Ductal Carcinoma In Situ

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Ductal carcinoma in situ (DCIS) is a malignant, clonal proliferation of cells growing within the basement membrane-bound structures of the breast, with no evidence of invasion into the surrounding stroma [1]. The increased use of screening mammography has led to a significant increase in the diagnosis of earlier stage breast cancers, including DCIS.

Specifically, DCIS is detected as mammographic microcalcifications in more than three quarters (75%) of cases, as a non-palpable mass in 11%, and as a combination of the above in 13%. Furthermore, DCIS constitutes 30–40% of breast cases diagnosed mammographically, with one case of DCIS detected in every 1300 screening mammograms. Ten to 20% of DCIS cases are seen bilaterally [2]. In some cases, DCIS presents clinically as nipple discharge, usually hemorrhagic, and is often seen in association with Paget disease of the nipple [3].

Risk factors for the development of DCIS are similar to those for invasive breast cancer, suggesting that these diseases are etiologically related and include increasing age (mean age at diagnosis for DCIS, 50–59 years), family history of a first-degree relative with breast cancer, nulliparity or late age of first birth, late age of menopause, long-term use of postmenopausal hormonal therapy, elevated body-mass index in postmenopausal women, BRCA mutational status, and high mammographic breast density [4, 5]. DCIS is considered a precursor lesion with a relative risk of 8–11 for the subsequent development of invasive carcinoma [1, 2].

11.1 Histologic Parameters

Ductal carcinoma in situ is a heterogeneous group of neoplastic intraductal lesions characterized by increased epithelial proliferation of different architectural patterns and various degrees of cytological atypia, ranging from mild to severe. The microscopic heterogeneity of DCIS has led to the development of several systems for classification. Historically, DCIS has been classified based on architectural patterns of proliferation, including comedo, cribriform, micropapillary, solid, or mixed subtypes [1, 6].

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11.2 Low-Grade Ductal Carcinoma In Situ

Low-grade DCIS is characterized by a proliferation of small cells with well-defined cell membranes that exhibit uniform size, shape, and placement. Cells are 1.5–2 times the size of a red blood cell, or similar in size to the adjacent ductal epithelial cells. In the solid growth pattern, cells completely fill ductal spaces (Figs. 11.1 and 11.2). The nuclei are small, with relatively homogeneous chromatin distribution and inconspicuous nucleoli (Fig. 11.3). Because of their polarized nature, these carcinomas cells consistently display better-developed glandular characteristics than hyperplastic cells. Cribriform and micropapillary architecture are more common than a solid growth pattern.

The cribriform pattern features extracellular lumens within the proliferation (Figs. 11.4 and 11.5). These are typically round and rigid with a punched-out appearance (Fig. 11.6).

Micropapillary DCIS consists of ducts lined by a layer of neoplastic cells giving rise to papillary/micropapillary fronds or arcuate formations protruding into the duct lumen (Fig. 11.7). Micropapillary DCIS is recognized to more often be multiquadrant (71%) than comedo-type disease (8%) [7]. Rare cases of low-grade DCIS may have comedo type necrosis (Fig. 11.8).

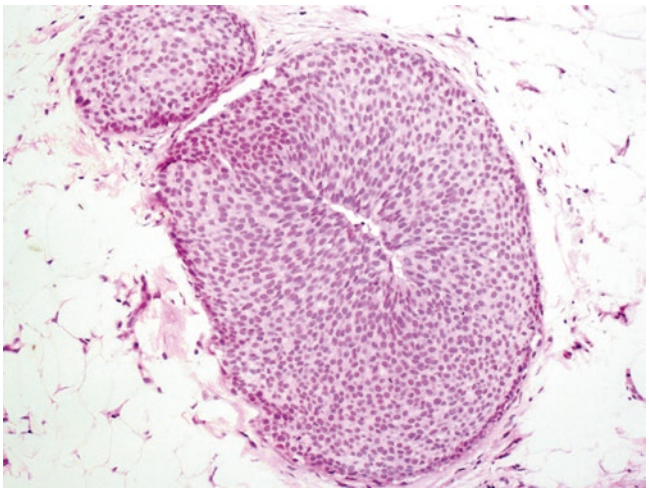


Fig. 11.1 Low-grade ductal carcinoma in situ, solid pattern. Involved ductal spaces are filled with solid sheets of cohesive cells; numerous microacini are present

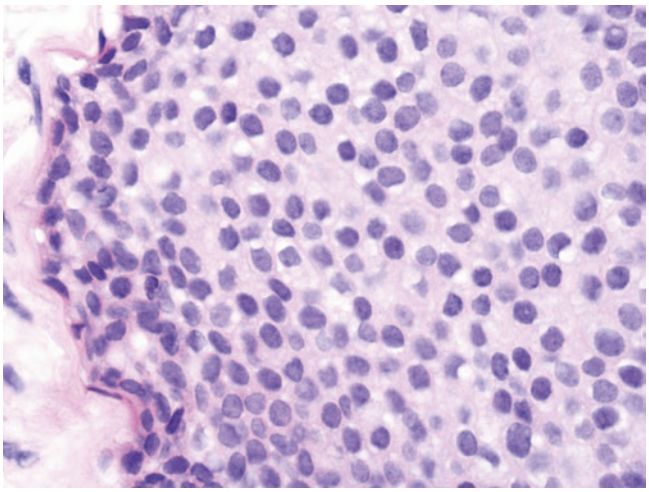


Fig. 11.3 Low-grade ductal carcinoma in situ. The nuclei are small, with small, relatively homogeneous chromatin distribution and inconspicuous nucleoli. The cells show a subtle increase in N:C ratio

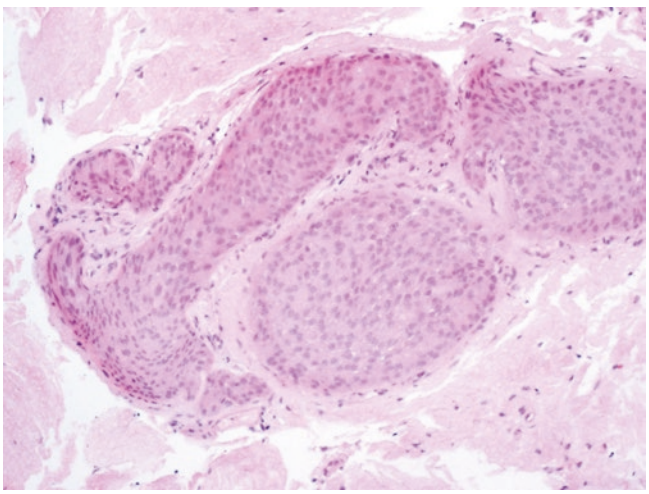


Fig. 11.2 Low-grade ductal carcinoma in situ, solid pattern

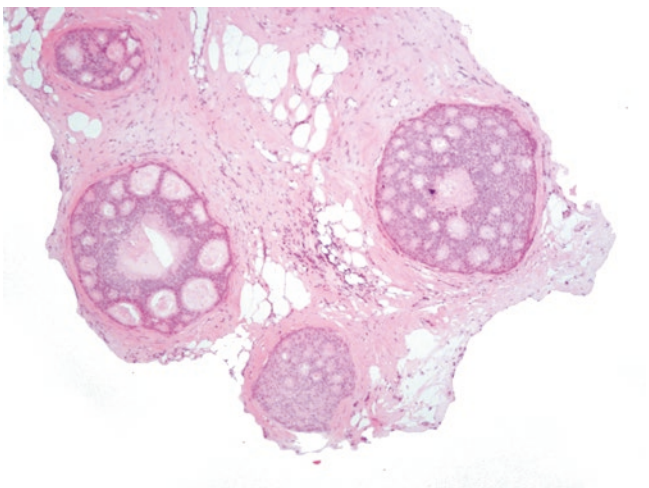


Fig. 11.4 Low-grade ductal carcinoma in situ, with cribriform pattern. Round lumens within the proliferation

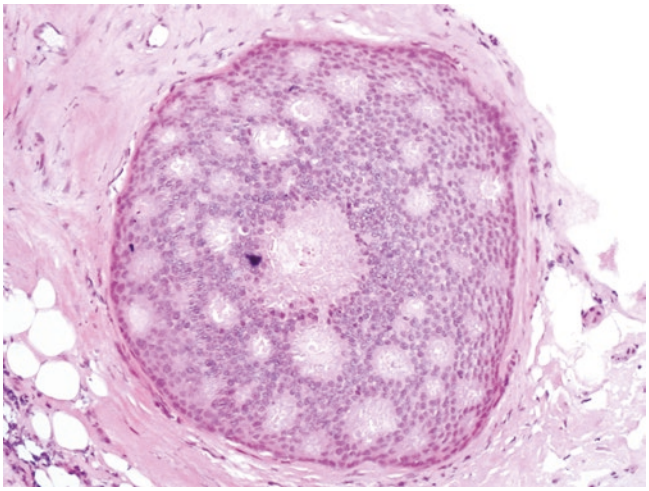


Fig. 11.5 Low-grade ductal carcinoma in situ with a cribriform pattern

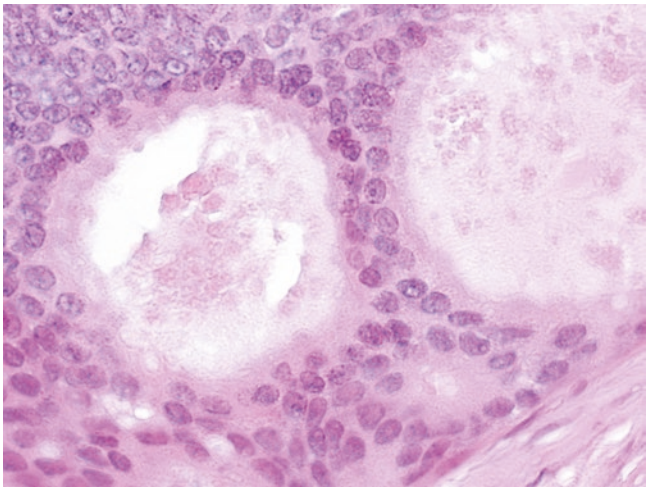


Fig. 11.6 Low-grade ductal carcinoma in situ with a cribriform pattern. The neoplastic cells show polarization around these lumens

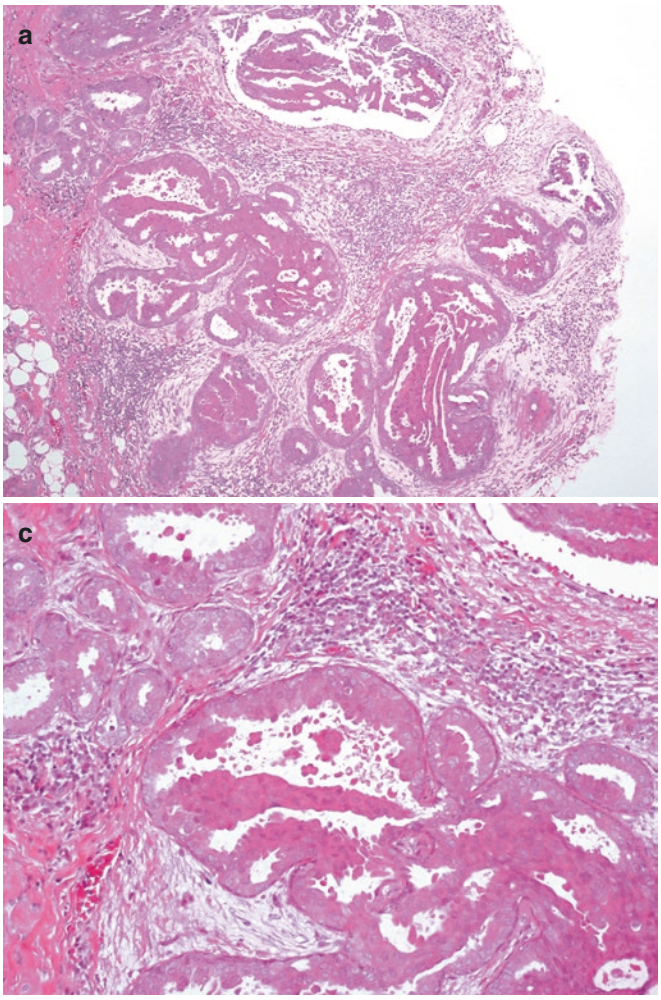


Fig. 11.7 Micropapillary carcinoma. (**a**, **b**) Slender fronds of micropapillary ductal carcinoma in situ form an irregular network of arches at the periphery. (**c**) Tufts of proliferating cells project into the lumen of the ducts

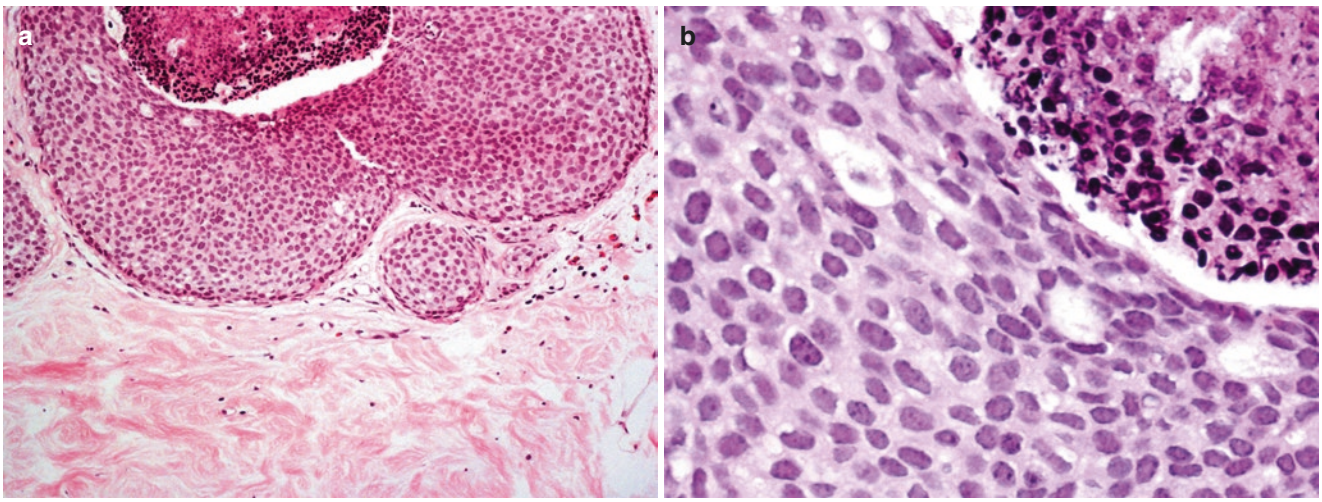


Fig. 11.8 (**a**, **b**) Low-grade ductal carcinoma in situ with comedo necrosis

11.3 High-Grade Ductal Carcinoma In Situ

High-grade DCIS consists of cells showing the archetypical characteristics of malignancy. The cells appear greatly enlarged and pleomorphic, and the nuclei and nucleoli usually look large, irregular, and pleomorphic (Fig. 11.9). Assessment of the size of the nuclei compared with adjacent normal cells (epithelial or red blood cells) provides particular assistance in classification. The nuclei of high-grade DCIS are typically more than 2.5 red-blood cells in diameter (Fig. 11.10) [8].

This grade of DCIS is often solid architecture, tends not to show polarization of cells, and frequently bears central (comedo-type) necrosis with or without associated microcalcifications (Fig. 11.11). Necrosis may be so extensive that only one layer or a few cell layers are present at the periphery of the involved space. Fibroblastic proliferation with collagen deposition (Fig. 11.12), chronic inflammation, and vascular proliferation are often seen in the stroma surrounding the involved spaces (Fig. 11.13).

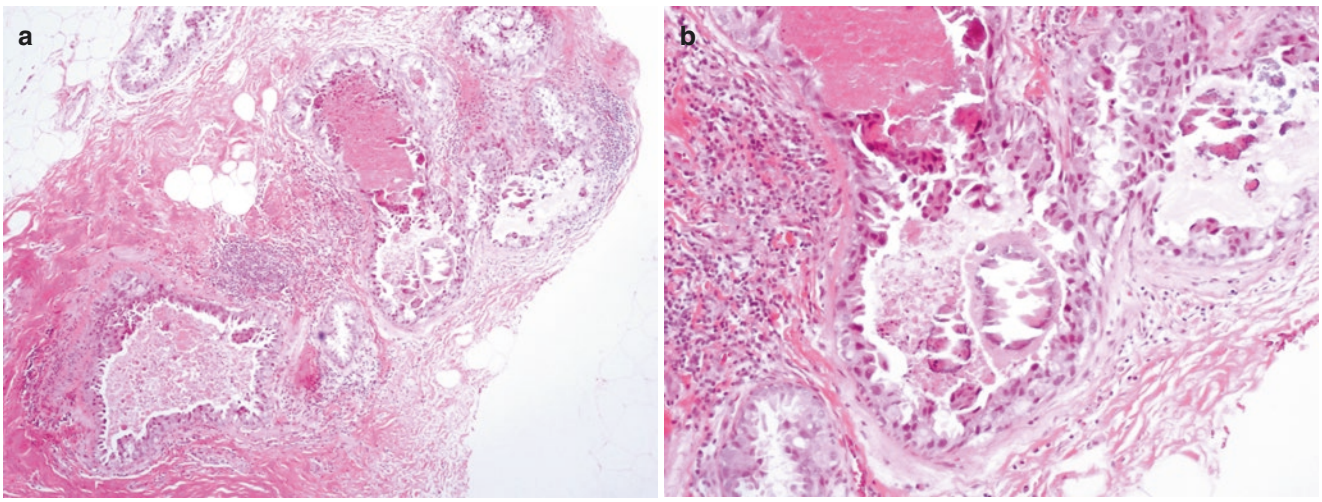


Fig. 11.9 High-grade ductal carcinoma in situ. (**a**, **b**) High-grade ductal carcinoma in situ with comedo necrosis and amorphous calcification

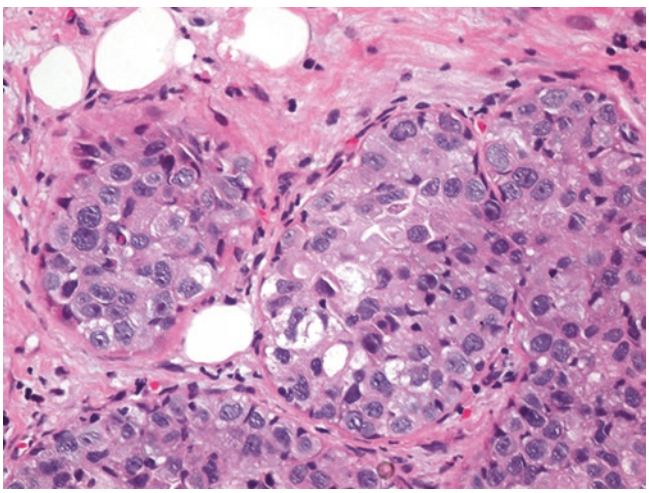


Fig. 11.10 High-grade ductal carcinoma in situ. Cells with large, pleomorphic nuclei that have vesicular or coarse chromatin and prominent nucleoli

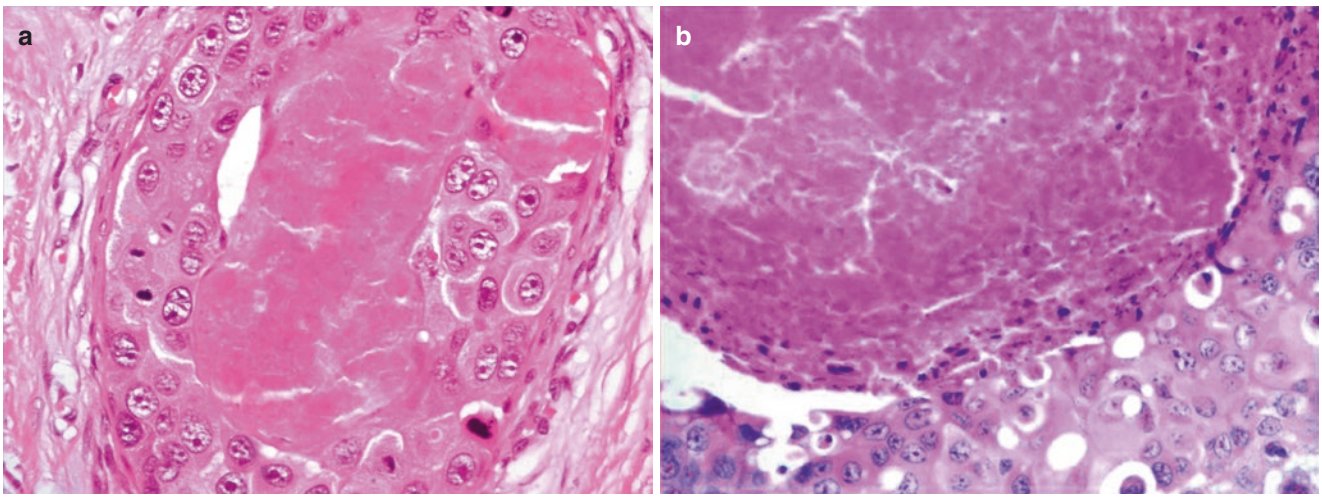
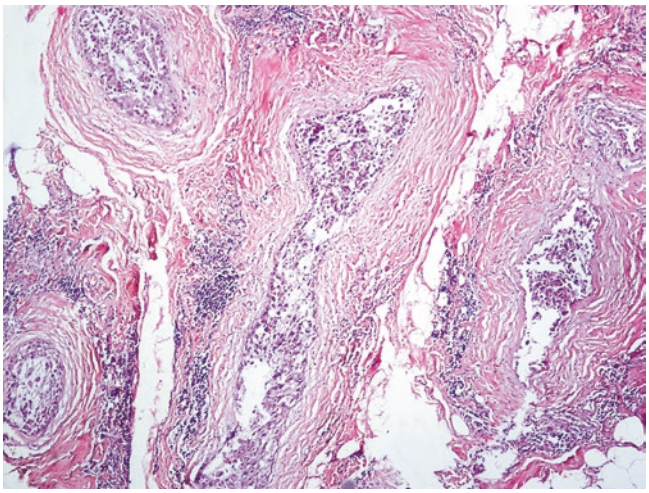


Fig. 11.11 High-grade ductal carcinoma in situ. (**a**, **b**) Ductal carcinoma in situ with comedo necrosis

Fig. 11.12 High-grade ductal carcinoma in situ. Marked periductal fibrosis can be associated with extensive obliteration of ducts, a process referred to as healing



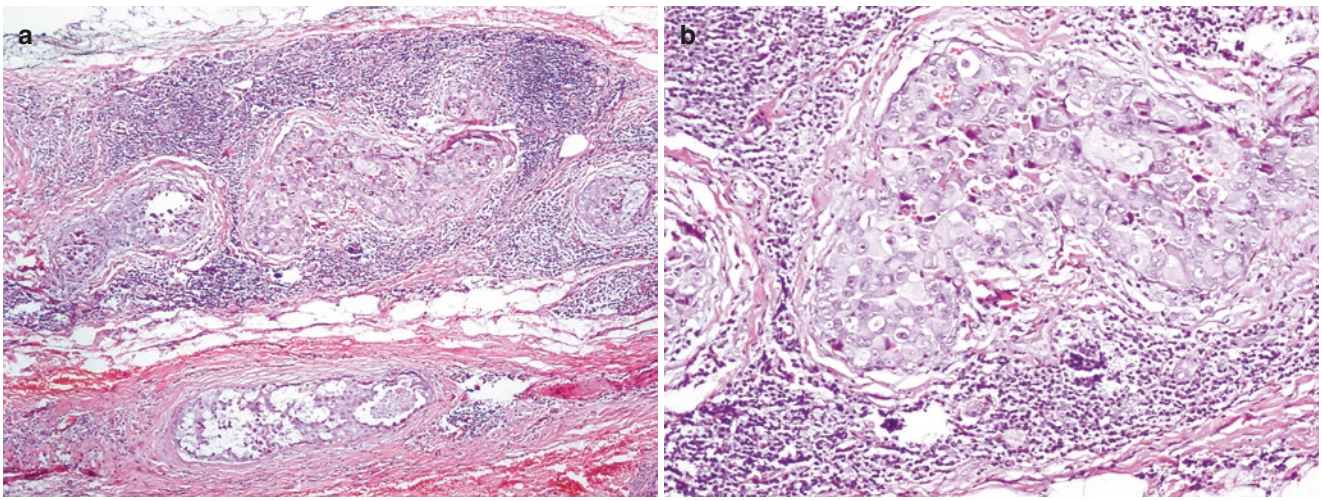


Fig. 11.13 (**a**, **b**) High-grade ductal carcinoma in situ with prominent chronic inflammation in the surrounding stroma

11.4 Intermediate-Grade Ductal Carcinoma In Situ

Intermediate-grade DCIS is diagnosed when the lesion cannot be assigned to high- or low-nuclear-grade categories. The cells may also grow in a cribriform pattern but without prominent cell polarization (Fig. 11.14). The nuclear–cytoplasmic (N:C) ratio is often high, and one or two small nucleoli may be present but are not prominent. The difference in ipsilateral recurrence rates between low- and intermediate-grade DCIS is not significant [9].

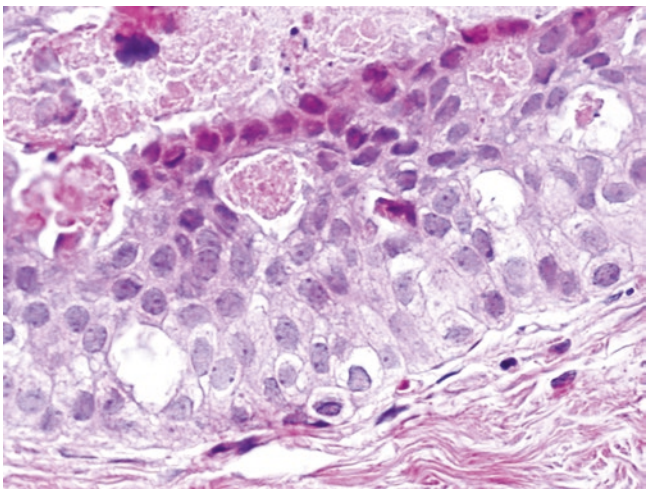


Fig. 11.14 Intermediate-grade cribriform DCIS. This duct is filled by cribriform DCIS without prominent cell polarization. N:C ratio is often high, and one or two small nucleoli may be present but are not prominent

11.5 Rare Variants of Ductal Carcinoma In Situ

A range of cell types is found in DCIS. Certain distinct variants have been identified and described by specific names. Signet ring cells, usually associated with lobular carcinoma, also occur in DCIS, most often in papillary and cribriform types [10]. Clear cell DCIS [11] is a poorly defined variant typically encountered with solid and "comedo" patterns (Fig. 11.15). The presence of a monomorphic clear cell population in a ductal proliferative lesion is highly suggestive of intraductal carcinoma.

Apocrine DCIS is characterized by cells that have abundant, eosinophilic cytoplasm (Fig. 11.16) [12]. The growth pattern may be solid, cribriform, or micropapillary, and necrosis can be present (either punctate or comedo).

Less commonly, DCIS may exhibit spindle cells (Fig. 11.17) [13], small cell, or adenoid cystic differentiation.

Cystic hypersecretory carcinoma is an uncommon variant of ductal carcinoma in situ that is recognized by its cystic appearance and characteristic luminal secretion. The cysts are lined by atypical epithelial cells, most often with a micropapillary pattern, but clinging, cribriform, and solid patterns may also be seen (Fig. 11.18) [14].

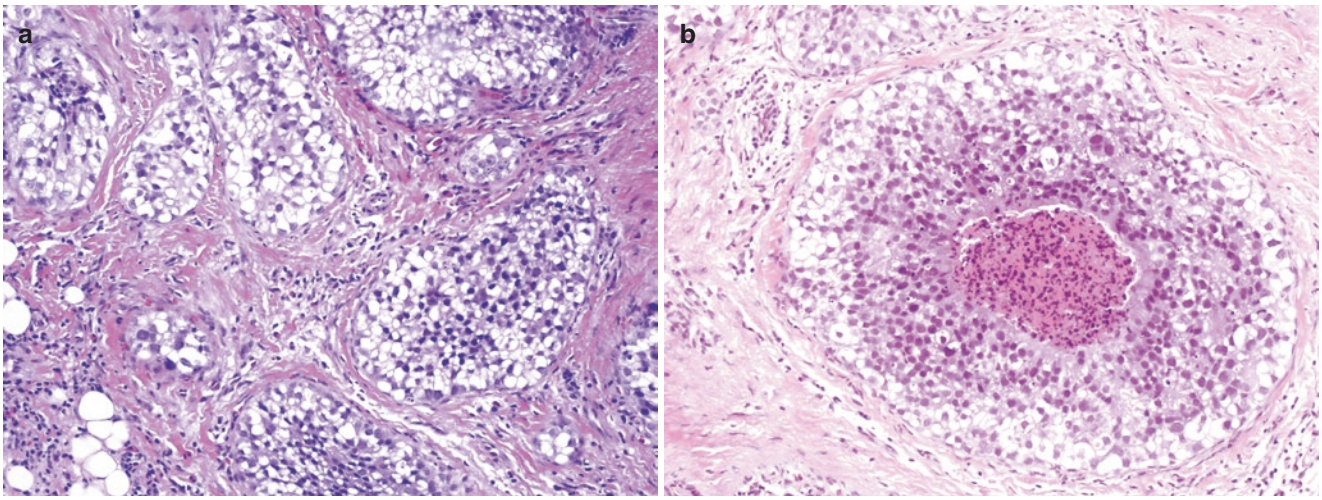


Fig. 11.15 (**a**, **b**) Ductal carcinoma in situ with clear cell features, the cells show prominent cytoplasmic clearing

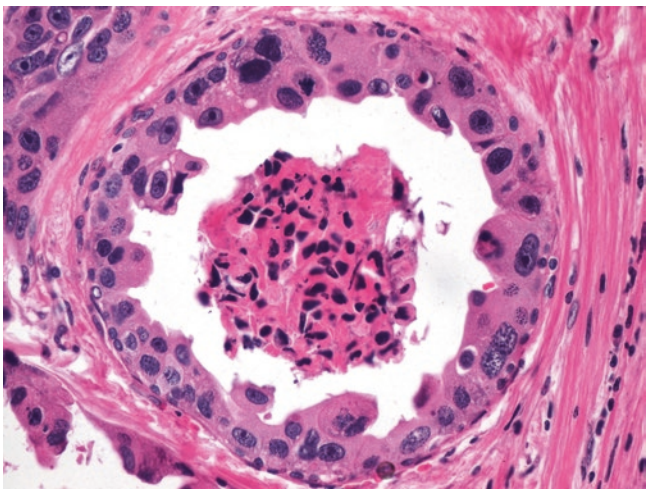


Fig. 11.16 High-grade ductal carcinoma in situ with enlarged nuclei and abundant eosinophilic cytoplasm

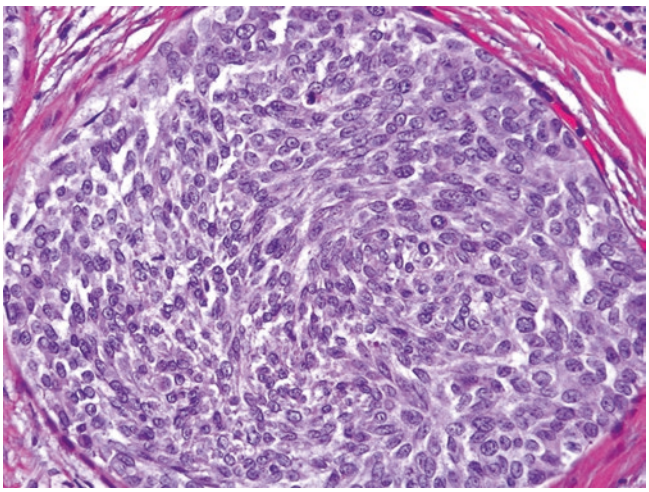


Fig. 11.17 Ductal carcinoma in situ with spindle cell features. The proliferation is composed of spindle-shaped cells with elongated nuclei that fill the involved space

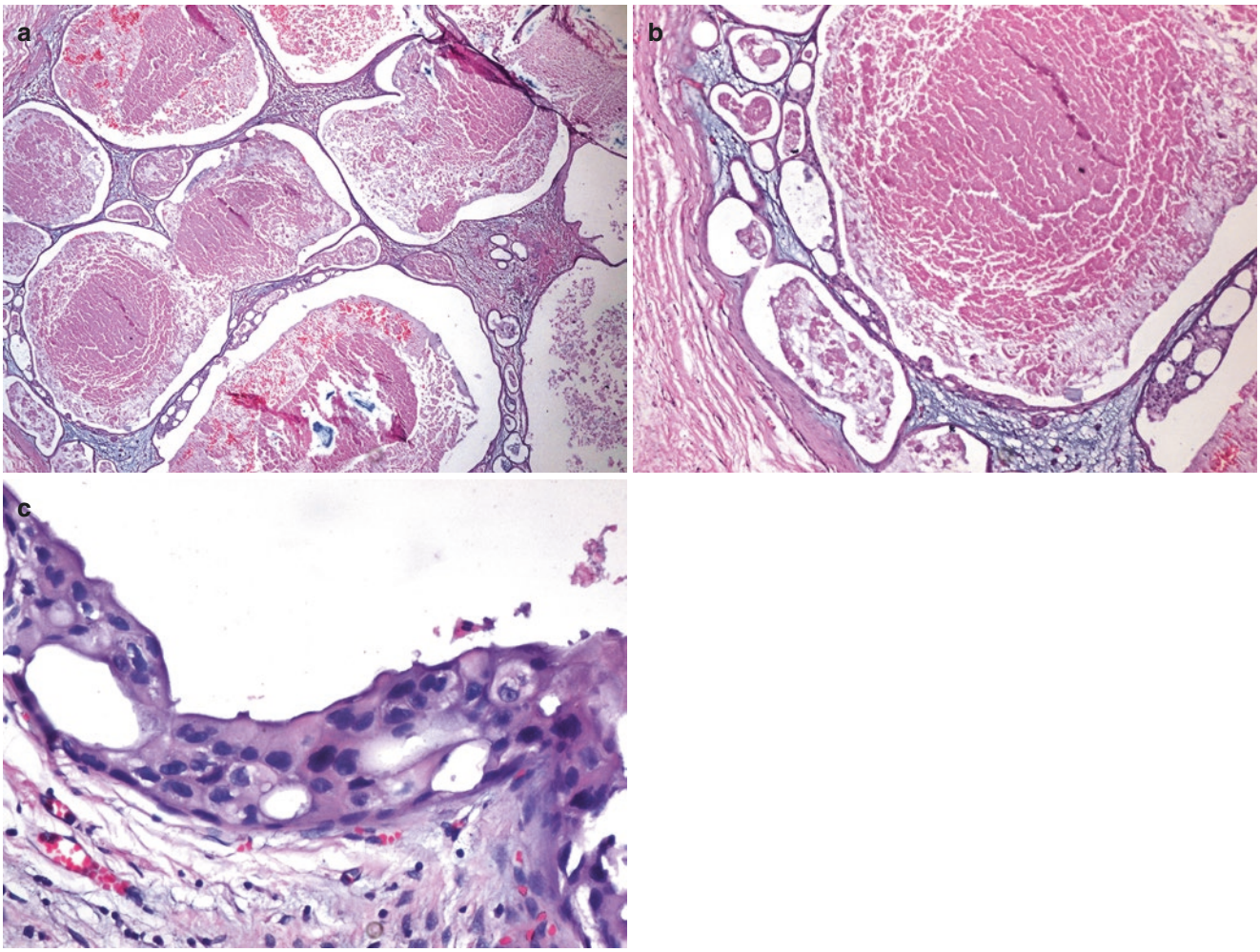


Fig. 11.18 Cystic hypersecretory ductal carcinoma in situ. (**a**) Low-power multiple cyst-like structures containing eosinophilic material and comedo necrosis. (**b**) The spaces are lined by epithelium with a cribriform pattern. (**c**) Epithelium with atypical cells

11.6 Immunohistochemistry

The distribution of receptor expression in DCIS is similar to that seen in invasive breast cancer. About 75–80% show positive nuclear staining for estrogen receptor (ER) (range, <1–100% of cells) (Fig. 11.19) [15]. The frequency of progesterone receptor (PR) expression in DCIS is somewhat lower.

Low-grade DCIS lesions typically show diffuse and strong ER and PR expression (Fig. 11.17). In contrast, high-grade DCIS lesions may be ER and PR positive or negative, have a high proliferative rate, and frequently show HER2 (human epidermal growth factor receptor 2) protein overexpression (Fig. 11.20) [16].

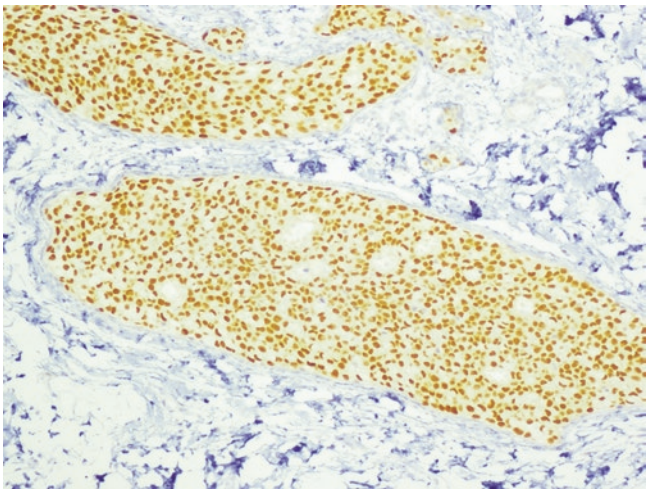


Fig. 11.19 Low-grade ductal carcinoma in situ and estrogen receptor immunostain**.** The neoplastic cells show intense strong nuclear staining

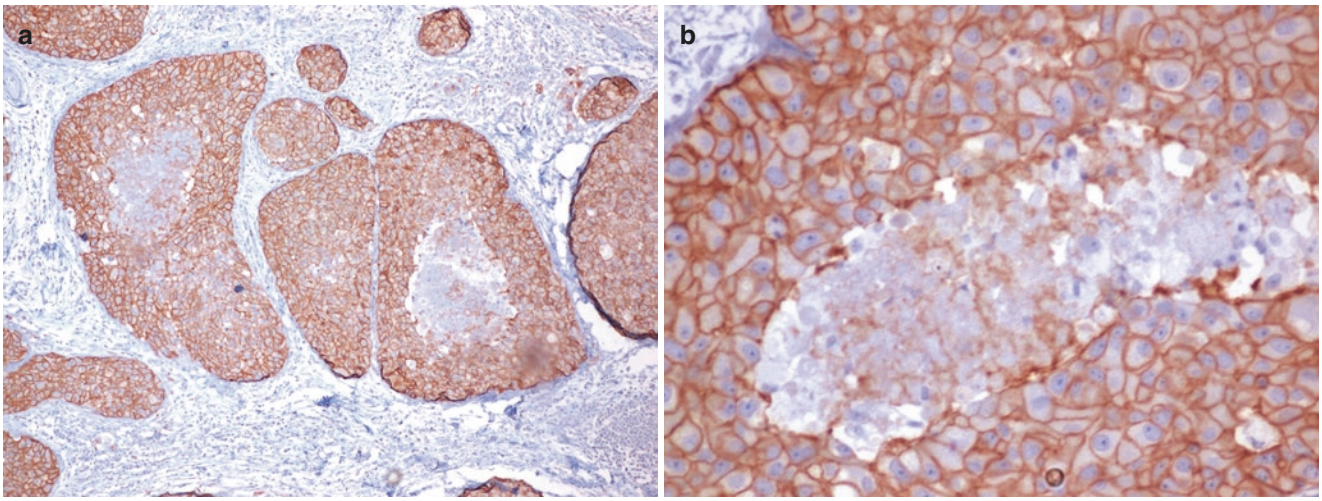


Fig. 11.20 High-grade ductal carcinoma in situ with comedo necrosis and HER2 immunostain. (**a**, **b**) The neoplastic cells show intense membrane staining (HER2 protein overexpression)

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