Lobular neoplasia: morphology, biological potential and management in core biopsies

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Lobular neoplasia has been traditionally recognized as a marker of increased risk for subsequent breast carcinoma development; however, molecular studies suggest that it also behaves in a non-obligate precursor manner. We do not know, as yet, how to identify the subgroup of cases that is most likely to progress, but the epidemiological data would indicate that this progression occurs after a long period of time. Thus, the current approach of conservative management of these lesions when identified in excision specimens is justified. Recently, several variants of lobular carcinoma *in situ* (LCIS), most notably pleomorphic LCIS, have been recognized and these can be difficult to differentiate from ductal carcinoma *in situ*. Application of strict diagnostic criteria and the judicious use of immunohistochemistry, particularly E-cadherin, can be helpful in this differential diagnosis. Another challenging issue is the management of lobular neoplasia when diagnosed on core biopsy. This controversial issue will be discussed in detail. The goals of this review are (1) to describe the morphological criteria used to diagnose the spectrum of lobular neoplastic lesions, including atypical lobular hyperplasia, LCIS and variants of LCIS; (2) to discuss the data exploring the biological potential of lobular neoplasia from an epidemiological and molecular viewpoint; and (3) to outline the recommendations for management of lobular neoplasia when encountered in core biopsies.

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The term 'lobular carcinoma *in situ*' (LCIS) was first coined by Foote and Stewart¹ over 65 years ago. Their description of the morphological appearance of the disease still holds true today: an entity composed of a monomorphic population of dysplastic cells expanding the terminal duct lobular unit. Almost 40 years after this first description of LCIS, Haagensen *et al*² published their own experience with this disease and concluded that 'lobular neoplasia' was a more appropriate term for this lesion as few cases appeared to progress to invasive carcinoma. With increasing recognition of LCIS, it became apparent that less well-developed forms were more frequently seen in the breast. Page *et al* used the term atypical lobular hyperplasia (ALH) for these lesions.^{3,4} In practice today, the term lobular neoplasia refers to both ALH and LCIS. Lobular neoplastic lesions have also been classified using an alternative nomenclature: lobular intraepithelial

neoplasia,⁵ although this classification is used less frequently in clinical practice.

There has been much debate in the literature regarding the natural history of lobular neoplastic lesions.^{6–10} Epidemiological studies have clearly shown lobular neoplasia as a marker of increased risk.^{11–14} However, in recent years, there is increasing evidence that LCIS may also act as a non-obligate precursor in the progression to invasive carcinoma.^{7,15–17}

Clinical features

Lobular neoplastic lesions (ALH and LCIS) are often multicentric and bilateral.^{1,18} They occur predominantly in premenopausal women, with most cases being diagnosed in women between 40 and 50 years of age.^{13,19–22} They are clinically occult, and although they are often also mammographically silent, a significant minority of lobular neoplasia cases diagnosed on core biopsy have associated microcalcifications.^{23–26}

Data derived from the Surveillance, Epidemiology and End Results Program²⁷ have shown that the age-adjusted, age-specific rates of LCIS among women in

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Figure 1 ALH: (a and b) Morphologically ALH and LCIS are composed of small, regular round, loosely cohesive cells originating in the terminal duct lobular unit. The diagnosis of ALH is made when the acini are only partially filled by these cells; if there is distension present, <50% of the acini are involved.

the United States has increased fourfold between the late 70s (0.9 per 100 000 person years) and late 90s (3.2 per 100 000 person years). Women aged between 50 and 59 years experienced the greatest absolute increase in incidence from 1978 to 1998. This rising incidence was not seen in premenopausal women or in women over 70 years of age.²²

Epidemiology

Although the morphological distinction between ALH and LCIS is quantitative and based on an arbitrarily set threshold, the epidemiological studies clearly indicate a significantly higher relative risk of subsequent carcinoma development associated with LCIS (eight- to ninefold) compared with ALH (four- to fivefold).^{2,3,12,28} The extent of LCIS in the breast does not seem to significantly affect risk.^{11,29,30} LCIS confers ~15% absolute risk of developing breast cancer at 15 years, but a significant number of subsequent carcinomas occur more than 15 years after a diagnosis of LCIS.^{2,12,19–21} Although lobular neoplasia has been linked to an increased risk of subsequent carcinoma in either breast,^{12,13,21} several studies have shown a higher, although not always statistically significant, risk in the ipsilateral breast.^{3,14,17,20,30,31} Cancer risk in ALH seems to vary with patient age; an initial diagnosis of ALH in postmenopausal women has been associated with a lower risk of subsequent carcinoma development than in premenopausal women.^{3,14,17,31}

The majority of invasive carcinomas that subsequently occur in cases of lobular neoplasia are ductal, no special type. But invasive lobular carcinomas constitute up to 45% of subsequent carcinomas;^{12,21,30,32} this is in sharp contrast to the expected rate (5–14%) of invasive lobular carcinomas in the general population.

Histopathology

Both ALH and LCIS are defined using the criteria of Page and colleagues^{3,33} by a population of cells that are small, round, monomorphic, dyshesive with an increased nuclear to cytoplasmic ratio; ALH is diagnosed when <50% of the acini in the affected terminal duct lobular unit are involved by the lobular proliferation and these cells do not completely occlude the lumen or produce marked distension of the acini (Figure 1). LCIS is diagnosed when >50% of the acini in the affected terminal duct lobular unit are completely filled and distended by the cellular proliferation (Figure 2). In practice, ALH and LCIS often coexist (Figure 3), and for this reason, along with the fact that it can be difficult to differentiate ALH from LCIS, some authorities would advocate using the term lobular neoplasia for both lesions. Intracytoplasmic vacuoles are often present in both ALH and LCIS and can be a prominent feature. Pagetoid extension along ducts producing a 'clover leaf' appearance is not uncommon. Although the majority of cells comprising these lobular neoplastic lesions are uniform with

Figure 2 LCIS: (a and b) A diagnosis of classic LCIS is made when the acini are not only completely filled by these cells but cause distension of at least 50% of the acini. In many cases, the neoplastic cells produce distension of all the acini within a lobule.

Figure 3 Lobules showing atypical lobular hyperplasia (ALH) (right) and lobular carcinoma *in situ* (LCIS) (left). This exemplifies the fact that ALH and LCIS often coexist in the same case.

bland nuclei and scant cytoplasm (referred to as 'type A' cells²), in some cases the cells are somewhat larger with more cytoplasm and show mild to moderate nuclear atypia ('type B' cells) (Figure 4). Lesions composed of either cell types are referred to as 'classic' lobular neoplasia and should be distinguished from variants of LCIS (see below).

Variants of LCIS

Several variants of LCIS have been recognized. These include pleomorphic LCIS, pleomorphic apocrine LCIS, LCIS with comedo necrosis and

carcinoma *in situ* with mixed ductal and lobular features. Clear cell and signet ring cell variants of LCIS have also been described.

PLCIS

Pleomorphic LCIS (PLCIS) was first identified as a distinct entity by Eusebi *et al*³⁴ in 1992. The few reports that have been published since then have described cases of pleomorphic LCIS associated with invasive lobular carcinoma.^{35–37} Sneige *et al*³⁸ described in detail the morphological features of pleomorphic LCIS not associated with invasive lobular carcinoma. The cytological appearances of these cells are quite different to those of classic LCIS. Although the cells appear dyshesive as in classic LCIS, they exhibit a greater degree of nuclear pleomorphism and usually contain abundant cytoplasm (Figure 5). Occasionally, the cytoplasm can appear eosinophilic and finely granular, giving the cells an apocrine appearance (pleomorphic apocrine LCIS) (Figure 6). Central, comedo necrosis and calcifications are quite commonly associated with this lesion and can be confused with comedo ductal carcinoma *in situ* (DCIS) (Figure 7).

LCIS with Comedo Necrosis

Lobular carcinoma with comedo necrosis³⁹ has recently been described. Before the widespread use of E-cadherin, such cases were categorized as mixed ductal and lobular carcinoma^{30,40,41} or carcinoma *in situ* with indeterminate features.⁴² These lesions are comprised of identical cells to those of classic LCIS;

Figure 4 Classic LCIS. (a) The lobular neoplastic cells are uniform and contain bland nuclei with inconspicuous nucleoli; type A cells. (b) Classic LCIS may exhibit cells with larger nuclei and more abundant cytoplasm. Nucleoli may be more conspicuous; type B cells.

Figure 5 Pleomorphic LCIS (PLCIS). (a) Low power shows spaces expanded by a dyshesive population of cells with central necrosis. (b) High power shows a greater degree of nuclear pleomorphism than is seen in classic LCIS (see Figure 4), but the cells show a similar degree of dyshesiveness as in classic LCIS. Intracytoplasmic vacuoles are evident.

namely, small, uniform cells with intracytoplasmic lumina and a dyshesive growth pattern, but in addition, contain central areas of comedo necrosis (Figures 8a and b). Calcifications are often associated with the areas of necrosis (Figures 8c and d). One study of 18 cases reported a strong association (67%) with invasive carcinoma. In all, 11 of these invasive carcinomas (92%) were either pure invasive lobular carcinomas or had focal lobular features.³⁹

***In Situ* Carcinoma with Mixed Ductal and Lobular Features**

Some *in situ* lesions show features that resemble both LCIS and DCIS. These cases often are comprised of small, monotonous cells typical of LCIS, but appear more cohesive. Alternatively, these cases

may resemble DCIS architecturally with the formation of microacinar-like structures but show dyshesion typical of LCIS (Figure 9). E-cadherin immunohistochemistry may show heterogeneous staining in such cases; in one study, roughly one third of cases were negative for E-cadherin, one third were positive and one third had both positive and negative cells within the same lobular unit.⁴² This latter pattern of staining should be differentiated from staining of residual benign epithelial cells in a space filled by lobular neoplastic cells (Figure 10).

Immunophenotype

Although both classic lobular neoplasia and the variants of LCIS are almost uniformly positive for

hormone receptors (estrogen and progesterone) and negative for E-cadherin,^{42–45} (Figure 8) there are important differences in their immunophenotype. Classic LCIS and LCIS with comedo necrosis are negative for HER2 protein overexpression/gene amplification, lack p53 mutations and have a low

Figure 6 Pleomorphic apocrine LCIS. The lobules are expanded by cells that contain abundant eosinophilic cytoplasm typical of apocrine cells. Intracytoplasmic vacuoles are conspicuous.

Ki67 labeling index. Conversely, pleomorphic LCIS may show HER2 protein overexpression/gene amplification (particularly if associated with invasive carcinoma), may show p53 positivity and has a moderate to high Ki67 labeling index.^{38,46} In addition, pleomorphic LCIS is often positive with gross cystic disease fluid protein-15, not surprisingly as these lesions often display apocrine features. High molecular weight cytokeratin positivity has been reported as a useful adjunct in differentiating morphologically ambiguous *in situ* lesions into ductal or lobular categories.⁴⁷ However, others have failed to reproduce these findings. Indeed, positive staining seen with the antibody 34betaE12 in lobular neoplasia may in fact be related to the antigen retrieval process.⁴⁸ In addition, although E-cadherin is very useful as an adjunct in differentiating ductal from lobular lesions, morphologically unequivocal cases of LCIS and invasive lobular carcinoma have been shown to demonstrate focal E-cadherin positivity.^{49,50}

Dabbs *et al*^{51,52} recently reported the utility of p120-catenin in both classic and pleomorphic variants of LCIS. Characteristically, this antibody is diffusely localized to the cytoplasm in cases of lobular neoplasia, whereas in ductal lesions it remains localized to the membrane.

Figure 7 PLCIS vs DCIS. (a) Low power of PLCIS showing prominent central necrosis and calcification. This pattern of growth can be particularly difficult to differentiate from DCIS with central necrosis at low power (b), although the cells in (a) appear more dysplastic than the cells in (b).

Figure 8 LCIS with comedo necrosis. (a) The degree of nuclear pleomorphism in this case is less than that seen in PLCIS, despite being associated with central necrosis. (b) E-cadherin in this shows no immunoreactivity. (c) Another case of LCIS with central necrosis and abundant calcifications. (d) E-cadherin in this case is also negative.

Figure 9 (a) *In situ* carcinoma with indeterminate features on hematoxylin and eosin. The cells appear dyshesive in the majority of spaces, although there is a suggestion of microacinar formations in a few spaces. (b) E-cadherin is completely negative supporting a diagnosis of LCIS in this case.

Figure 10 Lobular neoplastic cells partially filling ductular spaces. The residual luminal cells show strong membrane staining with E-cadherin.

Figure 11 Low-grade DCIS showing a prominent microacinar pattern.

Differential diagnosis

Low-grade DCIS forming a solid growth pattern can be very difficult to differentiate from classic LCIS, even in excisional biopsy specimens. The presence of a dyshesive growth pattern and prominent intracytoplasmic vacuoles favors a diagnosis of lobular neoplasia (Figure 4). On the other hand, the presence of microacinar formations in this setting would support a diagnosis of DCIS. (Figure 11) E-cadherin immunohistochemistry can be particularly helpful in such cases (Figure 12).

Myoepithelial cells may be confused with lobular neoplasia, particular when these cells extend in a pagetoid manner into ducts and show abundant clear cytoplasm. The morphological characteristics of the myoepithelial cell, particularly the small, pyknotic-appearing nucleus and the clear cytoplasm, should help with this differential diagnosis.

Pleomorphic LCIS is very easily confused with high-grade DCIS, particularly when there is associated central necrosis and calcifications. The dyshesive appearance of the cells is helpful in making this diagnosis, as is the lack of E-cadherin staining (Figure 13).

Lobular neoplasia extending into sclerosing adenosis can be challenging, especially on core biopsies. The use of myoepithelial markers, such as smooth muscle myosin heavy chain or p63, can be very helpful in differentiating this process from an invasive carcinoma.

Molecular studies

Much has been discovered about the molecular genetics of lobular neoplasia in recent years. Most of these studies have focused on *in situ* lobular lesions

associated with adjacent invasive lobular carcinoma. Studies investigating loss of heterozygosity, E-cadherin expression and mutations in the E-cadherin gene, *CDH1*, have shown a relationship between LCIS and invasive lobular carcinoma.^{43,53–57} The *CDH1* gene is inactivated in both *in situ* and invasive lobular carcinomas by genetic (inactivating mutations of deletions) or epigenetic (promoter methylation) mechanisms.^{43,54–58} E-cadherin is a cell adhesion molecule that forms complexes with β -, γ -, α -catenins and p120-catenin. Loss of E-cadherin-mediated cell adhesion is believed to account for the dyshesive nature of lobular neoplasia and invasive lobular carcinoma. Invasive lobular carcinomas with adjacent LCIS not only lose E-cadherin, but have also been shown to simultaneously lose β -, γ - and α -catenin protein expression.⁵² Aberrant cytoplasmic localization of p120-catenin

(which may have a role in mediating the oncogenic effects of E-cadherin loss) has also been shown to characterize lobular neoplasia.^{52,58}

The development of powerful molecular techniques such as comparative genomic hybridization (CGH) has led to further discoveries in the molecular genetics of lobular neoplasia.^{16,59} Lu *et al*⁵⁹ using conventional chromosomal CGH (cCGH) found alterations at chromosomes 6, 16, 17 and 22. These alterations were found in similar frequency in LCIS and ALH, and therefore, based on these chromosomal CGH profiles, ALH and LCIS were suggested to represent the same genetic stage of development. The alterations found by Lu *et al*⁵⁹ in lobular neoplasia using cCGH were also identified and further refined by a study using array CGH.¹⁶ Altered regions in this study included loss at 16p11.2-p11.1 and loss at 22q11.1. Genes within regions of alteration found in both ALH and LCIS were identified to be involved in the process of luminal morphogenesis.^{16,60} Both ALH and LCIS showed loss of 16q21-q23.1 (E-cadherin gene, *CDH1*;16q21.1); this region was lost in all matched pairs of LCIS and invasive lobular carcinoma in another study using array CGH.⁶¹

There have been few molecular genetic studies of PLCIS.^{46,62,63} Although PLCIS shows the characteristic molecular genetic changes of classic lobular neoplasia (gain of 1q and deletion of 16q along with E-cadherin inactivation), this variant of lobular neoplasia also shows HER2/neu amplification, MYC amplification, deletion of 13q and gain of 20q.^{46,62}

The molecular data described above suggest that ALH/LCIS behaves in a non-obligate precursor manner. Loss of 16q and gain at 1q in lobular neoplasia points to the possible progression toward a low-grade invasive phenotype, given the frequency of these alterations in low-grade invasive breast cancer.⁶⁴ Taken together, however, the molecular genetic and clinicopathological data support lobular neoplasia acting both as a precursor lesion

Figure 12 DCIS showing distinct membrane staining with E-cadherin.

Figure 13 PLCIS. (a) Low power showing expansion of a space by a dyshesive population of cells associated with central necrosis. (b) E-cadherin shows no immunoreactivity within the expanded space.

and as a risk indicator for subsequent carcinoma. We cannot, as yet, predict which lobular neoplastic lesions are likely to progress. Further studies are needed to understand and identify the subset of lobular neoplastic lesions that have the highest likelihood of progressing to invasive carcinoma.

Management of lobular neoplasia in core biopsies

The management of lobular neoplasia on core biopsy has received increased attention in the literature over recent years. Over 30 studies have addressed this issue since 1999.^{23–25,65–93} Upgrade rates to either DCIS or invasive carcinoma in as many as 40% of cases have been reported, but these studies showed variability in the degree of pathological–radiological correlation and variations in imaging techniques including the number and caliber of cores taken, and they also included variants of lobular neoplasia.^{94,95}

Nevertheless, there is a general consensus that excision should be performed in cases of lobular neoplasia identified on core biopsy when the following conditions apply:

- (1) when another lesion that would in itself lead to excision, such as atypical ductal hyperplasia, is also present in the core biopsy;
- (2) when there is discordance between the radiological and pathological findings;
- (3) when there is an associated mass lesion or area of architectural distortion;
- (4) if the lesion shows indeterminate features between a ductal and lobular proliferation; and
- (5) if the morphology is consistent with pleomorphic LCIS or other variants of LCIS.^{81,96}

However, some recent studies have shown that classic lobular neoplasia as the sole lesion identified on core biopsy has been associated with either DCIS or invasive carcinoma in 10–27% of cases.^{65,74,80,82,89} These studies were limited by the small numbers of cases included and by their retrospective nature, which may have lead to selection bias with respect to the patients who underwent immediate excision. More recently, three studies^{92,93,97} have reported much lower rates of upgrades (1–3%). These studies included relatively large numbers of patients with lobular neoplasia on core biopsy who had immediate excision; larger volumes of tissue were sampled and there was meticulous attention paid to pathological–radiological correlation. The upgrade rates in two of these studies^{92,93} would have been much higher if their cases showing discordant pathological and imaging findings had been included. Of particular note in one of these studies⁹³ is that, although few of these women with lobular neoplasia on core biopsy had DCIS or invasive carcinoma in the subsequent excision, up to 30% of these women developed DCIS or invasive carcinoma in either the

ipsilateral or contralateral breast before or after the core biopsy. Many of the subsequent ipsilateral carcinomas occurred in sites not related to the previous core biopsy.

In summary, the data clearly show that lobular neoplasia can behave both as a high-risk lesion and as a non-obligate precursor. But given the long latency period to progression, conservative management of these lesions when identified in excision specimens remains the mainstay of treatment. We are increasingly recognizing variants of lobular neoplasia, and although their management at present is identical to that of DCIS, it is important to separate these lesions from DCIS so that we can learn more about their biological behavior. Finally, the management of lobular neoplasia when diagnosed on core biopsy remains a controversial issue. But there is general agreement that patients who have a diagnosis of a variant of LCIS on core biopsy should undergo immediate excision. On the other hand, the evidence does not support routine excision following a diagnosis of classic lobular neoplasia on core biopsy when there is complete pathological–mammographic correlation and the suspicious area on imaging has been adequately sampled. Although women with classic lobular neoplasia on core biopsy have a low risk of having a carcinoma at the site of the biopsy, there is an increased risk of developing a subsequent carcinoma in either the ipsilateral or contralateral breast. Thus, these women need close ongoing follow-up.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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