

Chapter 2

The So Called Pre-Neoplastic Lesions and Carcinoma In Situ

2.1 Introduction

In situ breast cancer represents 15 % to 30 % of all diagnosed cancer, from all the *in situ* breast cancer 80 % of them are ductal carcinoma or DCIS [1, 2]. Similar to invasive breast cancer, DCIS is not a single disease but rather many different diseases, each with its own clinical, morphologic, and molecular characteristics [3]. Ductal carcinoma *in situ* of the breast is characterized by malignant epithelial cells confined to the ductal system of the breast without evidence of invasion through the basement membrane into the surrounding stroma [4, 5].

DCIS constitutes 30 % to 40 % of the breast cancer cases diagnosed mammographically, however, only 1 out 1300 screening mammograms are carcinoma *in situ*. The most prominent feature in the mammogram is the presence of micro calcifications or as non-palpable masses or combination of both [6–8].

2.2 The So Called Pre-neoplastic Lesions

Although the sequence from normal to ductal hyperplasia, atypical ductal hyperplasia, carcinoma *in situ* and invasive has been considered the natural progression of the disease [6], there are some evidence that the ductal hyperplasia has few similarities to ADH, DCIS, or invasive cancer. Whereas ADH was shown to have many similarities to low-grade DCIS, such as losses at 16q and 17p and gains at 1q.7 [9, 10] In contrast, low-grade DCIS appears to be genetically distinct from high-grade DCIS [9, 10].

2.2.1 Ductal Hyperplasia

Epithelial hyperplasia of ductal type, has been classified as *mild* (when made up of three or four epithelial cells in thickness), *moderate to florid* (when more pronounced), and *atypical*. Nuclei are oval, normochromatic and with slight overlap; small, single, indistinct nucleoli; scanty or no mitotic activity (Figs. 2.1, 2.2 and 2.3). The cytoplasm is acidophilic and finely granular (Figs. 2.4 and 2.5). An interesting feature is that cytoplasmic borders are not well demarcated giving a syncytial appearance. The intratubular lumina of ductal hyperplasia tend to be irregular in

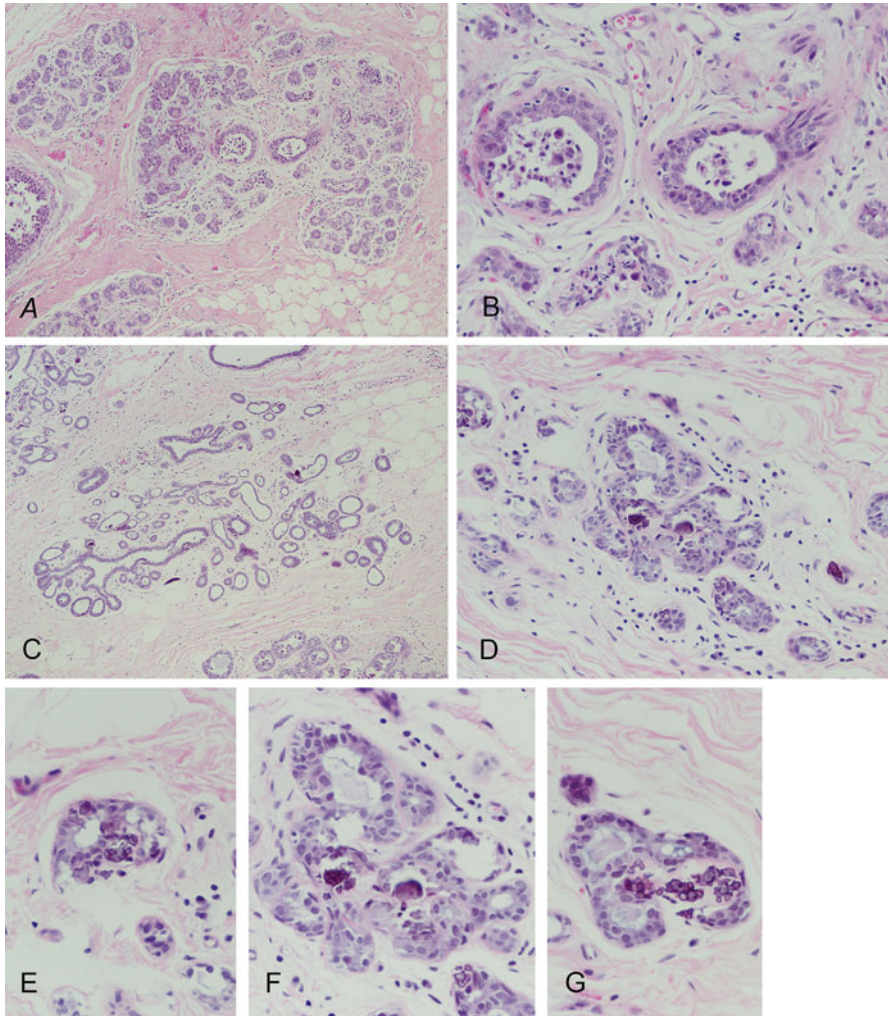


Fig. 2.1 Mild ductal hyperplasia. (a): 4×; (b): 10×; (c): 4×; Microcalcifications in the lumen are found in (d): 10×; (e, f and g): 10×

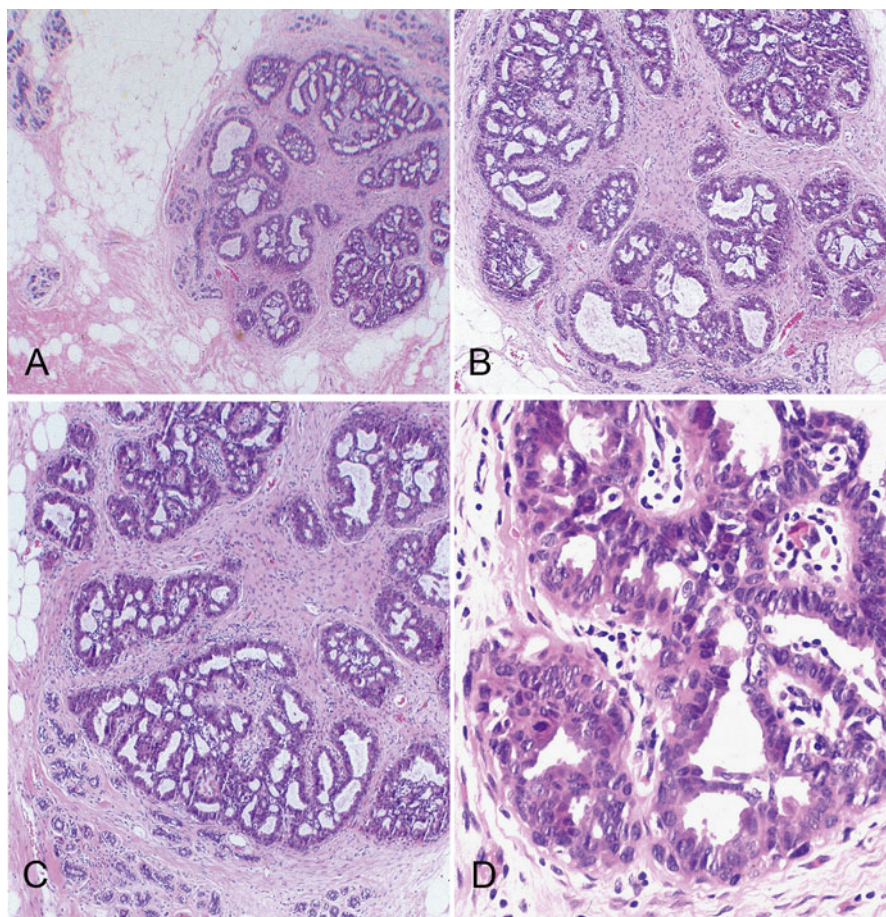


Fig. 2.2 Mid to moderate ductal hyperplasia. (a), 4 \times ; (b and c): 10 \times ; (d) 40 \times

size, and more elongated rather than rounded, and most often are located in the periphery. The cells have a “Tufts” and “mounds” projecting into the lumen [11] (Figs. 2.4, 2.5 and 2.6). This must not be confused with the cytoplasmic blebbing of the apocrine metaplasia. Presence of irregularly shaped bridges connecting opposite portions of the wall formed by cells with oval nuclei arranged parallel to the long axis of the bridge (Fig. 2.6). Their appearance is very different from that seen in the rigid trabecular bars and Roman bridges of intraductal carcinoma. The luminal cells of the ductal hyperplasia are surrounded by myoepithelial cells either forming a continuous layer or scattered in the basal surface (Figs. 2.3, 2.4, 2.5 and 2.6). There is absence of necrosis but is not uncommon the presence of calcifications either in the lumina or in the stroma (Figs. 2.1, 2.6, 2.7, and 2.8).

Ductal hyperplasia at difference of atypical ductal hyperplasia express high-molecular-weight (HMW) keratin associated with S-100 protein expression (Fig. 2.9) [12], whereas atypical ductal hyperplasia lack reactivity for HMW keratin.

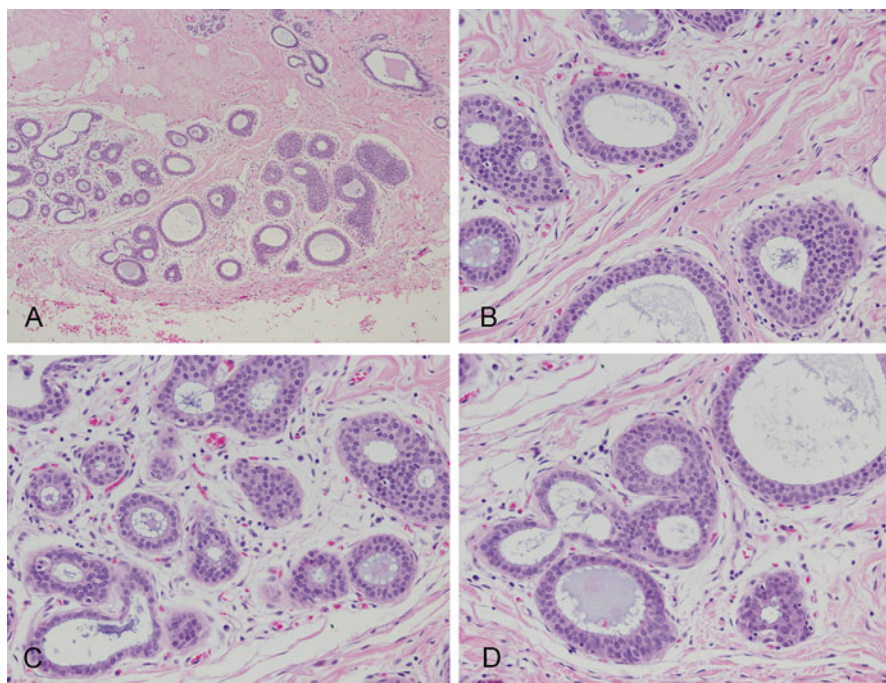


Fig. 2.3 Mild ductal hyperplasia with cystic changes. (a): 4x; (b, c and d) 10x

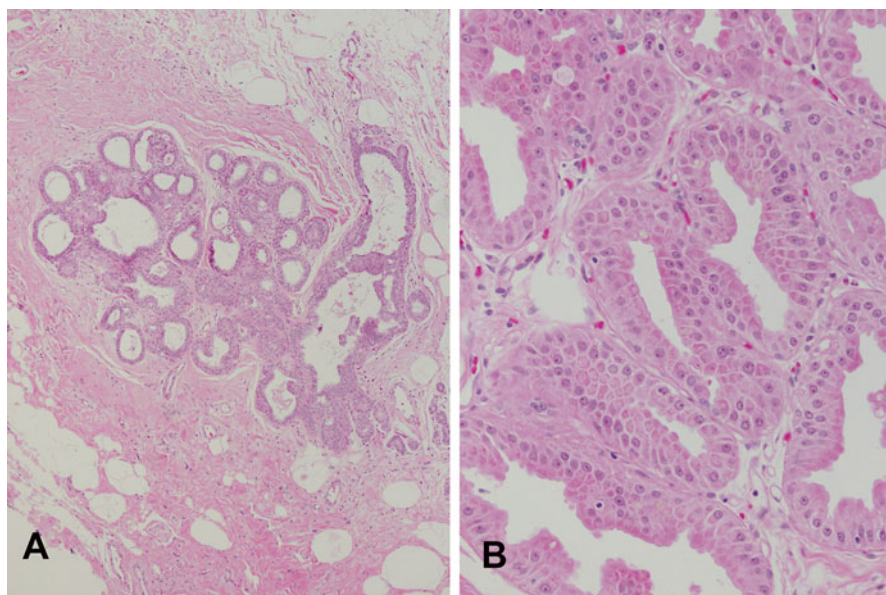


Fig. 2.4 Mild ductal hyperplasia. The cytoplasm is acidophilic and finely granular. (a): 4x and (b) 40x

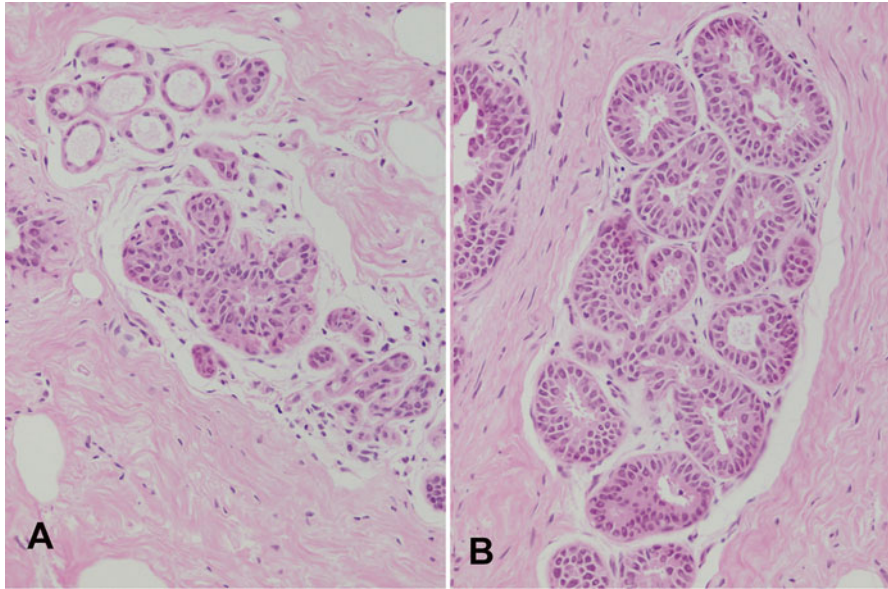


Fig. 2.5 Moderate ductal hyperplasia. (a): 4× and (b) 40×

2.2.2 Lobular Hyperplasia

The histological pattern of this lesion is characterized by abundant lobular formation and more cellular than usual (Fig. 2.10). These lesions do not fulfill the criteria for lobular CIS or even for atypical lobular hyperplasia (ALH). According to Rosai [11] the definition of ALH is rather vague itself.

2.2.3 Atypical Ductal and Lobular Hyperplasia

Page-Dupont [13–18] proposed the terms atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia (ALH) for proliferative lesions in which some but not all of the features of intraductal carcinoma or lobular CIS, respectively, are present. Using these criteria in a retrospective study, they diagnosed ADH and / or ALH in 3.6 % of the cases and concluded that these patients had a risk of invasive breast carcinoma that was four to five times that of the general population. The currently accepted definition of ADH is that of a lesion with cytologic (monomorphic cells with ovoid to rounded nuclei) and architectural (micro papillae, tufts, fronds, bridges, solid and cribriform patterns) features indistinguishable from those of low-grade DCIS, but (1) intimately admixed with usual ductal hyperplasia, and/ or (2) showing only partial involvement of the terminal ductal lobular

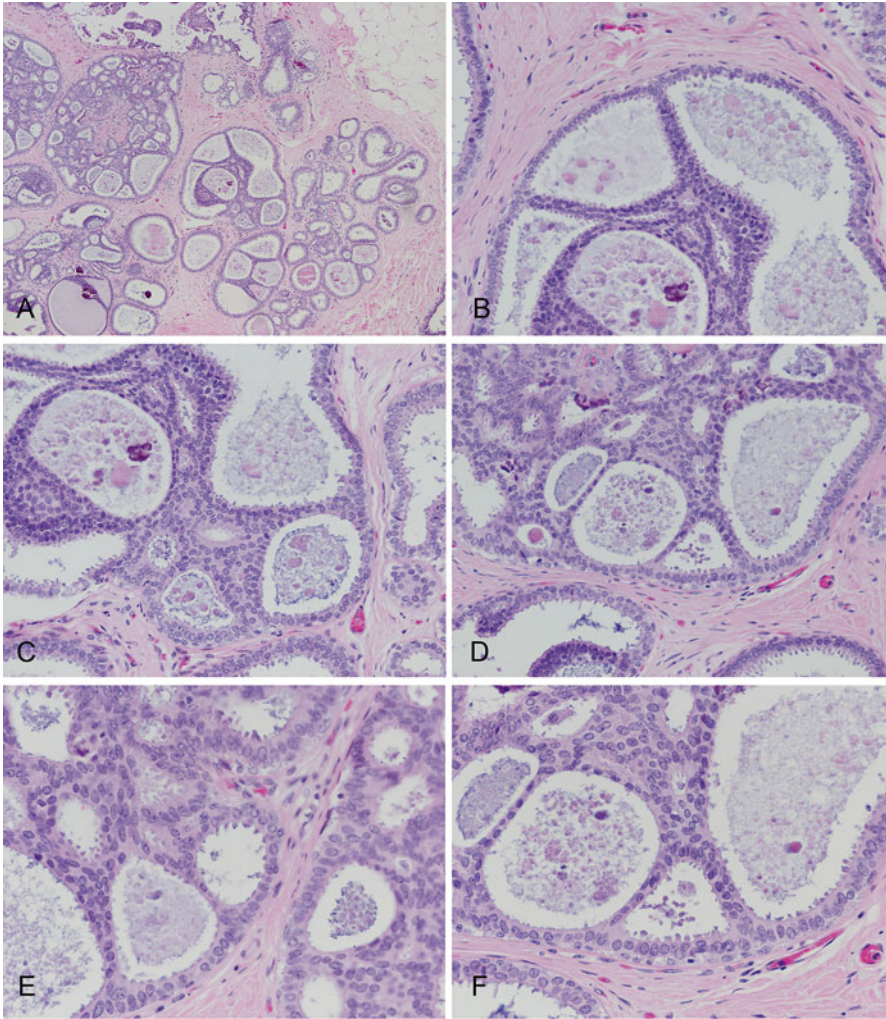


Fig. 2.6 Moderate ductal hyperplasia. (a): 4×, (b, c, d, e and f), 40×. The intratubular lumina of ductal hyperplasia tend to be irregular in size. The cells have a “Tufts” and “mounds” projecting into the lumen. Presence of irregularly shaped bridges connecting opposite portions of the wall formed by cells with oval nuclei arranged parallel to the long axis of the bridge

unit (TDLU) (Figs. 2.11 and 2.12). Quantitative requirements have been proposed (to measure <2 mm in aggregate or to be present in two spaces), but these have not been agreed upon [19–21]. The diagnosis of this type of lesions carries a significant subjectivity in the microscopic interpretation [22–24]. The intraductal proliferative lesions of the breast have been reformulated in the WHO book on Tumors of the Breast and Female Genital Organs and they are part of fibrocystic

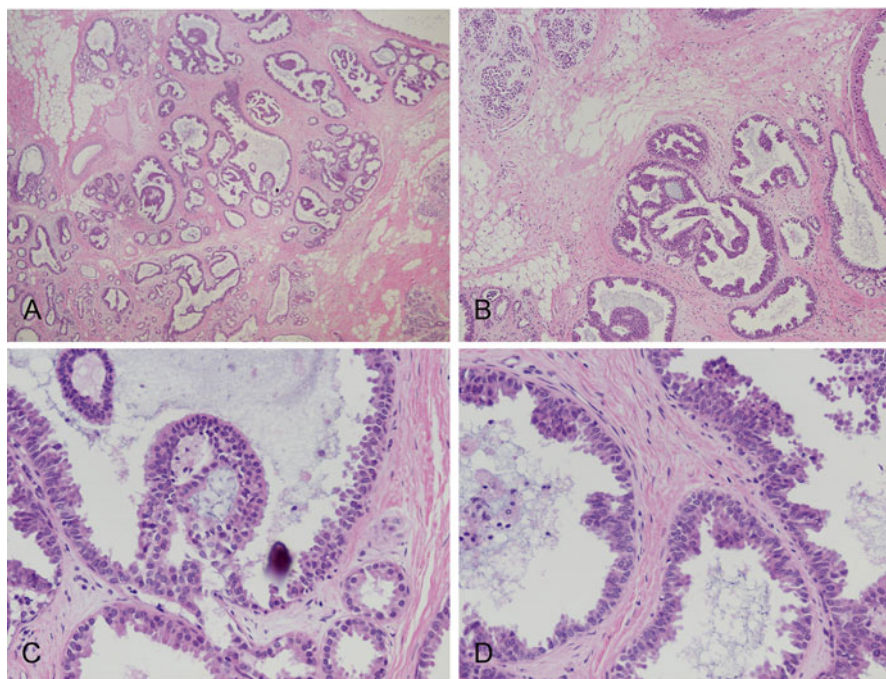


Fig. 2.7 Moderate ductal hyperplasia. (a): 4 \times ; (b): 10 \times ; (c): and (d): 40 \times . There is absence of necrosis but is not uncommon the presence of calcifications in the lumina

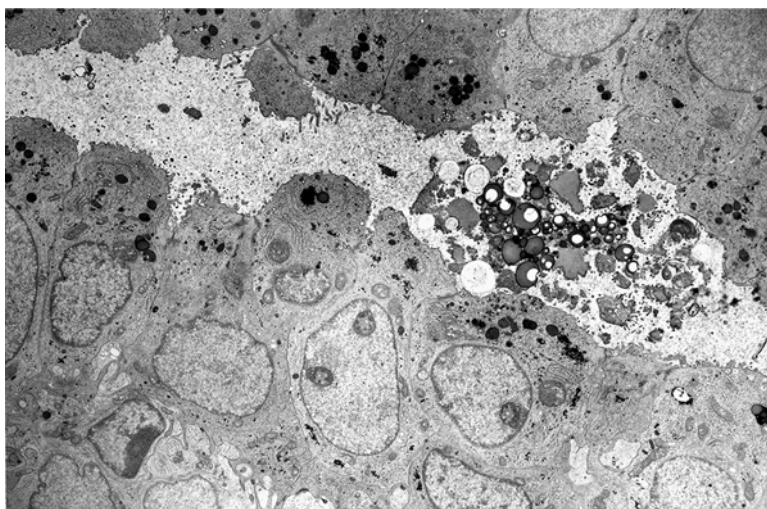


Fig. 2.8 Electron macrograph showing the multilayer epithelium and the presence of micro calcifications in the lumen. Stained with lead citrate and uranyl acetate; 5000 \times

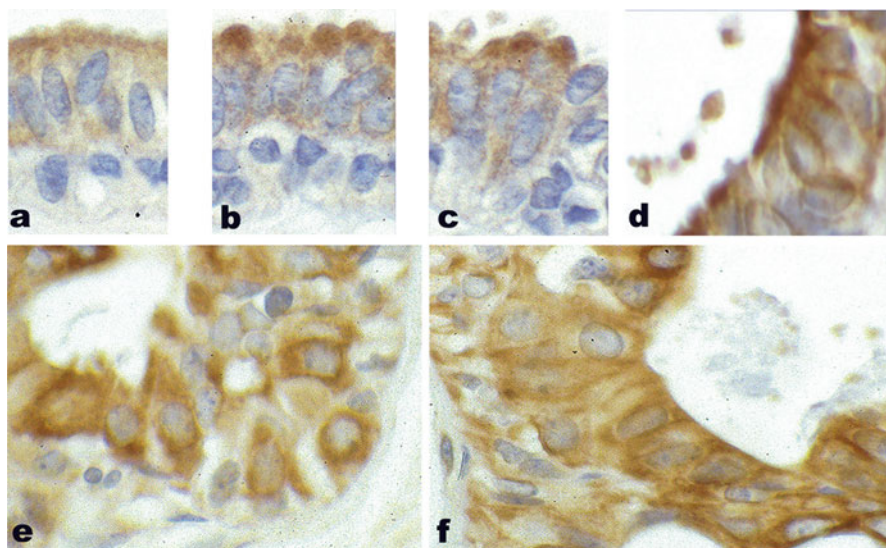


Fig. 2.9 Ductal hyperplasia showing intense reaction against S100 protein. (a, b, c, d, e and f): 40×

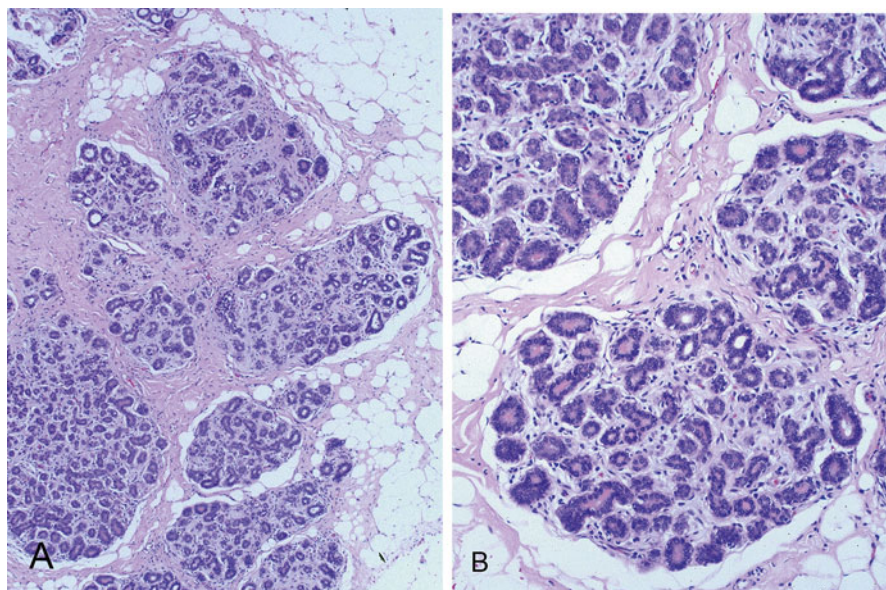


Fig. 2.10 Lobular hyperplasia is characterized by abundant lobular formation and more cellular than usual. (a): 4×, (b): 10×

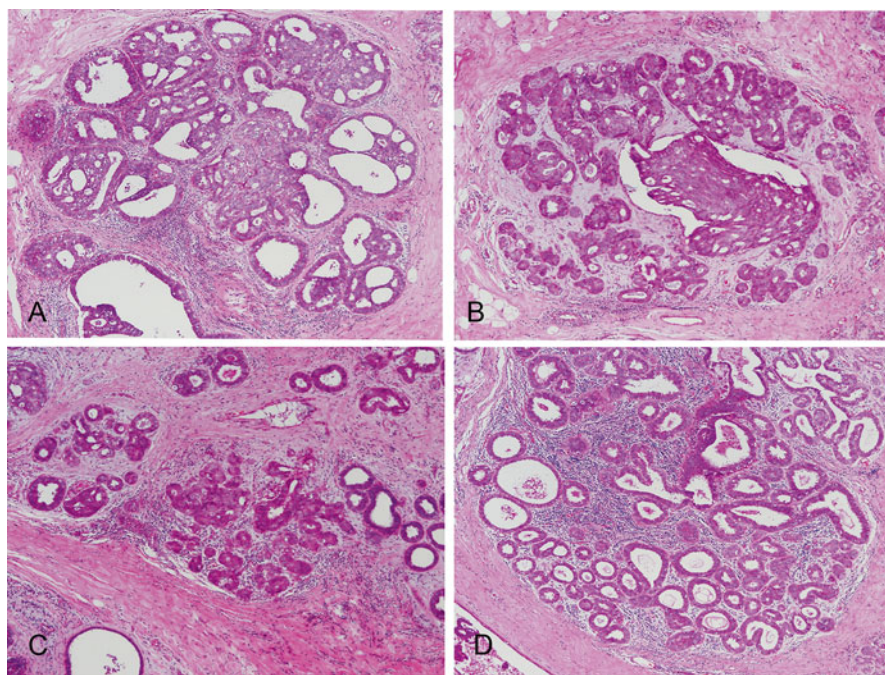


Fig. 2.11 Atypical ductal hyperplasia. It is characterized by architectural (micropapillae, tufts, fronds, bridges, solid and cribriform patterns) features indistinguishable from those of low-grade DCIS, but intimately admixed with usual ductal hyperplasia, and showing only partial involvement of the TDLU. (a, b, c and d): 4×

disease [25–28]. An important agreement is that the presence and type of proliferative epithelial disease determines the risk for subsequent carcinoma and that this risk seems to range from one to five times that of the control population [16, 22, 29–33].

2.3 The Histopathology of DCIS

The architectural subtypes of DCIS were classically divided into non-comedo (Fig. 2.13) and comedo subtypes (2.14); non-comedo subtypes were further subdivided into cribriform, micro papillary, solid and papillary, while the comedo subtype was defined by high-grade cells, prominent central necrosis, and associated pleomorphic micro calcifications [15, 34].

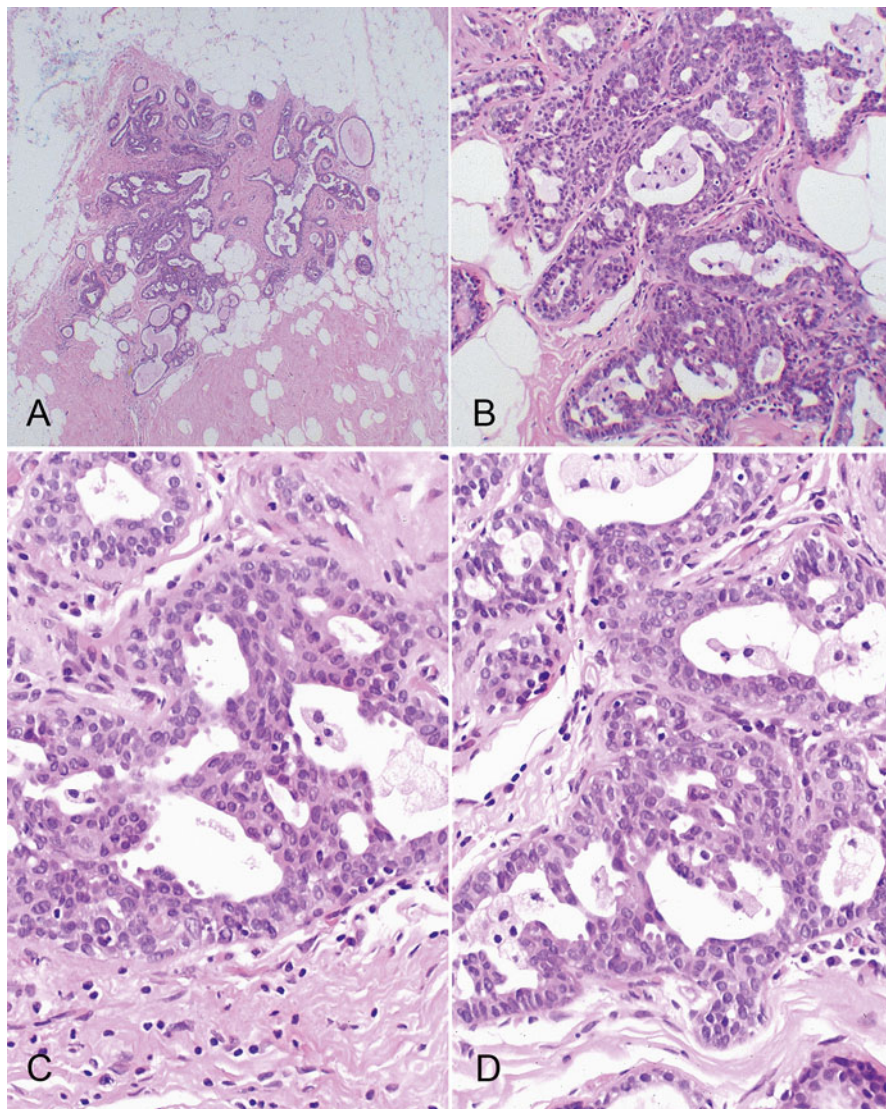


Fig. 2.12 Atypical ductal hyperplasia is characterized by atypical cytologic (monomorphic cells with ovoid to rounded nuclei) and architectural (micropapillae, tufts, fronds, bridges, solid and cribriform patterns) features indistinguishable from those of low-grade DCIS and showing only partial involvement of the TDLU. (a): 4x; (b) 10x; (c and d): 40x

2.3.1 Comedocarcinoma

Although comedocarcinoma are carcinoma in situ they may reach a relatively large size and become palpable [35]. They also can be multicentric and in 10% of the cases could be bilateral [36, 37]. The term comedo is derived from the extrusion of necrotic

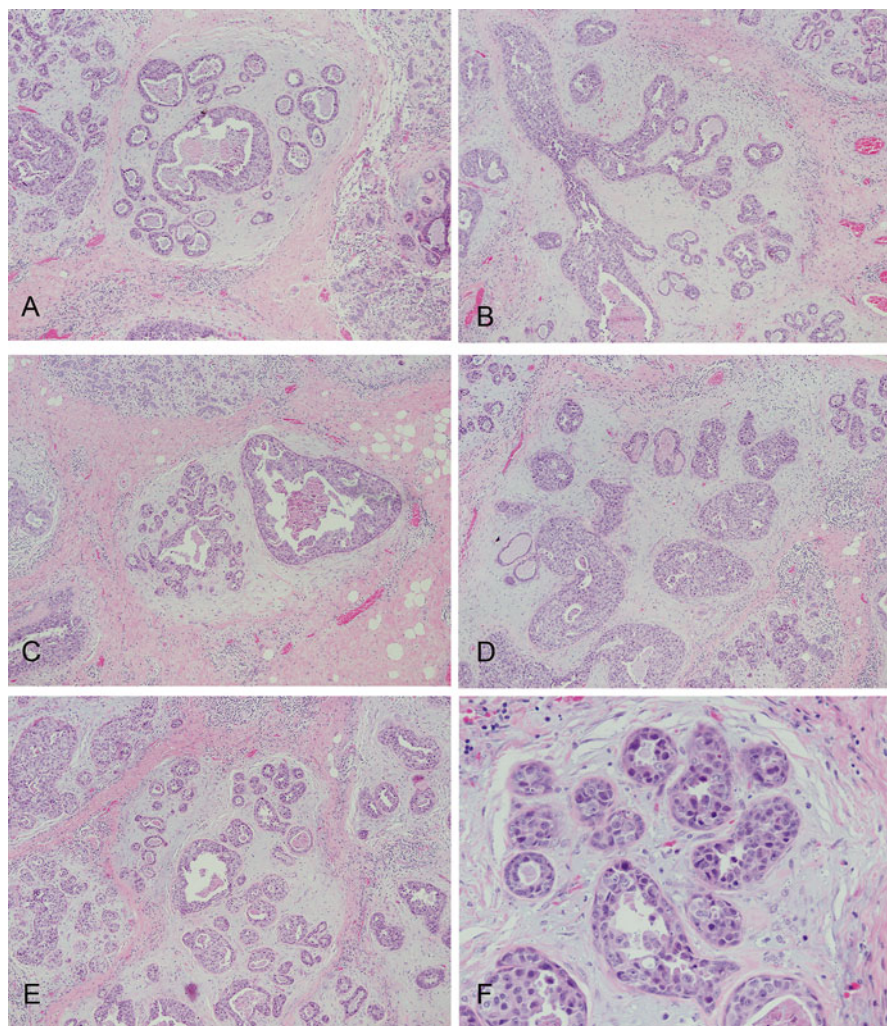


Fig. 2.13 DCIS noncomedo type. (a, b, c, d and e): 4×, (f): 10×

material or comedones upon compression of the lesion. Under the microscope the ducts show a solid growth of large pleomorphic tumor cells accompanied by generally abundant mitotic activity and lacking connective tissue support (Figs. 2.14 and 2.15). Most of these lesions are negative for hormone receptors and are expressing c-erbB-2 growth factors, P cadherin and mutation in P53 is a frequent finding [38–54]. In contrast, non-comedo subtypes are composed of cells with low-grade cytology, are very frequently positive for ER, negative for HER2/neu amplification, negative for p53 mutations, are not aneuploid, and have low proliferation rates [46, 49–54]. In the comedo carcinoma necrosis is always present and constitutes an important diagnostic sign, whether in the form of a large central focus or of individual tumor cells (Figs. 2.15 and 2.16).

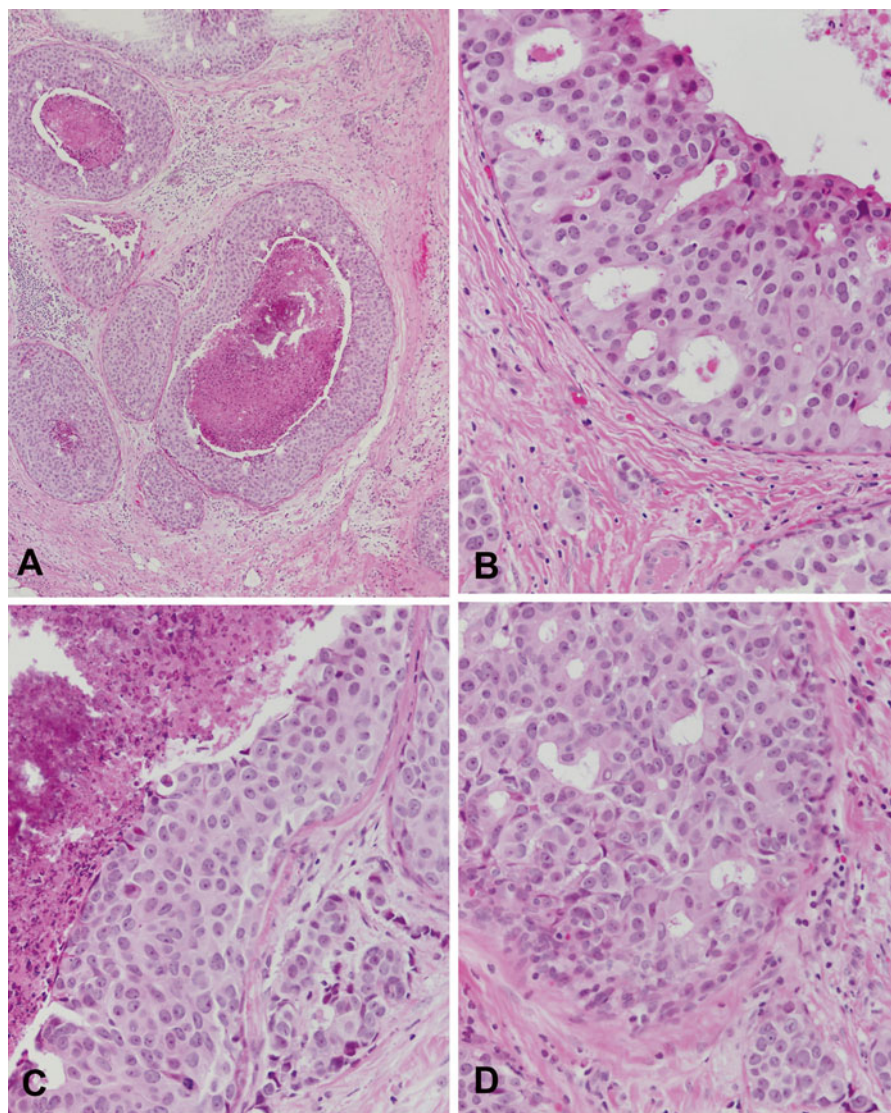


Fig. 2.14 DCIS comedo subtype. (a): 10x; (b, c and d): 40x

Calcification is often found in the center of the necrotic areas. The stroma around the involved ducts shows a characteristic concentric fibrosis accompanied by a mild to-moderate mononuclear inflammatory reaction.

In the European classification the pathologic report of comedocarcinoma is taking into account the degree of atypia of the nuclei that has a good correlation with clinical outcomes [55, 56]. In this system, the nuclear grade of the DCIS lesions is defined as low grade (grade 1), intermediate grade (grade 2), and high grade (grade 3) (Fig. 2.16),

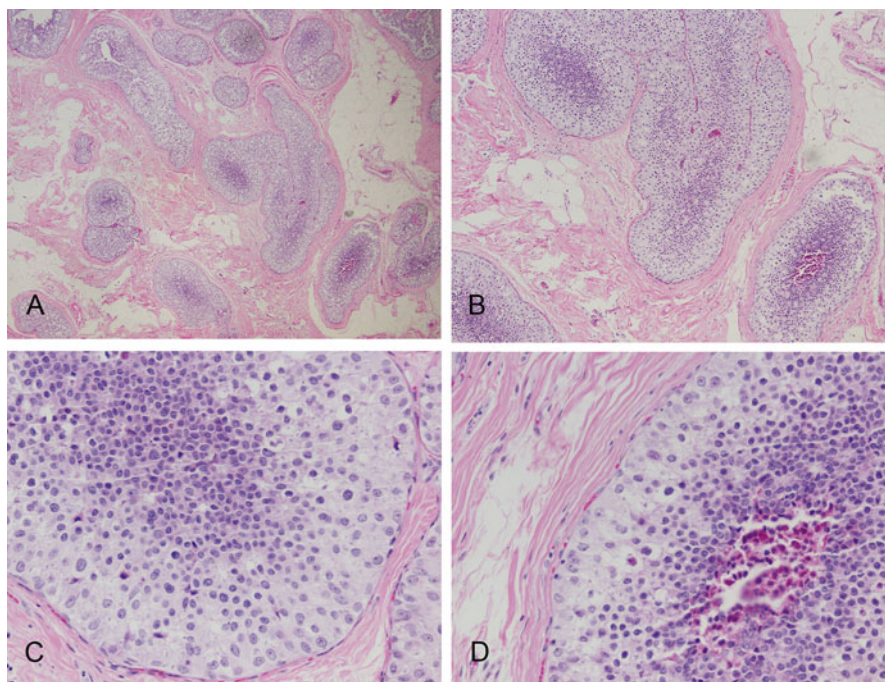


Fig. 2.15 DCIS comedo subtype. The ducts show a solid growth of large pleomorphic tumor cells accompanied by generally abundant mitotic activity and lacking connective tissue support. In the comedo carcinoma necrosis is always present and constitutes an important diagnostic sign, whether in the form of a large central focus or of individual tumor cells. (a): 4×; (b): 10×; (c and d): 40×

and this information is now one of the necessary components of a breast pathology report for DCIS, as emphasized in the 2009 College of American Pathologists-American Society for Clinical Oncology protocol for reporting of DCIS lesions [3].

2.3.2 *Papillary Carcinoma in Situ*

Papillary carcinomas occur in an older age group and are larger than papillomas. Microscopically, features favoring carcinoma are uniformity in size and shape of the epithelial cells, presence of one cell type only, nuclear hyperchromasia and high nucleocytoplasmic ratio, high mitotic activity, lack of apocrine metaplasia, cribriform and trabecular patterns, scanty or absent stroma, and lack of benign proliferative disease in the adjacent breast are the main features of this lesion (Figs. 2.17, 2.18 and 2.19).

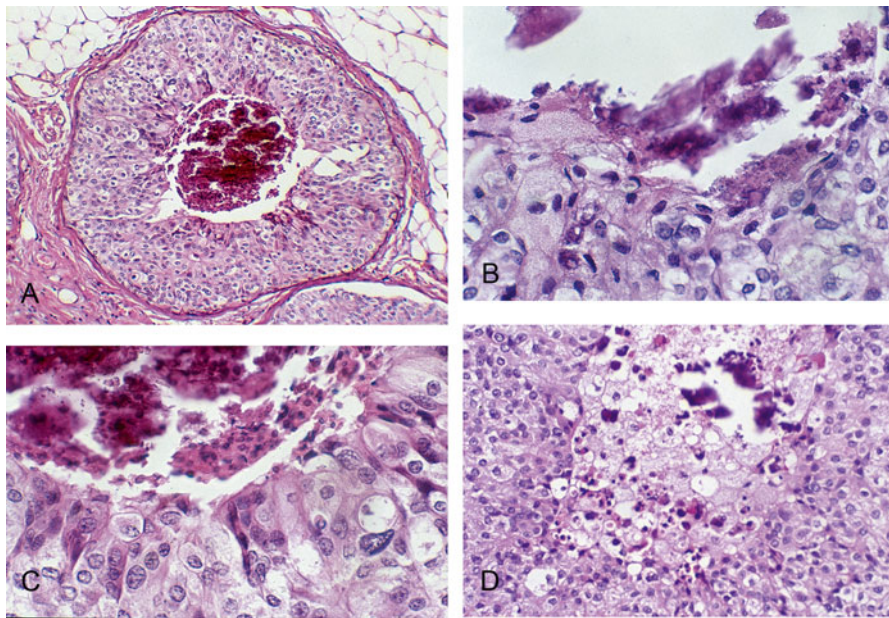


Fig. 2.16 DCIS comedo subtype high grade (grade 3). (a): 10×; (b, c and d): 40×

2.3.3 *Solid Form of DCIS*

In this type of carcinoma in situ, the glandular lumen is filled by the proliferation of medium-sized cells, which are larger than those found in lobular carcinoma in situ but smaller and more uniform than those of comedocarcinoma [57] (Fig. 2.20).

2.3.4 *Cribriform Carcinoma In Situ*

In this variety, round regular spaces are formed within the glands; the more regular these spaces are in terms of distribution, size, and shape, the more likely the lesion is to be malignant (Figs. 2.21 and 2.22). These spaces are often associated with formations of Roman bridges that are curvilinear trabecular bars connecting two portions of the epithelial lining (Figs. 2.23 and 2.24).

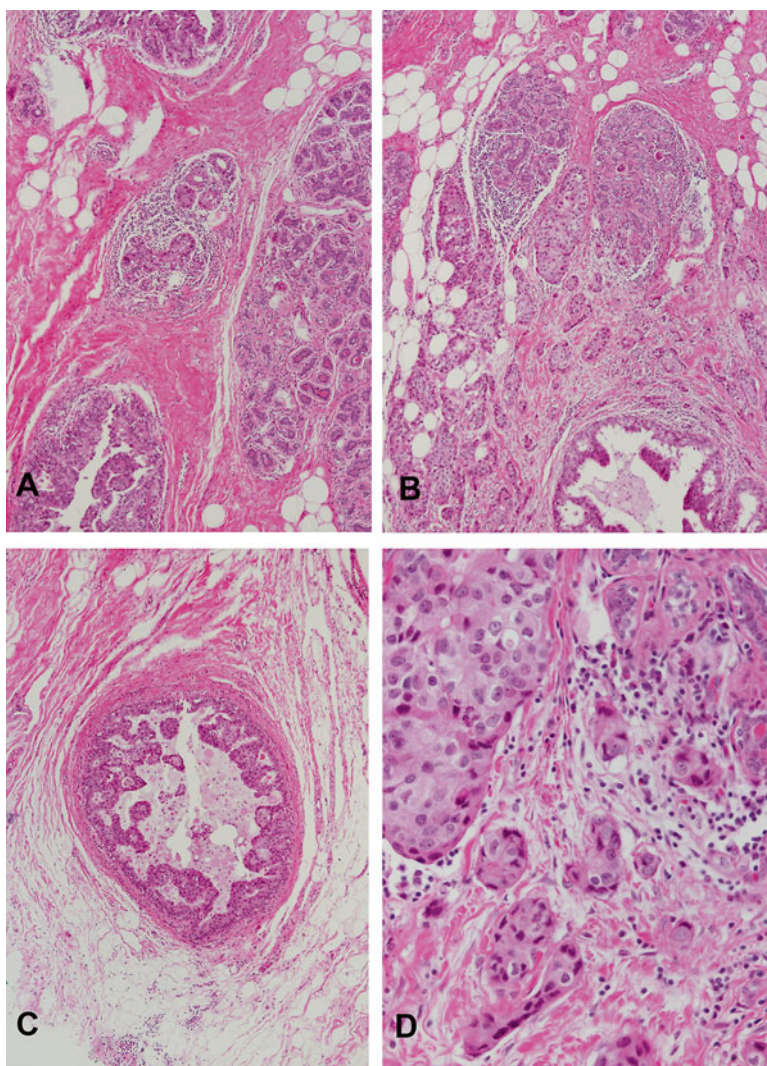


Fig. 2.17 Papillary carcinoma in situ with uniformity in size and shape of the epithelial cells, presence of one cell type only, nuclear hyperchromasia and high nucleocytoplasmic ratio, high mitotic activity, lack of apocrine metaplasia, cribriform and trabecular patterns, scanty or absent stroma. (**a** and **b**): 4 \times ; (**c**): 10 \times . (**d**) shows an area of invasive cells in and adjacent area of a solid DCIS in the same woman that shows the areas (**a**), (**b**), and (**c**)

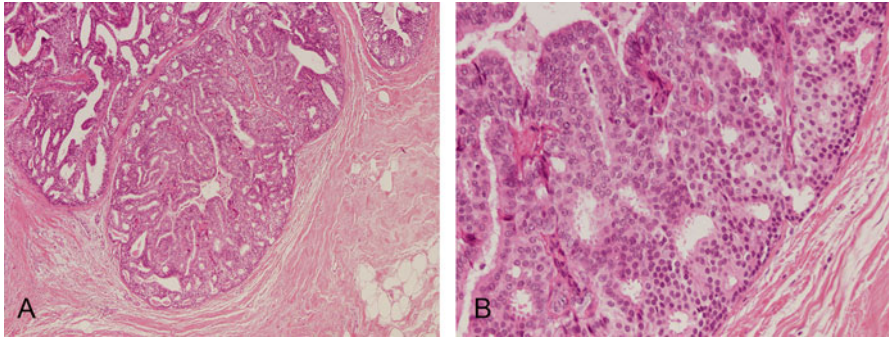


Fig. 2.18 Papillary carcinoma in situ. (a): 4× and (b): 10×

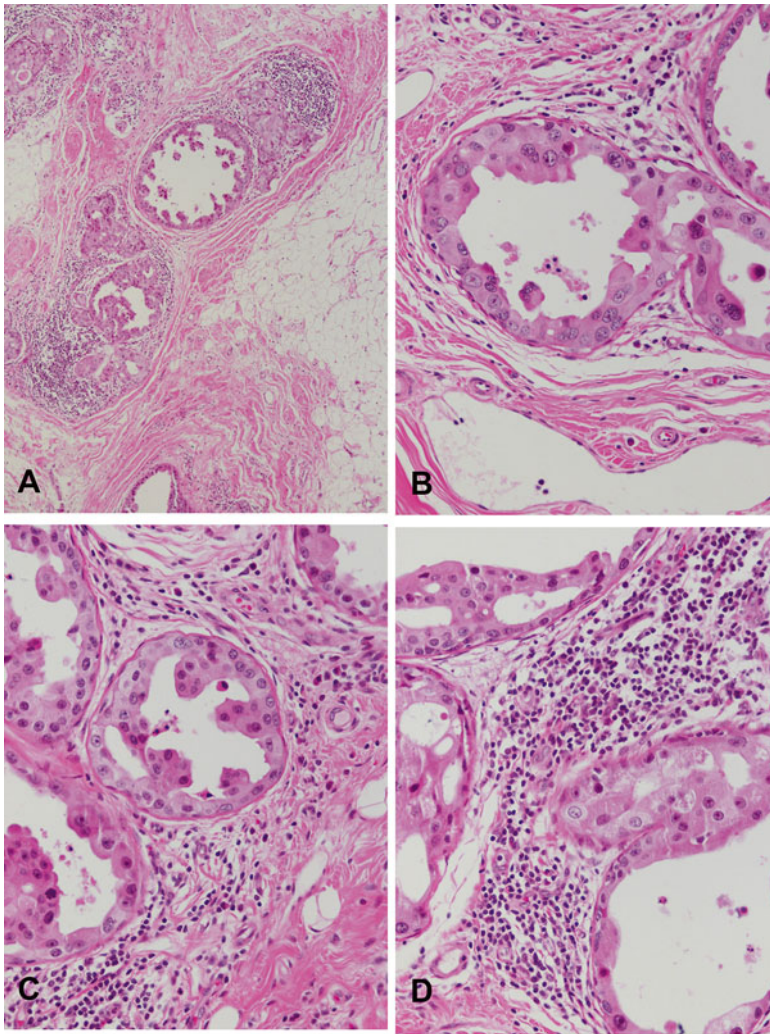


Fig. 2.19 Papillary carcinoma in situ. (a): 4×; (b, c and d): 40×. Observe the lymphocytic infiltration in (c) and in (d). In the figure (d) a tongue of invasive cells are seen

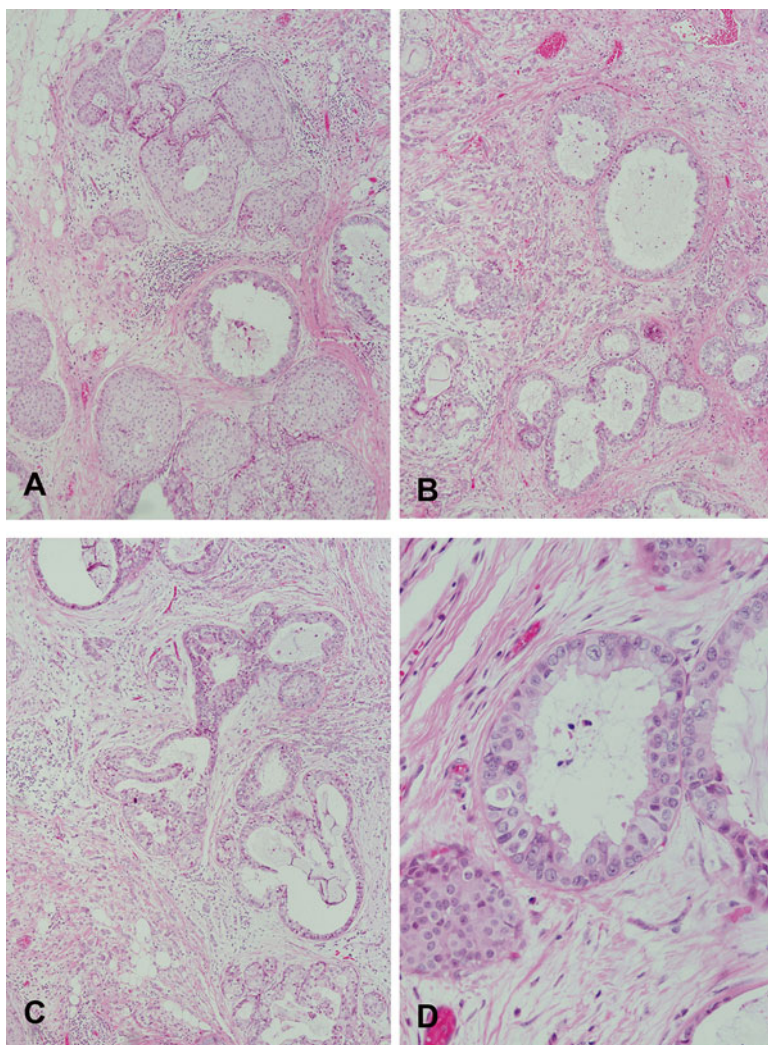


Fig. 2.20 Solid form of DCIS in which the glandular lumen is filled by the proliferation of medium-sized cells, which are larger than those found in lobular carcinoma in situ but smaller and more uniform than those of comedocarcinoma. (a, b and c): 10 \times ; (d): 40 \times

2.3.5 *Micropapillary Carcinoma In Situ*

This variety could be associated with the cribriform type (Fig. 2.25). Histologically shows elongated epithelial projections projecting into the glandular lumen; these lack connective tissue support, may have a space at the base, and often show a bulbous expansion at the tip. The micro papillary carcinoma may involve multiple quadrants of the breast.

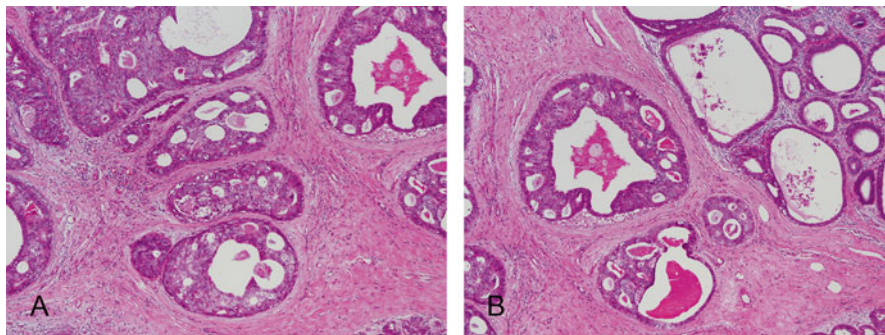


Fig. 2.21 Cribriform carcinoma in situ. (a and b): 4×

2.3.6 Other Forms of DCIS

The *clinging carcinoma* is a variety of DCIS showing one or two layers of malignant cells lining a glandular formation with a large empty lumen [57]. The *cystic hypersecretory* form is a variation of DCIS characterized by cystic formations induced by the abundant secretory material present [58]. Other morphologic variations of DCIS include cases with *signet ring cells* [59], with *apocrine differentiation* [60–62] and those with evidence of *endocrine differentiation* [63].

2.4 Lobular Carcinoma In Situ (LCIS)

The major characteristic of lobular CIS is its multicentricity in 70 % of cases [64] and bilateral in approximately 30 % to 40 % [65]. Microscopically, the lobules are distended and completely filled by relatively uniform, round, small- to medium-sized cells with round and normochromatic nuclei (Figs. 2.26, 2.27, 2.28). The *pleomorphic LCIS* has tumor cells of medium to large size, with moderate to marked pleomorphism, occasional prominent nucleoli, and moderate to abundant cytoplasm. According to Rosai [11] the diagnosis of LCIS should be made only in those cases in which the cellular proliferation has resulted in the formation of solid nests that have expanded the lobules, whereas the designation of atypical lobular hyperplasia is to be given to those lesions accompanied by normal-sized lobules in which central lumina are still identifiable. Staining for mucin show positivity in scattered tumor cells in about three fourths of cases [66, 67]. One immuno-cytochemical features of LCIS are the lack of reactivity for E-cadherin and the positivity for HMW keratin by contrast, DCIS is consistently positive for E-cadherin and shows significantly reduced or absent HMW keratin [68].

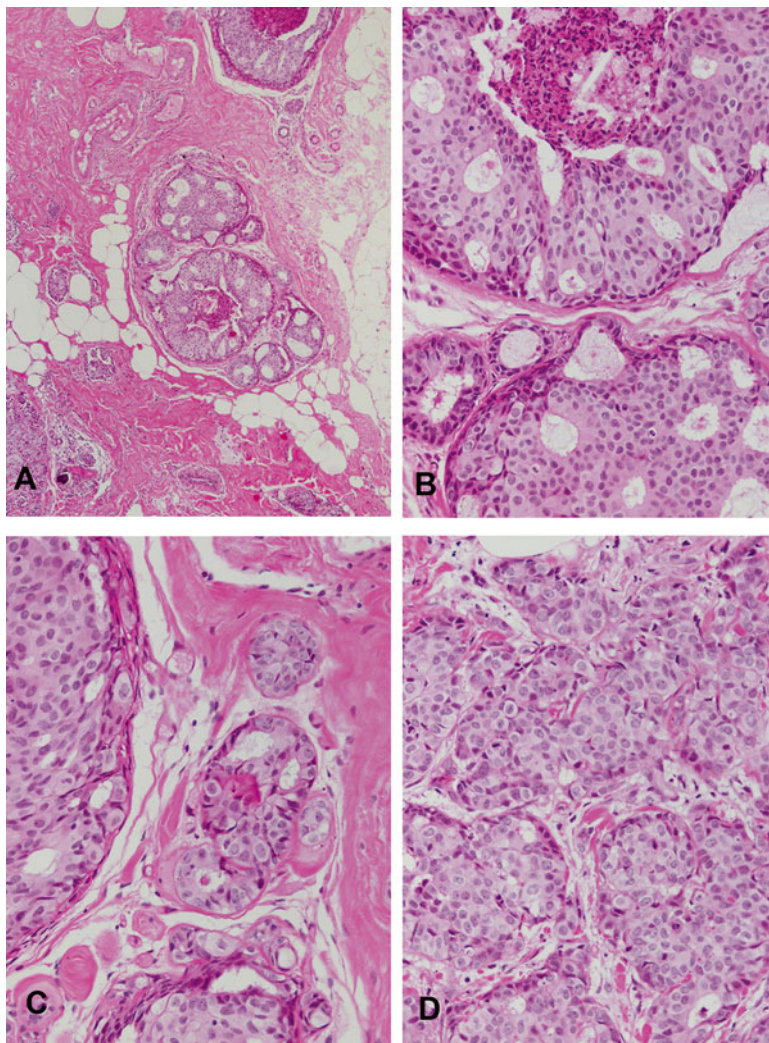


Fig. 2.22 Cribriform carcinoma in situ. Round regular spaces are formed within the glands; the more regular these spaces are in terms of distribution, size, and shape. (a): 10 \times ; (b and c): 40 \times . Area of invasion is observed in a cribriform carcinoma subtype 40 \times

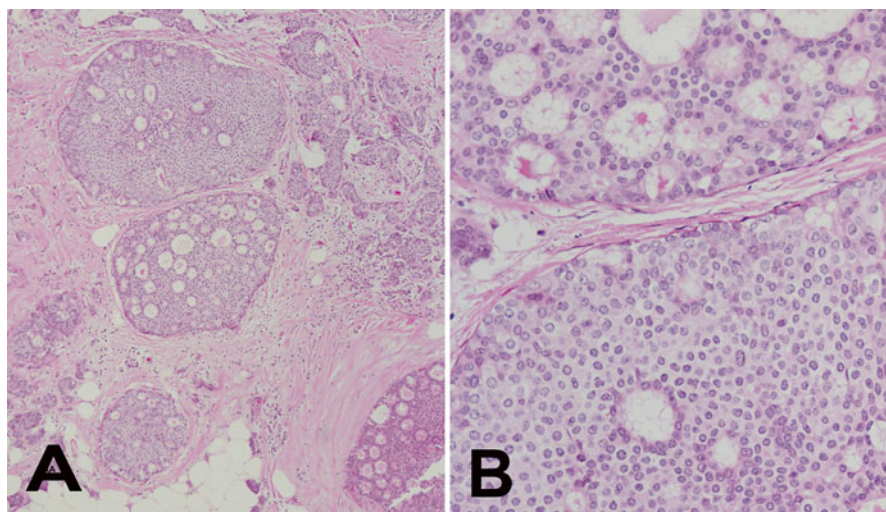


Fig. 2.23 Cribriform carcinoma in situ. Round regular spaces are formed within the glands and these spaces are often associated with formations of Roman bridges that are curvilinear trabecular bars connecting two portions of the epithelial lining. (a): 10× and (b): 40×

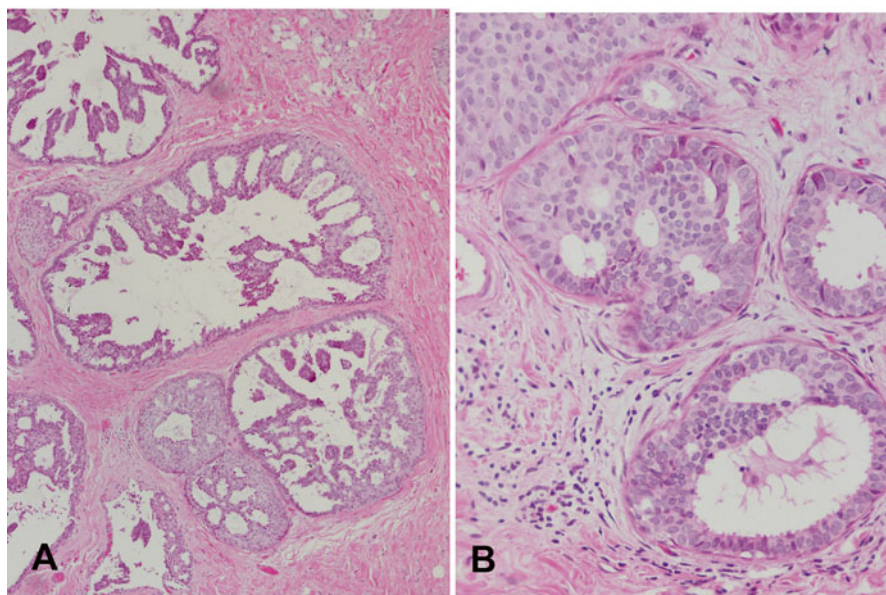


Fig. 2.24 Cribriform carcinoma in situ. (a): 10×; (b): 40×

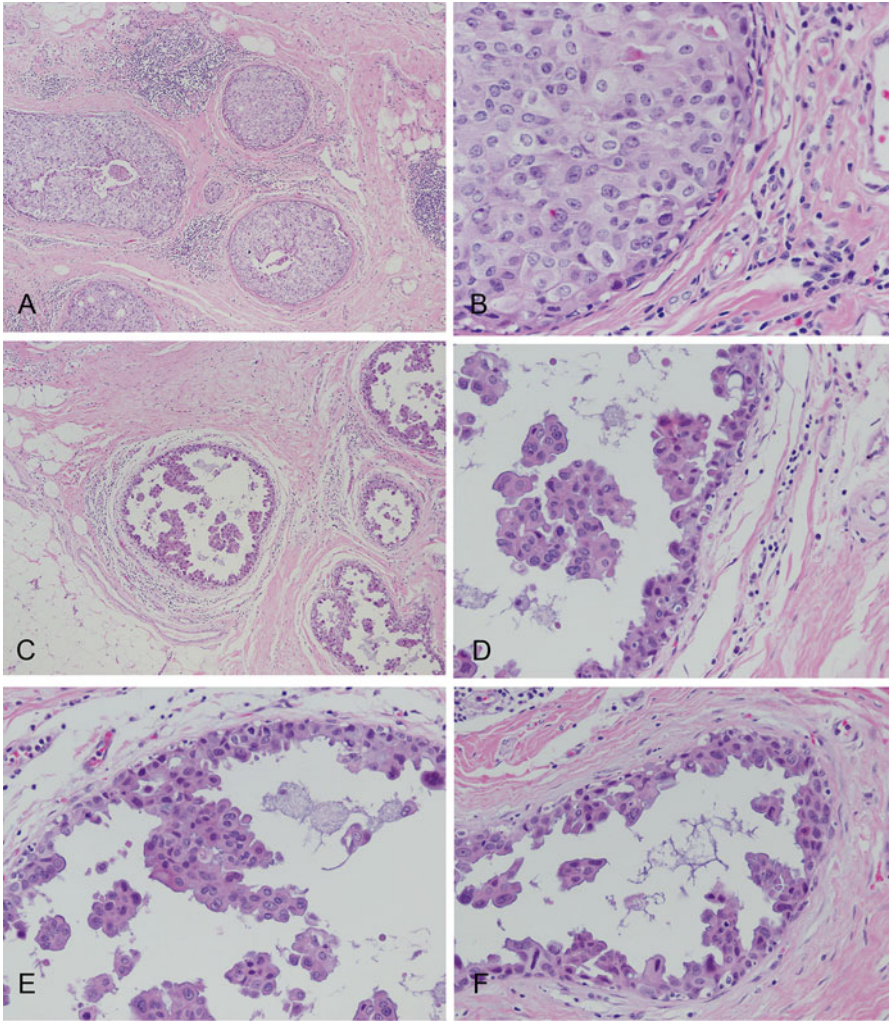


Fig. 2.25 Solid carcinoma in situ. (a): 4× and (b): 40×. Micropapillary carcinoma in situ showing elongated epithelial projections projecting into the glandular lumen; there is a lack of connective tissue support. (c): 4×; (d, e and f): 40×

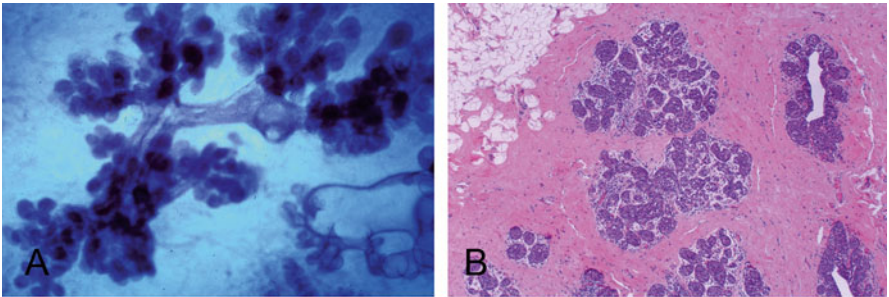


Fig. 2.26 (a): Whole mount of lobular carcinoma in situ (LCIS) originated in the lobules type 2 of the breast, 4×. (b): Lobular carcinoma in situ in which the lobules are distended and completely filled by neoplastic cells, 4×

Fig. 2.27 Lobular carcinoma in situ (LCIS) clearly showing the lobules completely filled by relatively uniform, round, small- to medium-sized cells with round and normochromatic nuclei, 40x

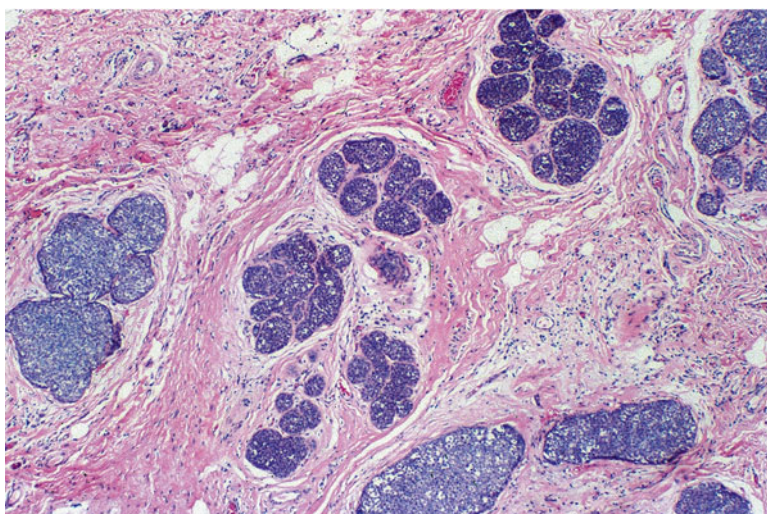
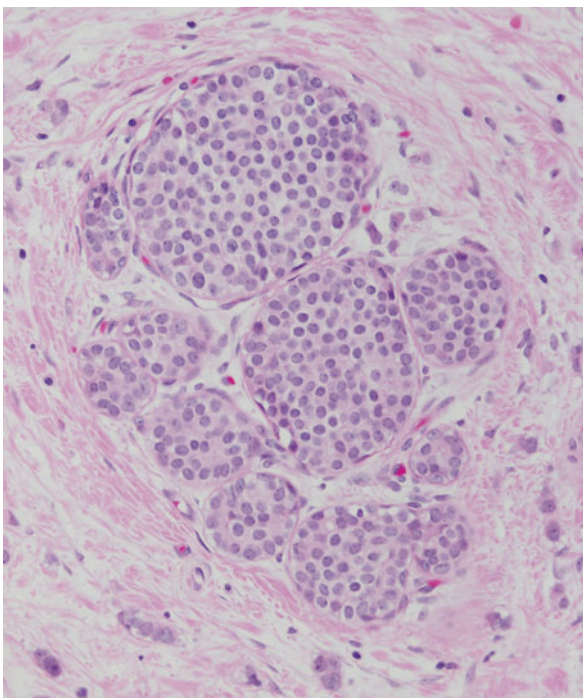


Fig. 2.28 Lobular carcinoma in situ (LCIS) involving several lobules of the breast, 4x

2.5 Differential Diagnosis

DCIS needs to be distinguished from atypical ductal hyperplasia (ADH) [7, 16, 29]. The difference lies in the extent of involvement of the ducts; specifically, ADH lesions occupy only part of the involved space, while low-grade DCIS occupies the entire duct space and often adjacent duct spaces as well [8, 17, 69]. Page et al. [17, 69] proposed that at least 2 spaces of uniformly present atypical cells should be seen in order to call a low-grade atypical epithelial lesion DCIS instead of ADH, while Tavassoli and Norris [21] proposed the 2-mm rule, namely, any low-grade atypical epithelial lesion smaller than 2 mm should be placed in the ADH category and larger than 2 mm, in the low-grade DCIS

DCIS lesions also need to be distinguished from invasive carcinomas; a frequent problem is invasive cribriform carcinoma that needs to be distinguished mostly from cribriform DCIS. Myoepithelial markers may help identify a basement membrane around cribriform DCIS and the absence of such barrier in invasive cribriform carcinomas is extremely helpful [8, 70–72]. Extension of cancer cells beyond the basement membrane with no focus larger than 0.1 cm in diameter is considered microinvasion. The presence of microinvasion is a frequent finding according to some authors [73]. Another problem is the differential diagnosis in which the DCIS extend in a benign lesion such as sclerosing adenosis, giving the morphologic impression of microinvasion [8, 70–72]. The use of immuno-cytochemical markers like myosin heavy chain or p63 are useful [8, 70–72]. The same confusion may occur when foci of cancer cells are in lymphatic and vascular spaces mimicking a carcinoma in situ. The use of markers such as CD31, CD34, or classic factor VIII immunostain are helpful to differentiate a DCIS from an intra- lymphatic or vascular invasion [8, 70–72].

Comedo-type DCIS lesions often need to be distinguished from the pleomorphic subtype of lobular carcinoma in situ lesions [42, 73–75]. The main difference between these two types of lesions is that LCIS subtype is the lobulocentric appearance of the lesion and the discohesive nature of the large atypical cells. Pleomorphic LCIS, as is the case with all other lesions of lobular histology are negative for E-cadherin expression [8, 70, 73–75].

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