

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

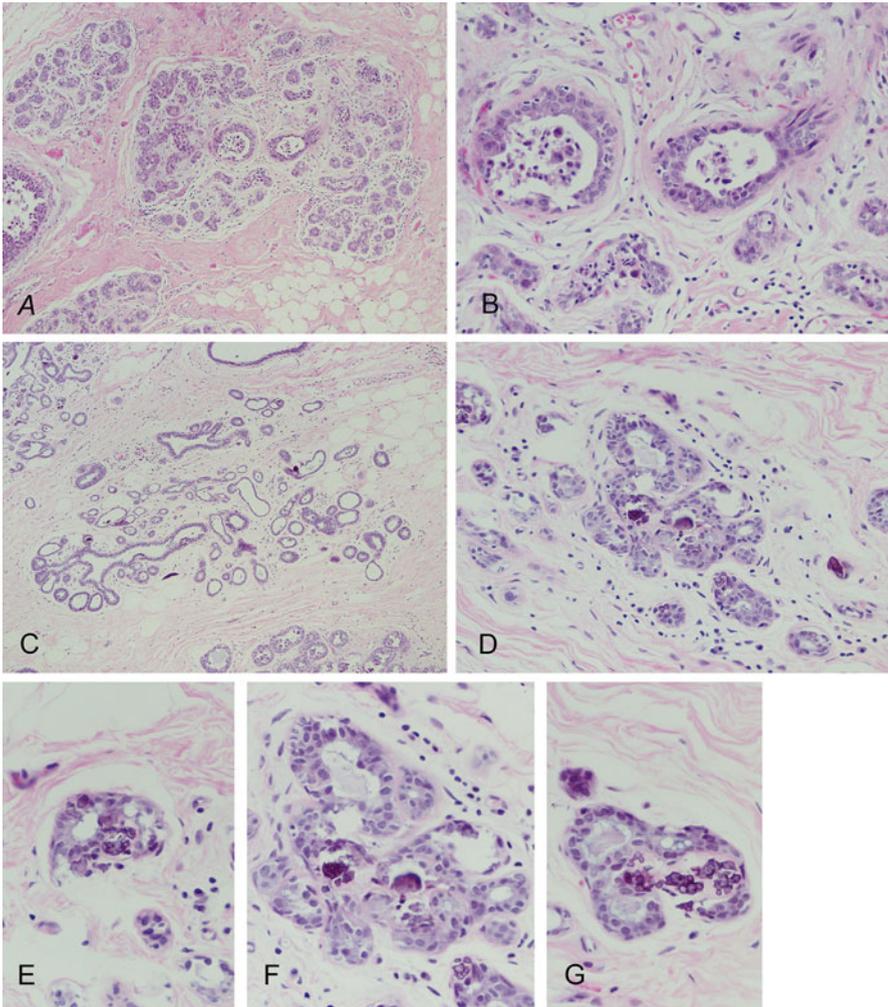


Fig. 2.1 Mild ductal hyperplasia. (a): 4 \times ; (b): 10 \times ; (c): 4 \times ; Microcalcifications in the lumen are found in (d): 10 \times ; (e, f and g): 10 \times

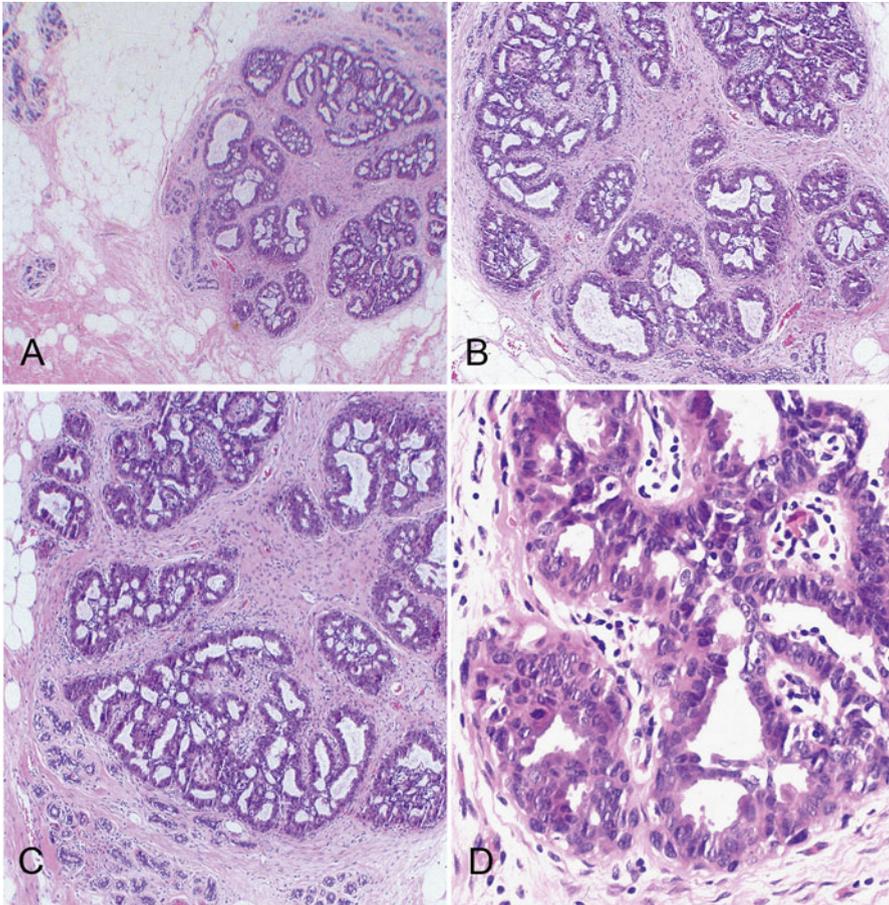


Fig. 2.2 Mid to moderate ductal hyperplasia. (a), 4x; (b and c): 10x ; (d) 40x

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.

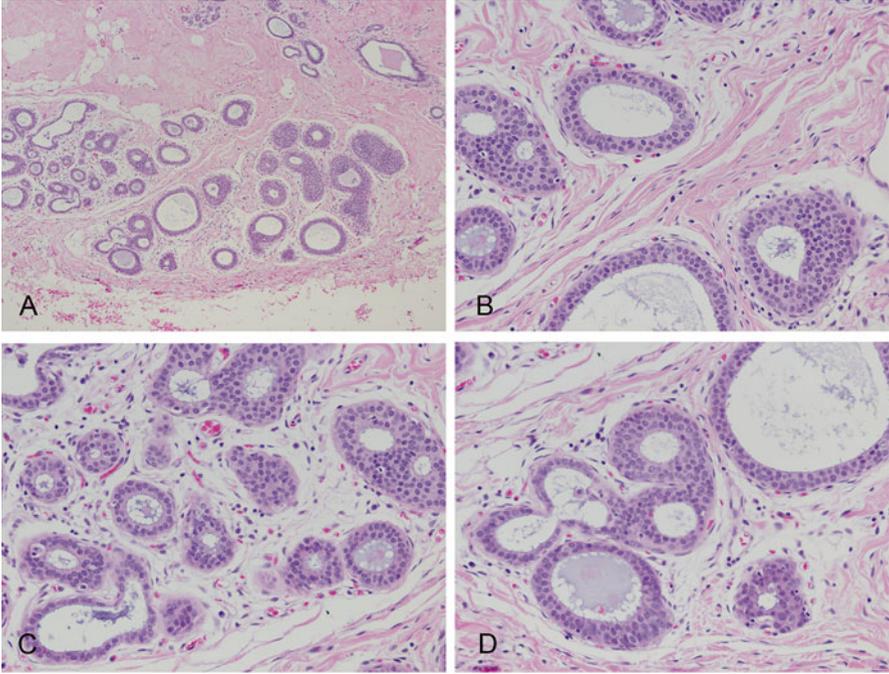


Fig. 2.3 Mild ductal hyperplasia with cystic changes. (a): 4x; (b, c and d) 10x

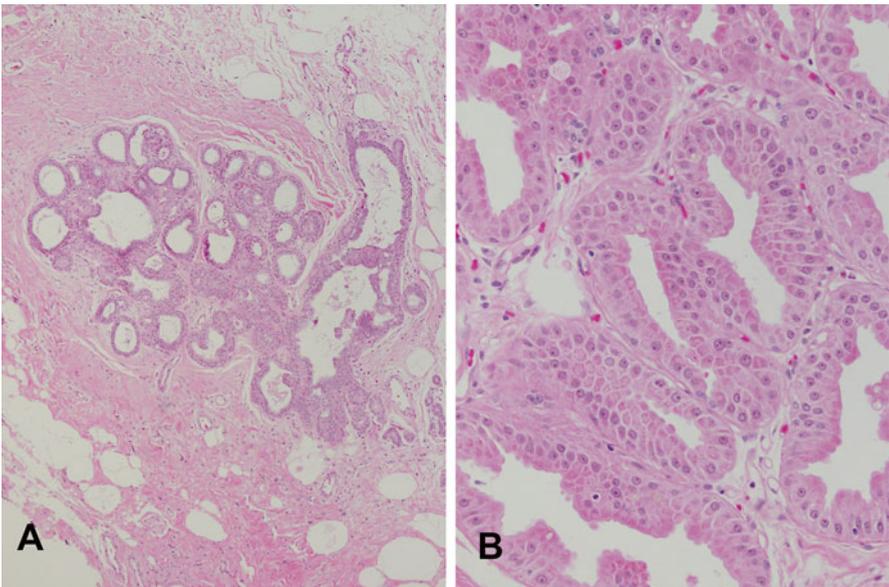


Fig. 2.4 Mild ductal hyperplasia. The cytoplasm is acidophilic and finely granular. (a): 4x and (b) 40x

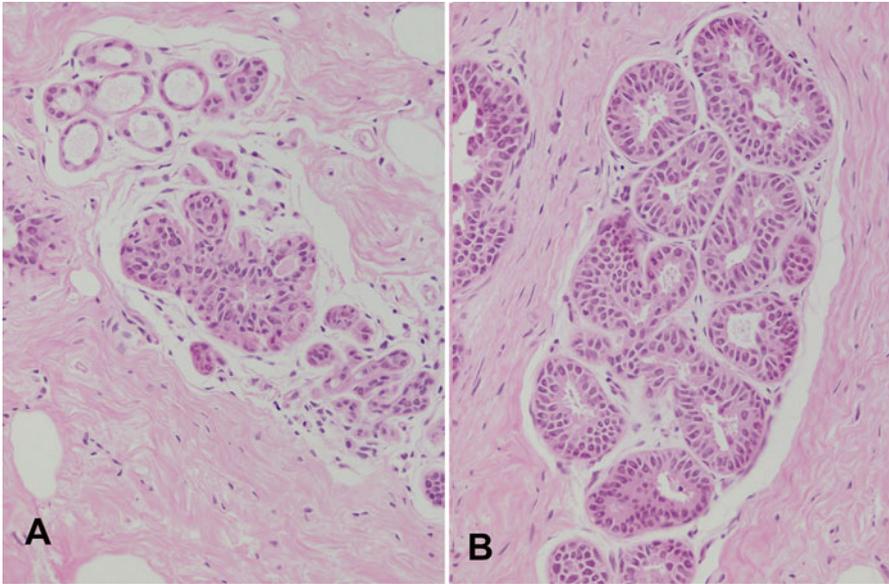


Fig. 2.5 Moderate ductal hyperplasia. (a): 4× and (b) 40×

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

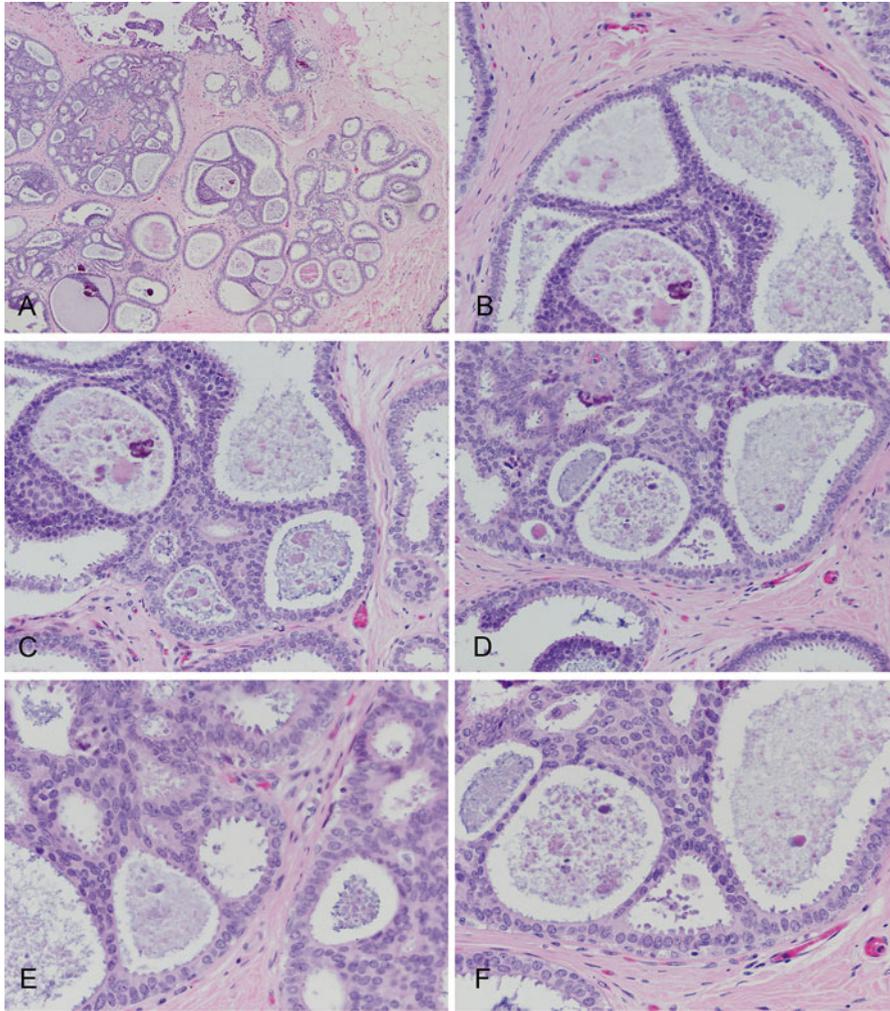


Fig. 2.6 Moderate ductal hyperplasia. (a): 4 \times , (b, c, d, e and f), 40 \times . The intratubular lumina of ductal hyperplasia tend to be irregular in size. The cells have a “Tufts” and “mounds” projecting into the lumen. Presence of irregularly shaped bridges connecting opposite portions of the 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

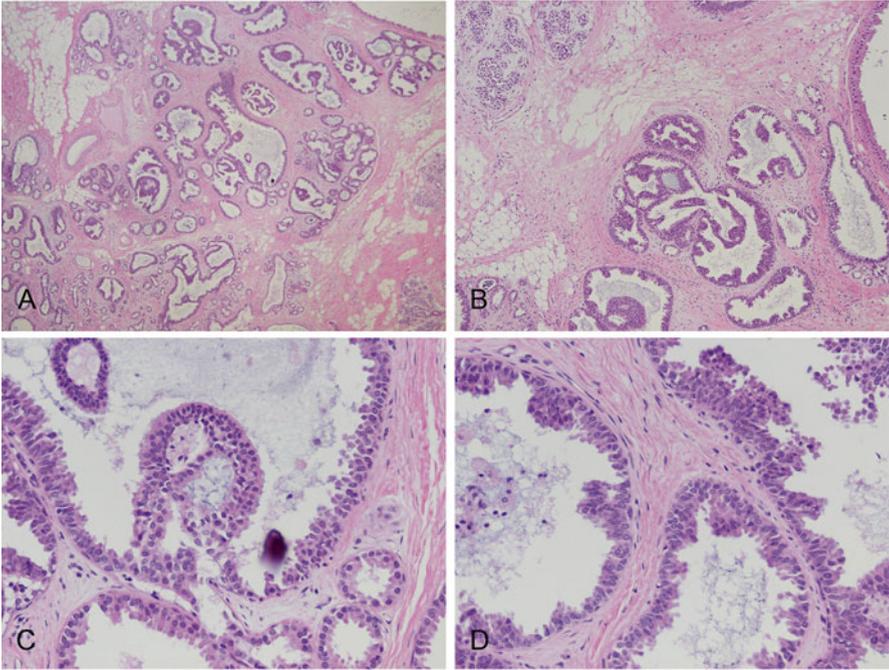


Fig. 2.7 Moderate ductal hyperplasia. (a): 4x; (b): 10x; (c): and (d): 40x. There is absence of necrosis but is not uncommon the presence of calcifications in the lumina

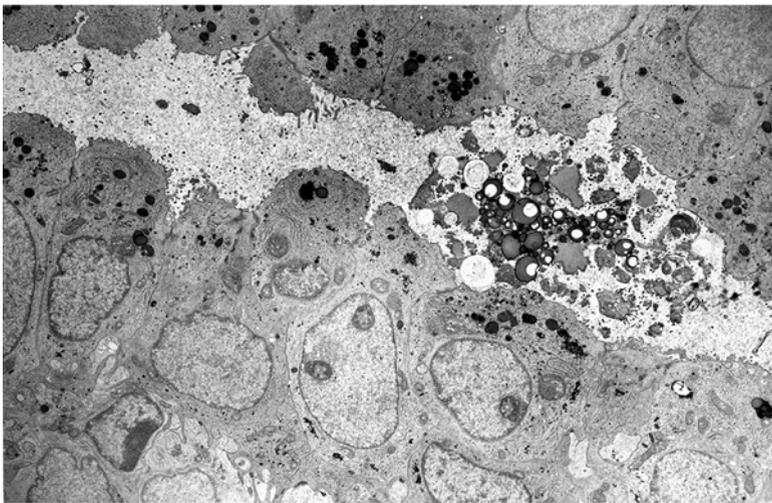


Fig. 2.8 Electron macrograph showing the multilayer epithelium and the presence of micro calcifications in the lumen. Stained with lead citrate and uranyl acetate; 5000x

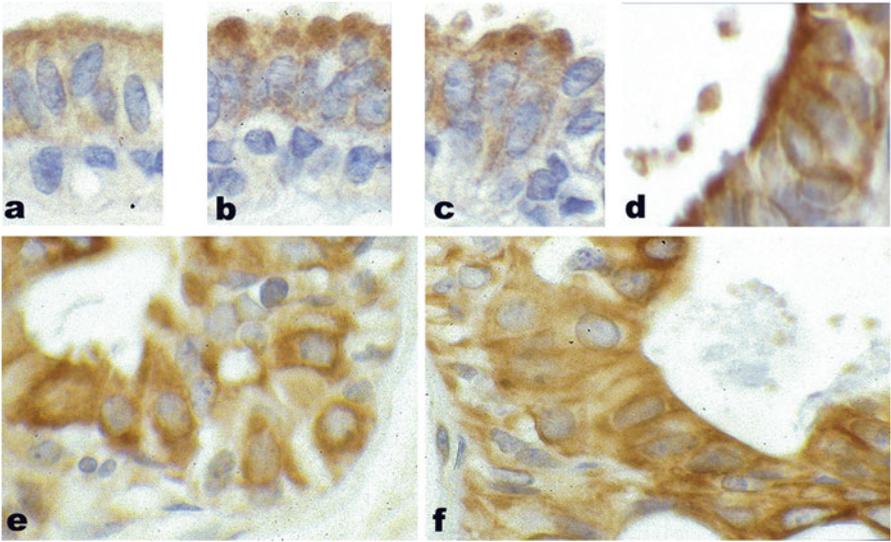


Fig. 2.9 Ductal hyperplasia showing intense reaction against S100 protein. (a, b, c, d, e and f): 40x

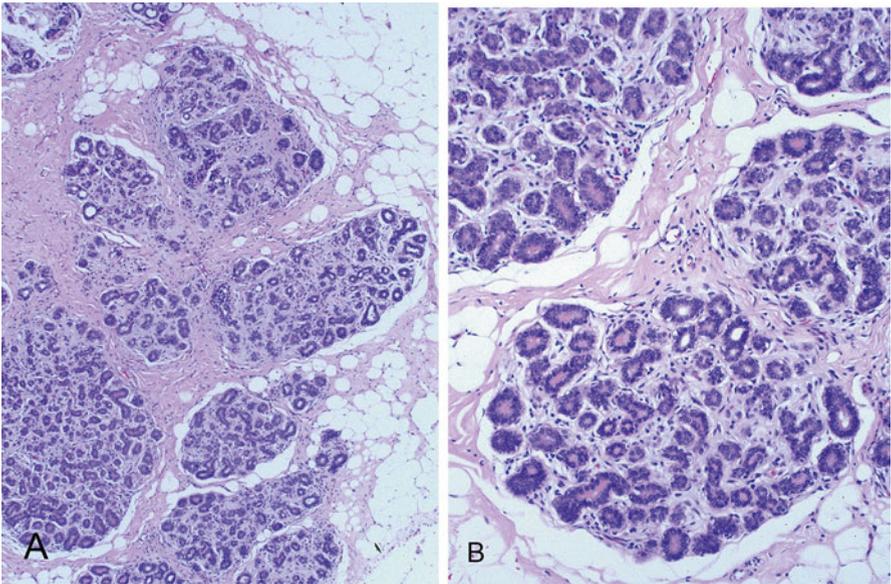


Fig. 2.10 Lobular hyperplasia is characterized by abundant lobular formation and more cellular than usual. (a): 4x, (b): 10x

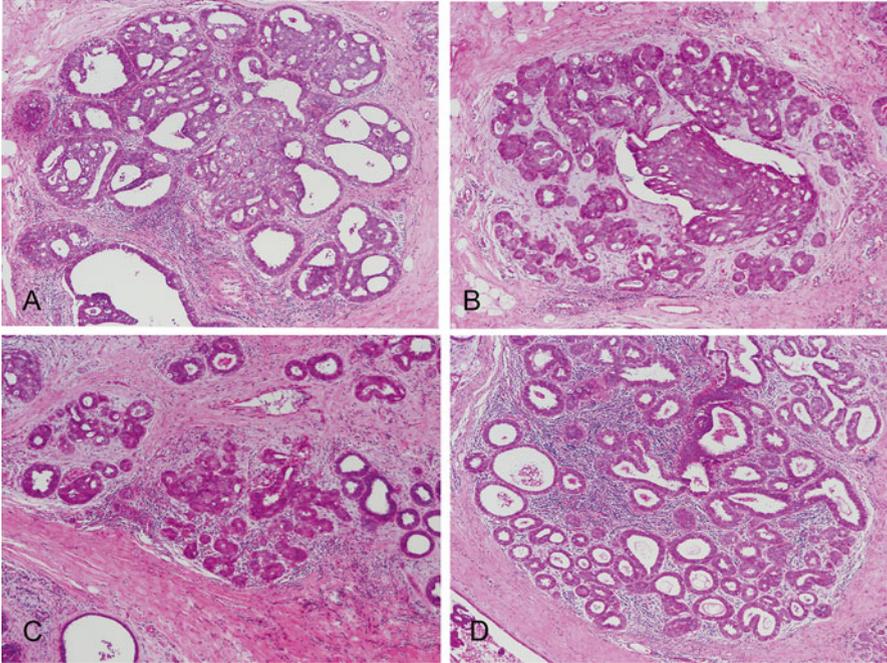


Fig. 2.11 Atypical ductal hyperplasia. It is characterized by architectural (micropapillae, tufts, fronds, bridges, solid and cribriform patterns) features indistinguishable from those of low-grade DCIS, but intimately admixed with usual ductal hyperplasia, and showing only partial involvement of the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

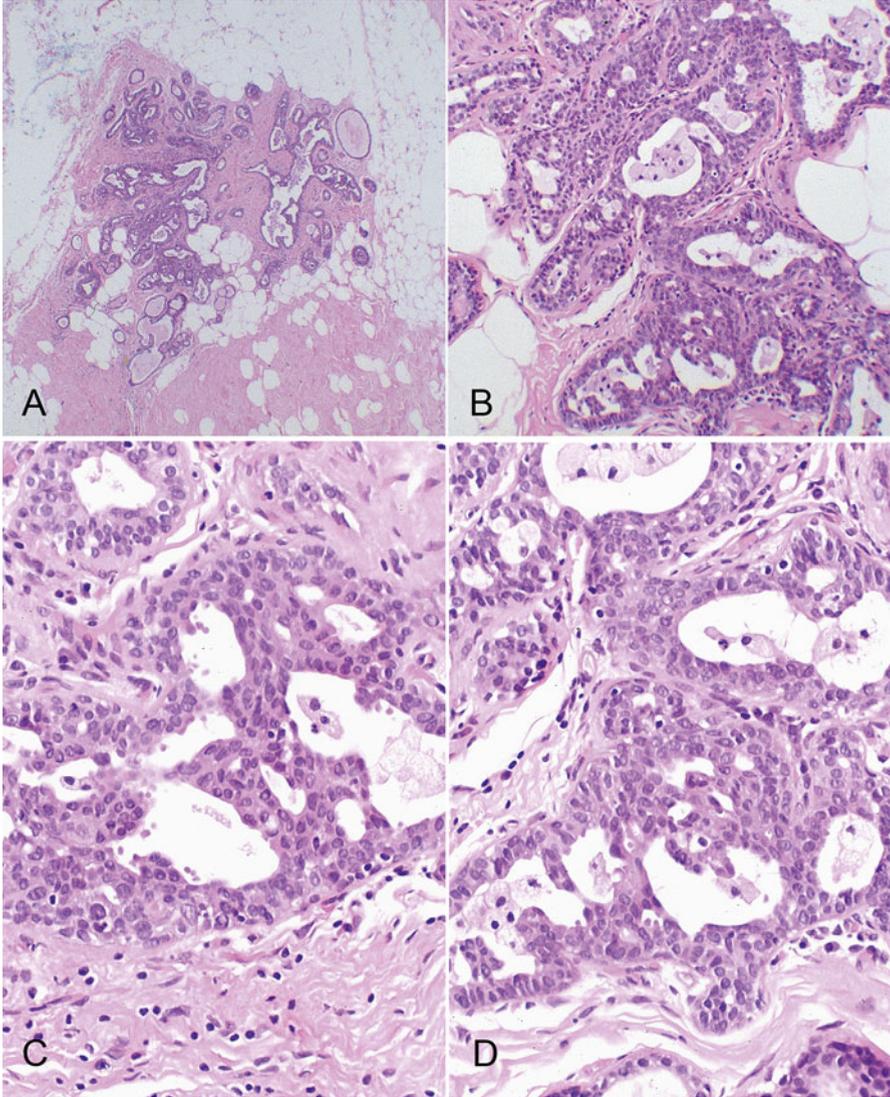


Fig. 2.12 Atypical ductal hyperplasia is characterized by atypical cytologic (monomorphic cells with ovoid to rounded nuclei) and architectural (micropapillae, tufts, fronds, bridges, solid and cribriform patterns) features indistinguishable from those of low-grade DCIS and showing only partial involvement 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 extraction of necrotic

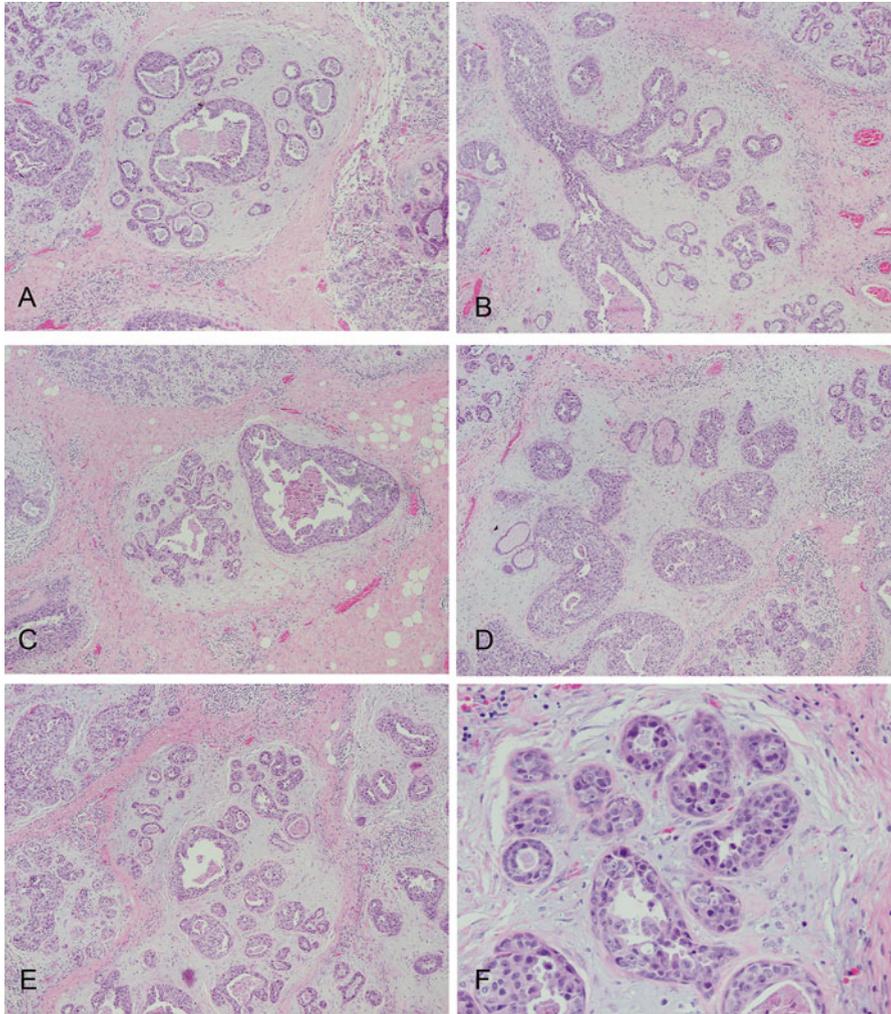


Fig. 2.13 DCIS noncomedo type. (a, b, c, d and e): 4x, (f): 10x

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).

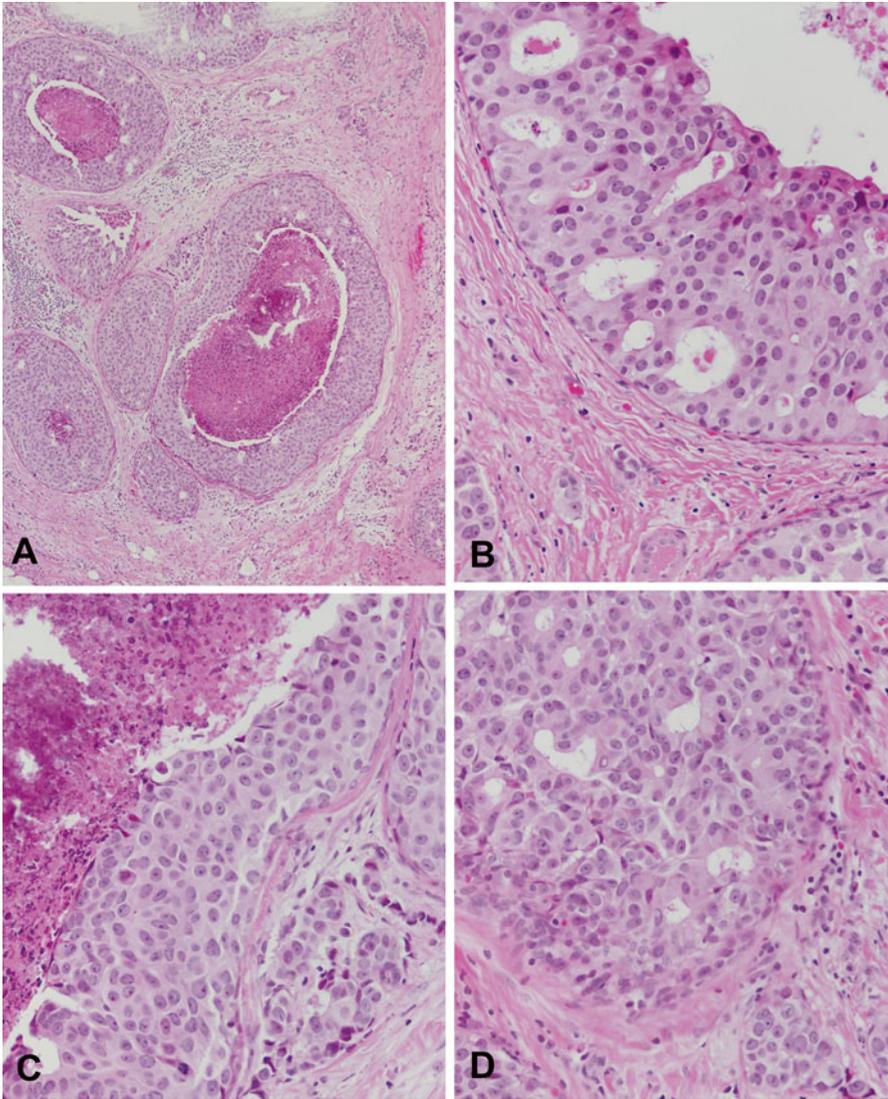


Fig. 2.14 DCIS comedo subtype. (a): 10 \times ; (b, c and d): 40 \times

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),

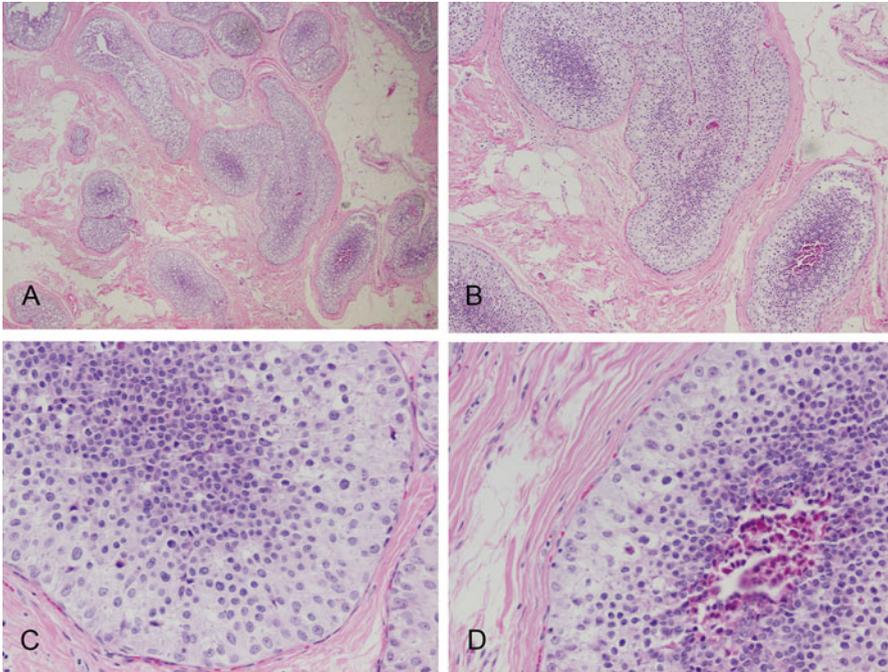


Fig. 2.15 DCIS comedo subtype. The ducts show a solid growth of large pleomorphic tumor cells accompanied by generally abundant mitotic activity and lacking connective tissue support. In the comedo carcinoma necrosis is always present and constitutes an important diagnostic sign, whether in the form 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).

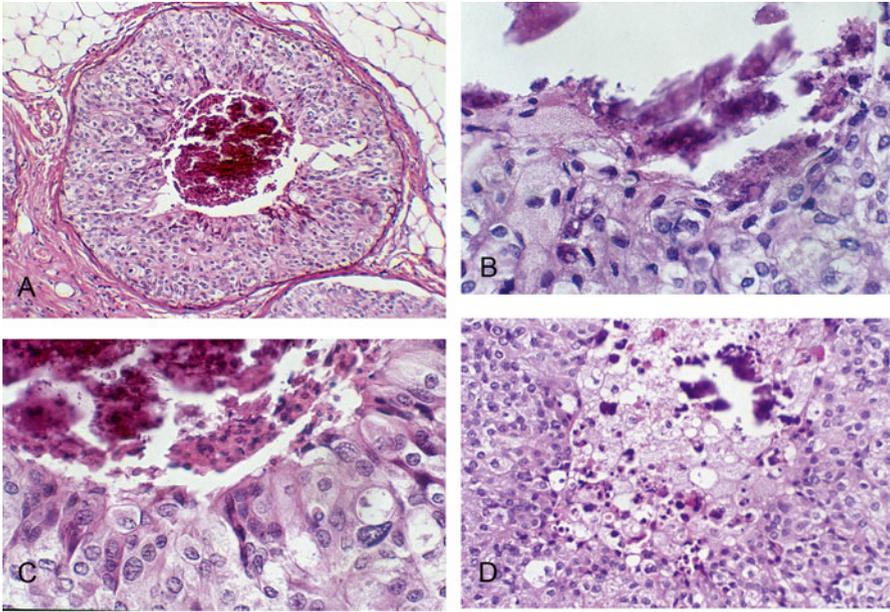


Fig. 2.16 DCIS comedo subtype high grade (grade 3). (a): 10×; (b, c and d): 40×

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).

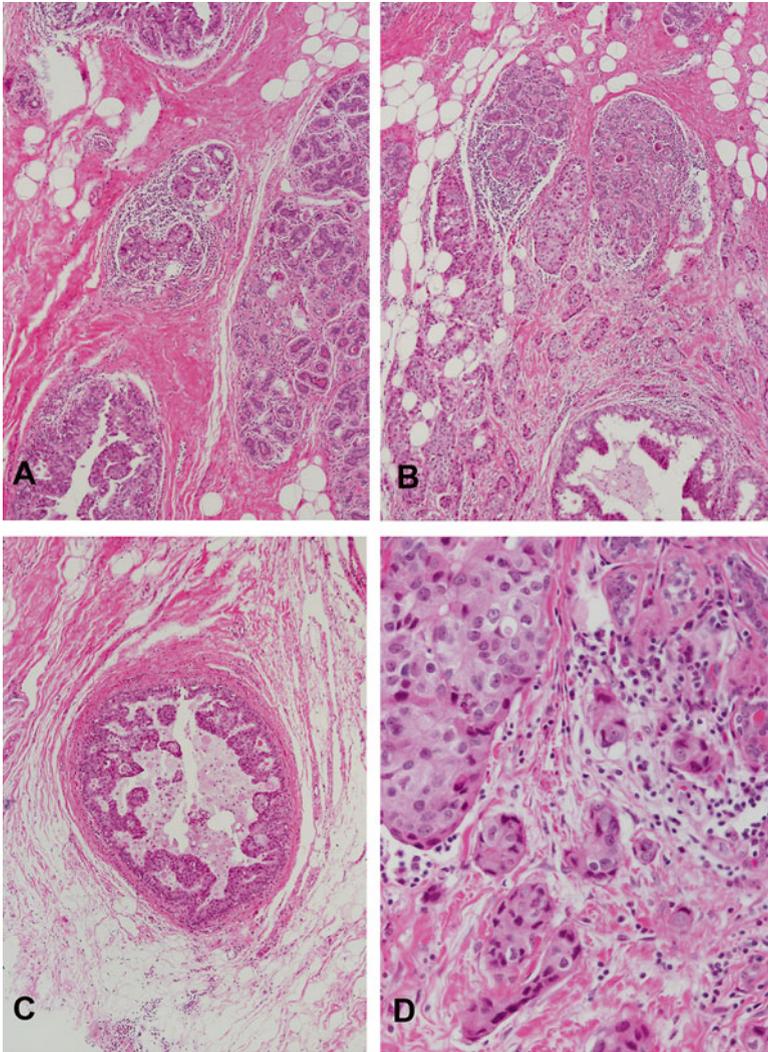


Fig. 2.17 Papillary carcinoma in situ with uniformity in size and shape of the epithelial cells, presence of one cell type only, nuclear hyperchromasia and high nucleocytoplasmic ratio, high mitotic activity, lack of apocrine metaplasia, cribriform and trabecular patterns, scanty or absent stroma. (**a** 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**)

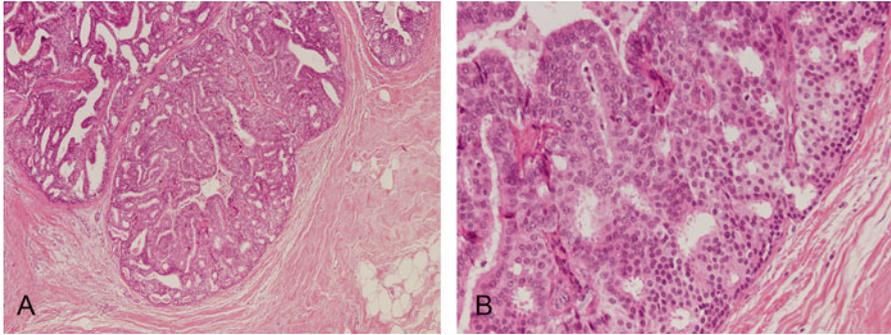


Fig. 2.18 Papillary carcinoma in situ. (a): 4× and (b): 10×

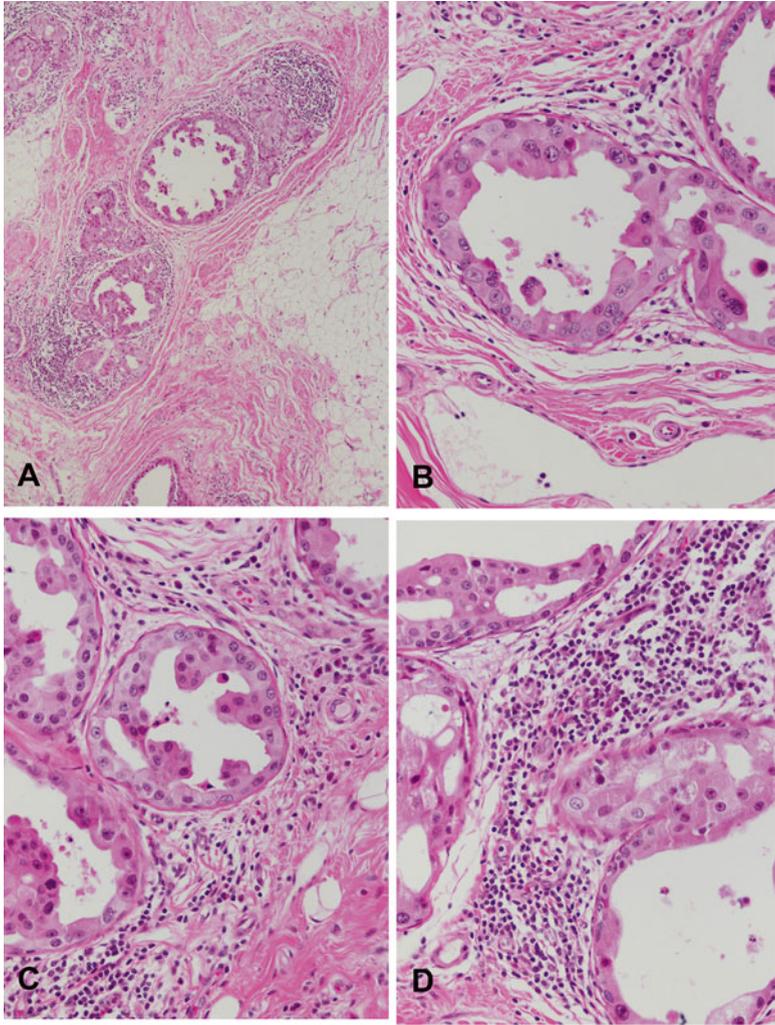


Fig. 2.19 Papillary carcinoma in situ. (a): 4×; (b, c and d): 40×. Observe the lymphocytic infiltration in (c) and in (d). In the figure (d) a tongue of invasive cells are seen

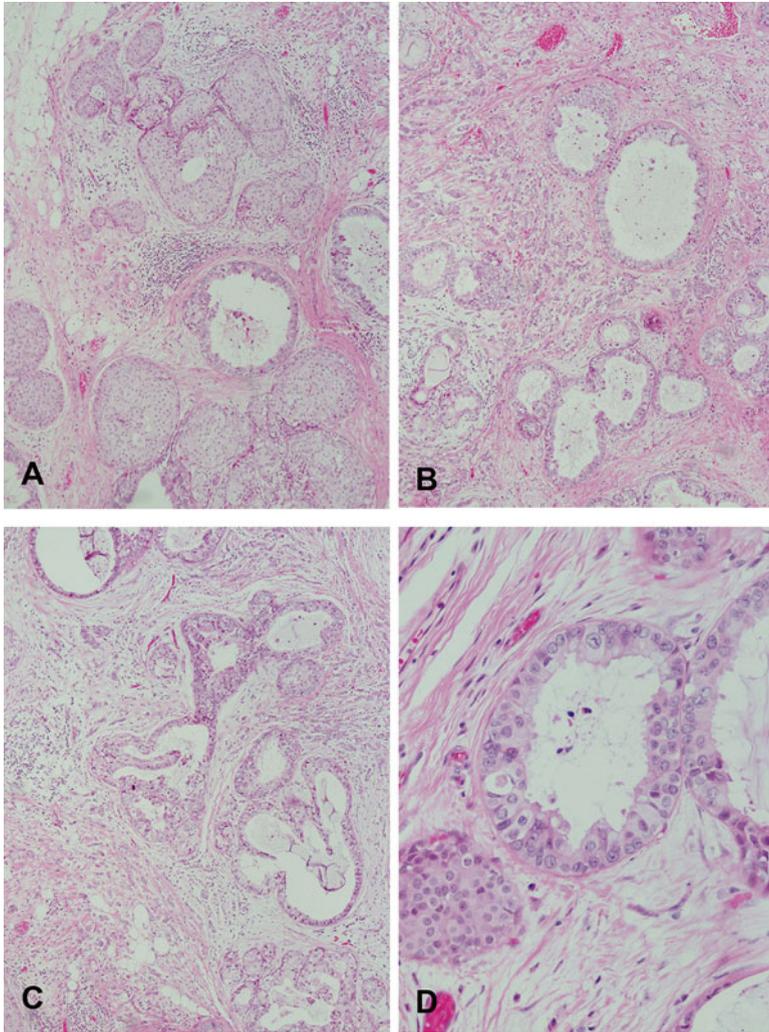


Fig. 2.20 Solid form of DCIS in which the glandular lumen is filled by the proliferation of medium-sized cells, which are larger than those found in lobular carcinoma in situ but smaller and more uniform than those of comedocarcinoma. (a, b and c): 10x; (d): 40x

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.

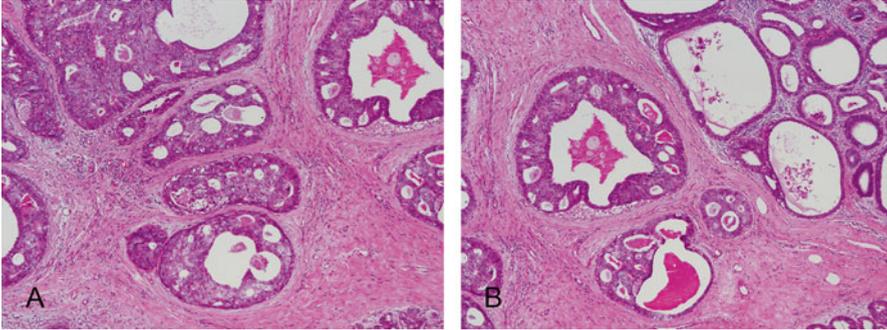


Fig. 2.21 Cribriform carcinoma in situ. (a and b): 4×

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].

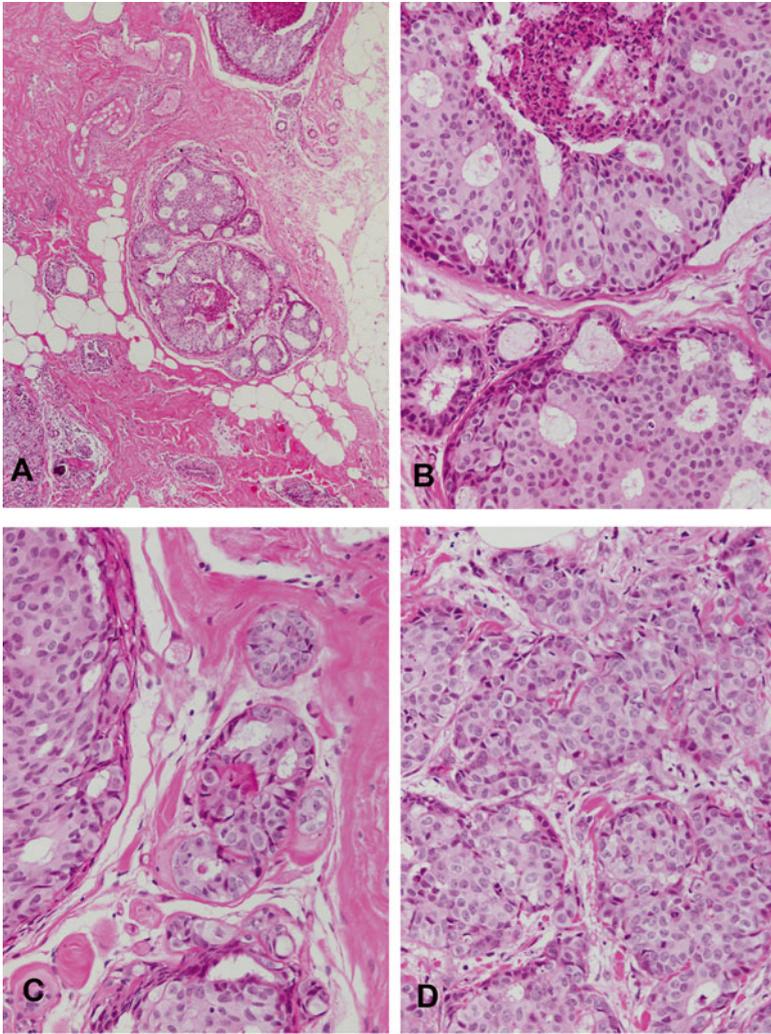


Fig. 2.22 Cribriform carcinoma in situ. Round regular spaces are formed within the glands; the more regular these spaces are in terms of distribution, size, and shape. (a): 10x; (b and c): 40x. Area of invasion is observed in a cribriform carcinoma subtype 40x

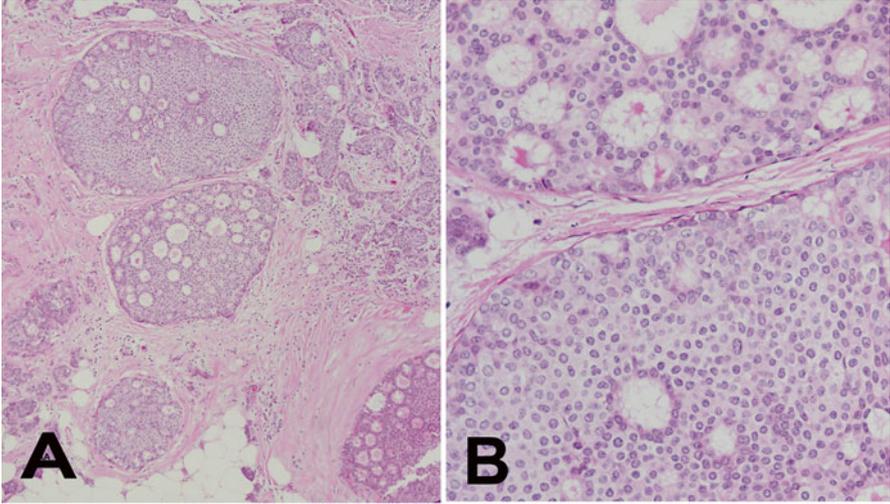


Fig. 2.23 Cribriform carcinoma in situ. Round regular spaces are formed within the glands and these spaces are often associated with formations of Roman bridges that are curvilinear trabecular bars connecting two portions of the epithelial lining. (a): 10× and (b): 40×

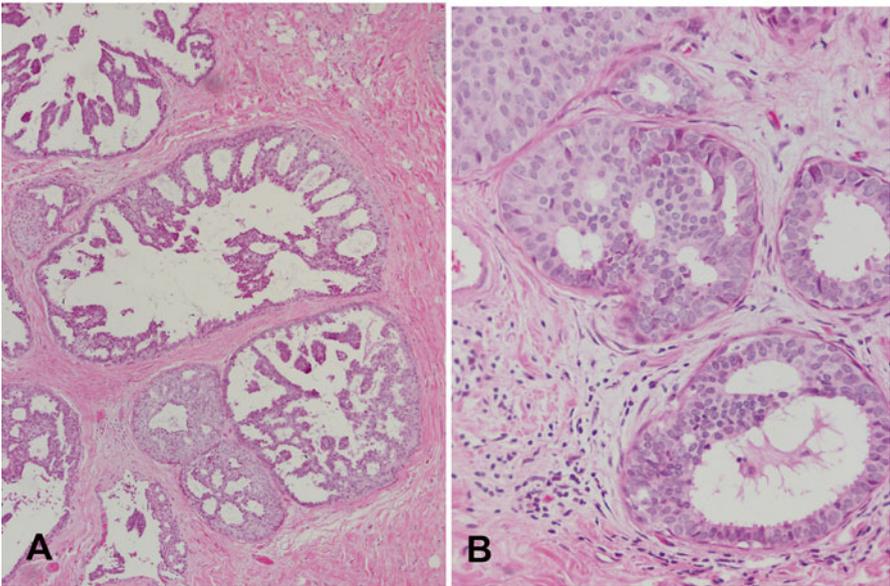


Fig. 2.24 Cribriform carcinoma in situ. (a): 10×; (b): 40×

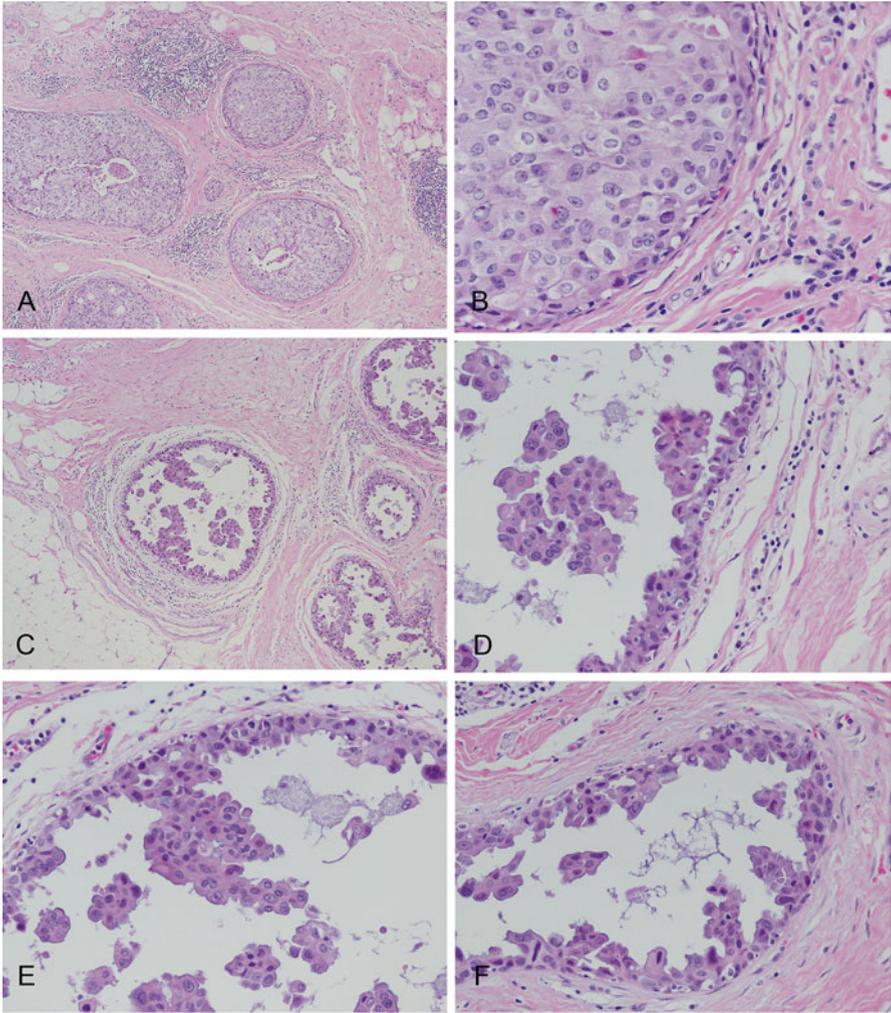


Fig. 2.25 Solid carcinoma in situ. (a): 4× and (b): 40×. Micropapillary carcinoma in situ showing elongated epithelial projections projecting into the glandular lumen; there is a lack of connective tissue support. (c): 4×; (d, e and f): 40×

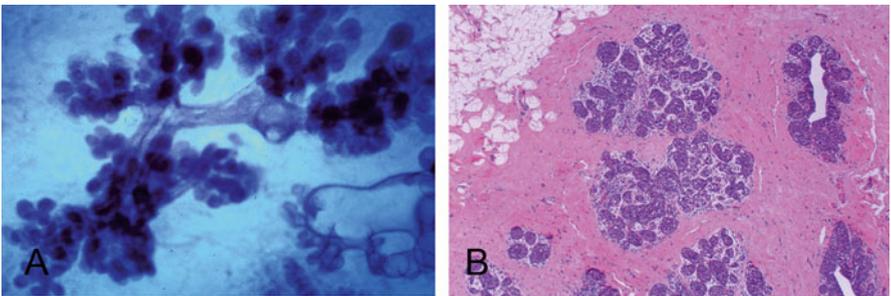


Fig. 2.26 (a): Whole mount of lobular carcinoma in situ (LCIS) originated in the lobules type 2 of the breast, 4×. (b): Lobular carcinoma in situ in which the lobules are distended and completely filled by neoplastic cells, 4×

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

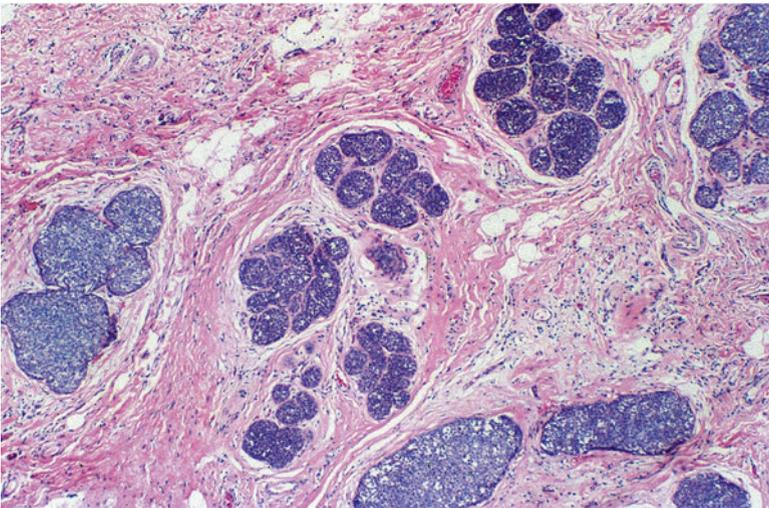
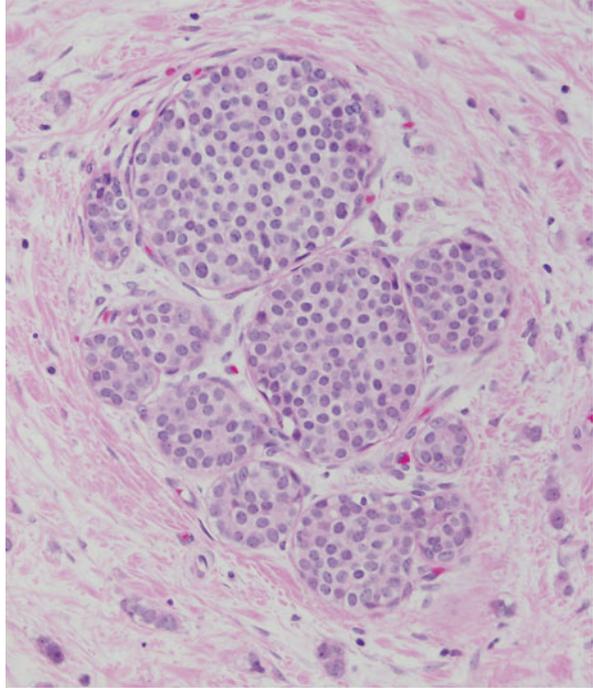


Fig. 2.28 Lobular carcinoma in situ (LCIS) involving several lobules of the breast, 4x

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].

References

1. SEER Cancer Statistics Review (2012) National Cancer Institute Web site. <http://seer.cancer.gov/>. Accessed April 16, 2012
2. Cancer Facts and Figures (2008) American Cancer Society Web site. www.cancer.org. Accessed June 1, 2012
3. Siziopikou Arch Pathol Lab Med—Vol 137, April 2013 Ductal Carcinoma In Situ of the Breast
4. Schnitt SJ, Silen W, Sadowsky NL et al (1988) Ductal carcinoma in situ (intraductal carcinoma) of the breast. *N Engl J Med* 318(14):898–903
5. Lester SC, Bose S, Chen Y et al (2009) Cancer Committee of the College of American Pathologists. Protocol for the examination of specimens from patients with ductal carcinoma in situ (DCIS) of the breast. *Arch Pathol Lab Med* 133(1):15–25

6. Harris J, Lippman ME, Morrow M, Osborne CK (2004) Diseases of the breast, 3rd edn. Lippincott Williams & Wilkins, Philadelphia
7. Stomper PC, Margolin FR (1994) Ductal carcinoma in situ: the mammographer's perspective. *AJR Am J Roentgenol* 162(3):585–591
8. Schnitt SJ, Collins LC (2009) Biopsy interpretation of the breast. Biopsy Interpretation Series. Lippincott Williams & Wilkins, Philadelphia, pp 51–95
9. Simpson PT, Reis-Filho JS, Gale T et al (2005) Molecular evolution of breast cancer. *J Pathol* 205(2):248–254
10. Burstein HJ, Polyak K, Wong JS et al (2004) Ductal carcinoma in situ of the breast. *N Engl J Med* 350(14):1430–1441
11. Rosai J (ed) (2004) Breast. Chapter 20. In: Rosai and Ackerman's Surgical Pathology. Mosby, New York, pp 1802–1818
12. Guerreiro Da Silva ID, Hu YF, Russo IH, Ao X, Salicioni AM, Yang X, Russo J (2000) S100P Ca²⁺-binding protein overexpression is associated with immortalization and neoplastic transformation of human breast epithelial cells *in vitro* and tumor progression *in vivo*. *Int J Oncol* 16:231–240
13. Dupont WD, Page DL (1985) Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med* 312:146–151
14. Fitzgibbons PL, Henson DE, Hutter RV (1998) Benign breast changes and the risk for subsequent breast cancer: an update of the 1985 consensus statement. Cancer Committee of the College of American Pathologists. *Arch Pathol Lab Med* 122:1053–1055
15. Page DL (1986) Cancer risk assessment in benign breast biopsies. *Hum Pathol* 17:871–874
16. Page DL, Dupont WD, Rogers LW, Rados MS (1985) Atypical hyperplastic lesions of the female breast. A long-term follow-up study. *Cancer* 55:2698–2708
17. Page DL, Kidd IE, Dupont WD, Rogers LW (1988) Lobular neoplasia of the breast (LN) has varying magnitudes of risk for subsequent invasive carcinoma (IBC) (abstract). *Lab Invest* 58:69A
18. Schnitt SJ, Connolly JL, Tavassoli FA, Fechner RE, Kempson RL, Gelman R, Page DL (1992) Interobserver reproducibility in the diagnosis of ductal proliferative breast lesions using standardized criteria. *Am J Surg Pathol* 16:1133–1143
19. Page DL, Rogers LW (1992) Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. *Hum Pathol* 23:1095–1097
20. Purcell CA, Norris HJ (1998) Intraductal proliferations of the breast: a review of histologic criteria for atypical intraductal hyperplasia and ductal carcinoma in situ, including apocrine and papillary lesions. *Ann Diagn Pathol* 2:135–145
21. Tavassoli FA, Norris HJ (1990) A comparison of the results of long-term follow-up for atypical intraductal hyperplasia and intraductal hyperplasia of the breast. *Cancer* 65:518–529
22. Rosai J (1991) Borderline epithelial lesions of the breast. *Am J Surg Pathol* 15:209–221
23. Bratthauer GL, Tavassoli FA (2002) Lobular intraepithelial neoplasia: previously unexplored aspects assessed in 775 cases and their clinical implications. *Virchows Arch* 440:134–138
24. Tavassoli FA, Hoefler H, Rosai J, Holland R, Ellis I, Schnitt S (2003) Intraductal proliferative lesions. Pathology and genetics of tumours of the breast and female genital organs. IARC Press, Lyon, pp 14–20
25. McDivitt RW (1978) Breast carcinoma. *Hum Pathol* 9:3–21
26. Schnitt SJ, Jimi A, Kojiro M (1993) The increasing prevalence of benign proliferative breast lesions in Japanese women. *Cancer* 71:2528–2531
27. Skolnick MH, Cannon-Albright LA, Goldgar DE, Ward JH, Marshall CJ, Schumann GB, Hogle H, McWhorter WP, Wright EC, Tran TD et al (1990) Inheritance of proliferative breast disease in breast cancer kindreds. *Science* 250:1715–1720
28. Steinhoff NG, Black WC (1970) Florid cystic disease preceding mammary cancer. *Ann Surg* 171:501–508
29. Dupont WD, Parl FF, Hartmann WH, Brinton LA, Winfield AC, Worrell JA, Schuyler PA, Plummer WD (1993) Breast cancer risk associated with proliferative breast disease and atypical hyperplasia. *Cancer* 71:1258–1265

30. Bianchi S, Palli O, Galli M, Zampi G (1993) Benign breast disease and cancer risk. *Crit Rev Oncol Hematol* 15:221–242
31. Bodian CA, Perzin KH, Lattes R, Hoffmann P, Abernathy TG (1993) Prognostic significance of benign proliferative breast disease. *Cancer* 71:3896–3907
32. Page DL, Dupont WD (1990) Anatomic markers of human premalignancy and risk of breast cancer. *Cancer* 66:1326–1335
33. Rosen PP (1993) Proliferative breast “disease.” An unresolved diagnostic dilemma. *Cancer* 71:3798–3807
34. The Consensus Conference Committee (1997) Consensus conference on the classification of ductal carcinoma in situ. *Cancer* 80(9):1798–1802
35. Millis RR, Thynne GSI (1975) In situ intraduct carcinoma of the breast. A long-term follow-up study. *Br J Surg* 62:957–962
36. Brown PW, Silverman J, Owens E, Tabor DC, Terz JJ, Lawrence W Jr (1976) Intraductal “noninfiltrating” carcinoma of the breast. *Arch Surg* 111:1063–1067
37. Lagios MD, Westdahl PR, Margolin FR, Rose MR (1982) Duct carcinoma in situ. Relationship of extent of noninvasive disease to the frequency of occult invasion, multicentricity, lymph node metastases, and short-term treatment failures. *Cancer* 50:1309–1314
38. Bacus SS, Ruby SG, Weinberg DS, Chin D, Ortiz R, Bacus JW (1990) HER-2/ neu oncogene expression and proliferation in breast cancers. *Am J Pathol* 137:103–111
39. Bhoola S, DeRose PB, Cohen C (1999) Ductal carcinoma in situ of the breast: frequency of biomarkers according to histologic subtype. *Appl Immunohistochem* 7:108–115
40. Bobrow LG, Happerfield LC, Gregory WM, Springall RD, Millis RR (1994) The classification of ductal carcinoma in situ and its association with biological markers. *Semin Diagn Pathol* 11:199–207
41. Bose S, Lesser ML, Norton L, Rosen PP (1996) Immunophenotype of intraductal carcinoma. *Arch Pathol Lab Med* 120:81–85
42. Douglas-Jones AG, Schmid KW, Bier B, Horgan K, Lyons K, Dallimore ND, Moneypenny IJ, Jasani B (1995) Metallothionein expression in duct carcinoma in situ of the breast. *Hum Pathol* 26:217–222
43. Killeen JL, Namiki H (1991) DNA analysis of ductal carcinoma in situ of the breast. A comparison with histologic features. *Cancer* 68:2602–2607
44. Leal CB, Schmitt FC, Bento MJ, Maia NC, Lopes CS (1995) Ductal carcinoma in situ of the breast. Histologic categorization and its relationship to ploidy and immunohistochemical expression of hormone receptors, p53, and *c-erbB-2* protein. *Cancer* 75:2123–2131
45. Lodato RF, Maguire HC Jr, Greene MI, Weiner DB, Li Volsi VA (1990) Immunohistochemical evaluation of *c-erbB-2* oncogene expression in ductal carcinoma in situ and atypical ductal hyperplasia of the breast. *Mod Pathol* 3:449–454
46. O’Malley FP, Vnencak-Jones CL, Dupont WD, Parf F, Manning S, Page DL (1994) p53 mutations are confined to the comedo type ductal carcinoma in situ of the breast. Immunohistochemical and sequencing data. *Lab Invest* 71:67–72
47. Paredes J, Milanezi F, Viegas L, Amendoeira I, Schmitt F (2002) P-cadherin expression is associated with high-grade ductal carcinoma in situ of the breast. *Virchows Arch* 440:16–21
48. Poller ON, Silverstein MJ, Galea M, Locker AP, Elston CW, Blamey RW (1994) Ellis 10. Ideas in pathology. Ductal carcinoma in situ of the breast. A proposal for a new simplified histological classification association between cellular proliferation and *c-erbB-2* protein expression. *Mod Pathol* 7:257–262
49. Bur ME, Zimarowski MJ, Schnitt SJ et al (1992) Estrogen receptor immunohistochemistry in carcinoma in situ of the breast. *Cancer* 69(5):1174–1181
50. Rudas M, Neumayer R, Gnant MF et al (1997) p53 protein expression, cell proliferation and steroid hormone receptors in ductal and lobular in situ carcinomas of the breast. *Eur J Cancer* 33:39–44
51. Mack L, Doig G, O’Malley FP (1997) Relationship of a new histological categorization of ductal carcinoma in situ of the breast with size and the immunohistochemical expression of p53, *c-erbB-2*, *bcl-2* and *ki-67*. *Hum Pathol* 28(8):974–979

52. van de Vijver MJ, Peterse JL, Mooi WJ et al (1988) Neu-protein overexpression in breast cancer: association with comedo-type ductal carcinoma in situ and limited prognostic value in stage II breast cancer. *N Engl J Med* 319(19):1239–1245
53. Bartkova J, Barnes DM, Millis RR et al (1990) Immunohistochemical demonstration of c-erbB-2 protein in mammary ductal carcinoma in situ. *Hum Pathol* 21(11):1164–1167
54. Poller DN, Roberts EC, Bell JA et al (1993) p53 protein expression in mammary ductal carcinoma in situ: relationship to immunohistochemical expression of estrogen receptor and c-erbB-2 protein. *Hum Pathol* 24(5):463–468
55. Holland R, Peterse JL, Millis RR et al (1994) Ductal carcinoma in situ: a proposal for a new classification. *Semin Diagn Pathol* 11(3):167–180
56. European Commission Working Group on Breast Screening Pathology (1998) Consistency achieved by 23 European pathologists in categorizing ductal carcinoma in situ of the breast using five classifications. *Hum Pathol* 29(10):1056–1062
57. Azzopardi JG (1979) Problems in breast pathology. In: Bennington JL (consulting ed.) *Major problems in pathology*, vol. 11. W.B. Saunders, Philadelphia
58. Guerry P, Erlandson RA, Rosen PP (1988) Cystic hypersecretory hyperplasia and cystic hypersecretory duct carcinoma of the breast. *Pathology, therapy, and follow-up of 39 patients. Cancer* 61:1611–1620
59. Andersen JA (1974) Invasive breast carcinoma with lobular involvement. Frequency and location of lobular carcinoma in situ. *Acta Pathol Microbiol Scand (A)* 82:719–729
60. Leal C, Henrique R, Monteiro P, Lopes C, Bento MI, De Sousa SP, Lopes P, Olson S, Silva MD, Page DL (2001) Apocrine ductal carcinoma in situ of the breast: histologic classification and expression of biologic markers. *Hum Pathol* 32:487–493
61. O'Malley FP, Page DL, Nelson EH, Dupont WD (1994) Ductal carcinoma in situ of the breast with apocrine cytology. Definition of a borderline category. *Hum Pathol* 25:164–168
62. Tavassoli FA, Norris HJ (1994) Intraductal apocrine carcinoma. A clinicopathologic study of 37 cases. *Mod Pathol* 7:813–818
63. Cross AS, Azzopardi JG, Krausz T, Van Noorden S, Polak JM (1985) A morphological and immunocytochemical study of a distinctive variant of ductal carcinoma in situ of the breast. *Histopathology* 9:21–37
64. Warner NE (1969) Lobular carcinoma of the breast. *Cancer* 23:840–846
65. Carter D, Smith RRL (1977) Carcinoma in situ of the breast. *Cancer* 40:1189–1193
66. Andersen JA, Vendelboe ML (1981) Cytoplasmic mucous globules in lobular carcinoma in situ. Diagnosis and prognosis. *Am J Surg Pathol* 5:251–255
67. Breslow A, Brancaccio ME (1976) Intracellular mucin production by lobular breast carcinoma cells. *Arch Pathol Lab Med* 100:620–621
68. Acs G, Lawton D, Rebbeck TR, LiVolsi VA, Zhang PJ (2001) Differential expression of E-cadherin in lobular and ductal neoplasms of the breast and its biologic and diagnostic implications. *Am J Clin Pathol* 115:85–98
69. Page DL, Anderson TJ (1987) *Diagnostic histopathology of the breast*. Churchill Livingstone, New York
70. Maluf HM (2004) Differential diagnosis of solid carcinoma in situ. *Semin Diagn Pathol* 21(1):25–31
71. Yaziji H, Gown AM, Sneige N (2000) Detection of stromal invasion in breast cancer: the myo-epithelial markers. *Adv Anat Pathol* 7(2):100–109
72. Lerwill MF (2004) Current practical applications of diagnostic immunohistochemistry in breast pathology. *Am J Surg Pathol* 28(8):1079–1091
73. Sneige N, Wang J, Baker BA et al (2002) Clinical, histopathologic and biologic features of pleomorphic lobular (ductal-lobular) carcinoma in situ of the breast: a report of 24 cases. *Mod Pathol* 15(10):1044–1050
74. Jacobs JW (2003) Recently recognized variants of lobular carcinoma in situ (LCIS) with an emphasis on management of LCIS on core needle biopsy. *Pathol Case Rev* 8(5):211–219
75. Fulford LG, Reis-Filho JS, Lakhani SR (2004) Lobular in situ neoplasia. *Curr Diagn Pathol* 10(3):183–192



<http://www.springer.com/978-3-319-40813-2>

The Pathobiology of Breast Cancer

Russo, J.

2016, XIV, 235 p. 126 illus., 109 illus. in color.,

Hardcover

ISBN: 978-3-319-40813-2