Non-operative breast pathology: lobular neoplasia

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Lobular neoplasia is a relatively uncommon lesion, which is frequently diagnosed in biopsy specimens taken for other reasons. Although the histological features of this lesion are well known, its biological significance as a “risk indicator” or “breast cancer precursor” has been a matter of debate. This review provides an update on recent clinicopathological and molecular data on lobular neoplasia and how these have changed the way these lesions are perceived and, most importantly, managed. Furthermore, the current recommendations for the management of lobular neoplasia diagnosed on core needle biopsies proposed in the National Health Service Breast Cancer Screening guidelines are discussed.

The first illustration of lobular neoplasia (LN) was published by Ewing, back in 1919, who described this lesion as an “atypical proliferation of acinar cells”.¹ However, it was Foote and Stewart, who, in 1941, first recognised this group of lesions as a distinct entity and coined the term “lobular carcinoma in situ” (LCIS).² Although this seminal study was published more than 65 years ago, the main characteristics of the disease were accurately described. Indeed, most are still accepted, including that LCIS: (i) originates from cells in the terminal duct-lobular unit or terminal ducts; (ii) is usually multicentric, often bilateral and not readily identifiable in gross examination; (iii) is composed of a monomorphic population of discohesive cells that expand the terminal duct-lobular units and disseminate through the ductal system in a way that recalls Paget’s disease (pagetoid spread, called “sandwich” pattern by Haagensen *et al*); and (iv) is almost never seen in association with true Paget’s disease of the nipple.² Even the associations with its invasive counterpart, invasive lobular carcinoma, and other types of low grade breast cancer (i.e., low grade ductal/no special type and tubular carcinomas) were described in that seminal paper.² The precursor nature of LN was also suggested by Muir, in 1941, who coined the term “intra-acinous carcinoma” to refer to these lesions.

In 1978, Haagensen *et al*³ published their own series of 211 patients and reviewed the literature on “lobular carcinoma in situ” not associated with other forms of breast cancer. Their conclusions were largely in agreement with those of Foote and Stewart,² however they considered the term “lobular carcinoma in situ”, when not associated with invasive cancer, a misnomer,³ given that the evidence available at that time suggested that

those lesions were in fact a “benign, noninfiltrating, special microscopical form of lobular proliferation of the mammary epithelium”.³ They suggested the use of the term “lobular neoplasia” (LN) instead. This term was subsequently widely accepted and played an important role in changing the management of the lesion, from mastectomy to follow-up. However, in hindsight, it is also arguable that this study,³ which called into question the precursor nature of this lesion, also delayed an understanding of the true biology and clinical behaviour of LN.

For a long time it has been debated whether LN is a non-obligate breast cancer precursor, or a mere risk indicator.^{2–17} The risk indicator nature of LCIS is not in dispute; in fact, it is widely accepted that LCIS confers an increased risk of development of invasive carcinoma of about 1–2%/year, a 10-year risk of 7–8%, a lifetime risk of 30–40% and a relative risk of breast cancer of 8–10.^{8 15 18} The term “atypical lobular hyperplasia” (ALH) was introduced to describe a morphologically similar but less well-developed lesion (see below), which confers a relative risk of breast cancer development of 4–5.^{16 19 20}

Although ALH and LCIS confer different relative risks of developing subsequent invasive breast cancer, distinguishing the two lesions is, at least partly, subjective. For some experts the differences between these two categories of lobular neoplasia are expressed more easily in words than in actual practice.¹³ Criteria for distinguishing the two are difficult to apply in some situations (e.g., core biopsies, when pagetoid spread only is present, when the LN involves another underlying lesion such as sclerosing adenosis). For these reasons, the term LN which encompasses both ALH and LCIS, has been accepted by many diagnostic pathologists.²¹ Of note, in the context of diagnostic core biopsies, the use of the term lobular neoplasia is recommended by the UK NHS BSP (National Health Service Breast Screening Programme) guidelines for non-operative diagnostic procedures and reporting in breast cancer screening.⁵²

LCIS is most frequently diagnosed in women aged between 40 and 55 years (less than 10% of patients with LN are postmenopausal).^{3 5} However, estimating the true incidence of LCIS is fraught with difficulty, given that, in the pre-breast cancer screening programme era, the majority of cases used to be incidental findings in biopsy specimens taken for other lesions and not associated with

Abbreviations: ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; CGH, comparative genomic hybridisation; CNB, core needle biopsy; DCIS, ductal carcinoma in situ; ILC, invasive lobular cancer; LCIS, lobular carcinoma in situ; LN, lobular neoplasia

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specific clinical or radiological findings (i.e., LN does not form a mass and <50% of cases are associated with microcalcifications).^{2, 3, 5} Although it is reported that the incidence of LN in otherwise benign biopsy specimens ranges from 0.5% to 3.8%,^{3, 4} an accurate assessment of the prevalence of LN in the general population is yet to be provided.

Consistent with the idea of LN being a risk indicator, early epidemiological studies suggested that a diagnosis of ALH/LCIS would confer an increased risk of developing invasive cancer anywhere in either breast and that the invasive breast cancer was not necessarily of lobular histology.^{3, 8, 22} However, it has recently been shown that this risk is higher in the ipsilateral breast and mainly at the site of the biopsied LN.^{10, 13} Furthermore, when cases of pure LCIS (i.e., without associated ductal carcinoma in situ (DCIS)) are followed, the subsequent invasive tumour is almost uniformly of lobular histology.^{12, 13}

HISTOPATHOLOGY OF LOBULAR NEOPLASIA

Although there is still controversy regarding the clinical implications of a diagnosis of LN, its morphological characteristics are well known. According to the latest World Health Organization classification of breast tumours, lobular neoplasia is defined as a “proliferation of generally small and often loosely cohesive cells originating in the terminal duct-lobular unit, with or without pagetoid involvement of terminal ducts”.²¹ Architecturally, these lesions are characterised by a variable enlargement of the acini, which are filled by a monomorphic population of small, rather discohesive, round, cuboidal or polygonal cells, with inconspicuous cytoplasm (fig 1A). Intracytoplasmic vacuoles, sometimes containing a central eosinophilic dot, are not uncommonly found^{2, 3, 5, 21} (fig 1B). Although the classic variant is composed of monomorphic cells, some variability in the cytomorphology between different cases, and frequently within the same case, has been reported. Thus the cells of classic LN can be classified into two sub-types, according to criteria laid down by Haagensen²³ and revised by Sneige *et al*:²⁴ type A, which are characterised by bland and mildly discohesive cells, with scant cytoplasm and nuclei approx 1.5× the size of that of a lymphocyte; and type B cells, which characteristically have more abundant cytoplasm, slightly bigger nuclei (2× the size of a lymphocyte nucleus), mild to moderate nuclear atypia (still falling into nuclear grade 1 or 2) and indistinct or absent nucleoli. This system of cytological categorisation, has not, however, proven of value and does not have a direct correlation with development of cancer; it has thus become more of an academic exercise.²⁵ Indeed, Haagensen *et al*²³ suggested that this would be too simplistic a classification.

The term ALH is used to refer to a partial involvement of acini by lobular neoplasia cells. According to Page *et al*,^{4, 9, 10, 16, 20} for a

diagnosis of LCIS, more than half of the acini in an involved lobular unit must be filled and distended by the characteristic cells, leaving no central lumina. However, the differences between ALH and LCIS at the morphological level (and molecular level, see below) appear to be merely quantitative with an arbitrarily set threshold; therefore, it is not surprising that there is a great degree of inter- and intra-observer variability in the differentiation between LCIS and ALH. Despite the morphological and molecular evidence to suggest that the differences between ALH and LCIS are negligible and the difficulties with reproducibility of diagnosis, given the acknowledged and significantly higher relative risk of breast cancer development associated with LCIS,^{4, 9, 10, 16, 19, 20} the value of the terms ALH, LCIS and LN remains controversial. As noted above, in the context of diagnostic core biopsy specimens, where limited sampling is a significant issue, the use of the term lobular neoplasia should be used as per the UK NHS BSP guidelines for non-operative diagnostic procedures and reporting in breast cancer screening.⁵²

More biologically and clinically important is the recognition of the recently described pleomorphic variant of lobular carcinoma in situ, which was first identified as a distinct entity by Eusebi *et al*²⁶ in 1992. In 2002, the first detailed analysis of pleomorphic LCIS not associated with invasive cancer was reported.²⁴ Pleomorphic LCIS is characterised by cells that are remarkably bigger than those of classic LN, have more abundant, pink and finely granular cytoplasm, frequently display features of apocrine differentiation and harbour more pleomorphic, atypical nuclei, with conspicuous nucleoli^{24, 26, 27} (fig 2). Central, comedo-type necrosis and microcalcifications are not uncommon in this variant. It is almost certain that some of these lesions were classified as high grade DCIS, in the past.^{24, 27} Other variants of LN are also on record, including endocrine, amphoteric, apocrine, histiocytoid, rhabdoid and the pleomorphic apocrine LCIS variant^{28, 29}; however, their biological and/or clinical significance remains uncertain.

ANCILLARY IMMUNOHISTOCHEMICAL MARKERS

Lobular neoplasia consistently shows positivity for oestrogen and progesterone receptors; even the pleomorphic variant is reported to show expression of these markers in >90% of cases.^{5, 24, 27, 30} However, some differences in the expression of classic biomarkers of aggressiveness have been observed between the classic and pleomorphic variants (table 1). While expression of p53 and HER2 is remarkably rare in classic LN, p53 expression (as defined by >10% of neoplastic cells) and HER2 overexpression are found in approximately 30% of pleomorphic LCIS.^{5, 24, 27, 30} Furthermore, *HER2* gene amplification and high MIB-1 labelling indices have been reported in the pleomorphic variant, while these are not features of classic

Figure 1 (A) Lobular carcinoma in situ; note the expansion of the terminal duct lobular unit by a monomorphic cell population. (B) High-power magnification of lobular neoplasia highlighting the discohesiveness of neoplastic cells and the presence of intracytoplasmic vacuoles.

Figure 2 Pleomorphic lobular carcinoma in situ associated with invasive pleomorphic lobular carcinoma. (A and B) Low power magnification of a rather extensive lesions with multiple areas of comedo necrosis. (C) Coarse microcalcifications are not uncommonly seen. Note the resemblance with high grade ductal carcinoma in situ; however neoplastic cells are more discohesive. (D) Some examples of pleomorphic lobular carcinoma in situ have marked apocrine features. (E) A terminal duct lobular unit affected by pleomorphic lobular carcinoma in situ. (F) Lack of E-cadherin expression is a common feature, as are: (G) HER2 3+ positivity (Herceptest/DAB, Dako, Glostrup, Denmark); and (H) *HER2* gene amplification (chromogenic in situ hybridisation, SpotLight *HER2* amplification probe, Zymed, South San Francisco, CA, USA).

LN.^{5 24 27 30} Given the high frequency of apocrine differentiation in the pleomorphic variant, it is not surprising that >60% of pleomorphic LCIS shows expression of gross cystic disease fluid protein-15,^{26 30} a marker of apocrine differentiation.

In recent years, the likeliest underlying molecular mechanism for the discohesiveness so typical of LN has been identified. There are several lines of evidence to suggest that this is due to a lack, or a significant reduction, of the expression of functional E-cadherin.^{5 31-44} This protein mediates homophilic-homotypic adhesions and is consistently expressed, as a membrane

marker, in luminal epithelial cells of the breast. Both classic and pleomorphic variants of LN fail to express this protein in >95% of cases,^{5 31-44} and some have reported that focal expression of this protein may be associated with higher recurrence rates.^{45 46}

E-cadherin has been used as a successful marker to differentiate ductal from lobular proliferations.⁴¹⁻⁴⁴ In fact, some authorities have suggested that solid in situ proliferations with indeterminate features are best classified according to the pattern of E-cadherin expression: those with E-cadherin

Table 1 Summary of ancillary markers for the diagnosis of lobular neoplasia

Marker	Classic LN	Low-grade DCIS	Pleomorphic LN	High-grade DCIS
ER	+	+	+/- (often weak)	-/+
PgR	+	+	+/- (often weak)	-/+
HER2	-	-	+/-	+/-
p53	-/+	-/+	+	+
Ki-67	Low	Low	Medium/high	High
E-cadherin	-	+	-	+
β -catenin	-	+	-	+
GCDFP-15	-/+	-/+	+/-	-/+*

ER, oestrogen receptor; PgR, progesterone receptor; GCDFP-15, gross cystic disease fluid protein 15.

*Positivity is observed in cases with apocrine differentiation.

expression should be considered DCIS, whereas cases that lack the expression of this adhesion molecule are best classified as LN⁴¹⁻⁴⁴ (fig 3). In addition, some cases of carcinomas in situ with indeterminate features may harbour a mixed pattern of E-cadherin expression and should be classified as mixed lesions.⁴³ Interestingly, molecular data in support of this approach have recently been published.²⁷

High molecular weight cytokeratins identified by the clone 34 β E12 (i.e., cytokeratins 1, 5, 10 and 14) were reported to be consistently expressed in LN and it has been suggested that this antibody could be used to differentiate it from ductal lesions.⁴⁴ However, there is strong evidence to suggest that LN cells do not express cytokeratins 1, 5, 10 and 14 and that 34 β E12 positivity in LN may be an artefact of antigen retrieval.⁴⁷ In addition, up to 15% of ductal carcinomas may express basal keratins,⁴⁸ and low-grade ductal/no special type and tubular neoplasms are also reported to show positivity for 34 β E12.⁴⁹ Therefore, we would recommend caution when using the 34 β E12 for a diagnosis of lobular neoplasia.

More recently, other proteins that form complexes with E-cadherin have been successfully used to differentiate between ductal and lobular neoplasms. These new markers include β - and α -catenin,³⁹ which are also lost in the majority of LNs, and p120 cadherin,⁵⁰ which is expressed in the membrane of non-neoplastic luminal cells and ductal proliferations, and shows cytoplasmic rather than membranous expression in LN. Of note, this expression pattern is present from the early stages of lobular breast cancer but is maintained during tumour progression and is seen in metastatic deposits. However, further studies are required to accurately define the use of these ancillary markers to differentiate LN from its mimics.

DIFFERENTIAL DIAGNOSIS

The main pitfalls that can pose problems in the identification of LN have been described elsewhere.²⁸⁻⁵¹ Poor tissue fixation, not uncommonly seen in mastectomy specimens, can lead to an artefactual appearance of discohesion within a lobular unit, resulting in an overdiagnosis of LCIS. Fortunately, this is an

infrequent problem in diagnostic core biopsy specimens. It should be noted that in core biopsy samples the pathologist should not strive to distinguish ALH from LCIS⁵²; their categorisation lies in an assessment of the extent and degree of expansion of lobular units, which is not possible in the limited amount of tissue often received. The lesion in a core biopsy specimen should be diagnosed as LN and classified as B3, of uncertain malignant potential, and multidisciplinary discussion should take place.

Differentiating low grade, solid DCIS from LN is, sometimes, an exceedingly difficult task,⁴¹⁻⁴⁴ even in surgical excisional samples. In cases of carcinoma in situ with indeterminate features, it has been suggested that the presence of a mosaic growth pattern with prominent intracytoplasmic vacuoles is more suggestive of LN, whereas the presence of microacinar-like structures would favour a diagnosis of solid low-grade DCIS.⁴³ However, as discussed above, in this context E-cadherin staining is particularly helpful.⁴¹⁻⁴⁴ Nevertheless it may simply not be possible to unequivocally distinguish LN from low grade DCIS in limited core biopsy specimens; such a lesion can be classified as B4, suspicious, and further investigations such as repeat (11 gauge) biopsy or diagnostic surgery undertaken.

In the non-operative setting in particular, the other important differential diagnosis of LN is cancerisation of the lobules by DCIS. Cancerisation of the lobules by DCIS is a well known phenomenon, which was included in the definition of "intra-acinous carcinoma" by Muir.⁶ In fact, that author failed to appreciate that LN and cancerisation of the lobules were distinct pathological processes and stated that "intra-acinous carcinoma is often merely the result of the spread of cancer cells from terminal ducts in which the malignant process has started". However, since Fechner's report⁵³ on this phenomenon, it has become clear that LN and cancerisation of the lobules are completely separate entities and should be differentiated. This phenomenon is particularly troublesome in cases where the differential diagnosis is between lobular cancerisation and pleomorphic LCIS. Again, immunohistochemistry with anti-E-cadherin antibodies is helpful; a lack of

Figure 3 (A) Carcinoma in situ with indeterminate features. (B) Lack of E-cadherin staining helps classify these lesions as variants of lobular neoplasia.

membranous E-cadherin staining would strongly militate against a diagnosis of cancerisation of the lobules by high grade DCIS.

It is also important to remember that benign lesions in core biopsy specimens may sometimes be misleading; for instance, foci of clear cell metaplasia or lactational change containing intracytoplasmic lipid droplets may bear some resemblance to ALH/LCIS. LN is not infrequently seen in association with coexisting benign lesions, including radial scar, sclerosing adenosis and fibroadenoma (fig 4), which clinically and radiologically may present as a mass. The histological appearance of LN in association with these lesions may cause difficulties for the unwary.

MOLECULAR PATHOLOGY

Molecular genetic studies have provided a wealth of increasingly more coherent data on the pathways of breast cancer evolution and how these findings correlate with morphological features. It is currently believed that at the molecular genetic level, breast cancer can be classified into two groups. The low grade group is characterised by low nuclear grade, consistent positivity for oestrogen and progesterone receptors, lack of HER2 overexpression and, at the genetic level, quite simple, diploid or near diploid karyotypes. The most frequent genomic changes in lesions of this group comprise deletions of 16q, and gains of 1p and 16p.⁵⁴ High grade lesions are characterised by much more complex karyotypes, which are frequently aneuploid. Although these lesions have many more unbalanced genomic changes, deletions of the whole 16q arm are seen in <10% of these cases. Even when these are present, they are reported to occur through distinct genetic mechanisms,⁵⁵ suggesting that progression from low to high grade breast cancers is an unlikely, or at least a rare, phenomenon.^{54 55}

Conversely, the molecular data have blurred the boundaries between low-grade ductal and lobular proliferations. These lesions have remarkably similar immunohistochemical and molecular genetic profiles, the main difference being the target

gene of 16q deletions.^{34 56 57} While in low-grade ductal lesions the target gene remains as yet unidentified,^{34 56–58} in LN it has been shown to be the *CDH1* gene, which encodes E-cadherin. The *CDH1* gene is reported to be inactivated in both LCIS and invasive lobular cancer (ILC), through a variable combination of genetic (deletions and inactivating mutations) and epigenetic (gene promoter methylation) mechanisms.^{32 33} In addition, Vos *et al*³⁶ have shown concurrent identical truncating mutations in the E-cadherin gene in matched LCIS and adjacent ILC. Noteworthy, although *CDH1* mutations appear to be more frequent in LCIS, they have even been found in ALH not associated with invasive cancer.³⁹ On the other hand, comprehensive surveys of low grade ductal carcinomas have failed to identify *CDH1* truncating gene mutations or E-cadherin down-regulation.^{5 36 42–44 56 58} Another level of evidence linking *CDH1* gene inactivation and LN comes from studies of families with *CDH1* germline mutations, who are reported to have a remarkably high risk of development of signet ring gastric cancer and lobular carcinoma.⁵⁹ More recently, by introducing conditional *cdh1* gene mutations into a conditional mouse tumour model based on epithelium-specific knockout of *p53*, Derksen *et al* have shown that E-cadherin inactivation leads to the genesis of neoplasms morphologically identical to human invasive lobular carcinomas.⁶⁰ Taken together, these data provide strong evidence to suggest that LCIS is a non-obligate precursor of ILC and that *CDH1* gene inactivation is paramount for the pathogenesis of lobular lesions.

Comparative genomic hybridisation (CGH) analysis of LN has shown that ALH and LCIS harbour strikingly similar unbalanced chromosomal changes, with the most frequent aberrations comprising deletions of 16p, 16q, 17p, and 22q and gains of 6q.⁶¹ Interestingly, more recent chromosomal^{62 63} and microarray-based^{40 64 65} CGH studies have shown that deletions of 16q, 8ptel-p12 and 11q14-qtel and gains of 1q, 8p12-p11.2, 11q13 and 16p are the most frequent molecular genetic changes found in lobular carcinoma. Most importantly, array CGH and mitochondrial DNA analyses have confirmed the similarities

Figure 4 Troublesome cases of lobular neoplasia. (A) Lobular neoplasia arising in sclerosing adenosis. (B) Note the continuous layer of calponin-positive, myoepithelial cells. (C) Lobular neoplasia arising in a fibroadenoma. (D) Neoplastic cells consistently lack E-cadherin and β -catenin.

between matched LN and ILC at the molecular genetic level,^{64–66} providing additional, circumstantial evidence in support of a precursor role for LN.

Although molecular data on the pleomorphic variant are scant, deletions of 16q, mapping to the *CDH1* gene locus have been shown.⁶⁷ In a recent study, a case of matched pleomorphic LCIS and invasive pleomorphic lobular carcinoma revealed remarkably similar molecular genetic profiles, with a similarity of 72%, as defined by high resolution CGH and a correlation index of 0.784 as assessed by microarray-based CGH.²⁷ Furthermore, it is now well accepted that pleomorphic LCIS harbours the hallmark genetic features of LN, namely gain of 1q and deletion of 16q coupled with E-cadherin inactivation. However, pleomorphic LCIS has proven to be a genetically advanced lesion, with complex karyotypes. Amplification of *HER2* and *MYC*, gain of 20q and deletion of 13q may account for the high grade nuclear features and the reported more aggressive behaviour of this variant.²⁷

MANAGEMENT OF LOBULAR NEOPLASIA IN CORE NEEDLE BIOPSY SPECIMENS

Contrary to initial descriptions,^{2–3, 23} LN is reported to be associated with microcalcifications in up to 40% of cases diagnosed on core needle biopsy (CNB).^{68–70} However, LN is infrequently seen as the sole diagnostic finding in such specimens, accounting for 0.5–2.9% of biopsy specimens taken for histological assessment of mammography detected lesions.^{69–80} There is a paucity of peer reviewed data and prospective analyses on this topic in the literature; most management recommendations have therefore been based more on pragmatism than scientific evidence. Until recently,^{5–69} most authors agreed that excision should be performed in cases of LN diagnosed on a CNB in the following instances: (i) another lesion, which would itself be an indication for surgical excision, was also present on the core biopsy (such as ADH or a radial scar); (ii) there was discordance between clinical, radiological and pathological findings; (iii) there was an associated mass lesion or an area of architectural distortion; (iv) the ALH or LCIS showed mixed histological features with difficulty in distinguishing the lesion from DCIS, or showed a mixed E-cadherin staining pattern; and (v) the morphology was consistent with that of the pleomorphic variant of lobular neoplasia.^{51–69}

The above method of selection of cases that should undergo further assessment has not been universally applied; some UK breast units have been recommending and undertaking surgical diagnostic surgical excision of all LN for many years,⁷¹ while other groups have been excising only those cases defined as above, and in particular those with radiological/surgical/pathological discordance. In the last two years, North American authors have suggested that LN should be perceived as “high-risk” and recommended excision of all cases due to the underestimation of cancer in up to 33% of LN diagnosed on CNB.^{78–79}

In summary, while it is of utmost importance to avoid unnecessary diagnostic surgery for patients where LN is the sole finding in a core biopsy specimen, the risk of associated malignancy in the adjacent breast at the time of diagnosis should be noted. Some have advocated that a multidisciplinary approach for such cases is essential⁸¹ and that each case must be assessed individually. Although there is a paucity of large prospective studies to define accurately the risk of underestimating the presence of more aggressive lesions in patients where classic LN is the sole diagnosis in a core biopsy specimen, based on the evidence currently available we would recommend diagnostic surgical excision of all such lesions. Despite the rather limited data on the pleomorphic variant of LN, there is

Take-home messages

- Lobular neoplasia is both a risk indicator and a non-obligate precursor of invasive breast cancer.
- In core biopsies, atypical lobular hyperplasia and lobular carcinoma in situ should be diagnosed as lobular neoplasia and classified as B3.
- E-cadherin, B-catenin and p120 catenin are useful markers to differentiate lobular from ductal proliferations.
- Pleomorphic lobular carcinoma in situ is a high grade and more aggressive variant of lobular neoplasia.

circumstantial evidence to suggest that these lesions are more frequently associated higher risk lesions and may have a more aggressive clinical behaviour than classic LN; therefore, many would recommend that such cases should be subjected to further excision.

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