fill acinar lumina (Figure 1, A and B). Partial involvement of acini, defined as less than one-half of the acini of an involved lobule, is classified as ALH (Figure 1, C and D). More often than not, the cells of LN are also present interspersed between the basement membrane and native epithelium of ducts (pagetoid spread). When present alone, this latter finding is classified as ALH by some authorities and LCIS by others.\(^9\)

In most cases of LN, at least some of the cells have characteristic intracytoplasmic vacuoles, often with eosinophilic mucin globules. The cells of classic LN have been divided into 2 subtypes: those exhibiting scant cytoplasm and nuclei roughly 1.5 times the size of a lymphocyte (type A) and those with more abundant cytoplasm and somewhat larger nuclei (type B).\(^10\) This distinction is important in defining the cytologic spectrum of LN; however, it bears no documented clinical significance.\(^11\)

Some authorities advocate using the term LN for the entire spectrum of ALH/LCIS. This is appealing in that it avoids the term carcinoma for a lesion that is, for the most part, a...
Figure 2. Pleomorphic lobular carcinoma in situ (PLCIS). A and B, PLCIS is characterized by larger nuclei than are present in conventional lobular carcinoma in situ (LCIS). In addition, there is marked nuclear pleomorphism (nuclear Scarff-Bloom-Richardson grade 3). These lesions may be associated with necrosis, microcalcifications, or a high mitotic index (hematoxylin-eosin, original magnifications ×100 [A] and ×200 [B]). C, The cells in PLCIS can exhibit apocrine features (hematoxylin-eosin, original magnification ×200). D, Similar to conventional LCIS, E-cadherin immunostain is negative (original magnification ×200).

risk factor for carcinoma. However, the established variation in relative risk for subsequent development of carcinoma between ALH (relative risk 5.5) and LCIS (relative risk 8–10), along with more recent studies showing differences between molecular alterations in ALH and LCIS, supports maintaining this subclassification.

PLEOMORPHIC LOBULAR CARCINOMA IN SITU

Recently, a pleomorphic subtype of LN (pleomorphic lobular carcinoma in situ [PLCIS]) has become more widely recognized. This form exhibits larger cells with the characteristic discohesive nature of LN but with pleomorphic nuclei, typically grade 3 using modified Scarff-Bloom-Richardson grading criteria, and more obvious nucleoli (Figure 2, A and B). These cells often exhibit apocrine differentiation and can show necrosis and microcalcifications mimicking high-grade ductal carcinoma in situ (DCIS; Figure 2, C). Pleomorphic lobular carcinoma in situ is best recognized by its association with classic LN in the nearby vicinity. The frequent coexistence of these 2 subtypes of LN suggests a common genetic pathway shared by classic and pleomorphic LN. In fact, recent molecular profiling studies comparing invasive classic and pleomorphic lobular carcinomas support this notion as well.

DISTINGUISHING CLASSIC LCIS FROM LOW-GRADE DCIS

Distinguishing classic LCIS from DCIS is essential, given that LN generally dictates close follow-up and chemoprevention with tamoxifen, whereas DCIS requires eradication with surgery and radiotherapy. Most cases of LCIS are readily distinguished from low-grade DCIS with hematoxylin-eosin stain. In ambiguous cases, use of E-cadherin immunostain is useful to distinguish these 2 entities. Lobular neoplasia generally exhibits loss of membrane staining due to inactivation of the E-cadherin gene, located on chromosome 16q (Figure 3, A). Ductal carcinoma in situ, on the other hand, lacks this inactivation, and hence retains linear, membranous staining (Figure 3, B). E-cadherin stains should be interpreted in the context of morphologic features, because rare cases of ductal carcinoma in situ with reduced or complete loss of E-cadherin expression have been reported, and aberrant expression of E-cadherin in LN has been reported as well.
In rare cases (10%–15%), E-cadherin stain may be equivocal. These cases are often categorized as “mammary carcinoma in situ with mixed ductal and lobular features” and are managed as ductal carcinoma. In such cases, p120 catenin has been suggested as a useful immunomarker for LN. The p120 catenin binds E-cadherin on the internal aspect of the cell membrane, aiding in stabilization of the E-cadherin complex.28–32 Disregulation of the E-cadherin complex in LN results in cytoplasmic redistribution of p120 catenin.33 Ductal carcinoma in situ maintains the E-cadherin complex, and hence p120 catenin remains membranous in distribution.

Finally, expression of high–molecular weight keratins may also be useful in characterizing LN. The clone 34bE12 (cytokeratins 1, 5, 10, and 14) is commonly expressed by LN and is usually absent or minimally expressed by ductal carcinoma.34,35 However, optimal use of this antibody requires heat-retrieval tissue preparation, because other methods may result in false-negative staining.34,35

DISTINGUISHING PLCIS FROM HIGH-GRADE DCIS

Pleomorphic lobular carcinoma in situ and high-grade DCIS are currently managed similarly, and hence distinguishing between these 2 entities is not of the clinical importance discussed above. Again, PLCIS is most readily identified by the presence of classic LCIS in the nearby vicinity. Like LCIS, PLCIS exhibits loss of E-cadherin staining (Figure 2, D) and cytoplasmic redistribution of p120 catenin, and hence these 2 stains are useful to confirm a suspected diagnosis.36

SIGNIFICANCE OF LN ON CORE BIOPSY

Evidence suggesting that some LN is a nonobligate precursor for invasive carcinoma has raised concerns about the need for follow-up surgical excision when LN is present on core needle biopsy. Studies vary in detection rates of a more advanced lesion (up to 20%) when follow-up surgical excision is performed after diagnosis of LN on biopsy.37–48 Although many of these studies are limited by size and selection bias, they do provide some practical guidelines that suggest when a more advanced lesion is most likely to be detected. Excision is prudent when there is discordance between pathologic changes present on biopsy and radiographic or clinical findings, when LN with atypical features is present (eg, PLCIS), or when LN is associated with another generally excised lesion (eg, atypical ductal hyperplasia) in the core.

The role of magnetic resonance imaging screening in patients diagnosed with LN on needle biopsy is unclear. However, one recent, institutional, retrospective study showed detection of subsequent cancer in a small subset of patients previously diagnosed with LCIS who underwent further screening by magnetic resonance imaging.46 No cases of cancer on magnetic resonance imaging–generated follow-up biopsies were found in patients previously diagnosed with ALH. Further studies in this area are warranted.

RECENT ADVANCES IN UNDERSTANDING THE PATHOGENESIS OF LN

The future management of LN may rely on dissecting the molecular pathways involved in the development of these lesions. Genomic and molecular studies have provided necessary insight into the pathogenesis and biology of LN. Atypical lobular hyperplasia exhibits more genomic alterations compared with LCIS, suggesting that they represent distinct biologic entities.12 However, both ALH and LCIS exhibit copy number gains in regions that harbor the AKT1 and CSF1R genes. These genes can disrupt cell polarization,47,48 possibly effecting an early common molecular pathway involved in LN maintenance. Only LCIS shows a gain in copy number of a region harboring the CCAAT/enhancer-binding protein (CEBP) beta, which may influence LCIS progression through its effect on cell proliferation and differentiation.

The loss of E-cadherin is not sufficient for tumorigenesis, as highlighted by the requirement for p53 inactivation in murine invasive lobular carcinoma development.19 Thus, loss of other tumor-suppressor genes may be involved in the pathogenesis of LN. Interestingly, CCCTC-binding factor (CTCF) and Dipeptidase 1 (DPEP1), both candidate tumor-suppressor genes, were found to have decreased expression in LCIS versus normal breast lobules.50 Both genes are found on chromosome 16q.

**Figure 3. E-cadherin immunostain.** A, Lobular neoplasia (LN) lesions are negative for E-cadherin (original magnification ×100). B, Ductal carcinoma in situ is strongly positive for E-cadherin (original magnification ×100). In order to rule out LN, E-cadherin stain must be strongly positive with distinct membrane staining, because some LN lesions can show weak and/or diffuse cytoplasmic E-cadherin expression.
whether the loss or gain of the above genes influences initiation or promotion of LN remains to be determined. However, these findings should encourage further identification of candidate tumor-suppressor genes or oncogenes through a targeted search in areas of common genomic aberrations.

CONCLUSION

Our understanding of the clinical outcomes and biology of LN has evolved during the past century, and it will continue to evolve with the combined, synergistic efforts of both basic and translational research. The histologic (hematoxylin-eosin) and immunohistochemical (E-cadherin, p120) characterizations of LN were important first steps in defining and understanding the pathogenesis of these lesions. Furthermore, the identification of PLCIS as a distinct, aggressive subtype of LN has increased the spectrum of lesions within LN. Given the histologic and biologic heterogeneity of LN, it is likely that genomic and molecular studies will guide our future handling of these lesions both pathologically and clinically. In summary, although not as much is known about LN as its ductal counterparts, namely, ADH and DCIS, the future holds promise in deciphering these seemingly indolent lesions.

References

13. Fadare O, Dadmanesh F, Alvarado-Cabrero I, et al. Lobular intraepithelial neoplasia (lobular carcinoma in situ) of the breast: a spectrum of lesions within LN. Given the histologic and biologic heterogeneity of LN, it is likely that genomic and molecular studies will guide our future handling of these lesions both pathologically and clinically. In summary, although not as much is known about LN as its ductal counterparts, namely, ADH and DCIS, the future holds promise in deciphering these seemingly indolent lesions.

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