Atypical Lobular Hyperplasia and Lobular Carcinoma In Situ

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Despite the earlier description by Ewing [1], the term lobular carcinoma is largely credited to Foote and Stewart [2] who, in 1941, published their seminal paper describing a detailed morphologic analysis of a distinctive subgroup of in situ carcinoma of the breast. Almost 40 years after the first description of lobular carcinoma in situ (LCIS), Haagensen et al. [3] 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. [4] used the term atypical lobular hyperplasia for these lesions.

Lobular neoplasia has also been termed lobular intraepithelial neoplasia (LIN), which divides these lesions using a 3-tiered grading scale based on extent and degree of lobular involvement and/or nuclear atypia (LIN1, LIN2, LIN3) [5]. Lobular neoplasia and LIN nomenclatures have not been widely adopted, and use of the terms ALH and LCIS is still prevalent in the literature as well as in patients' diagnostic reports today.

The incidence of both in situ and invasive forms of lobular carcinoma has increased over the last decades [6]. Between 1978 and 1988, the incidence of LCIS increased from 0.90/100,000 person-per-years to 3.19/100,000 person-per-year in the North American population [7]. Lobular neoplastic lesions (ALH and LCIS) are often multi-centric and bilateral. They occur predominantly in premenopausal women, with most cases being diagnosed in women between 40 and 50 years of age [8].

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 [9]. Epidemiologic studies have clearly shown lobular neoplasia as a marker of increased risk [10]. In recent years, however, there is increasing evidence that LCIS may also act as a non-obligate precursor in the progression to invasive carcinoma [11].

Atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) are not associated with any grossly recognizable features.

Lobular carcinoma in situ is composed of acini filled with a monomorphic population of small, round, polygonal, or cuboidal cells, with a thin rim of clear cytoplasm and a high nuclear-to-cytoplasmic rate. The nuclei are round-to-oval. The nuclei have homogeneous chromatin and nucleoli that are inconspicuous to absent, and mitoses are infrequent (Fig. 13.1).

The distinction between ALH and LCIS is quantitative. More than half of the acini of a lobular unit needs to be distended (not just filled) and distorted by the neoplastic cells for a diagnosis of LCIS; anything less than that is ALH. In objective terms, criterion to distinguish LCIS from ALH is based on extent; at least 50–75% of acini in a lobular unit must be filled and distended with no residual lumina (Fig. 13.2). Involved lobules may be compared to uninvolved lobules to estimate degree of distension.

In classical LCIS, two types of cells may be seen: (1) type A cells with small-to-slightly enlarged nuclei (1.5× size of lymphocyte), with uniform round nuclei and inconspicuous nucleoli (Fig. 13.3); and (2) type B cells with larger nuclei (2× size of lymphocyte), more abundant cytoplasm, and more prominent nucleoli (Fig. 13.4). Type A and B cells can coexist in the same lesion (Fig. 13.5). Regardless of cell nuclear size, the cytoplasm of LCIS cells is typically pale-to-lightly eosinophilic.

Most cases of LCIS have a discohesive growth pattern and the presence of intracytoplasmic vacuoles (Fig. 13.6). These vacuoles may be so subtle that special histochemical stains for mucin are required for their demonstration. At the other end of the spectrum, the vacuoles may be large enough to produce signet ring cell forms. Signet ring cells can have low, intermediate, or high-grade nuclei (Fig. 13.7).

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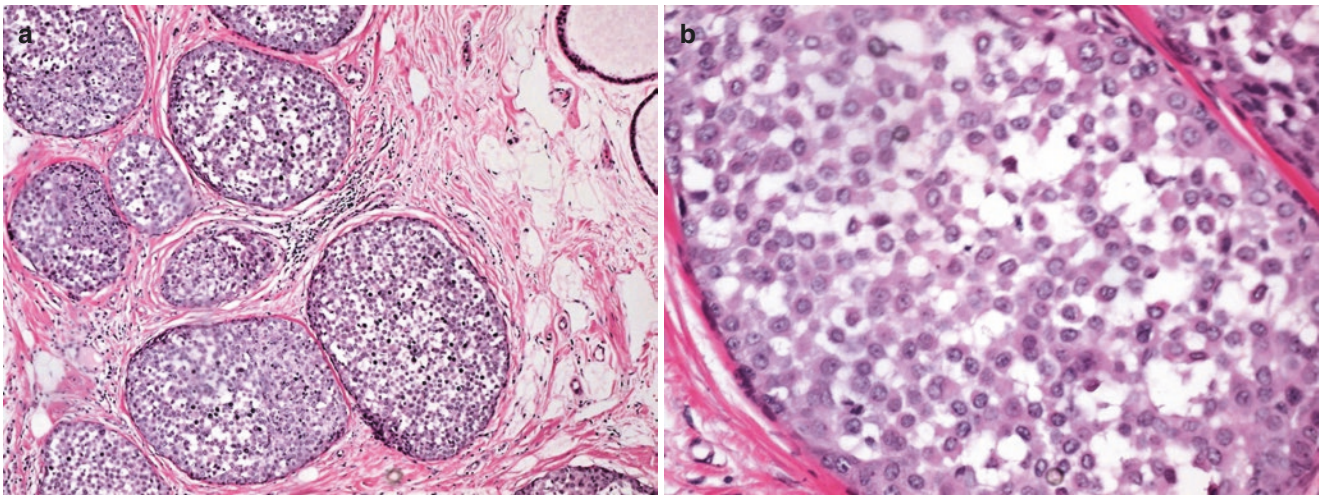

Fig. 13.1 Lobular carcinoma in situ. (**a**) A low-power view illustrating several enlarged terminal duct. (**b**) Lobular units in which the acini are filled with and distended by a population of uniform cells

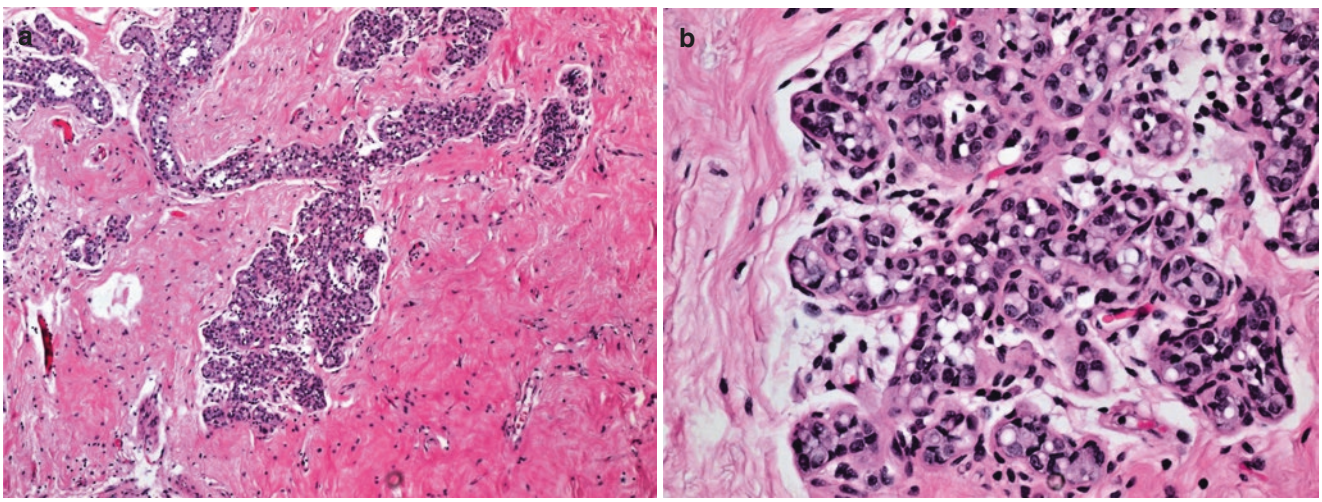

Fig. 13.2 Atypical lobular hyperplasia. (**a**) Involved terminal duct-lobular units are not completely distended by neoplastic cells. (**b**) Duct lobular unit contains a cellular proliferation that only minimally distends the involved acini

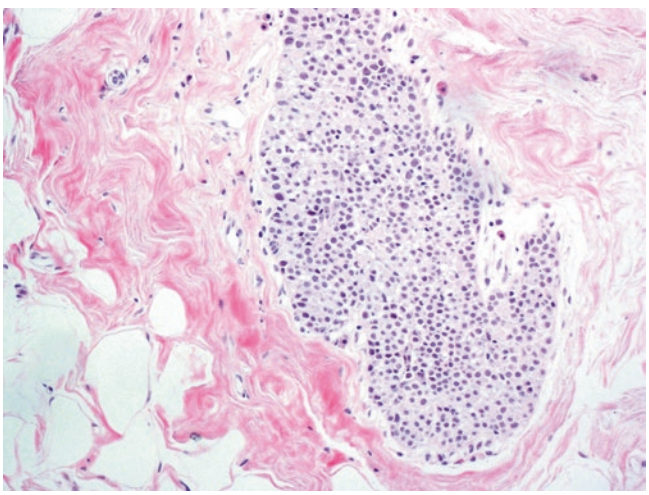

Fig. 13.3 Lobular carcinoma in situ with small cells with uniform nuclei often referred as type A

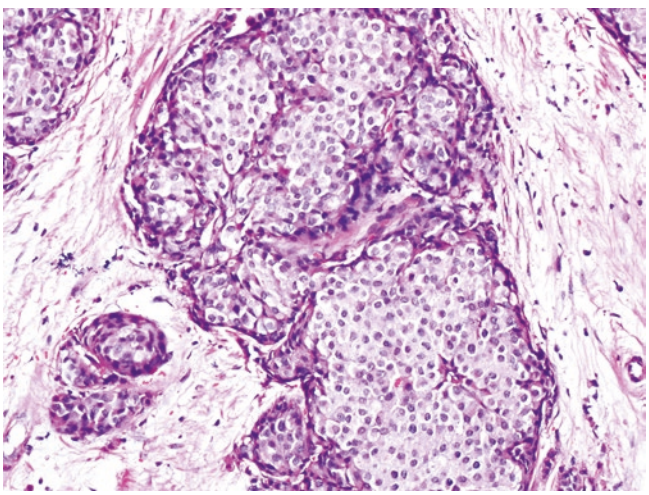

Fig. 13.4 Lobular carcinoma in situ with cells that show more abundant cytoplasm and slightly more variation in cell and nuclei size and shape, and by the presence of nucleoli. These have been referred as type B

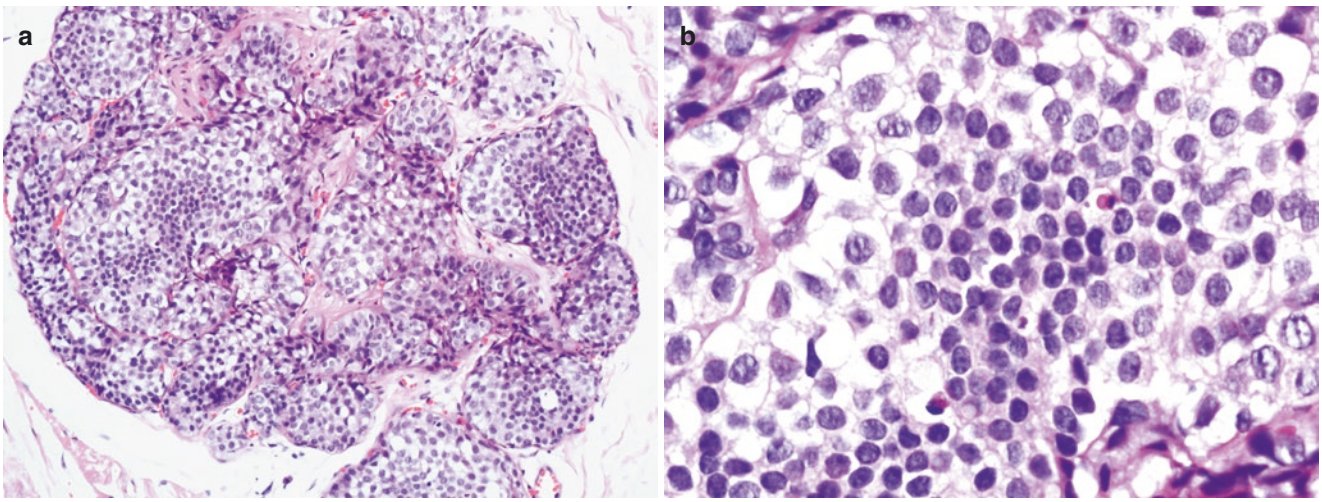

Fig. 13.5 Lobular carcinoma in situ with a mixture of two cell types. (**a**) Small cells with small uniform nuclei or smaller, central type A cells and larger, peripheral type B cells (**b**)

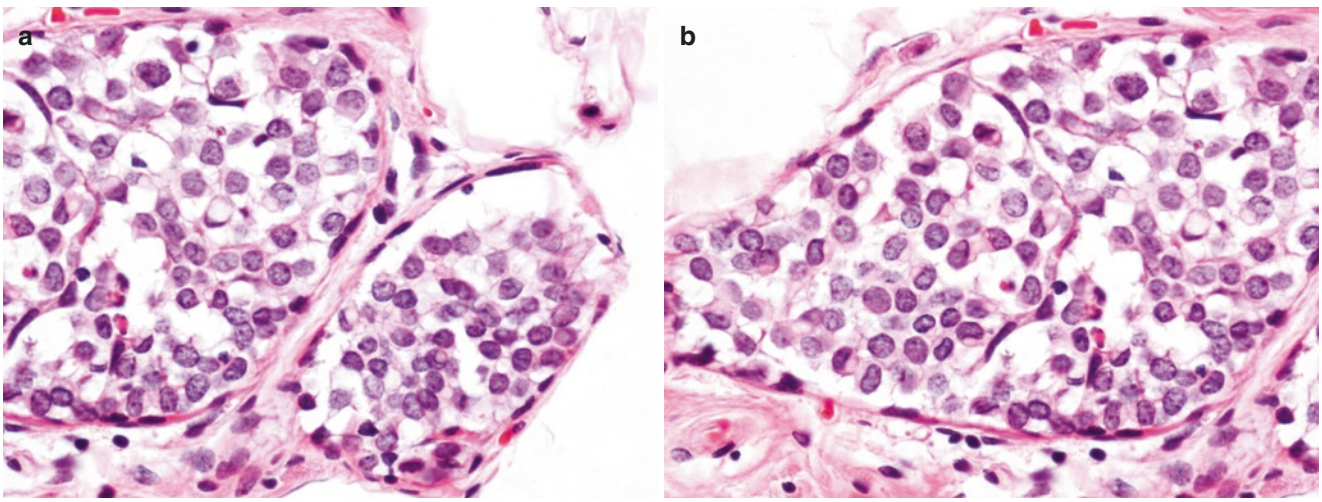

Fig. 13.6 (**a**, **b**) Most cases of LCIS are readily distinguished from low-grade DCIS with hematoxylin-eosin stain. Dyscohesive growth pattern and the presence of prominent intracytoplasmic vacuoles favor the diagnosis of LCIS

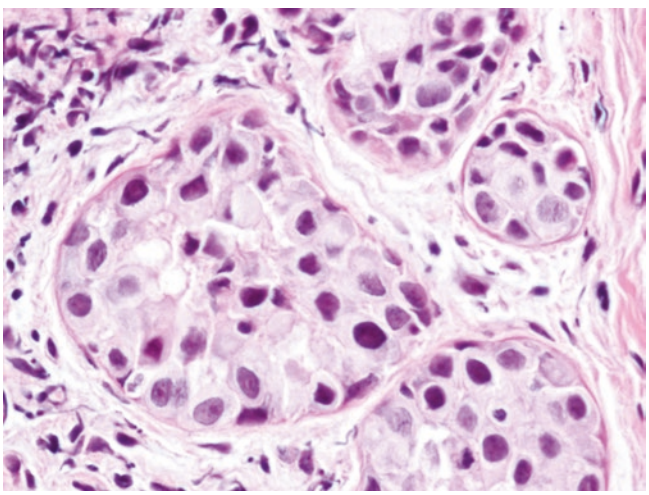

Fig. 13.7 Lobular carcinoma in situ with signet ring cells. Spaces expanded by a discohesive population of cells. Intracytoplasmic vacuoles are evident

Lobular carcinoma in situ typically involves intralobular and extralobular or terminal ductules as well as acinar units within the lobule. The irregular configuration of ductules affected by LCIS has been described as "saw-toothed" or as resembling a cloverleaf (Fig. 13.8). Pagetoid LCIS growing beneath the non-neoplastic ductal epithelium may be distributed continuously or discontinuously along the ductal system, undermining, and ultimately displacing, the normal ductal epithelium (Fig. 13.9). LCIS can also involve lactiferous ducts, but usually does not extend to epidermis. On the other hand, LCIS may colonize preexisting breast lesions such as fibroadenomas (Fig. 13.10), sclerosing adenosis, radial sclerosing lesions, collagenous spherulosis, and papillomas.

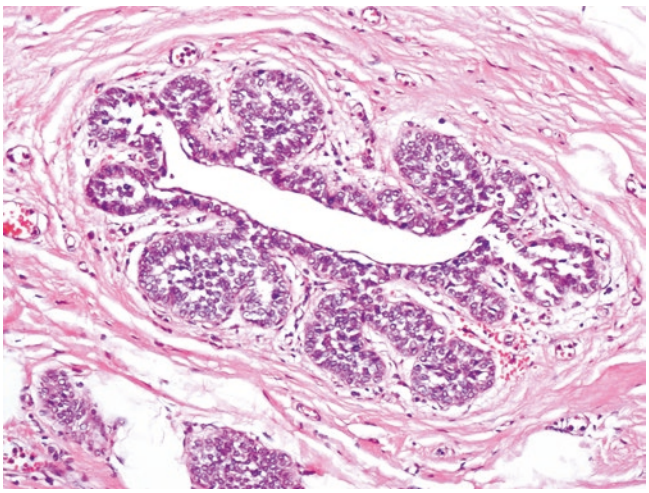

Fig. 13.8 Lobular carcinoma in situ with duct involvement in a cloverleaf pattern

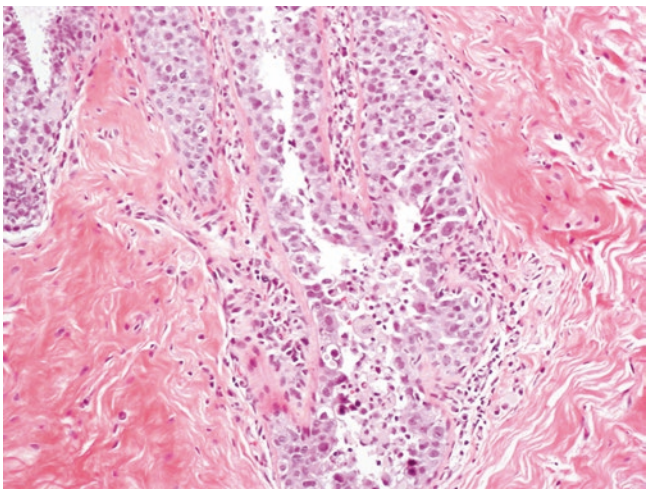

Fig. 13.10 LCIS involving an area of lobular units in a fibroadenoma

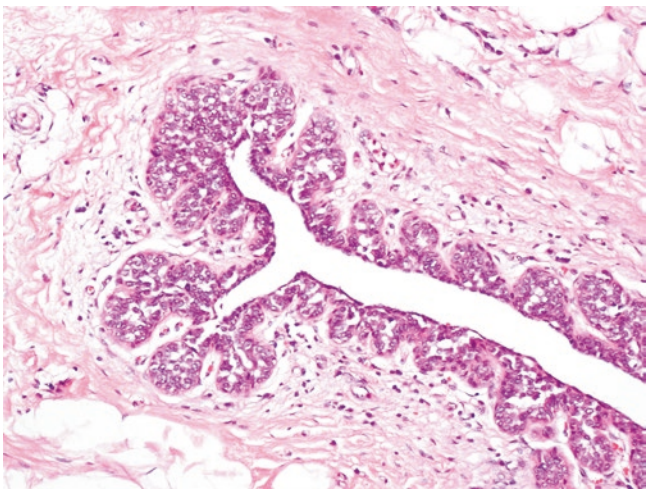

Fig. 13.9 Lobular carcinoma in situ. Pagetoid spread in ducts may be present. The neoplastic cells extend along ducts between intact overlying epithelium and underlying basement membrane

13.1 Variants of Lobular Carcinoma In Situ

Several variants of LCIS have been recognized. These include florid LCIS with comedo necrosis, Florid LCIS with signet ring cells, central necrosis and calcifications, and pleomorphic LCIS.

- **Lobular Carcinoma In Situ with Comedonecrosis**

LCIS with comedonecrosis has recently been described. Before the widespread use of E-cadherin, such cases were categorized as mixed ductal and lobular carcinoma or carcinoma in situ with indeterminate features. These lesions are comprised of cells identical to those of classic LCIS; namely, small, uniform cells and a discohesive growth pattern, but which also contain central areas of comedonecrosis (Fig. 13.11). An associated invasive carcinoma was present in 12 (67%) of 18 cases described by Fadare et al. (seven classic lobular, one pleomorphic lobular, one ductal, one mixed lobular and ductal, one tubular, and one case with ductal and lobular carcinomas as separate foci) [12]. Because LCIS with comedonecrosis is rare in its pure form, re-excision is recommended when this lesion is detected in isolation in a core biopsy or at the margin of an excision specimen.

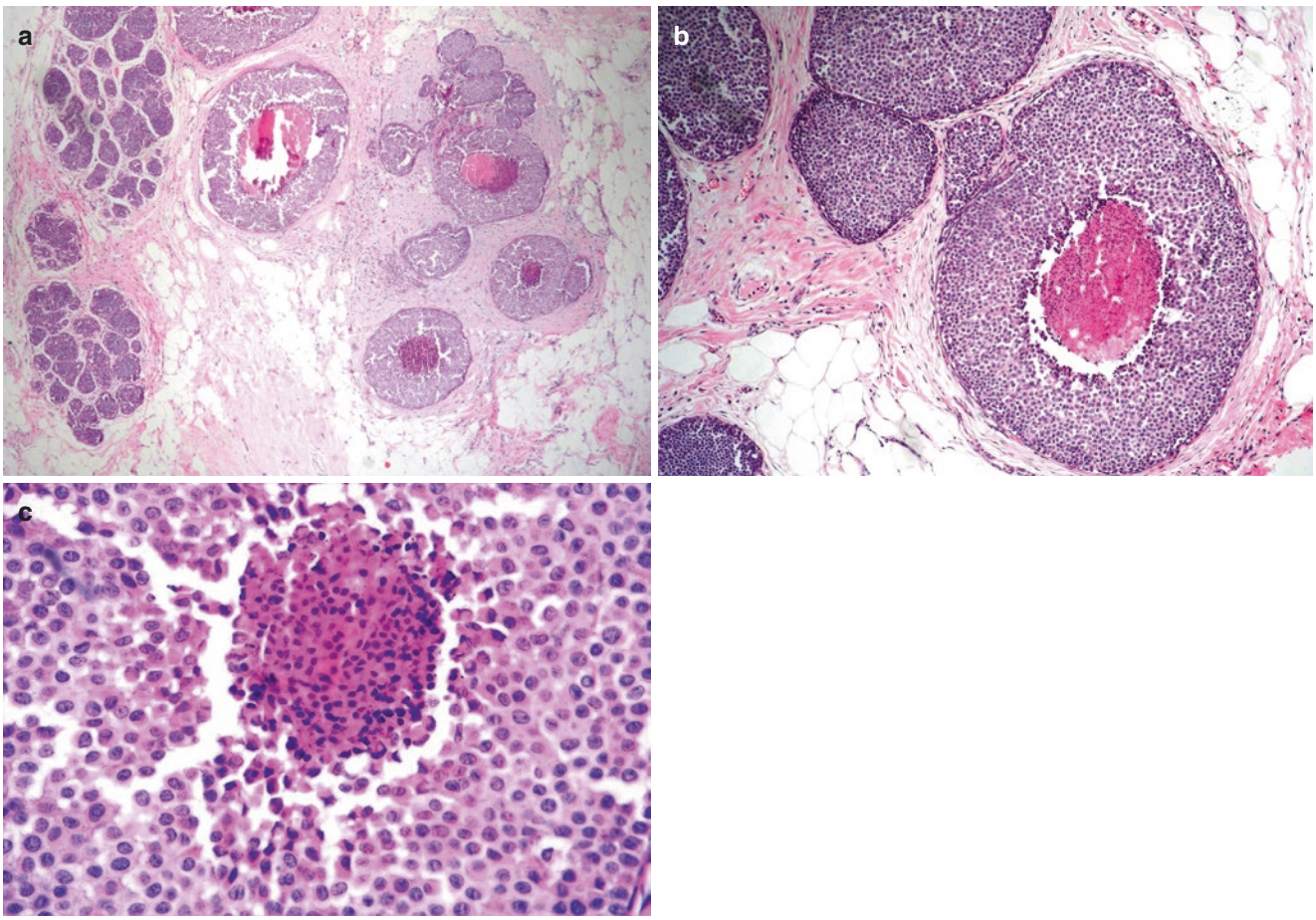

Fig. 13.11 Lobular carcinoma in situ with necrosis. (**a**) Low-power showing LCIS with necrosis in a background of classical LCIS. (**b**, **c**) Same lesion showing typical cytologic features of classical lobular carcinoma in situ

- **Lobular Carcinoma In Situ (Lobular Intraepithelial Neoplasia) with Signet Ring Cells, Central Necrosis, and Calcifications**

Alvarado-Cabrero et al. [13] described ten cases of LCIS (lobular intraepithelial neoplasia), composed of signet ring cells with central necrosis and calcifications. In this series, eight patients had associated invasive carcinoma (six lobular carcinomas and one mixed lobular and ductal) (Fig. 13.12).

- **Pleomorphic Lobular Carcinoma In Situ**

Pleomorphic lobular carcinoma in situ was first identified as a distinct entity by Eusebi et al. [14] in 1992. The cytological appearances of these cells are quite different to those of classic LCIS. Although the cells appear discohesive, as in classic LCIS, they exhibit a greater degree of nuclear pleomorphism and usually contain abundant cytoplasm. Occasionally, the cytoplasm can appear eosinophilic and finely granular (Fig. 13.13).

Regarding the immunohistochemical (IHC) profile, almost all cases of LCIS express estrogen receptors (ER) and progesterone receptors (PR) and lack for membranous E-cadherin (Fig. 13.14) and p120 expression by IHC. Classic LCIS is usually negative for HER2 protein overexpression/gene amplification, lack p53 mutations, and has a low ki-67 labeling index. In contrast, PLCIS may show HER2 protein overexpression/gene amplification, p53 expression, and moderate-to-high Ki-67 labeling index [15].

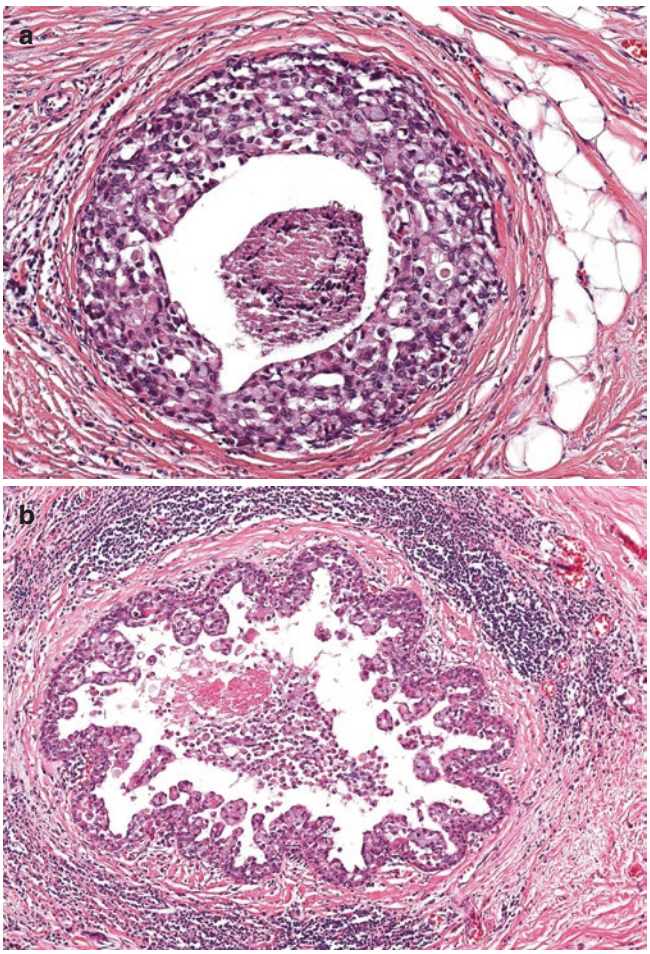

Fig. 13.12 Lobular carcinoma in situ. (**a**) Low-power microscopic examination of this case reveal distention of a duct by a population of signet ring cells. Foci of comedo type necrosis (central). (**b**) Duct involvement in a cloverleaf pattern (same case)

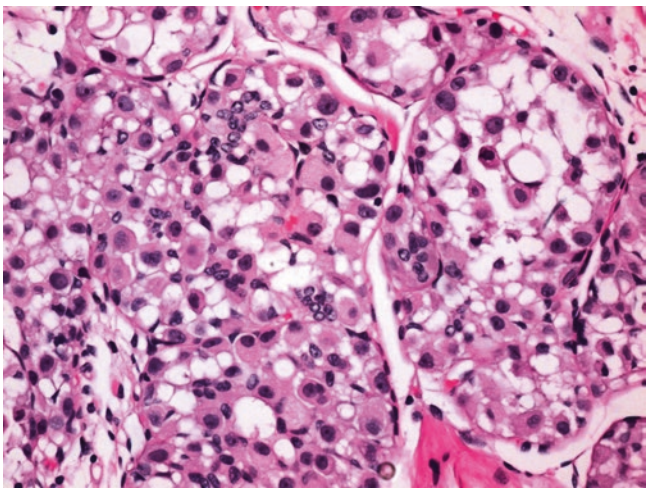

Fig. 13.13 Pleomorphic lobular carcinoma in situ (PLCIS). The neoplastic cells in PLCIS show marked pleomorphism and are larger with abundant eosinophilic cytoplasm. Signet-ring cells may be found in some cases

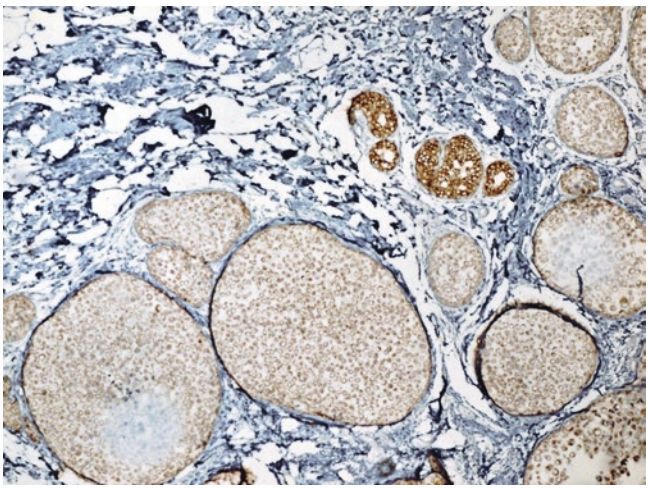

Fig. 13.14 Lobular carcinoma in situ (LCIS). The lack of membranous E-cadherin expression characterizes LCIS and is useful for distinction from ductal proliferations

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