Intraductal Proliferations (DCIS, ADH, and UDH)

9

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Introduction

Intraductal epithelial proliferations of the breast can present a diagnostic challenge to pathologists because of subtle differences in the diagnostic features and biologic characteristics of these proliferations. These lesions include ductal carcinoma in situ (DCIS), atypical ductal hyperplasia (ADH), and usual ductal hyperplasia. Each of these diagnostic categories carries a different risk of development of invasive carcinoma and has different treatment strategies. While diagnostic agreement rates on the diagnosis of high-grade ductal carcinoma are excellent, low-grade intraductal proliferations have notoriously low diagnostic agreement rates because these lesions present with a spectrum of very similar histologic findings [1, 2]. Reproducible evaluation of these lesions on core needle biopsy requires using current diagnostic criteria but also often must take into account clinical context. Figure 9.1 shows an overview of the main diagnostic categories and their characteristics.

The diagnosis of intraductal proliferative lesions on core biopsy requires evaluation of the cytologic and architectural features present as well as the extent of the process. Figure 9.2 shows an overview of the steps in this evaluative process. If the cytology is intermediate to high grade, a diagnosis of high-grade DCIS and its mimics should be considered, regardless of the extent or architecture. However, for lesions with low or borderline intermediate grade cytology, evaluation of the architecture of the proliferation is the next step in establishing the most accurate diagnosis. Are there architectural structures being formed that are associated with low-grade neoplasia, such as cribriform structures with polarized spaces, club-shaped micropapillae, or rigid bridges of uniform thickness? Or is the architecture more typical of a polyclonal process like usual ductal hyperplasia with swirling, overlapping cells, and non-polarized slit-like spaces?

The architectural and cytologic features are not always straightforward. Solid or spindled proliferations can be diagnostically challenging, but additional immunohistochemical studies can often help clarify the nature of the process and will be discussed. Lesions with a papillary architecture can also present a particular challenge in this diagnostic spectrum but will be discussed separately in Chap. 6.

When a diagnosis of low-grade DCIS versus ADH is being considered based on the cytologic and architectural features present, evaluation of the extent of the lesion becomes important when deciding which diagnostic category to assign. Both the uniformity of the process and the size of the lesion enter into the evaluation of extent. Are the spaces partially or completely involved by the atypical proliferation (is the process uniform or non-uniform)? Is the lesion larger than 2 mm, the size threshold used by Tavassoli and Norris to diagnose low-grade DCIS (when cytologic and architectural criteria are met) [3]? When in doubt, particularly on core needle biopsies where the entire extent of the lesion is still unclear, assigning a borderline diagnosis such as "ADH bordering on low-grade DCIS" or "ADH suspicious for low-grade DCIS" may be the most appropriate diagnosis to render to avoid overdiagnosis and overtreatment.

This chapter will begin with a discussion of DCIS and then follow with ADH and usual ductal hyperplasia.

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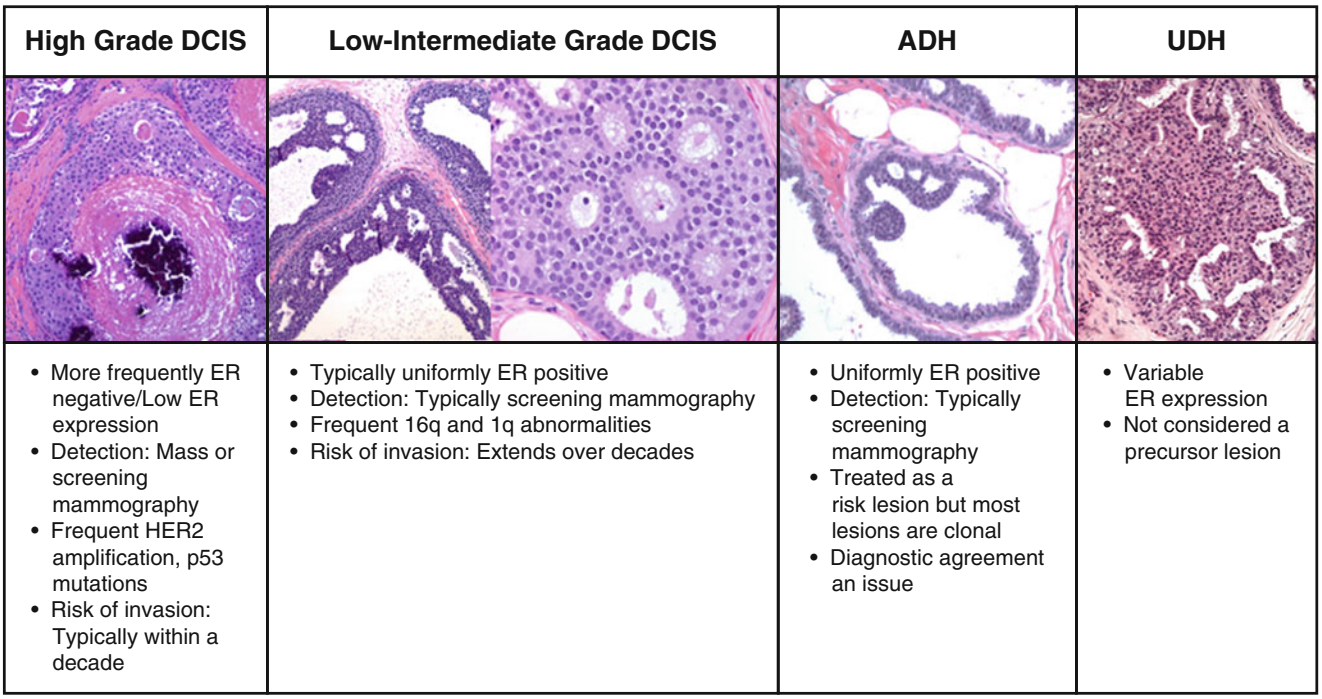

Fig. 9.1 Spectrum of intraductal proliferative lesions

Ductal Carcinoma In Situ

Overview

DCIS is a non-obligate precursor to invasive breast cancer. In contrast to atypical lesions, which carry a bilateral risk of developing invasive cancer, DCIS is classically treated as an ipsilateral precursor to invasion with complete surgical removal for local control purposes. Natural history studies on DCIS detected in the pre-screening era indicate that when left completely untreated, it can evolve into invasive carcinoma in the same area in the majority of patients. However, high-grade DCIS has a more immediate risk of invasion within 5 years, while low-grade DCIS has a much longer time-course to invasion that extends over many decades [4–8]. These differences imply a spectrum of biology and behavior for lesions classified as DCIS. In fact, DCIS is a heterogeneous group of noninvasive neoplastic lesions with different clinical presentations, risks, and potential management strategies.

The incidence of DCIS and its frequency on breast biopsy has increased dramatically in the era of mammographic screening [9–11]. In 1975, 5.8 US women per 100,000 were diagnosed with DCIS, while in 2012, this rate had climbed to 32.5 women per 100,000 [12]. This increase has largely been due to detection of smaller, low-grade, non-comedo DCIS with the incidence of high-grade DCIS remaining relatively stable [13, 14]. In population-based studies, 5–6% of breast core biopsies contain DCIS as the clinically most significant diagnosis, but the proportion of breast biopsies with DCIS increases with age and will also depend on practice characteristics and patient demographics [9].

Gross and Radiologic Features

In general, 80–85% of DCIS is detected by mammography with the remainder presenting as a mass and some in high-risk patients as MRI findings [15, 16]. Less commonly, DCIS can be present initially as bloody nipple discharge, Paget's disease of the nipple or as an incidental finding in breast tissue removed for other reasons. If core biopsies were performed for calcifications, radiographs of the cores are typically performed by radiology to confirm the presence of calcifications in the samples. The presence of calcifications in these films should be correlated with the presence of calcifications microscopically. If the targeted calcifications are not identified on histology, additional levels or radiography of the tissue blocks should be performed.

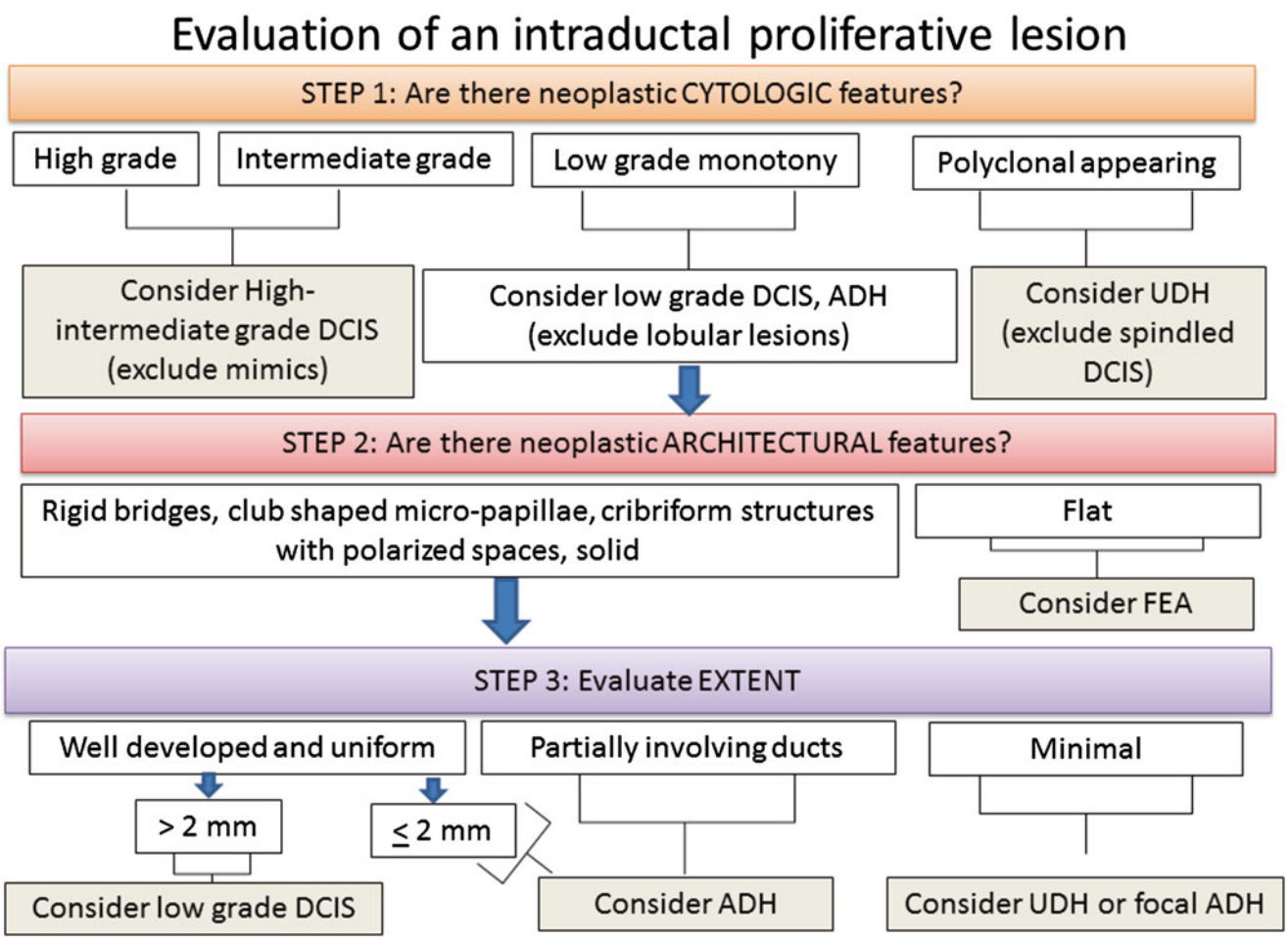

Fig. 9.2 Algorithm for diagnosing intraductal proliferative lesions

With any case of DCIS, the gross examination and tissue sampling procedures will be key to determining if there is also invasive carcinoma present. The College of American Pathologists recommends serial sequential sampling of the entire area of interest to exclude invasion, evaluate margins, and determine an accurate extent of disease [17]. This is especially true in cases of high-grade DCIS, where the presence of occult invasive carcinoma is higher. Creating a "map" of where tissue is submitted from is also crucial to determining an accurate size of both the DCIS and any occult-invasive carcinomas identified.

High-Grade DCIS Spectrum

While most high-grade DCIS is detected as calcifications on screening mammography, in contrast to low-grade DCIS, it can also frequently present as a mass or architectural distortion [18]. Less commonly, it presents as Paget's disease of the nipple or nipple discharge. On screening mammography, high-grade DCIS appears most commonly as abundant, linear, pleomorphic, or course heterogeneous calcifications, while granular segmental calcifications are more frequently associated with low-grade DCIS. Calcifications in high-grade DCIS are often associated with necrosis histologically.

MRI has become a useful imaging adjunct to mammography in high-risk patients and has a higher sensitivity for detection and evaluation of DCIS extent [19]. On MRI, high-grade DCIS presents as non-mass enhancement, a finding that can also be present in benign disease. MRI is particularly sensitive for high-grade DCIS with studies showing sensitivities of up to 98% on MRI versus only 56% on mammography [20]. The extent of DCIS on MRI is also often larger than the extent noted on mammography, but it can also be occult on MRI and only apparent as calcifications on mammography [21]. The largest lesion size on any imaging modality should be used to determine the extent of gross tissue sampling so that the true extent of disease present microscopically can be accurately measured.

Grossly, high-grade DCIS frequently has a gritty texture due to the comedo-necrosis and associated calcifications

present. Comedo-necrosis can be grossly apparent as punctate secretions. However, these gross findings will be difficult to appreciate on a non-surgical, core needle biopsy specimen.

Low-Grade DCIS Spectrum

Low-intermediate grade DCIS is largely a screen-detected lesion. Granular segmental calcifications are the finding that prompts biopsy, with only rare cases presenting as a mass, architectural distortion or nipple discharge. Paget's disease of the nipple is not associated with low-grade DCIS but may be intermediate-high grade DCIS.

While the span of the calcifications on screening mammography is used to estimate extent, these calcifications do not always correlate with the microscopic extent. Calcifications can also be present in adjacent risk lesions, columnar cell change, and fibro-proliferative changes, resulting in an overestimate of the extent of DCIS. DCIS can also extend far beyond the area of calcifications. Therefore, it is essential to closely correlate the imaging, gross and macroscopic findings when estimating size/extent of DCIS. On a core biopsy, reporting the presence of calcifications and if they are in the DCIS or surrounding changes can be helpful in guiding preoperative surgical treatment options.

Microscopic Features

High-Grade DCIS Spectrum

High-grade DCIS is characterized by its high nuclear grade, with pleomorphic nuclei. Mitotic figures are frequently seen, including atypical mitotic figures. Unlike low-grade DCIS, there is no requirement for a specific architectural pattern or extent and the diagnosis is made when there is an intraductal proliferation with high-grade cytology (see below for differential diagnosis).

High-grade DCIS can take on a variety of histologic growth patterns, many of which are also common in low-intermediate grade DCIS. The classic, "comedo-DCIS" is most characteristic of high-grade DCIS (Fig. 9.3a–c). It is typically solid in growth pattern with central areas of comedo-necrosis. The stroma around high-grade DCIS is often desmoplastic, with increased cellularity and prominent lymphocytic inflammation. Sometimes, the involved ducts become quite sclerotic and there are only small amounts of residual high-grade epithelium. On a core biopsy sample, if sclerotic ducts with associated lymphocytic inflammation are seen, additional levels can reveal diagnostic areas with more high-grade epithelium.

High-grade DCIS can extend from the ducts into the lobules, a process referred to as "cancerization of the lobules" (Fig. 9.4a–d). When there is a background of sclerosing adenosis involved by DCIS, the process can mimic invasion (Fig. 9.5a–d). Usually on H&E there are low-power, pattern-based clues that the process is more consistent with the nodular, "windswept" pattern of sclerosing adenosis involved by DCIS than the more infiltrative and diffuse pattern of invasive carcinoma. However, some cases are very challenging to distinguish from invasion. Examination of the patterns of sclerosing adenosis, atrophy, and fibro-proliferative changes in the background can be helpful for comparison. On higher power, close inspection often confirms the presence of basement membrane surrounding these areas. Myoepithelial cell stains can be very useful in this setting to confirm that the process is in situ (see "Differential Diagnosis" section below).

Cribriform growth patterns are also common in high-grade DCIS, frequently with at least focal, single cell necrosis (Fig. 9.6). In contrast to low-grade DCIS, the spaces formed by the cribriform pattern in high-grade DCIS are not necessarily "punched out" or polarized. Micropapillary growth patterns can occur in high-grade DCIS (Fig. 9.7a, b) but are more common in low-intermediate grade DCIS.

Clinging carcinoma is a pattern specific to high-grade DCIS where a single or few cell-thick layers of pleomorphic cells (Fig. 9.8). The ducts are frequently dilated and filled with comedo-type necrosis. The high-grade cytologic atypia is key to diagnosing this pattern. Care should be taken to exclude mimics such as atypical cystic hypersecretory or atypical pregnancy-like (pseudolactational) changes (see "Differential Diagnosis" section).

High-grade DCIS frequently has apocrine cytologic features, with obviously high-grade nuclei and abundant eosinophilic, sometimes granular cytoplasm (Fig. 9.9). High-grade DCIS can have other less common types of cytologic differentiation including clear cell change (Fig. 9.10) and mucinous differentiation (although this is more common in low-grade DCIS). Rarely, small cell forms of high-grade DCIS are recognized. These specific histologic types have not been consistently shown to have outcomes different from other high-grade DCIS.

Cystic hypersecretory DCIS (also frequently called "cystic hypersecretory carcinoma") is a form of DCIS that is characterized by the dense eosinophilic, colloid-like secretions present in cystically dilated ducts/lobules (Fig. 9.11a–d). These lesions need to be distinguished from forms of cystic hypersecretory hyperplasia with or without atypia. An in-depth discussion of cystic hypersecretory carcinoma is discussed in Chap. 13.

Low-Grade DCIS Spectrum

The diagnosis of low-grade DCIS requires adherence to strict criteria that includes evaluation of the cytology, architecture, and extent. The nuclei of low-grade DCIS are small, very round, and have homogenous chromatin (Fig. 9.12a, b). The cell borders are well-defined and evenly spaced. Mitotic figures are rare but may be present and the monotony present

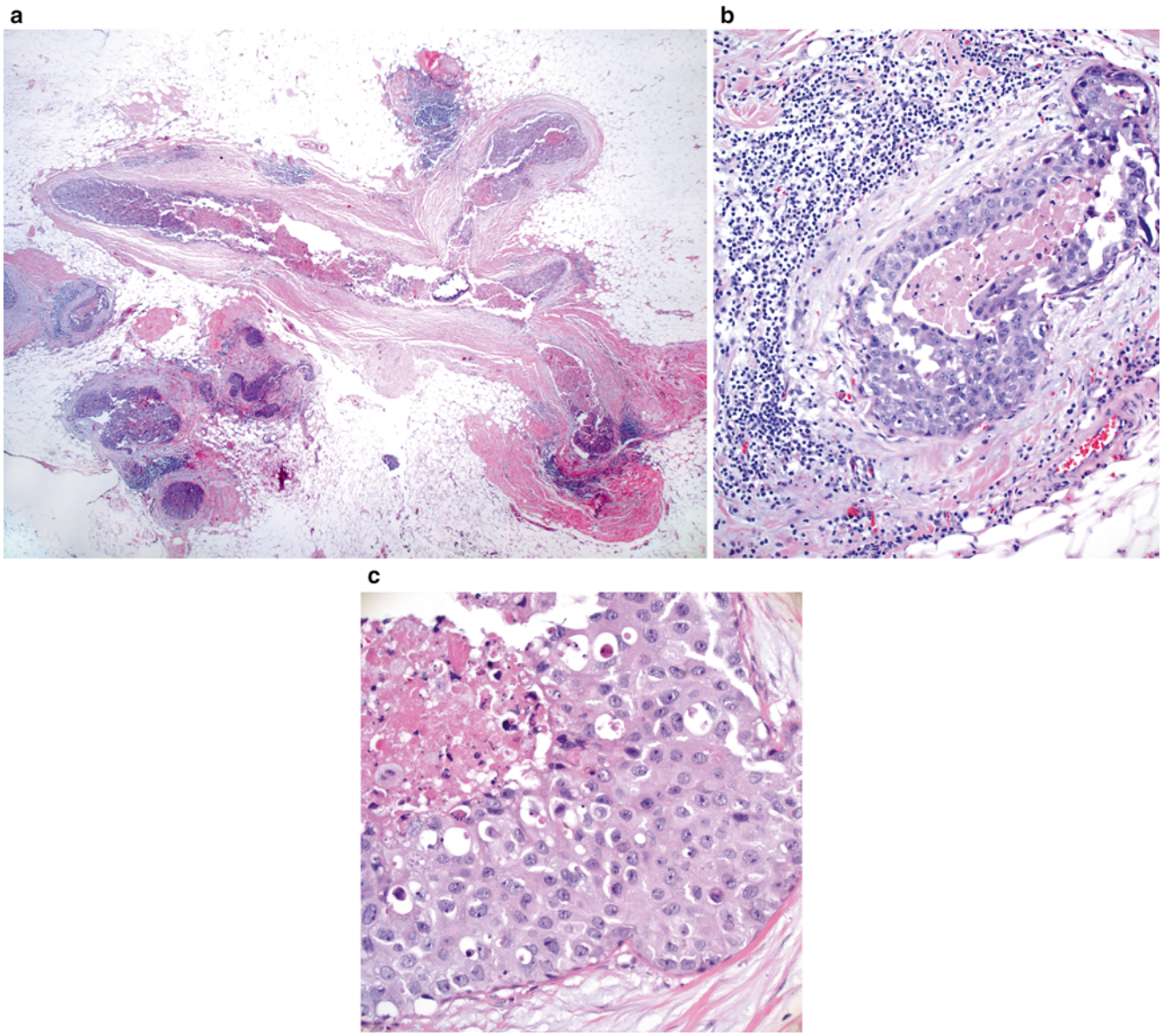

Fig. 9.3 High-grade DCIS, comedo-type with sclerosis around the ducts (**a**), and inflammation (**b**). The nuclear grade is high and there is central comedo-necrosis (**c**)

is typically uniform. When the nuclear grade is intermediate, architectural and the extent criteria are not used.

The architectural features of low-grade DCIS include several characteristic patterns, many of which can be present in the same case. Cribriform spaces tend to be crisp and "punched out" appearing, but not always uniformly. The formation of polarized neo-lumens with the nuclei oriented away from the spaces is a reliable feature associated with low-grade neoplasia in this setting (Fig. 9.13a–d). Solid patterns of low-grade DCIS fill the involved ducts and lobules involved and can have only subtle polarized micro-acini present within it (Fig. 9.14a–d). Rarely, necrosis is present in association with this form of low-grade DCIS.

Low-intermediate grade micropapillary structures are club-shaped and maintain their uniform nuclei throughout the processes (Fig. 9.15a–d). The micropapillae can vary in length and development from club-shapes to elongate projections and rigid arcades. When extensive, the micropapillary projections can become maze-like in complexity. In contrast to micropapillary ADH, these micropapillae need to more completely involve the lesional ducts for a diagnosis of low-grade micropapillary DCIS (see below section on micropapillary ADH). This pattern of DCIS tends to be more extensive and multifocal, is more often pure in pattern and can be more challenging to excise to negative margins. In other instances, low-grade micropapillary DCIS arising

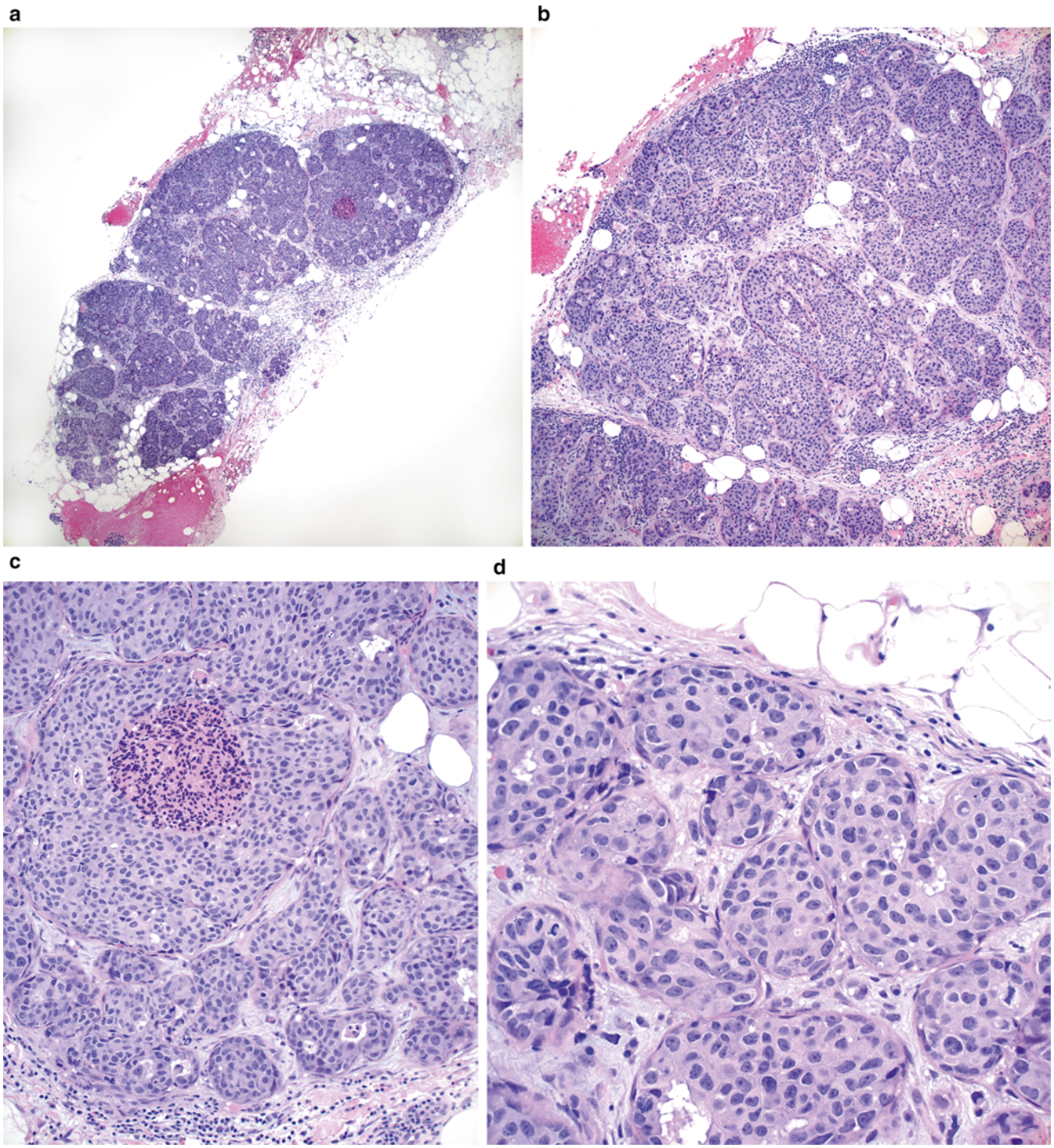

Fig. 9.4 High-grade DCIS with cancerization of lobules

intermittently in a background of micropapillary ADH can be seen. These cases are particularly difficult as the full spectrum of micropapillary proliferation is present and multifocal in distribution. Quantifying the extent of DCIS in these instances is particularly problematic. Despite similarities in nomenclature, micropapillary DCIS is *not* more frequently associated with micropapillary invasive carcinoma.

Low-grade DCIS is often present within a spectrum of low-grade neoplasia that includes ADH, flat epithelial atypia (FEA) and sometimes lobular lesions (Fig. 9.16a–d).

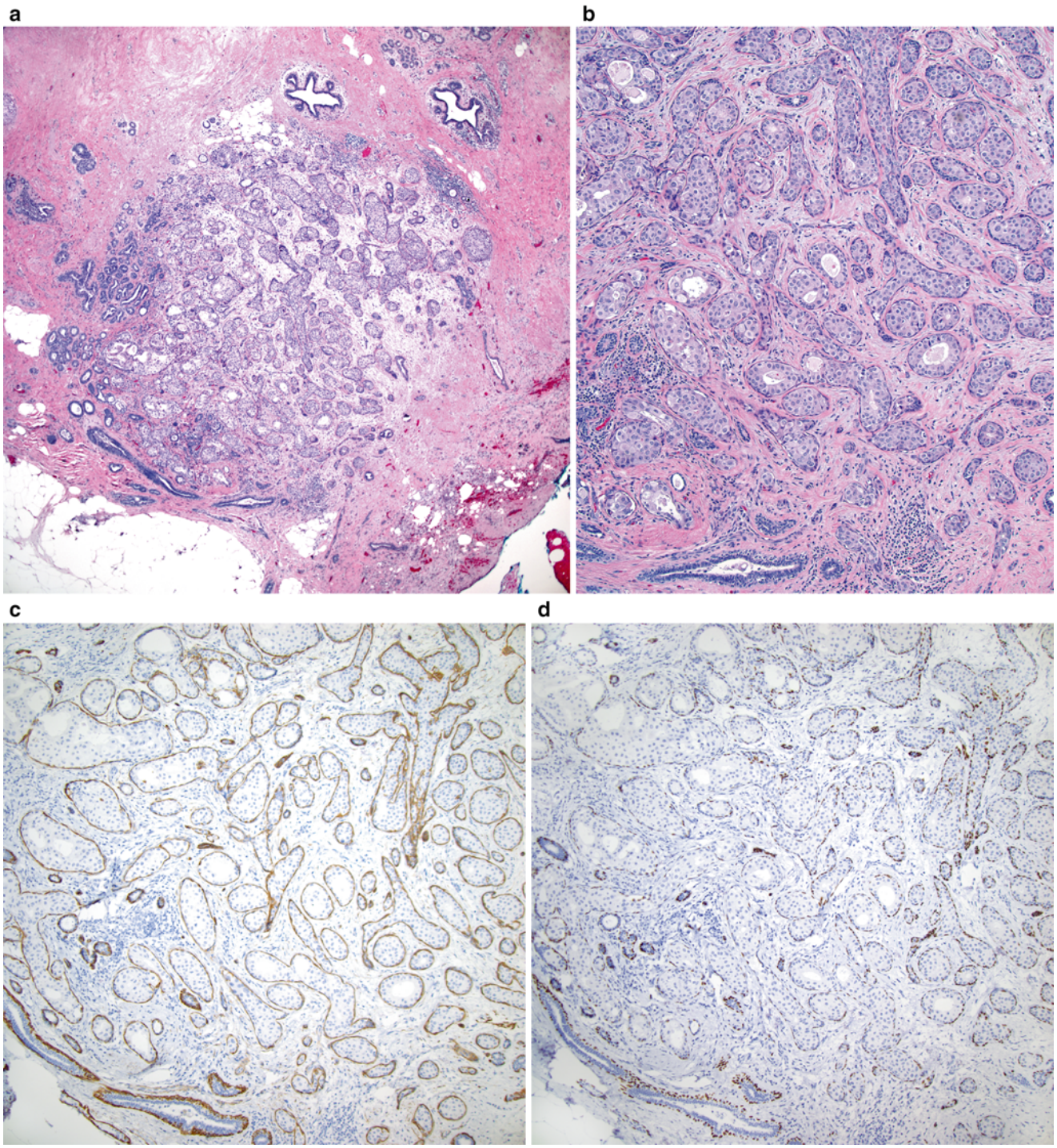

Fig. 9.5 High-grade DCIS involving sclerosing adenosis. On low power (**a**) the underlying architecture of sclerosing adenosis is more apparent that on higher power (**b**). Calponin (**c**) and p63 (**d**) stains will outline the myoepithelial layer, ruling out an invasive process

On a core needle biopsy, description of this combination of findings and which lesions contain the targeted calcifications can be helpful to surgeons when planning surgical excision options. On excisional specimens, it can be challenging to differentiate between areas that qualify as low-grade DCIS versus lesions that are background ADH, etc. when evaluating size/extent and margin status of low-grade DCIS. Terminology such as "spectrum of low-grade in situ

neoplasia, including low-grade DCIS, ADH, and FEA" can be helpful to describe these cases and their diagnostic challenges to clinicians. Pathologists must both use diagnostic criteria and their clinical judgment on such cases as these are more susceptible to higher interobserver variability.

The low-grade spectrum of DCIS also includes a papillary growth pattern which is characterized by monotonous tall columnar to rounded epithelial cells lining papillary structures containing fibrovascular cores (Fig. 9.17a, b). Myoepithelial cells are typically lacking within these fibrovascular cores but are maintained in the surrounding basal layer of the duct. This growth pattern of DCIS can be seen as a pure form but is also frequently admixed with micropapillary and cribriform patterns (Fig. 9.18a, b). When present, papillary DCIS can have a nodular growth pattern and be identified as multiple nodular areas on imaging. Low-grade DCIS can also involve benign papillary lesions or form dominant nodules ("encysted" or "encapsulated" papillary carcinomas). The spectrum of these more frequently solitary lesions are discussed in Chap. 6. On a core needle biopsy, for lesions that are predominantly papillary with a differential that includes papillary DCIS, encysted papillary carcinoma, or ADH/DCIS involving a papilloma, a diagnosis of "atypical papillary lesion" can be most appropriate to defer evaluation of the entire lesion to an excisional specimen.

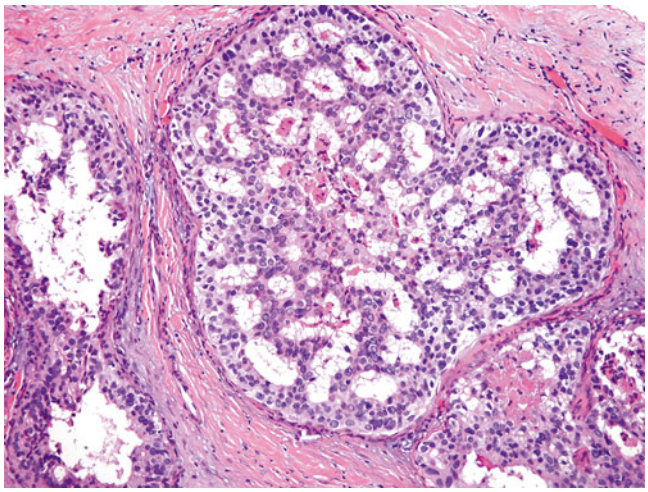

Fig. 9.6 Cribriform pattern high-grade DCIS

Low-grade apocrine DCIS is an uncommon DCIS variant characterized by abundant eosinophilic cytoplasm and bland but enlarged nuclei with prominent nucleoli. Because these cytologic features are similar to apocrine metaplasia and apocrine atypia, emphasis on the architectural growth patterns seen in other forms of DCIS is emphasized for a diagnosis. Most often, low-grade apocrine DCIS has a solid or cribriform growth pattern (Fig. 9.19). Caution should be used when evaluating micropapillary structures since benign apocrine metaplasia frequently forms club-shaped papillae. In addition, for lesions that only involve sclerosing adenosis without additional diagnostic areas, a diagnosis of atypical apocrine adenosis should be strongly considered.

Low-intermediate grade DCIS can take on a spindled growth pattern that mimics florid usual ductal hyperplasia. The cells contain nuclei that are elongated and hyperchromatic rather than rounded and are present in streaming patterns with solid growth (Fig. 9.20a, b). The more intermediate-grade nuclear features are critical to the recognition of this form of DCIS. See the differential diagnosis section below which includes a discussion of features and immunohistochemical techniques used to distinguish between these two entities.

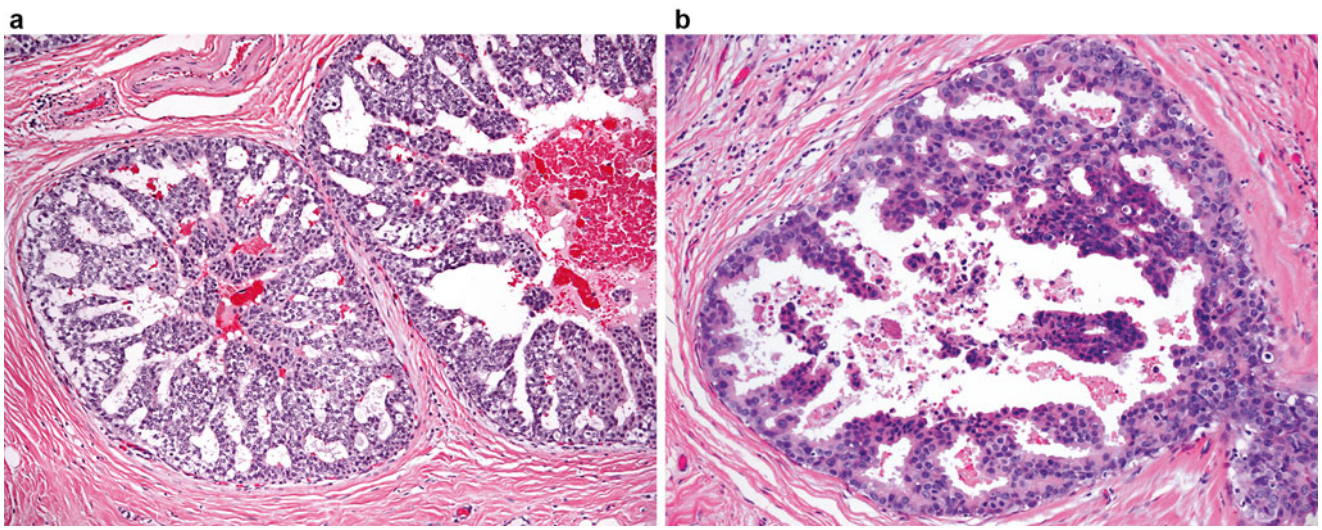

Fig. 9.7 High-grade micropapillary DCIS. (**a**) Extensive micropapillary projections are present with high-grade nuclei. (**b**) Single cell necrosis is present

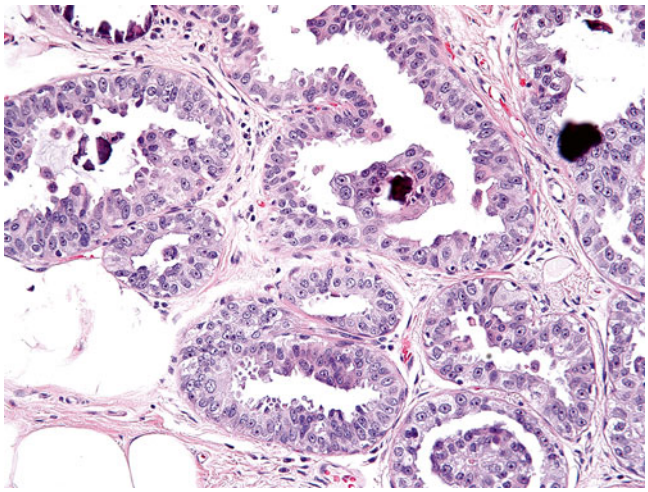

Fig. 9.8 Clinging carcinoma has a flat growth pattern but high-grade nuclei. Many cases also have central comedo-necrosis (not shown)

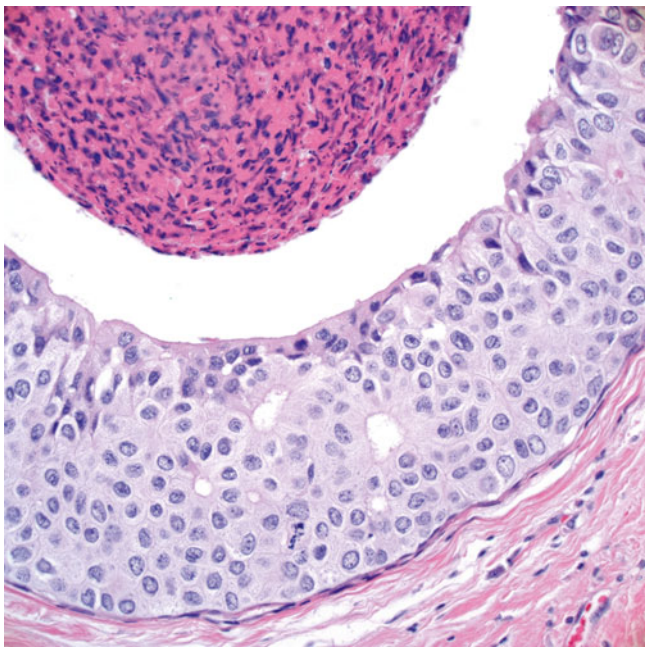

Fig. 9.9 High-grade DCIS with apocrine features (abundant eosinophilic cytoplasm) and comedo-necrosis

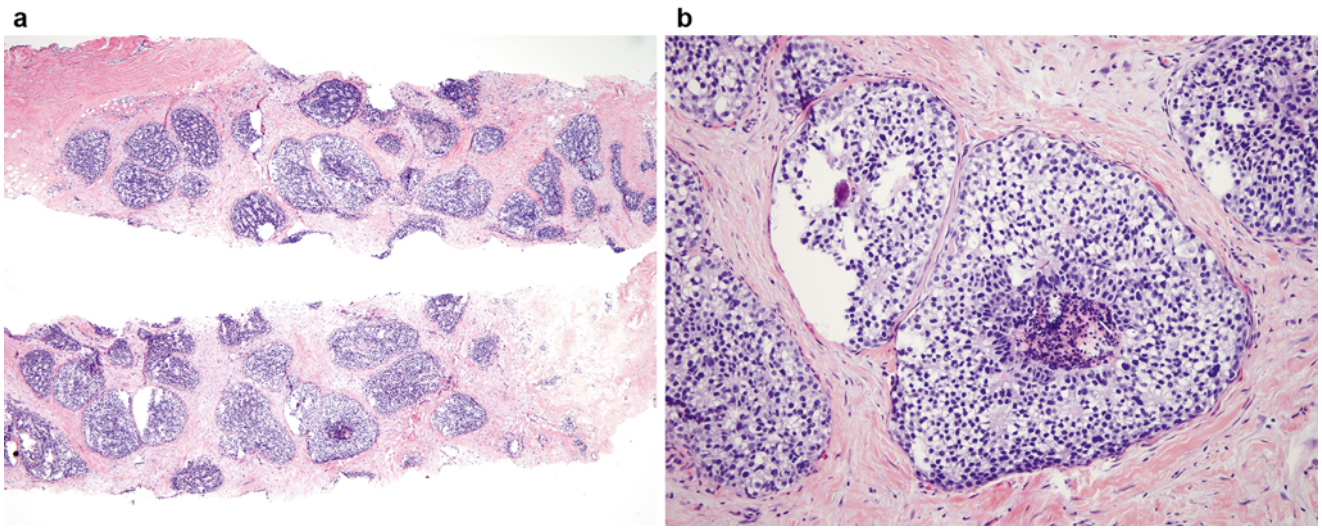

Fig. 9.10 Clear cell change in high-grade DCIS on core biopsy. (**a**) 1× magnification, (**b**) 10× magnification

Differential Diagnosis

High-Grade DCIS Spectrum

Invasion versus high-grade DCIS: When high-grade DCIS is extensive, it can be very challenging to rule out or differentiate from invasion due to the density of DCIS and the commonly present surrounding inflammation and sclerosis (Fig. 9.21a, b). However, because invasion in the setting of extensive high-grade DCIS is frequently also of high grade and HER2 positive, ruling out invasion is a critical job of the pathologist examining such a case [22] (Fig. 9.22a, b). A sentinel lymph node may be performed if invasion of any size is identified. According to the NCCN breast cancer treatment guidelines, treatment with chemotherapy (plus

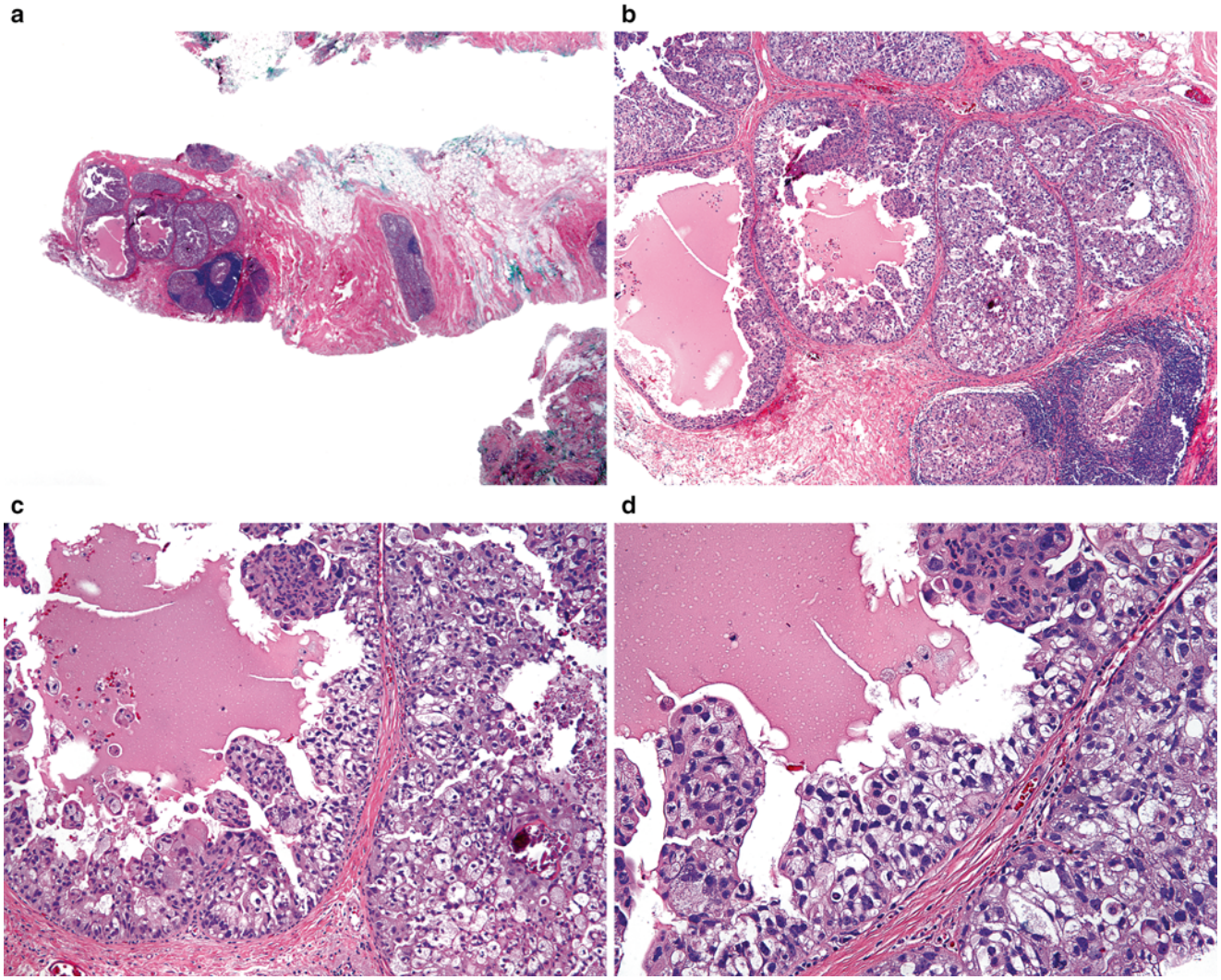

Fig. 9.11 Cystic hypersecretory DCIS on core biopsy at low-power magnification (**a**), intermediate (**b**) and high-power magnifications (**c**, **d**). Note the dense colloid-like secretion that has scalloped borders and is characteristic of hypersecretory lesions. The nuclei in this example are hyperchromatic, pleomorphic, and irregular

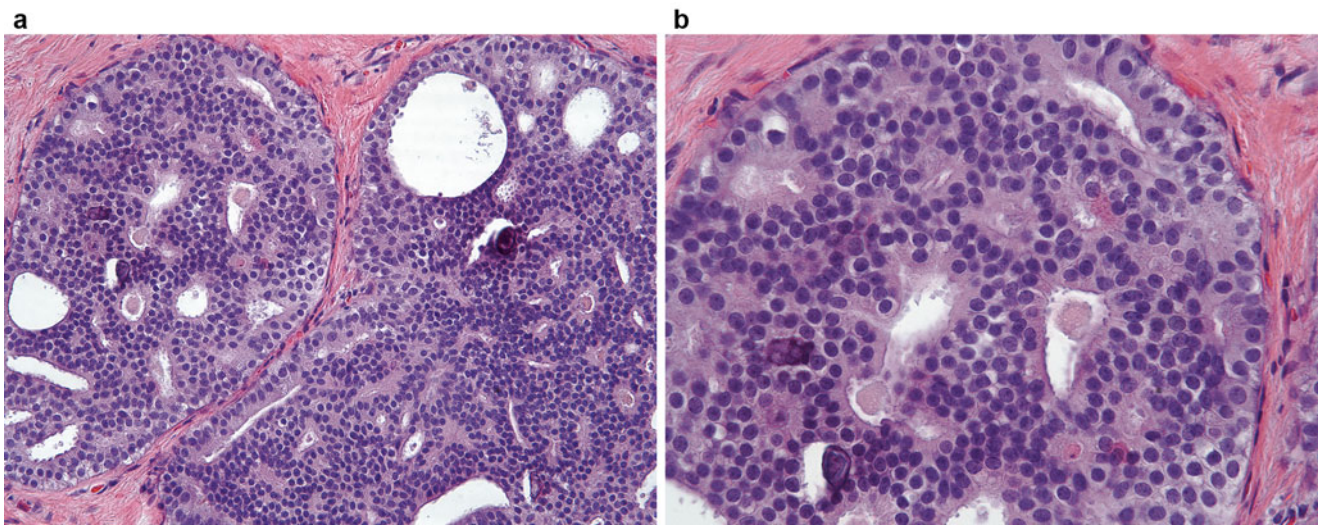

Fig. 9.12 Low-grade DCIS has cells with rounded, monotonous nuclei evenly distributed throughout the proliferation. (**a**) 20× magnification, (**b**) 40× magnification

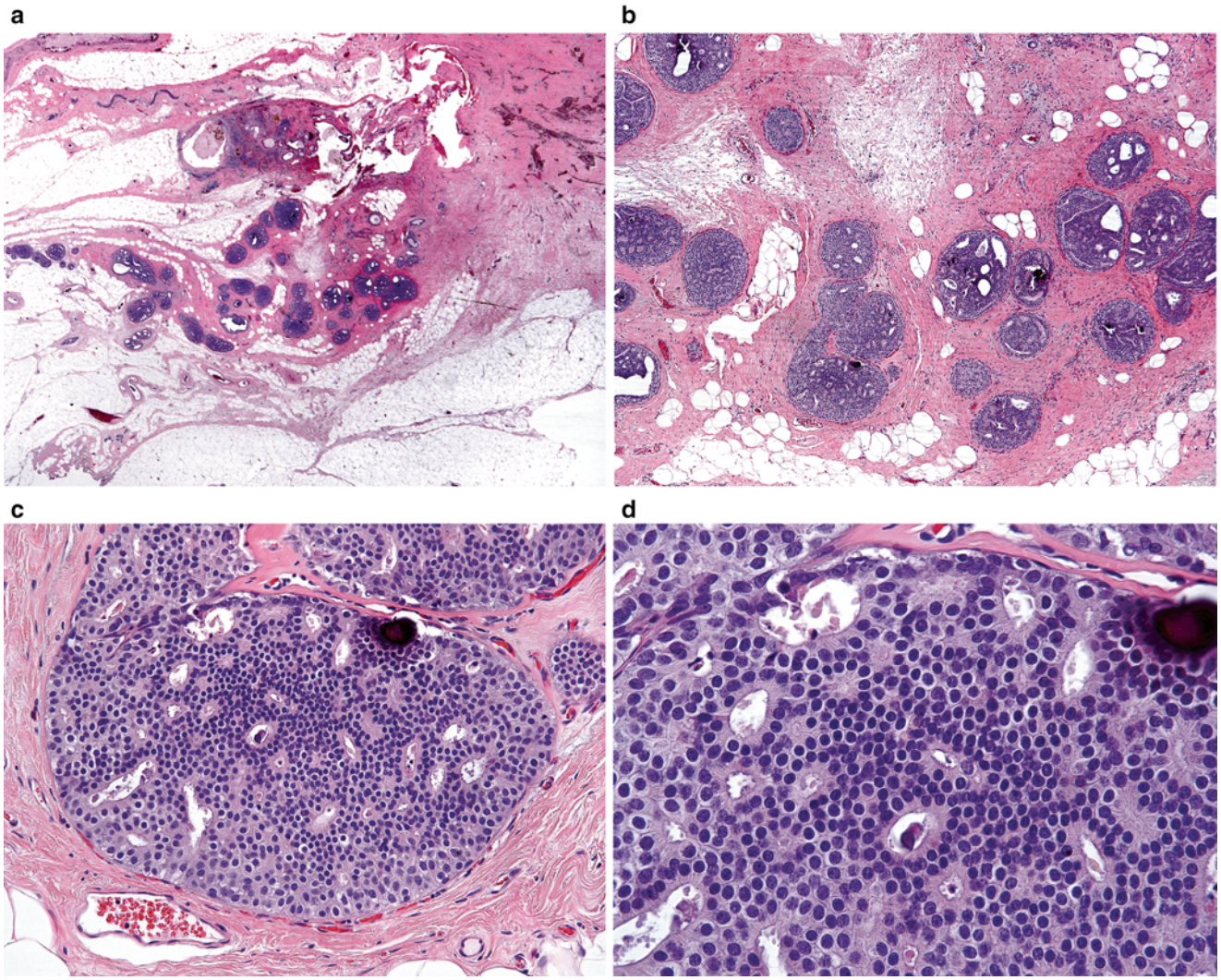

Fig. 9.13 (**a**–**d**) This case is an example of a core needle biopsy with a low-grade intraductal proliferation with cytologic monotony and cribriform architecture that is uniformly involving an area larger than 2 mm. These findings meet criteria for a diagnosis of low-grade DCIS on core needle biopsy. The targeted calcifications are present within the low-grade DCIS. Note the polarized lumens being formed despite not all spaces being perfectly "punched out"

HER2 targeted therapy when HER2+) is standard for hormone receptor-negative or HER2-positive invasion greater than 0.5 cm [23]. Oncologists may also consider these therapies when there are multiple smaller foci of invasion, but the evidence of benefit in this group is more limited.

Microinvasive foci of carcinoma (<1 mm) and larger foci can be masked in the lymphocytic background surrounding high-grade DCIS. Close examination of areas with more dense inflammation for single cells and clusters is recommended. A pan-cytokeratin stain, in addition to myoepithelial stains, can also be very useful to highlight the pattern of single cells and clusters of epithelial cells that lack myoepithelial cells (Fig. 9.21c–f). Some labs use combination stains that include two to three of these markers. Because these small foci can appear and disappear on immunostained levels and recuts, all additional material should be closely examined for invasion. In the context of a core needle biopsy with possible invasion, caution should be used if there is not 100% certainty about smaller foci of invasion. In this setting it can be appropriate to diagnose "DCIS with foci suspicious for microinvasion" and defer final classification of the process to the subsequent surgical specimen.

Solid, nested forms of high-grade invasive carcinoma can mimic DCIS (Fig. 9.23a–d). Because these foci are often larger than microinvasion, they are even more critical to diagnose and distinguish from clusters of DCIS. Clues to the diagnosis of invasion in these cases are the presence of a more complex, "puzzle-piece" pattern of growth than might

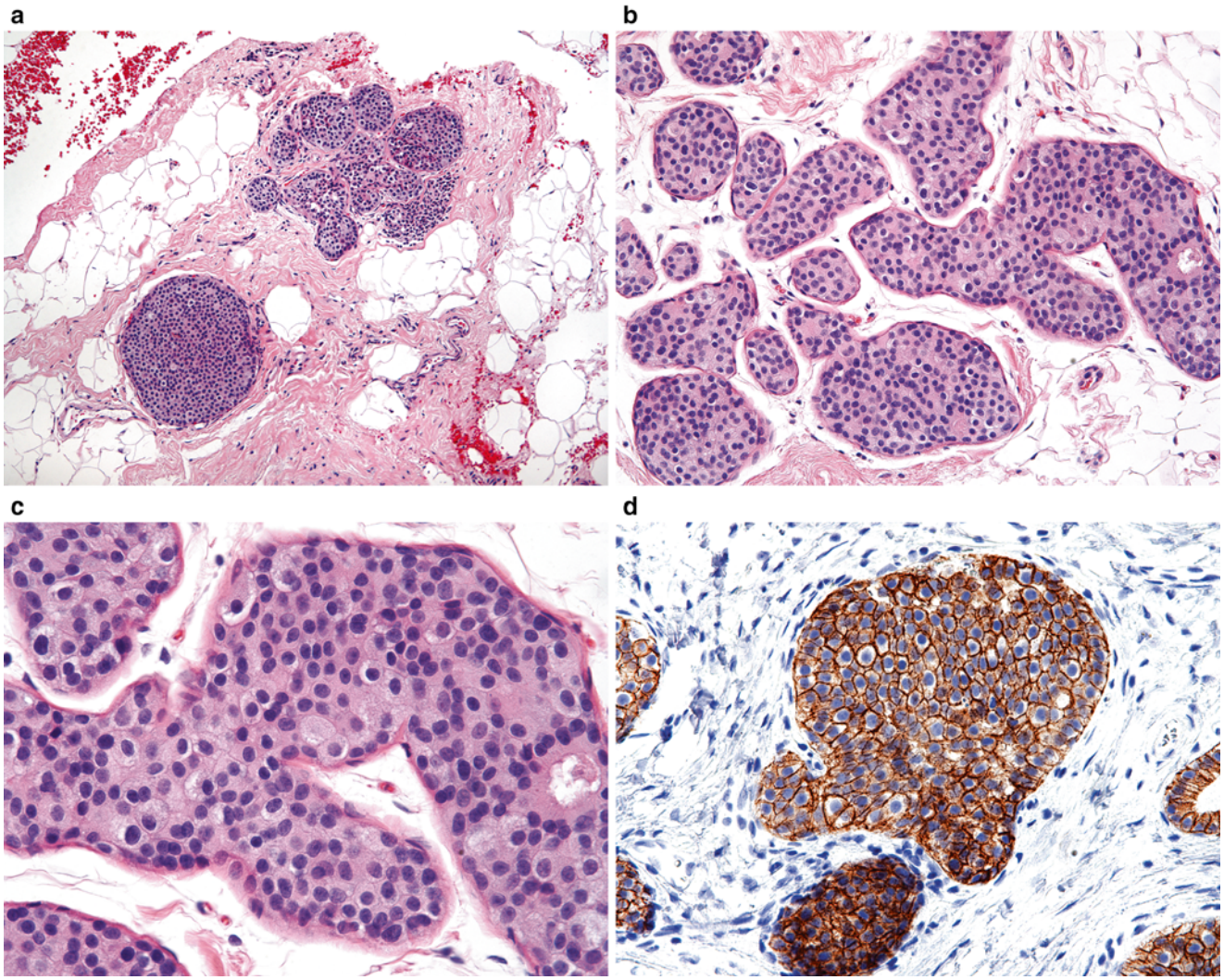

Fig. 9.14 (**a**–**d**) Examples of solid pattern, monotonous proliferations that raise the differential diagnosis of a low-grade DCIS versus lobular carcinoma in situ. Extension of the process into lobules can make this differential particularly challenging. Subtle clues to ductal differentiation include more crisp cell membranes and formation of subtle microacinar spaces (note a microacinar polarized space in the far left of image **c**). E-cadherin staining will be positive in a membranous pattern in a ductal process, as in this case (**d**)

be expected by diffuse involvement of ducts and lobules by DCIS. The edges of these nests are often more irregular than the rounded contours of DCIS. Myoepithelial stains will help in this differential. For cytoplasmic myoepithelial stains such as smooth muscle myosin heavy chain (SMM) and calponin, care should be taken not to interpret surrounding stromal positivity as a myoepithelial cell layer (Fig. 9.24a–d). The myoepithelial staining should be present within the outermost layer of the malignant cells in DCIS. This layer may be discontinuous and very attenuated in DCIS. Using a nuclear myoepithelial stain such as p63 in conjunction with a cytoplasmic one can help exclude "false positive" stromal staining. Some cases are very challenging and if there is uncertainty even after additional stains, consultation should be considered or this uncertainty should be clearly expressed in the report.

Pleomorphic LCIS: Pleomorphic lobular carcinoma (PLCIS) can also closely mimic high-grade DCIS. PLCIS will have high-grade nuclei and can also have central comedo-necrosis (Fig. 9.25a–d). Subtle areas of cellular discohesion or admixed areas of classical low-grade lobular carcinoma in situ (LCIS) or atypical lobular hyperplasia can be clues that raise this differential diagnosis. An E-cadherin stain can be used to determine the immunophenotype of the cells, with loss of expression being characteristic of PLCIS. This distinction can make big treatment differences since there is currently debate about whether PLCIS requires excision to negative margins, radiation or hormonal therapy.

Atypical cystic hypersecretory or atypical pregnancy-like (pseudolactational) changes: Another less common mimic of high-grade DCIS is atypical cystic hypersecretory or

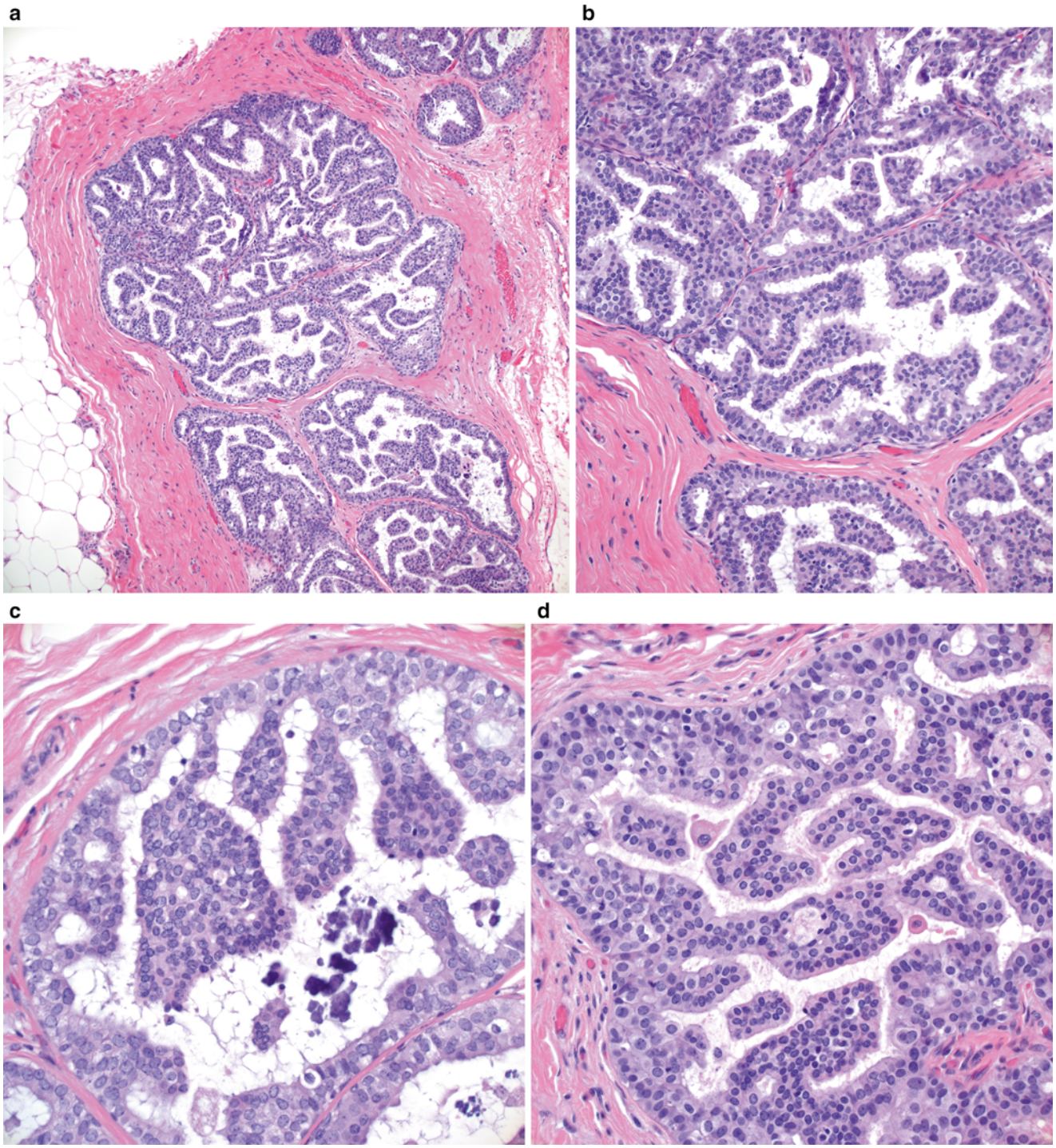

Fig. 9.15 (**a**–**d**) Micropapillary low-grade DCIS

pregnancy-like (pseudolactational) change. This differential often arises when considering the diagnosis of "clinging carcinoma" or isolated lobular involvement by high-grade DCIS. Pregnancy-like (pseudolactational) change is characterized by its focal or patchy lobular distribution and vacuolated, bubbly cytoplasm. It can accumulate calcifications and be a reason for core biopsy [24]. These calcifications are often laminated or layered. Cystic hypersecretory change is characterized by the presence of dense eosinophilic secretion that appears similar to thyroid colloid. The secretion frequently has scalloped edges. Pregnancy-like (pseudolactational) change and cystic hypersecretory change can be

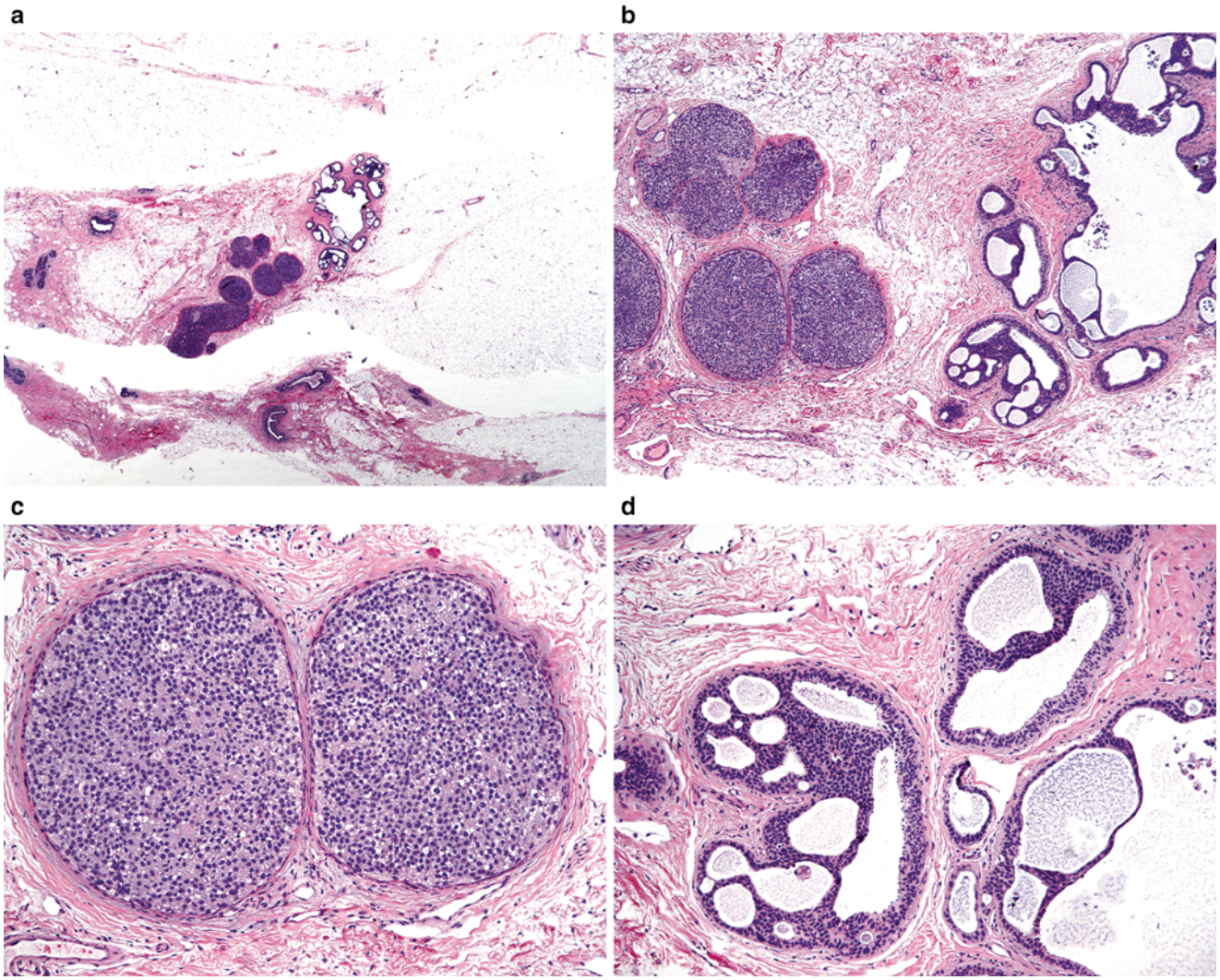

Fig. 9.16 Core needle biopsy with both low-intermediate grade DCIS and atypical ductal hyperplasia. On low-power images (**a**) and (**b**) the DCIS is on the left hand side and is distinguished by its complete involvement of multiple ducts by a solid pattern proliferation of cells with intermediate grade cytology (**c**). The ADH is on the right hand side of the low-power images and is seen in image (**d**). In contrast to the DCIS in this case, it has a lower nuclear grade and only early architectural forms that are incompletely involving the ducts in this area

present together. On a core biopsy, when there is only a focal lobule-based cytologically atypical process, caution should be used if there are features of pregnancy-like (pseudolactational) change or cystic hypersecretory change (Fig. 9.26a, b). This change is similar to the Arias-Stella reaction in the endometrium and can be present focally, in isolation and not associated with lactation. Cystic hypersecretory lesions and pregnancy-like lesions including their malignant counterparts are each discussed in Chaps. 13 and 21, respectively.

Posttreatment changes: Radiation therapy can result in scattered cytologically atypical cells being present within ducts and lobules (Fig. 9.27). However, in contrast to high-grade DCIS, these changes are typically present as scattered enlarged cells with hyperchromatic nuclei rather than a proliferation of atypical cells as is typically seen in high-grade DCIS. In the post-chemotherapy setting, residual "treated" DCIS can also present as atrophic sclerotic ducts lined by residual atypical epithelium. These ducts are often filled with histiocytes and debris as well. Knowing the clinical history is key to recognizing this as treated DCIS.

Low-Grade DCIS Spectrum

Limited extent low-grade DCIS versus ADH: Limited extent low-grade DCIS (2–3 mm) has many overlapping features with ADH, and determining the most appropriate of these diagnoses to use on a core biopsy sampling can be challenging. When either the cytologic or architectural features are considered borderline to qualify for a diagnosis of low-grade DCIS, a diagnosis of ADH is most appropriate. When there

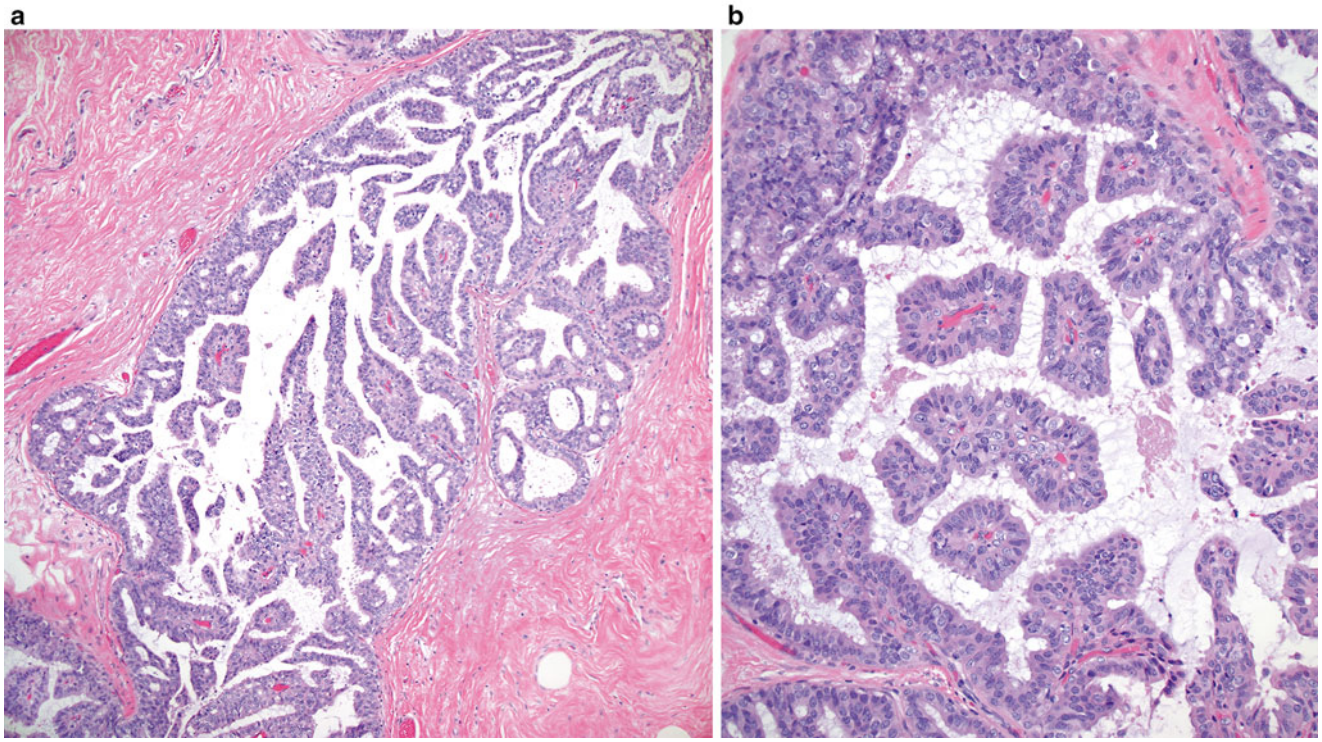

Fig. 9.17 (**a**, **b**) Papillary pattern DCIS contains papillary cores lined by low-grade cells with monotonous tall columnar to rounded nuclei. Despite its similarity to a benign papilloma, a myoepithelial layer is not apparent within the majority of the fibrovascular cores on H&E or myoepithelial cell stains (not shown here) but should surround the involved ducts

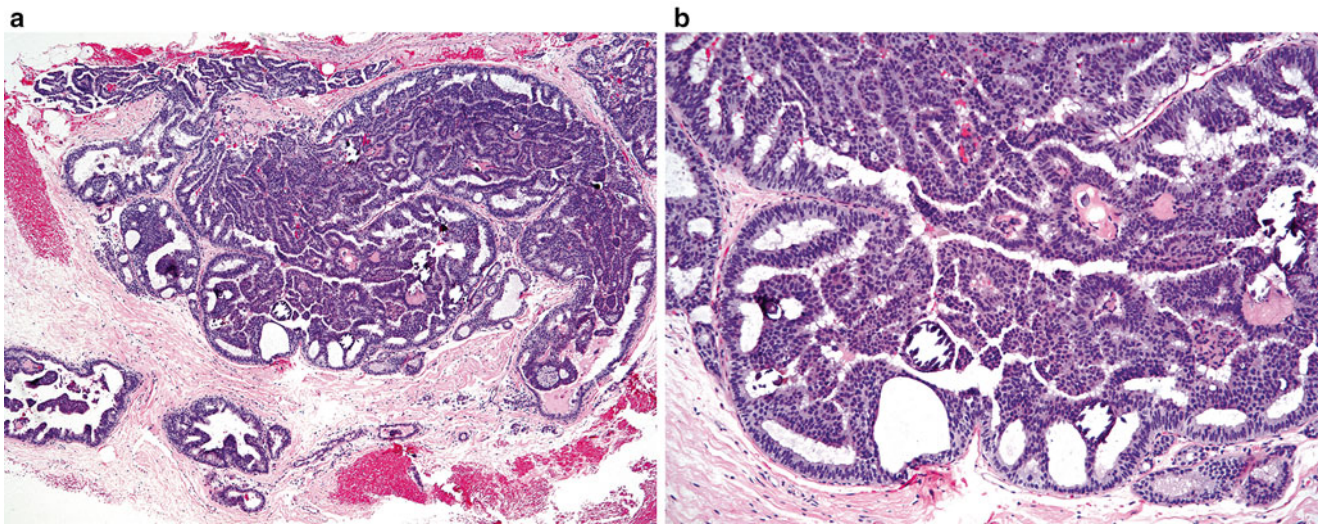

Fig. 9.18 (**a**, **b**) Low-intermediate grade DCIS with mixed papillary and micropapillary patterns

is clear cytologic monotony and there are early architectural forms characteristic of low-grade DCIS but not completely involving ducts or limited in development, again a diagnosis of ADH on core biopsy is more appropriate. Although originally developed in the excisional biopsy setting, the >2 mm threshold for a diagnosis of low-grade DCIS (when ducts are uniformly involved by a monotonous process with well-developed architecture) can serve as another useful threshold in the core biopsy setting. When close to this size threshold, a conservative approach should be used in the core biopsy setting. Diagnoses that reflect the borderline nature of the lesion should be utilized such as "ADH bordering on

low-grade DCIS," "At least ADH, suspicious for low-grade DCIS," and "Severely atypical intraductal proliferation." An example of a borderline lesion on core biopsy is shown in Fig. 9.28a–d. A definitive diagnosis of low-grade DCIS on core biopsy should be reserved for those cases where, if there are subsequently no additional findings on surgical excision, the pathologist can be confident that the extent of the lesion on core biopsy is enough to make treatment decisions that may include radiation.

Solid patterns: Monotonous solid proliferations based on the terminal-duct/lobular unit can raise the differential diagnosis of low-grade DCIS versus LCIS (Fig. 9.14). The formation of subtle micro-acini can sometimes be evident and is supportive of ductal differentiation. The cell borders of low-grade DCIS also tend to be more crisp, while discohesion and indistinct cell borders are more suggestive of LCIS. However, often E-cadherin staining can be used to resolve this differential with loss of expression characteristic of lobular lesions. Occasionally, E-cadherin (or p120) staining has a mixed pattern of partial loss. In these cases, correlation with the histologic features (such as the presence of atypical lobular hyperplasia, pagetoid growth in a lobular pattern) may help favor one process over the other. It should be recognized that classification of a case as "in situ carcinoma with mixed ductal and lobular features" will result in treatment as DCIS by most clinicians and in cases that are thought to be fundamentally lobular (i.e., pleomorphic LCIS), this term should not be used.

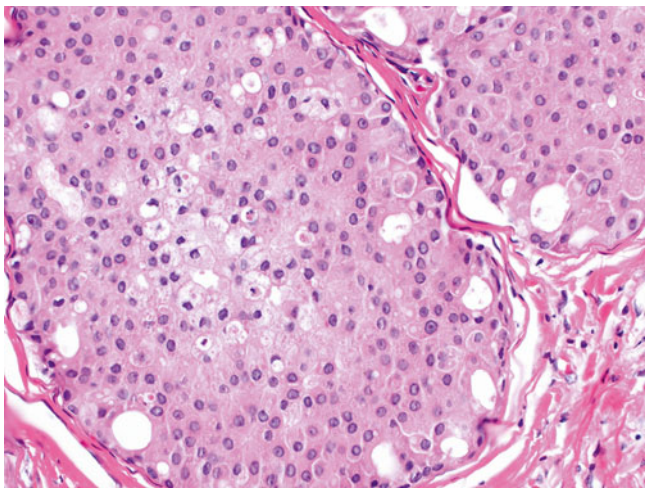

Fig. 9.19 Low-intermediate grade DCIS with apocrine differentiation

Cribriform patterns: Cribriform DCIS can be mimicked by collagenous spherulosis, especially when there is concurrent LCIS present in the lesion (Fig. 9.29). Collagenous spherulosis is characterized by the formation of "punched out" spaces that are filled with basement membrane material and lined by myoepithelial cells. On H&E the basement membrane material is often evident but sometimes it degenerates and is only present as myxoid change or thin fibrils detached from the spaces. When there is the cytologic monotony of LCIS present in the background of these cribriform-like spaces, the appearance of low-grade DCIS can be quite striking. Because collagenous spherulosis is composed of a proliferation of both luminal epithelial and myoepithelial cell types, myoepithelial cell stains can aid in this diagnosis. In collagenous spherulosis, the myoepithelial cells should line the spaces formed, a pattern of staining not seen in DCIS. E-cadherin staining can also be helpful in cases to identify concurrent involvement by LCIS.

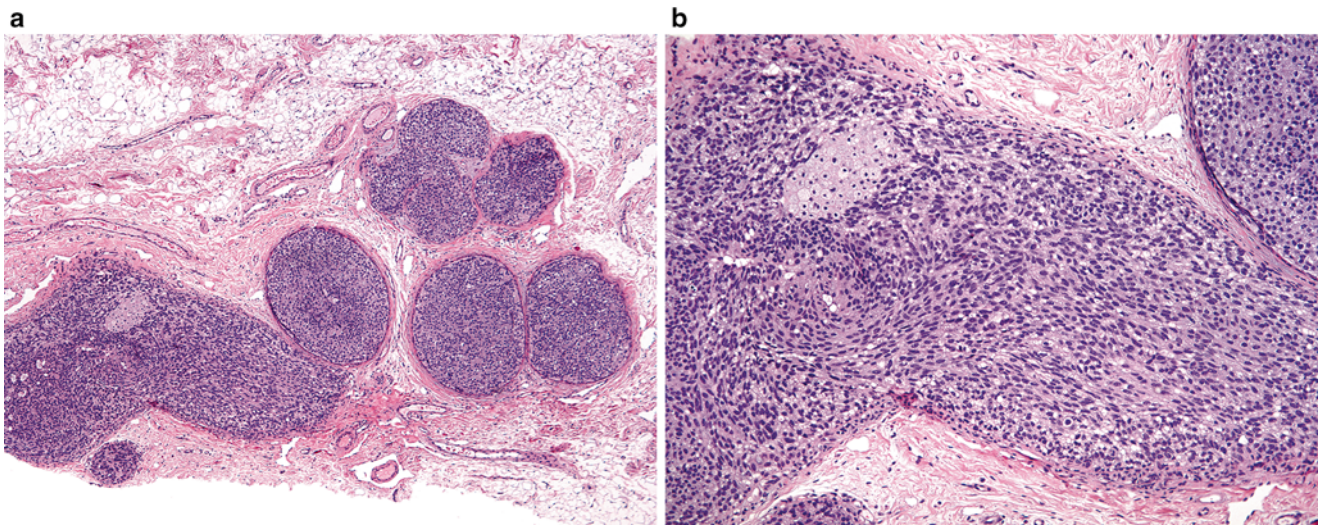

Fig. 9.20 (**a**, **b**) Spindled pattern low-intermediate grade DCIS

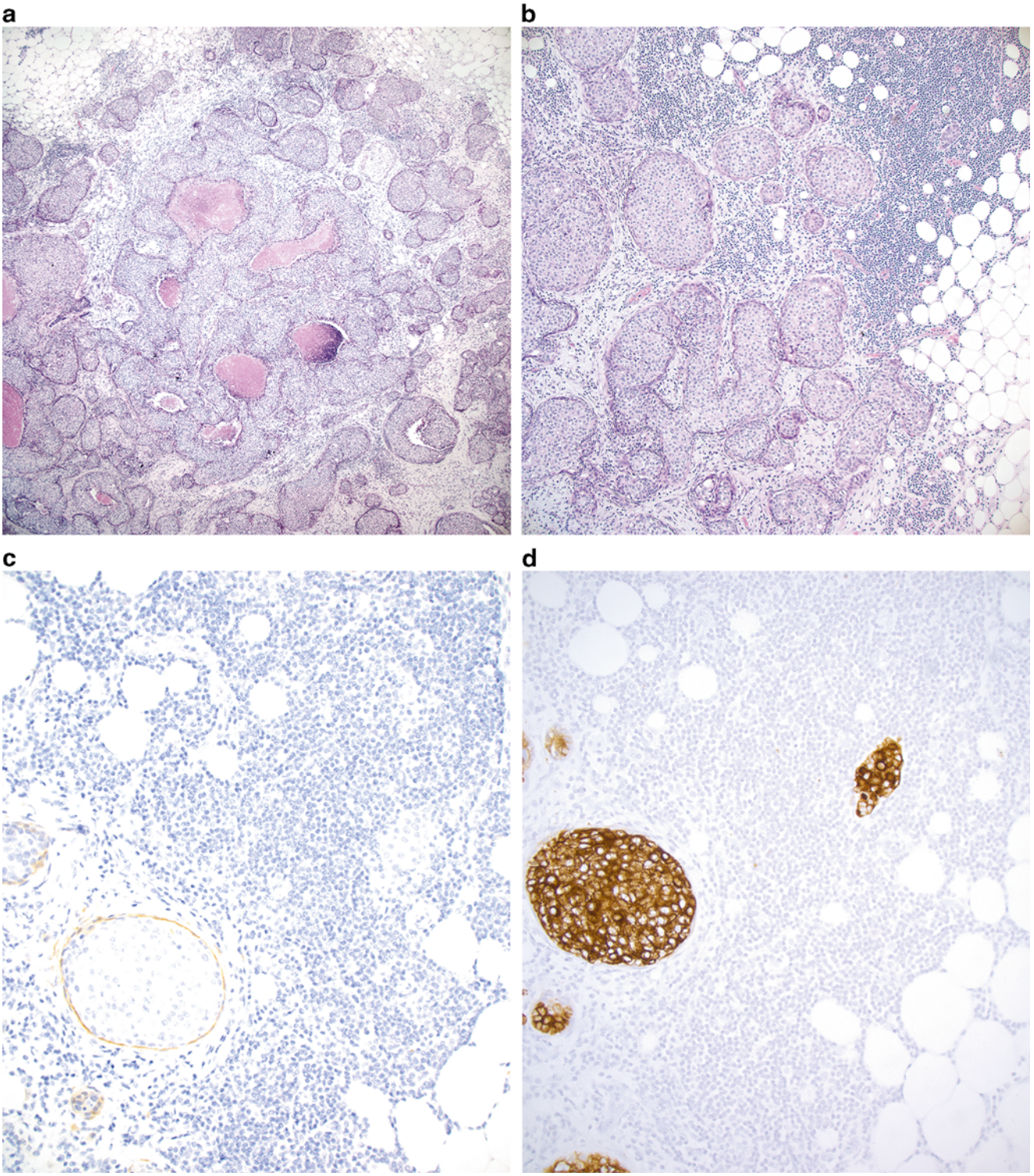

Fig. 9.21 (**a**) Low-power image of a case with extensive high-grade DCIS. The density of the DCIS with cancerization of lobules, surrounding sclerosis and areas of inflammation can mask small foci of invasion. (**b**) Careful examination of areas with inflammation or irregular borders should be undertaken. There is a small focus of microinvasion present that is not easily visualized on H&E (**b**) or calponin immunostain (**c**), but is highlighted well on a pan-cytokeratin statin (**d**). Often more than one focus of microinvasion is present. Another focus of microinvasion is pictured in images (**e**) (calponin stain) and (**f**) (cytokeratin stain)

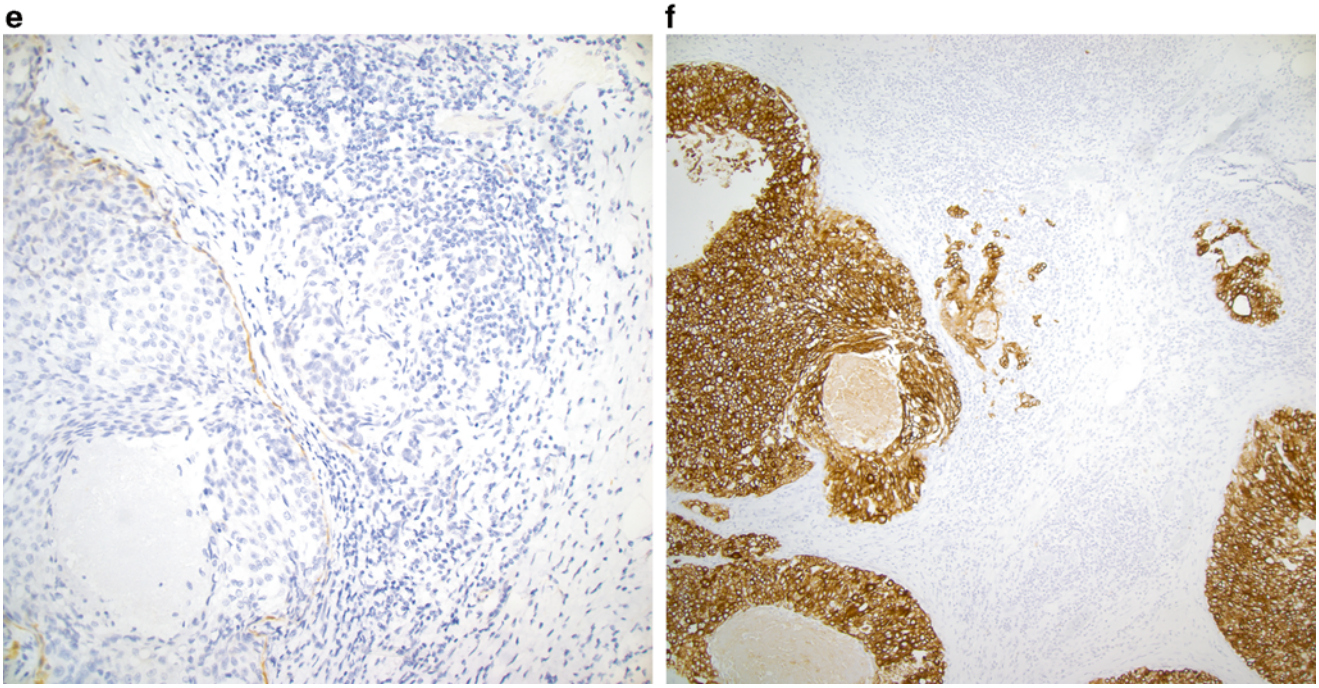

Fig. 9.21 (continued)

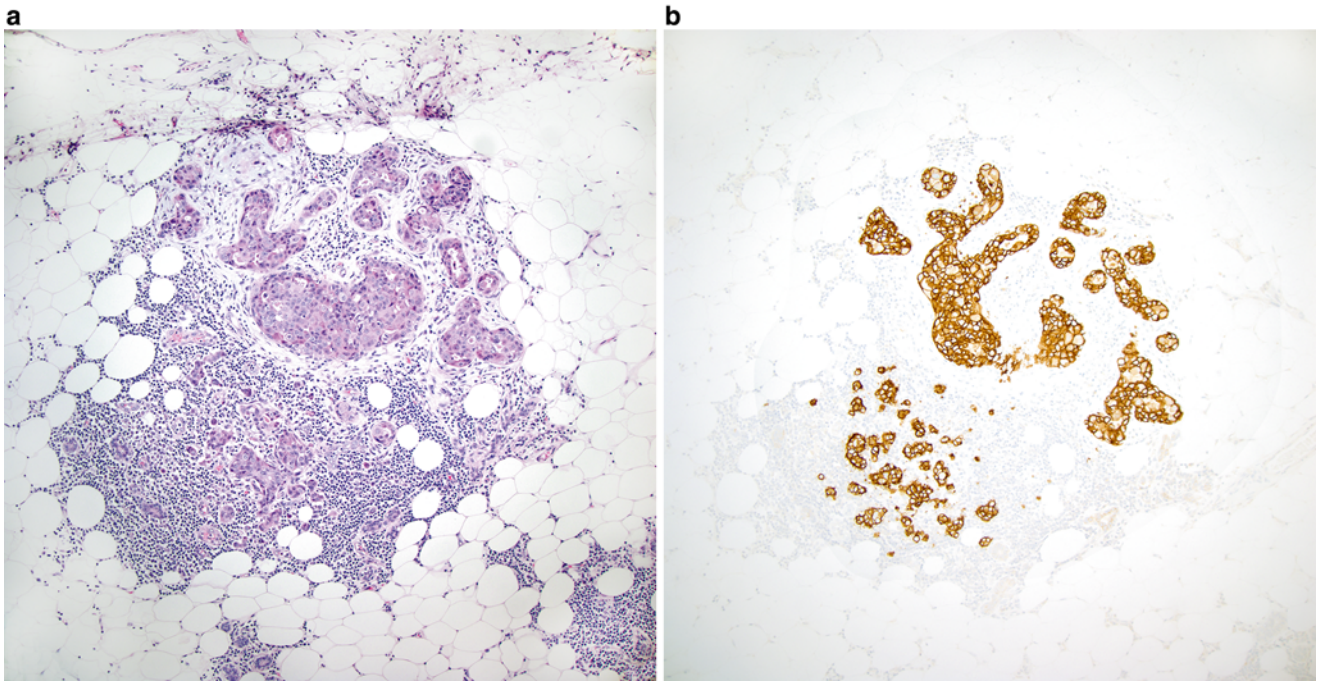

Fig. 9.22 Extensive high-grade DCIS is frequently associated with HER2-positive invasive disease. In this case, the scattered cells present in the inflammation adjacent to the DCIS (**a**) are positive for HER2 overexpression as well as the DCIS (**b**)

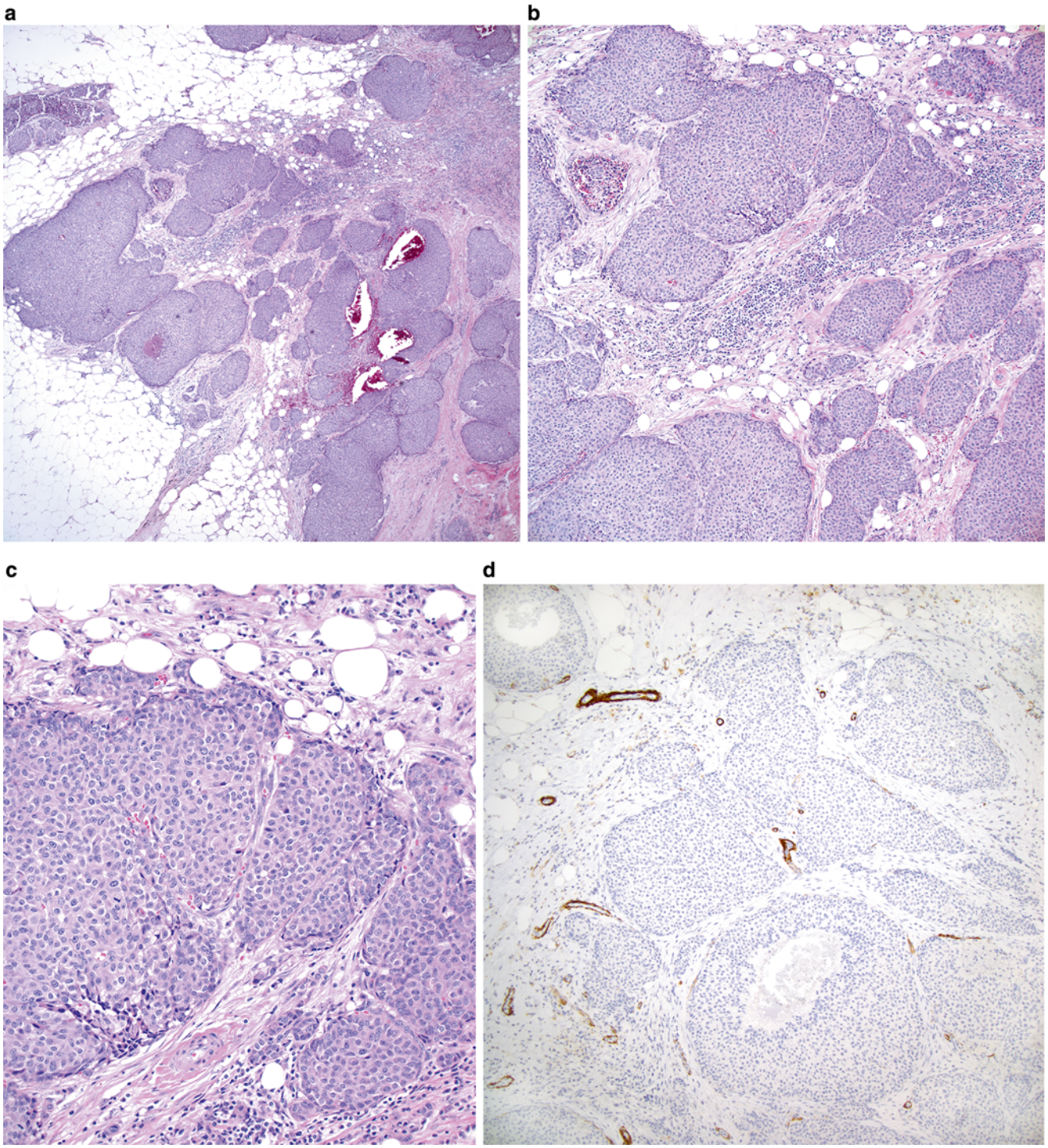

Fig. 9.23 The differential diagnosis between DCIS and solid, nested forms of invasive carcinoma can be a challenge. A diagnosis of invasive carcinoma should be considered even when the nests of carcinoma have rounded contours (similar to DCIS) when these areas appear to "fit" together like puzzle pieces in more complex patterns than that typically seen in DCIS (**a**). Some nests of carcinoma may have more irregular borders (**b**) or wrap around normal structures like adipocytes (**c**) or normal ducts. A negative result using myoepithelial cell markers will confirm the invasive nature of the process (**d**)

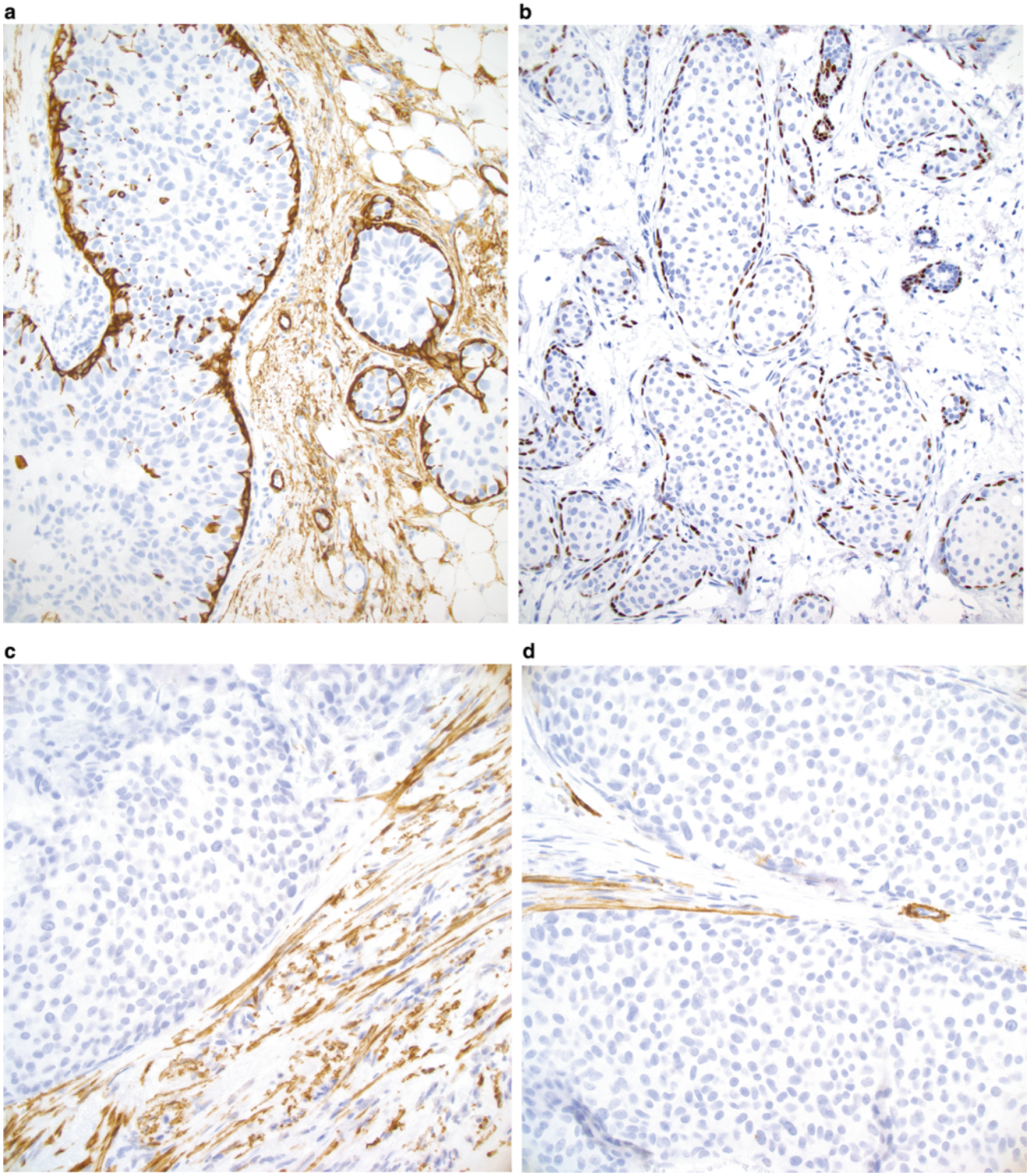

Fig. 9.24 A cytoplasmic myoepithelial stain such as smooth muscle myosin (SMM) should stain the cytoplasm of the basal myoepithelial cell layer in DCIS but may also stain surrounding stromal cells or small vessel walls (**a**). Note that the cells with cytoplasmic staining for SMM are located above the basement membrane and contain malignant appearing nuclei, in contrast to the stromal cells staining in the surrounding tissue. A nuclear myoepithelial cell marker such as p63 (**b**) can be helpful in conjunction since should not stain the surrounding stromal cells. (**c**, **d**) show rounded nests of invasive carcinoma that lack a myoepithelial cell layer but on SMM stain there is stromal staining that is below the basement membrane that does not contain cells with malignant nuclei, and should not be interpreted as a myoepithelial cell layer. (**d**) Also shows SMM staining of a small vessel

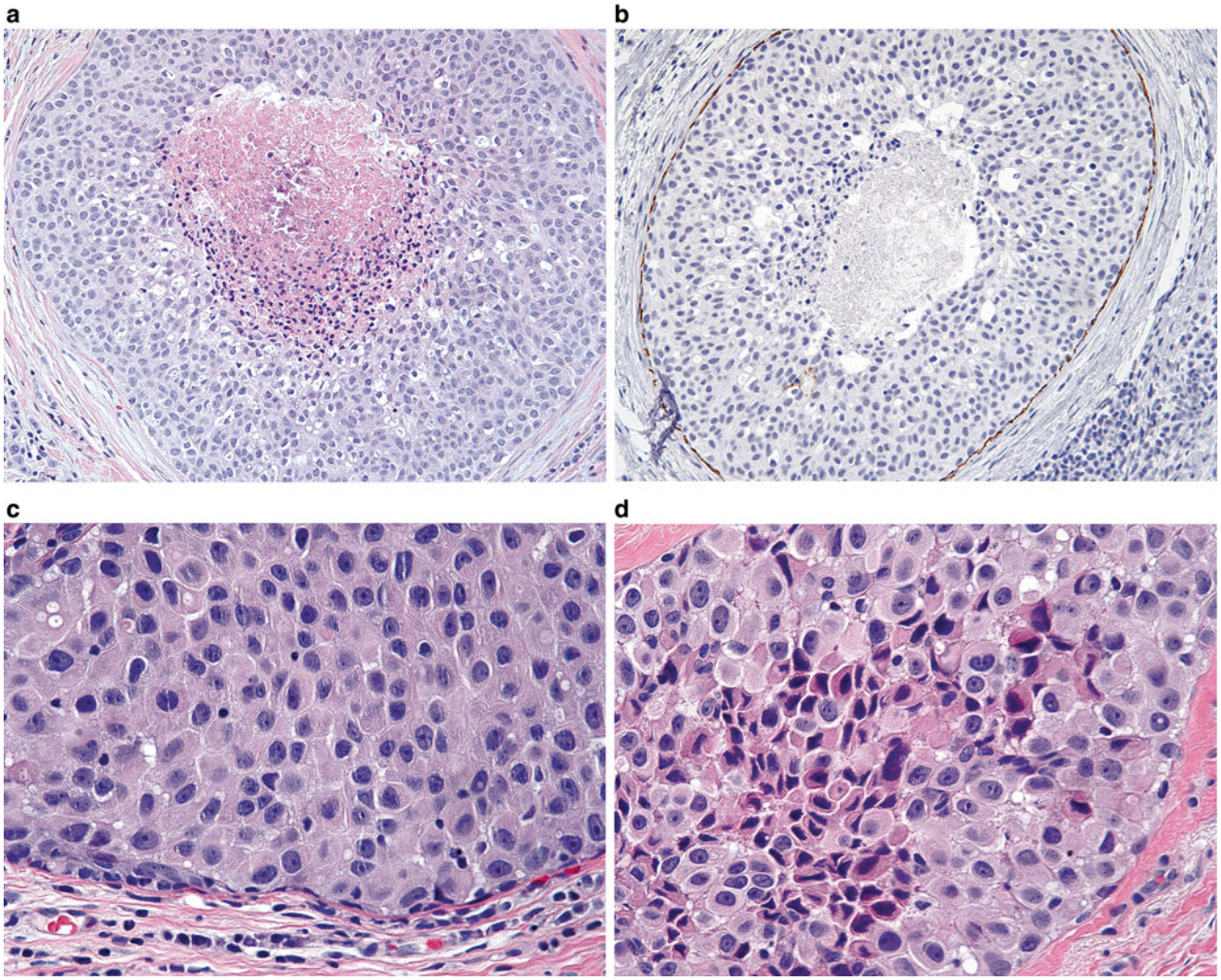

Fig. 9.25 Pleomorphic lobular carcinoma in situ (PLCIS) has high nuclear grade and can have central comedo-necrosis very similar to comedo-type DCIS (**a**). However, PLCIS will have loss of E-cadherin (**b**), in contrast to DCIS which should retain its E-cadherin expression. Subtle clues on H&E to a lobular process include intracytoplasmic lumens, less distinct cell borders and rounding up of cells with discohesion (**c**, **d**, 40× magnification)

Invasive mimics of cribriform low-grade DCIS include adenoid cystic carcinoma and cribriform carcinoma. It is important to recognize the patterns of myoepithelial staining in adenoid cystic carcinoma, which has both luminal and basal/myoepithelial phenotypes admixed throughout the process, rather than only around the rim as in DCIS.

Spindled patterns: Spindled forms of DCIS are challenging to diagnose due to their similarity to florid forms of UDH (Fig. 9.30a–d). When other more recognizable architectural patterns of DCIS are present, this can be helpful because it raises the differential of DCIS with a spindled pattern component. Spindled DCIS tends to have a more evenly distributed cellularity in involved ducts than compact forms of UDH, and should have more hyperchromatic, irregular, and enlarged nuclei. However, some cases are very difficult to differentiate without the help of immunohistochemistry. A CK5/6 stain is particularly useful when the differential diagnosis includes intermediate-grade DCIS versus UDH. DCIS will be negative in the epithelial proliferation (while maintaining staining in the surrounding myoepithelial cell layer) while UDH will have a mixed, or "mosaic" staining pattern. Including an ER stain can also be helpful since the cells of low-intermediate grade DCIS should be fairly uniformly and strongly positive, while the pattern of ER expression in UDH is more patchy and irregular.

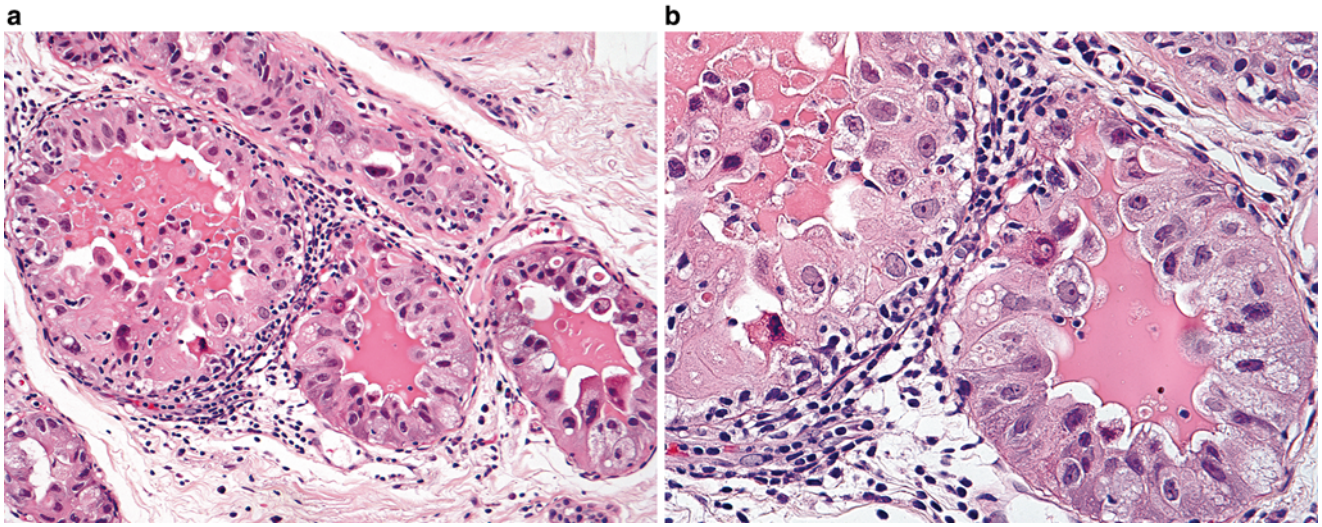

Fig. 9.26 Atypical cystic hypersecretory change (**a** at 20× magnification, and **b** at 40× magnification) can mimic high-grade DCIS involving a lobule. The dense thyroglobulin-like secretion with scalloped edges, which is characteristic of hypersecretory processes, should not be mistaken for necrosis. The cytoplasm in these images is bubbly and contains small granular secretions, suggesting a lactation-related phenotype. Although the nuclear atypia is marked, with prominent nucleoli and occasional multinucleated cells, if these changes are isolated to a few lobules in a core needle biopsy a diagnosis of "severely atypical intraductal proliferation with hypersecretory features" should warrant excision to further clarify the extent and nature of the process. Cystic hypersecretory DCIS should be considered if there is more extensive proliferation involving ducts (see Fig. 9.11)

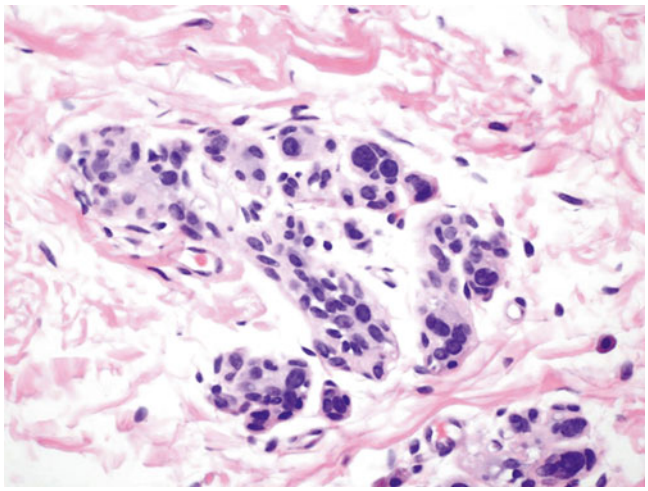

Fig. 9.27 Postradiation atypia can be seen in patients who were previously treated for breast cancer or other intrathoracic malignancies. In contrast to DCIS, the atypia is present as scattered hyperchromatic cells without significant proliferation

Papillary patterns: Papillary forms of DCIS can mimic benign papillomas especially when the lining epithelium is a single layer. The epithelium lining of papillary DCIS will appear darker at low power than a benign papilloma. This is due to the increased nuclear hyperchromasia and nuclear stratification present in papillary DCIS. Benign papillomas also have thicker fibrovascular cores than the thin ones that characterize papillary DCIS. High-power inspection of papillary DCIS will not identify obvious myoepithelial cells, as should be seen in a benign papilloma. When there is doubt, myoepithelial stains can be performed to differentiate, with myoepithelial layer present around the fibrovascular cores of benign papilloma but not the cores of papillary DCIS. Care should be taken not to interpret the staining of small vessels compressed around the edges of the fibrovascular cores as staining of a myoepithelial cell layer. Nuclear p63 staining should also be present in the myoepithelial cells. When in doubt, or if the differential includes other papillary lesions (such as encysted papillary carcinoma or papilloma involved by ADH or DCIS), a diagnosis of "atypical papillary lesion" can be appropriate on a core needle biopsy sample. Papillary lesions are discussed in more detail in Chap. 6.

Immunohistochemistry

Estrogen receptor staining is the only clinically relevant stain currently used in DCIS. Although high-grade DCIS is less likely to be ER positive than low-intermediate grade DCIS, an estimated 57% of comedo-DCIS is ER positive [25]. Patients with ER-positive DCIS can be offered Tamoxifen (or other hormonal-targeted therapies), to reduce the risk of recurrence in any residual breast tissue [26]. The threshold for ER positivity is 1% of cells with weak intensity staining, similar to criteria for invasive carcinoma [27]. A low-grade DCIS should be ER positive, and if it is not, this is considered a discordant result (Fig. 9.31). Both a re-evaluation of the histology as well as evaluation of possible testing error or a pre-analytical issue should be considered.

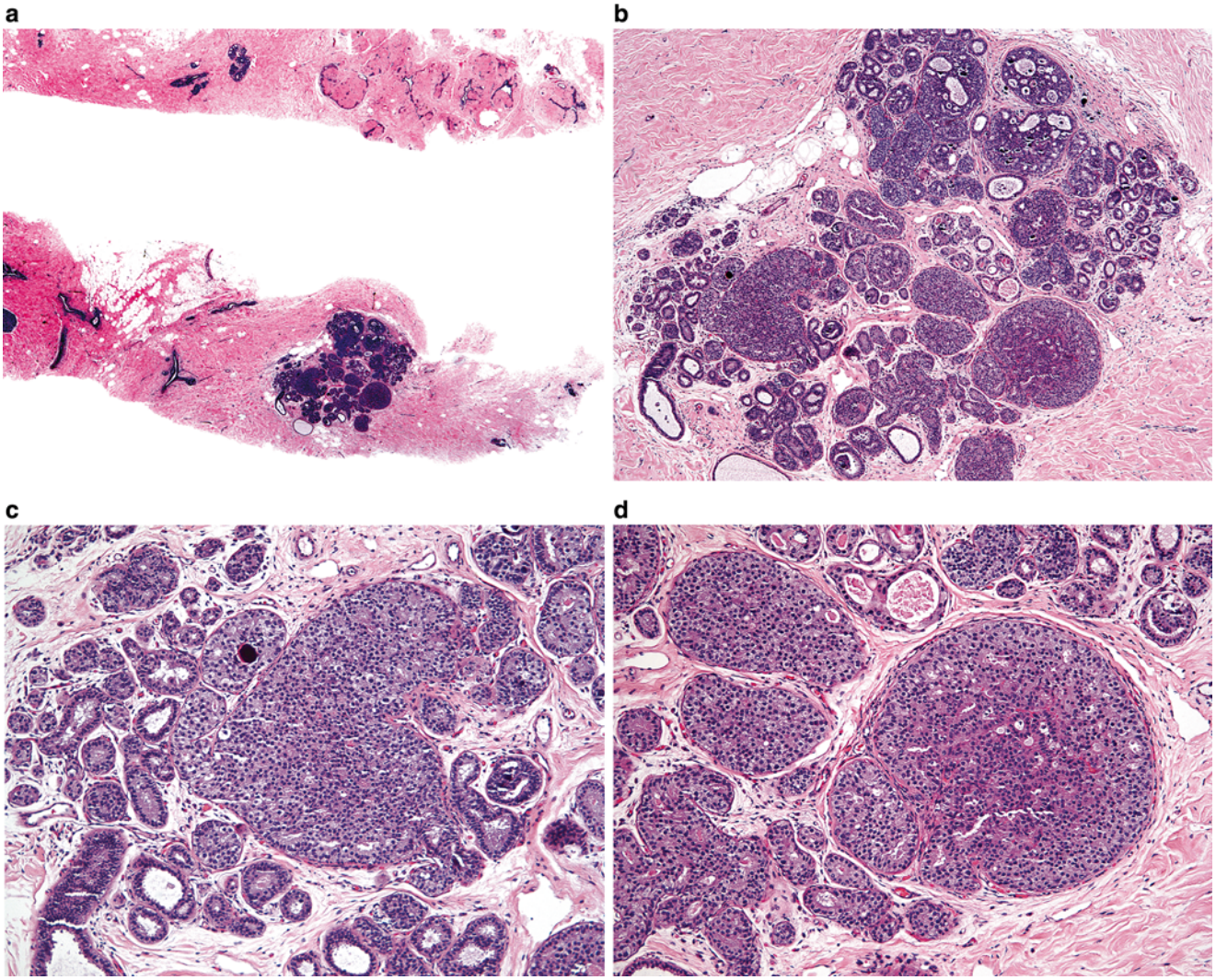

Fig. 9.28 (**a**–**d**) A core biopsy with an intraductal proliferation showing low-grade cytologic monotony and cribriform architecture. The process is well-developed in several ducts but the process is not completely uniform throughout the lesion and it measures <2 mm. When changes straddle between those of low-grade DCIS and ADH are present on a core biopsy, a diagnosis of "atypical ductal hyperplasia bordering on low-grade DCIS" (or similar terminology) should be considered. These borderline lesions will have high diagnostic disagreement so consideration should also be given to a second pathologist review

When a concurrent invasive carcinoma is hormone receptor negative and there is ER expression noted in the associated DCIS, both results should be reported since hormone-based treatment may be offered on the basis of the ER expression of the DCIS [26]. If a core biopsy sample contains only very limited ER-negative DCIS (or another factor limits the evaluation of ER expression), consideration for repeat testing on DCIS present in the subsequent surgical specimen is recommended if clinically relevant. Although progesterone receptor (PR) is frequently performed with ER on DCIS cases, there is not currently evidence that PR expression is clinically relevant in DCIS.

HER2 staining is not standard in DCIS since there is currently no role for HER2 targeted therapies for pre-invasive disease. However, as mentioned earlier, high-grade DCIS is frequently HER2 positive with 60–100% HER2 positivity in high-grade, comedo-type DCIS [28, 29]. Twelve percent of ER-positive DCIS is estimated to be HER2 positive as well [30]. The vast majority of Paget's disease of the nipple is HER2 positive, ER negative, and high grade [31]. Extensive HER2-positive high-grade DCIS is more likely to harbor small foci of invasion, which has important implications for more extensive tissue sampling to identify any and possibly larger foci of invasive cancers [32] (Fig. 9.32).

Some argue that using IHC surrogates for molecular subtyping, including hormone receptors, HER2 and Ki-67, can help stratify DCIS patients by risk of upgrade [33]. High-grade DCIS is more often p53 positive and has higher proliferative rates on Ki-67 staining than low-grade DCIS.

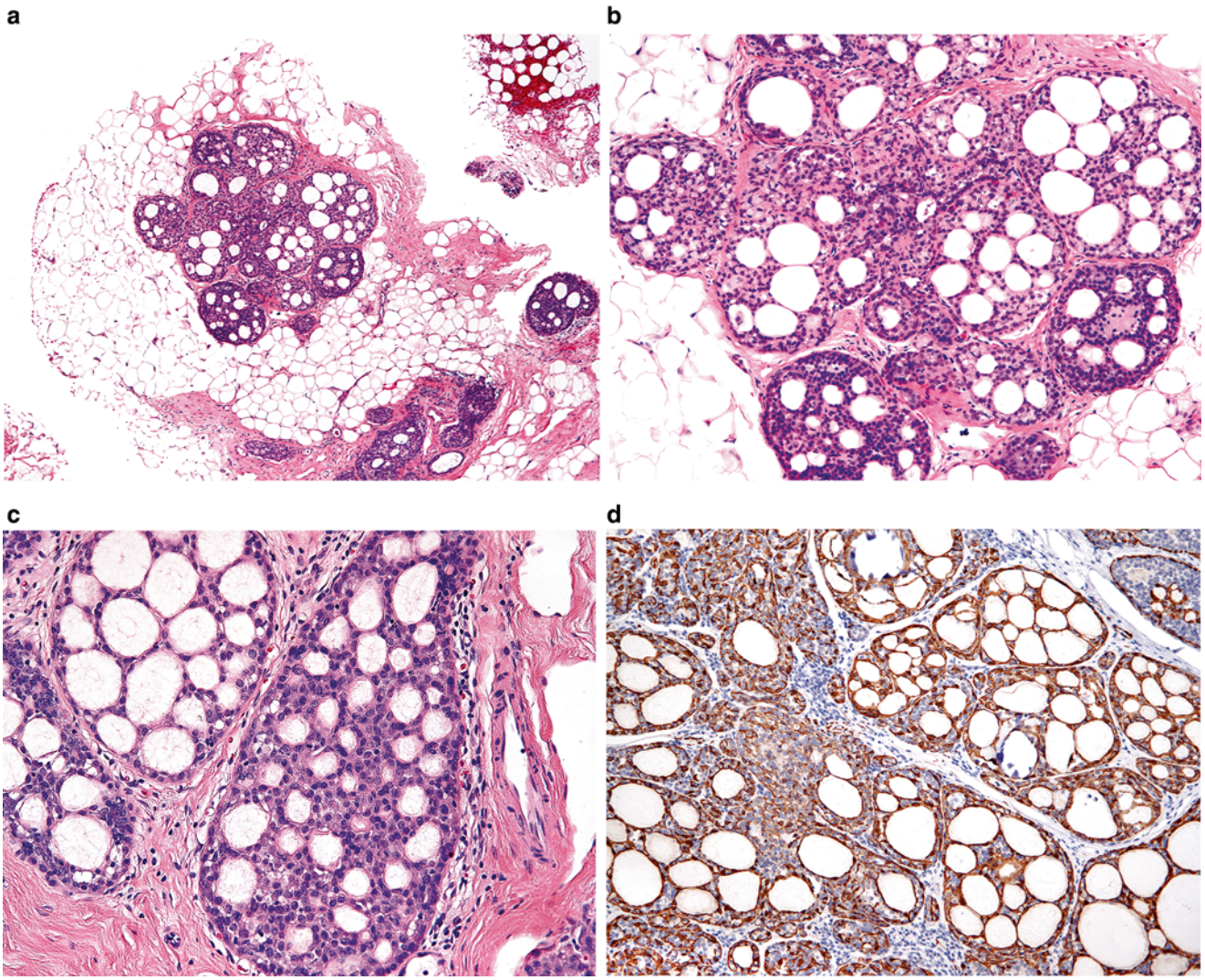

Fig. 9.29 (**a**–**d**) Collagenous spherulosis involved by LCIS mimicking low-grade cribriform DCIS. Collagenous spherulosis forms "punched out" crisp spaces within an intraductal proliferation. These spaces are lined or filled with basement membrane material that can be seen as a subtle "cuticle" surrounding the spaces or extending across the center of the space. Myoepithelial stains will highlight the mixed population of myoepithelial cells present that line these spaces. The monotony seen in this case is due to involvement of the process by LCIS (an E-cadherin stain—not shown—was negative in this cell population)

CK5/6 staining is most often used to differentiate low-intermediate grade DCIS or ADH (CK5/6 negative) from UDH (mosaic pattern CK5/6 staining) and is less often useful in the diagnosis of high-grade DCIS. However, if used, it is important to recognize that some high-grade DCIS, especially the basal-like subtype, will be CK5/6 positive [34]. However, less than 10% of DCIS is estimated to be basal-like with the vast majority of invasive basal-like breast cancers not found to be associated with DCIS [35].

See the above differential diagnosis section for the utility of myoepithelial or E-cadherin staining in specific settings.

Pathogenesis

Just as it has become clear that there are distinct subtypes of invasive breast cancer with different molecular/phenotypic profiles and outcomes, there is also evidence that DCIS can be grouped into similar categories with differing pathogenesis [33, 36].

Estrogen receptor-positive DCIS is frequently low-intermediate grade and is associated with luminal-type invasive breast cancers that are most often low-intermediate grade and ER positive. It is considered a part of the "low-grade neoplasia family" which includes FEA, ADH, ALH, LCIS, low-grade DCIS, and low-grade invasive carcinomas [37, 38].

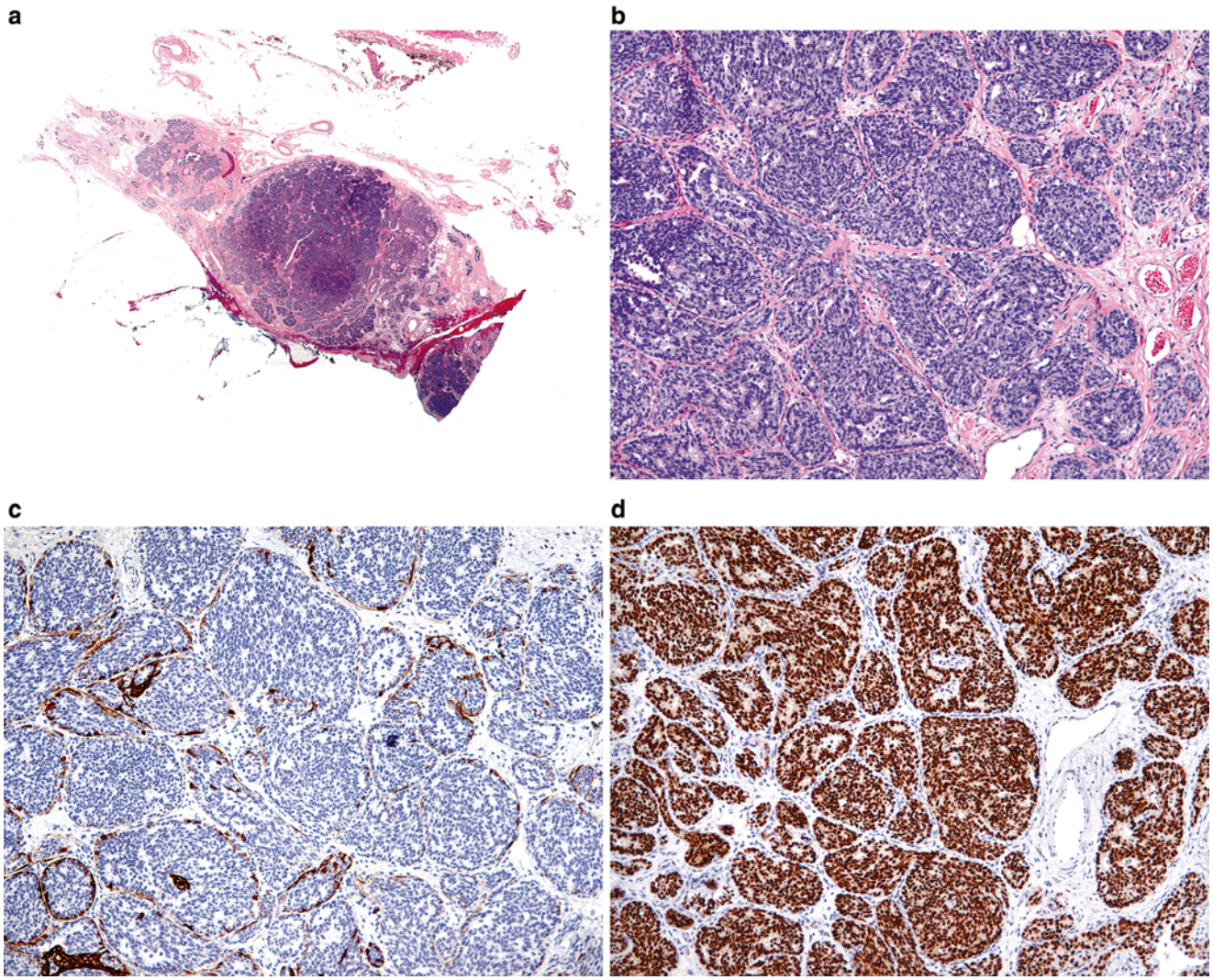

Fig. 9.30 (**a**, **b**) Spindled forms of DCIS can raise the differential of a florid usual ductal hyperplasia. When in doubt, additional immunohistochemistry can be helpful in this differential. Low-intermediate grade spindled DCIS should be negative for CK5/6 staining (**c**) and uniformly positive for ER expression (**d**). This is contrast to the "mosaic" CK5/6 staining pattern seen in UDH and more variable ER expression (see Fig. 9.41)

Low-grade DCIS contains recurrent losses of 16q and 17p as well as gains of 1q that are characteristic of this low-grade neoplasia family [39–41].

In contrast, hormone receptor negative (to low ER expressing) DCIS is typically high grade and is associated with the HER2 enriched and occasionally basal subtypes of high-grade invasive cancers [36]. When compared to the low-grade neoplasia family, high-grade DCIS more frequently has HER2 amplification, basal marker expression, aneuploidy, and complex karyotypes [42, 43]. Of note, <30% of high-grade lesions have deletions of 16q, which is strongly associated with the low-grade pathway [36, 38, 44]. This finding suggests that most high-grade lesions have a different pathogenesis and do not evolve from low-grade ones. However, this pathway can occur in the minority of cases and the process of progression to invasion is complex [45].

Outcomes

The standards for treatment of DCIS are evolving as more is understood about its biology and outcomes. The most standard therapy is either partial mastectomy followed by whole-breast irradiation or a total mastectomy. Hormone targeting therapies are also commonly used to reduce recurrence rates in either breast in patients with hormone receptor-positive DCIS. However, as more is understood about the risks of the increasingly common low-grade DCIS spectrum, there is interest in more minimally treating this group by omitting radiation, performing partial breast irradiation or even employing active surveillance protocols [46]. Although differences in local recurrence rates are apparent when radiation is added after lumpectomy for DCIS, there is not clear evidence of differences in overall survival using

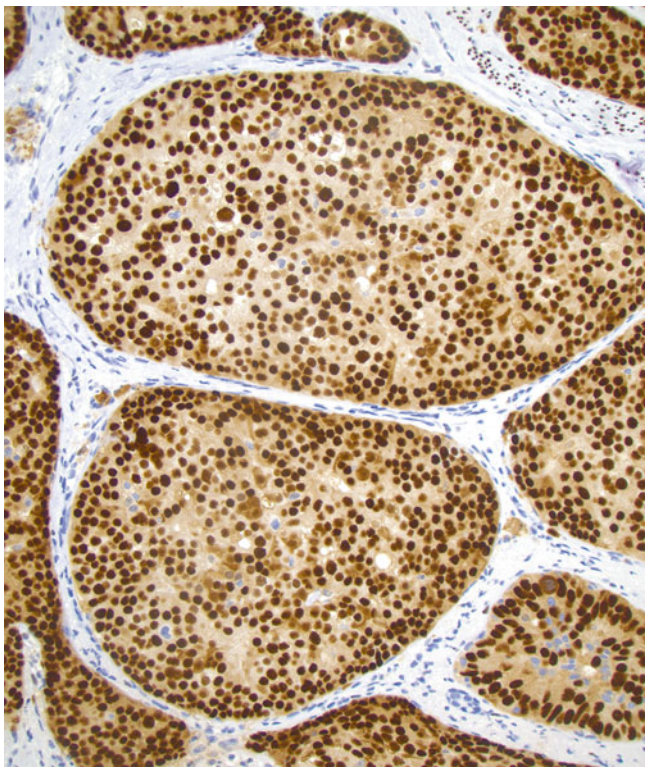

Fig. 9.31 Low-grade DCIS is typically uniformly and strongly ER positive

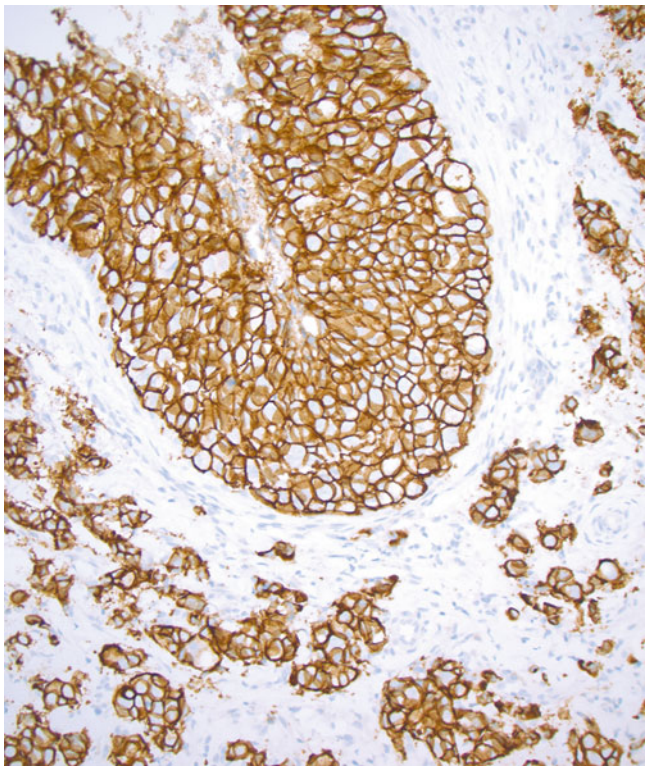

Fig. 9.32 High-grade invasive HER2-positive cancers are frequently associated with concurrent HER2-positive DCIS

radiation [47–49]. Because benefits to overall mortality in treating this group of screen-detected low-grade cancers are currently unclear, there has been some recent concern that these lesions are overdetected or "overdiagnosed" and "overtreated" [50, 51].

There are many factors that have been associated with an increased risk of recurrence for DCIS, including margin status, age, and size, but one of the most powerful predictors appears to be nuclear grade. In one study with a median follow-up of 8.5 years, there was a 6.8% risk of recurrence of DCIS, 73% of which were in patients with high-grade DCIS [52]. After local therapy for DCIS, nuclear grade has been shown to be a predictive factor for ipsilateral breast cancer recurrence in a randomized clinical trial and meta-analysis [53–55].

The Van Nuys prognostic index, which combines size, margin width, nuclear grade, necrosis, and age is used to calculate a score that predicts recurrence in conservatively treated DCIS [56, 57]. There is now at least one commercially available reverse transcriptase PCR-based assay that aims to determine which cases of DCIS are more likely to locally recur and respond to radiation therapy, however, its role in clinical practice is still unclear [58].

Given the currently evolving clinical management strategies for DCIS, a detailed, accurate pathologic diagnosis is and will continue to be key to individualizing treatment. Diagnostic agreement is estimated to be approximately 85% for breast biopsy samples containing DCIS (in a test set setting), with the majority of disagreements occurring in the low-grade end of the spectrum [1]. There is also a growing interest in developing biomarkers and clinical tests on DCIS tissue that can predict behavior and help determine treatment benefit [58, 59].

Atypical Ductal Hyperplasia

Overview

ADH on core needle biopsy accounts for only 3–15% of breast biopsy diagnoses, but is a frequent topic in breast disease discussions because of the challenges presented by both their diagnosis and clinical management [60, 61]. ADH is a borderline lesion that has significant overlap of its diagnostic and molecular features with low-grade DCIS and UDH. Because ADH exists within this spectrum of changes and has no biologically distinct characteristics, its diagnosis is frequently problematic.

Diagnostic agreement rates for biopsies with ADH are quite low (40–60%), especially when compared to the much higher agreement for DCIS, invasive carcinoma, and benign breast lesions [1, 62]. Because the differences in diagnosis are frequently related to subtle differences of professional opinion and diagnostic thresholds, simply knowing the diag-

nostic criteria may not be enough to ensure a reproducible diagnosis of ADH [2]. These cases should be shown to colleagues or consultants such that a reproducible diagnostic consensus can be reached in these challenging lesions, particularly in the lesions that are considered to be borderline with either low-grade DCIS or UDH.

ADH is considered a bilateral "risk lesion" because it has been associated with 3–5× increased risk of developing invasive carcinoma in either breast [63, 64]. From a clinical perspective, when a lesion increases the risk of developing invasive cancer in either breast, it is managed as a generalized "risk lesion" rather than as a localized lesion that can be surgically excised. However, because of its association with low-grade DCIS and invasive cancers, when identified on core needle biopsy, an excision is typically performed to rule out unsampled carcinoma.

Patients with ADH as the clinically most significant lesion on a core biopsy are told that they have an increased risk of developing an invasive breast cancer, a risk which spans and slowly increases over several decades, and some are offered risk hormonal agents such as Tamoxifen to non-surgically reduce this risk [65]. Occasionally, a patient with ADH with or without other high-risk features may choose to reduce their future cancer risk surgically with bilateral mastectomies, although this is considered by most to be overtreatment. As such, although ADH is considered "benign," it is a diagnosis that can have a significant clinical impact for any given patient and its diagnosis should be made with caution and with as much certainty as possible.

Gross and Radiologic Features

Similar to low-grade DCIS, ADH is most frequently diagnosed on core needle biopsy when calcifications are identified on screening mammogram. ADH does not present as a mass, unless it is involving a mass-forming lesion such as a papillary lesion or fibroadenoma. There are no radiologic features that help distinguish ADH and other risk lesions from calcifications present in low-grade DCIS or invasive carcinoma. Excisional biopsy is performed after identification of ADH as the clinically most significant lesion on a core biopsy to exclude the possibility of adjacent non-sampled DCIS or invasive carcinoma.

Microscopic Features

ADH is broadly described as a lesion that has "some but not all of the features of low-grade DCIS." The cytologic features of ADH are those of low-grade DCIS, with monotonous cells containing rounded nuclei with even chromatin (Fig. 9.33). Intermediate-to-high grade nuclear features are not considered to be in the spectrum of ADH. The cell borders are well-defined and the nuclei are evenly spaced; classical features of low-grade neoplasia.

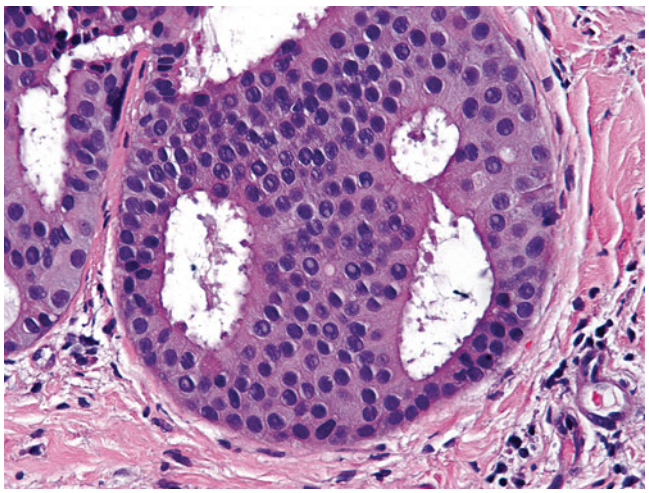

Fig. 9.33 Cytologic monotony with rounded and evenly spaced nuclei is present in a focus of atypical ductal hyperplasia. Similar nuclear monotony is present in low-grade DCIS

The architectural features typical of ADH are earlier/less well developed than in low-grade DCIS, such as rigid bridges or bars of uniform thickness or "roman" arches and arcades. Partial involvement of a duct with more developed cribriform architecture or micropapillary structures also can be a feature (Fig. 9.34a–d). Solid patterns of ADH can be present if focal and occasionally have subtle polarized lumens present. The involved spaces may also contain admixed cell populations with features more suggestive of UDH, FEA, or non-proliferative epithelium. Two examples of core needle biopsies with ADH are shown in Figs. 9.35a–d and 9.36a–d.

When the cytologic and architectural features of low-grade DCIS are present, many authors agree that smaller lesions with these findings should still be classified as ADH. There are different extent and size thresholds suggested by different authors. Page et al. proposed a system where these proliferations, if confined to no more than two duct spaces, could be classified as ADH instead of low-grade DCIS [66]. However, some authors argue that this low threshold would result in overtreatment of very limited extent low-grade DCIS that may not have significantly different outcomes from ADH. Tavassoli and Norris proposed that 2 mm (in size) be the threshold below which lesions with low-grade DCIS characteristics could be classified as ADH [3]. However, since both of these systems were developed in excisional biopsies, their use in core needle biopsies where the entire lesion may not be visualized should be done with caution. The WHO Working Group recommends a conservative approach when a core needle biopsy contains ADH

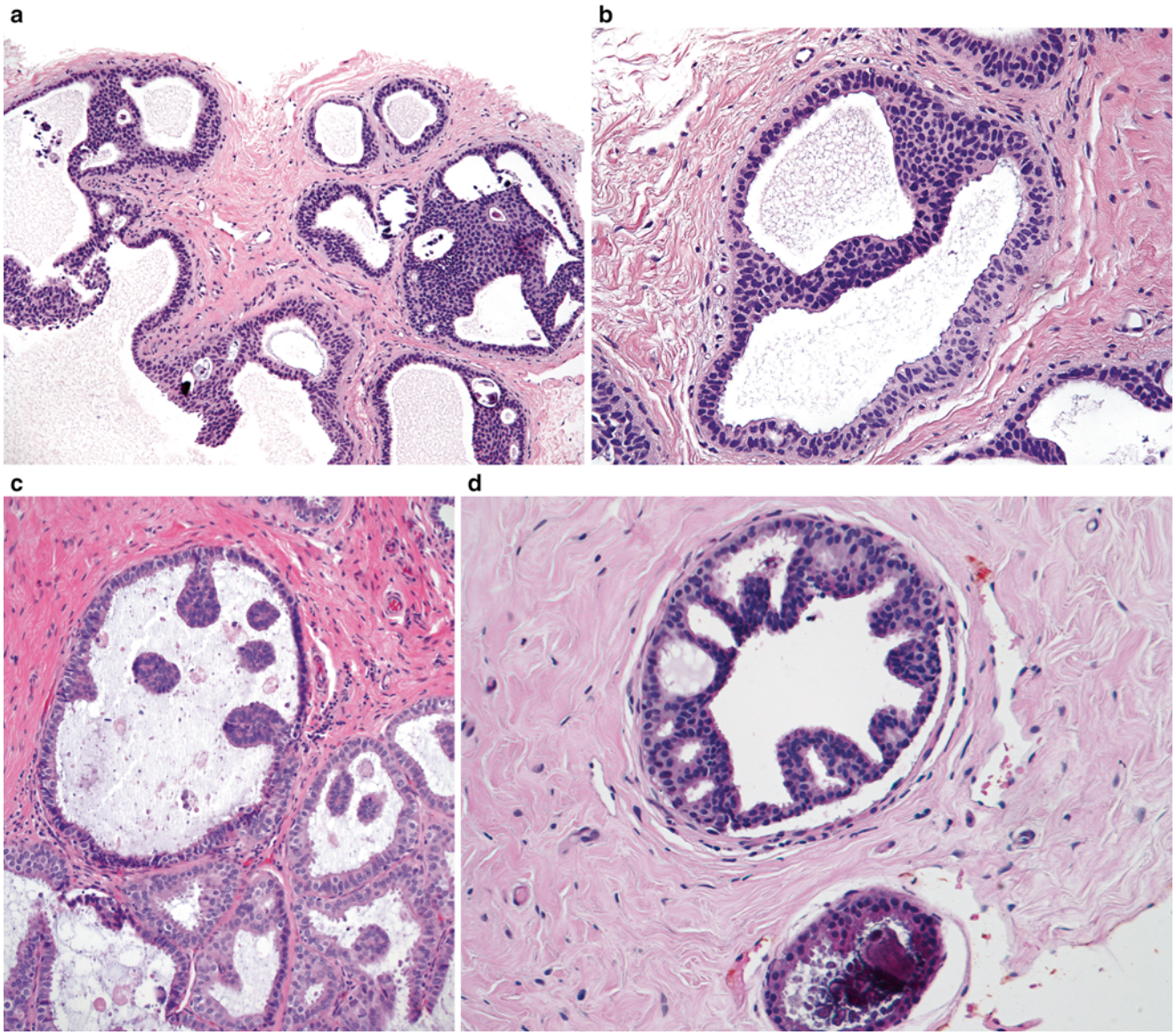

Fig. 9.34 (**a**, **b**) Architectural characteristics of ADH include the formation of rigid bridges or bars across duct spaces and early cribriform structures. (**c**) Micropapillary forms of ADH will have only a few early micropapillary structures present. (**d**) Roman bridges or arches can also be present. These early neoplastic structures do not uniformly fill the duct spaces or are limited in extent compared to low-grade DCIS

versus limited extent low-grade DCIS, favoring classification as ADH or "at least ADH" with various qualifiers until the entire lesion can be evaluated on surgical excision [67].

Differential Diagnosis

ADH borderline with low-grade DCIS: As mentioned above, this diagnostic differential is very challenging since there are no additional stains or molecular markers to aid in the distinction of ADH from limited extent low-grade DCIS. This differential most frequently arises when the cytology is clearly monotonous but the architecture is not uniformly well developed or the size of a lesion with uniform well-developed architecture is small (<2 mm). In general, if the lesion borders between ADH and low-grade DCIS, a diagnosis of ADH should be made on core needle biopsy. Figure 9.28a–d, shows an example of a case with features that border on low-grade DCIS. Cytologic monotony is present and some early neoplastic architecture is evident. Two of the involved ducts have more complete involvement by the process. However, given the lack of uniformity of the architectural changes throughout the lesion, on a core needle biopsy this lesion should be classified as "ADH borderline with low-grade DCIS, with associated calcifications" and include a comment such as the following: "There is an atypical

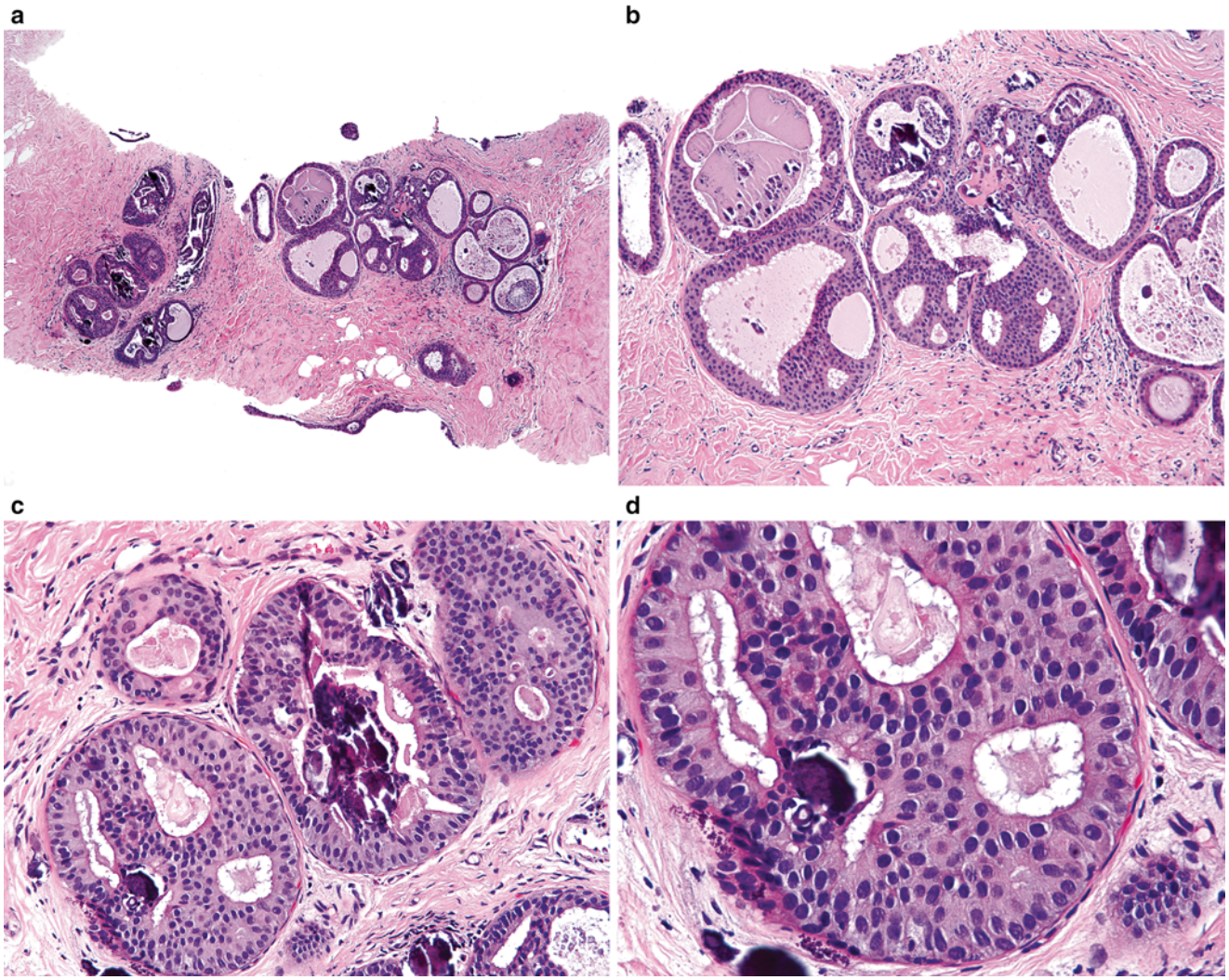

Fig. 9.35 (**a**–**d**) This core needle biopsy contains an intraductal proliferation with low-grade cytologic monotony and early, partially developed architectural changes. The architecture is not well-developed or uniform enough for a diagnosis of low-grade DCIS. These findings on core needle biopsy are most consistent with atypical ductal hyperplasia. The targeted calcifications are present within the ADH

intraductal proliferation with features that border on a diagnosis of low-grade DCIS. However, given the limited extent present in this core biopsy sampling, we would classify the findings as ADH and recommend correlation and final classification of the process on the anticipated excisional specimen." It is our policy to have a second pathologist review of all diagnoses of ADH on core biopsy (as the clinically most significant lesion), which would also be noted in the comment.

ADH versus UDH: The other end of the spectrum of ADH includes the differential with non-atypical proliferative lesions such as UDH. UDH is characterized by a more polyclonal appearance, in contrast to the monotony seen in ADH. Sometimes cases have borderline cytologic features that can raise this differential. Evaluation of the architecture can offer clues to help resolve this differential. The spaces formed in ADH are frequently polarized, with the nuclei oriented away from the lumen of the space. This is in contrast to UDH, where the peripherally located spaces are non-polarized with nuclei immediately abutting the slit-like spaces that are formed. Bars and bridges formed in ADH should be rigid and contain cells without significant nuclear overlap. In contrast, UDH can form cellular bridges but they should be tapered and contain overlapping nuclei. When there are micropapillary structures being formed, ADH is favored when they are club-shaped and contain regularly spaced monotonous nuclei. UDH can form tufted or gynecomastoid hyperplastic structures that mimic micropapillae but they contain overlapping nuclei that are smaller at the ends

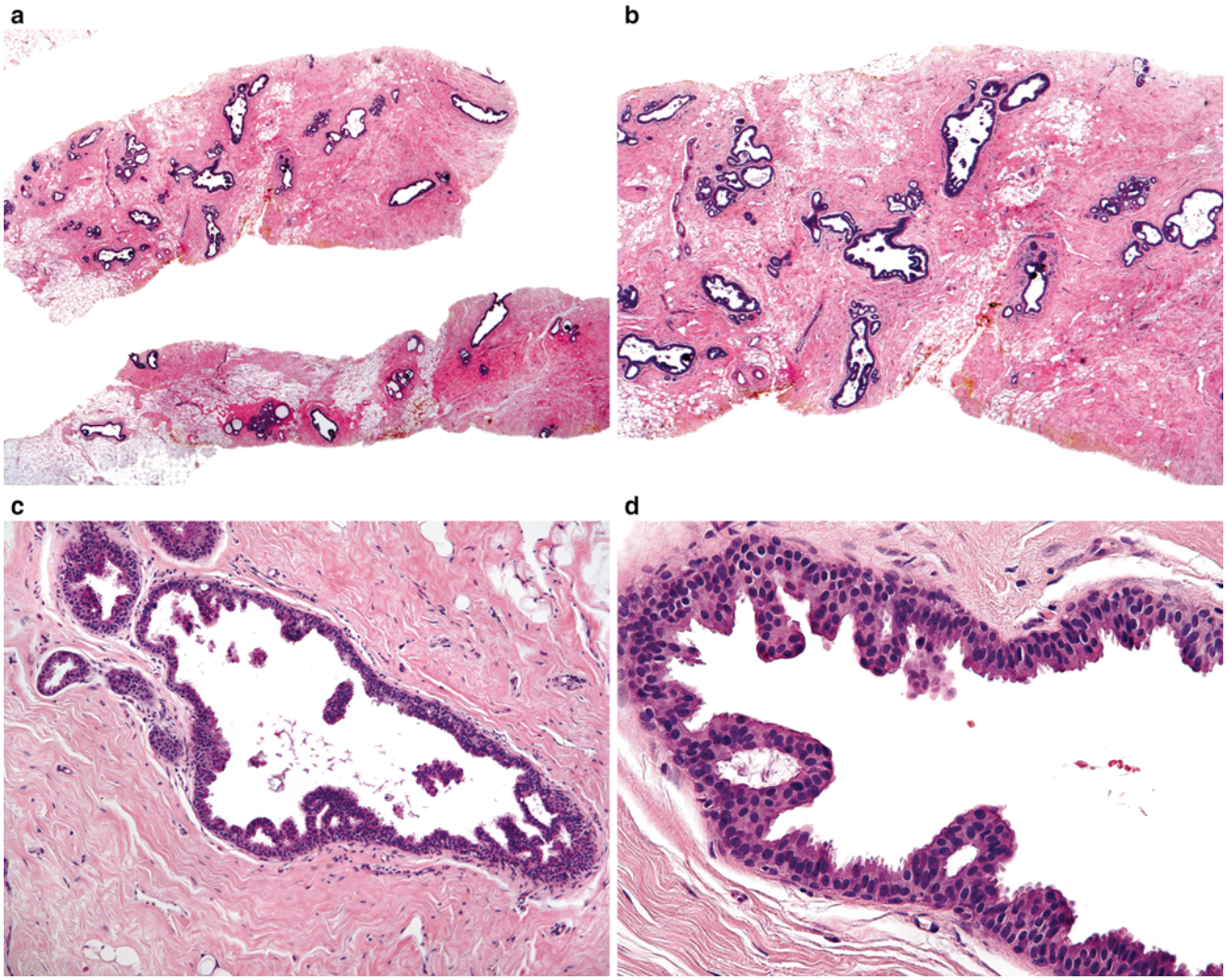

Fig. 9.36 (**a**–**d**) This core needle biopsy contains scattered ducts involved by a cytologically monotonous process that is forming early bridges and arches in portions of these ducts. Despite multiple ducts being involved, the development of the architectural forms is not considered sufficient for a diagnosis of low-grade DCIS (no definite club-shaped micropapillae, etc.). These findings are most consistent with a diagnosis of atypical ductal hyperplasia on core biopsy

of these structures and are non-uniform. Figure wwa–f shows side-by-side comparisons of these features in ADH versus UDH.

CK5/6 and ER staining, or ADH-5 (see below) can be helpful in cases when features are borderline. The cell population of ADH will stain similar to low-grade DCIS with loss of CK5/6 expression and uniform, strong ER staining within the proliferation. In contrast, UDH will have a mixed "mosaic" pattern of staining and variable ER expression.

When in doubt about the diagnosis of UDH versus ADH on a core biopsy, a review by a second pathologist can be helpful, but in general the low-grade diagnosis should be favored. A comment can be included that the diagnosis of ADH was considered but that the changes were insufficient for this diagnosis in this sample.

Minimal extent ADH versus FEA or non-atypical columnar cell change/benign: ADH is frequently seen admixed with FEA and non-atypical columnar cell change. The targeted calcifications can be present throughout all of these lesions. When columnar cell change becomes monotonous with more rounded nuclei and there are early architectural formations, the diagnosis of minimal extent ADH should be considered (Fig. 9.38a, b). When FEA is seen on a core biopsy sampling as the highest order diagnosis, because it is still unclear if excisional biopsy should follow, additional levels should be considered to identify any areas that are diagnostic of ADH. These areas are often minimal, early architectural formations such as a few rigid bridges or micropapillations within ducts lined by FEA. CK5/6 and ER stains are not useful in columnar cell lesions versus ADH since they can have very similar staining patterns.

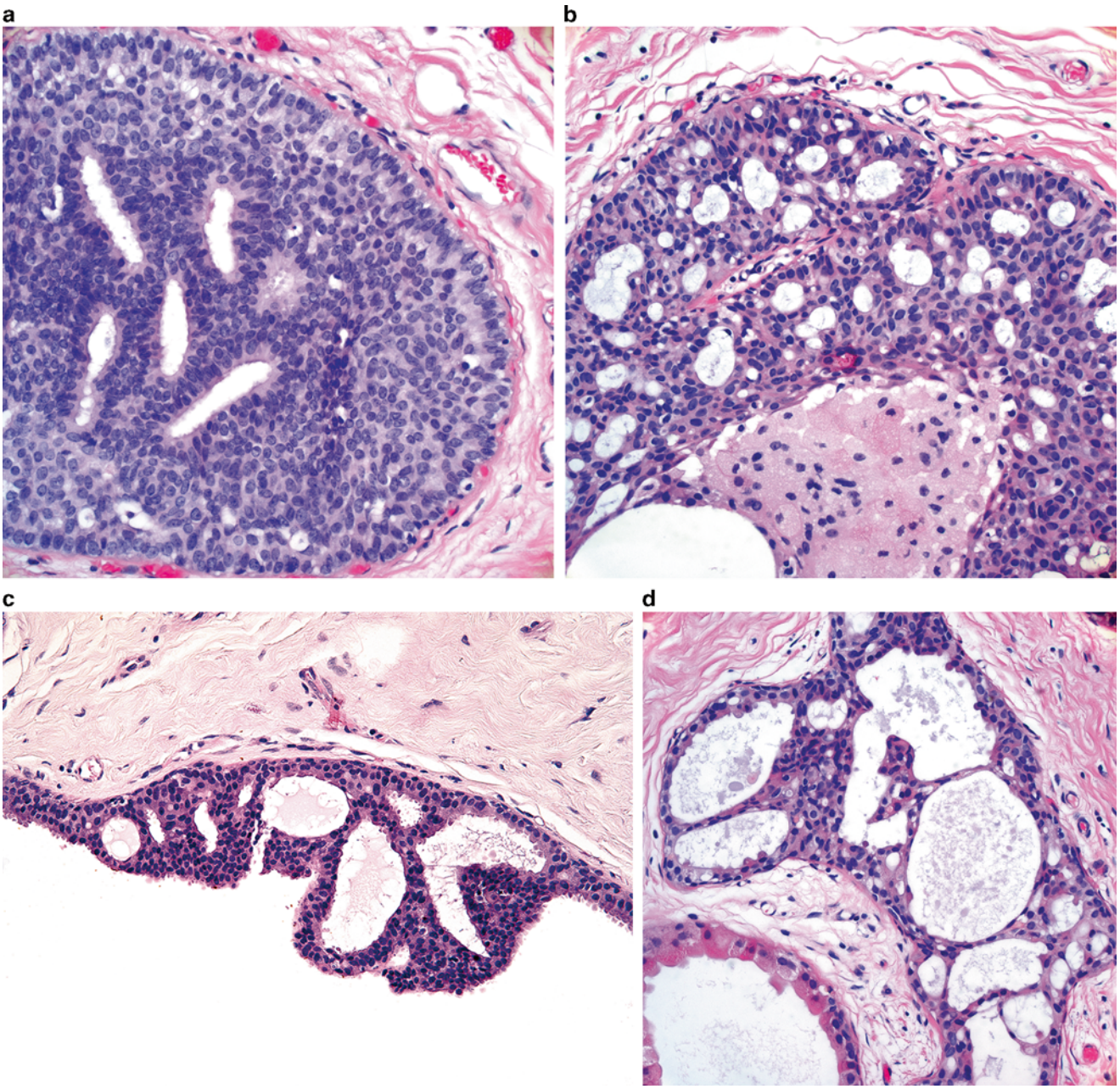

Fig. 9.37 (**a**) ADH with cytologic monotony and formation of early lumens that are slit-like but are polarized. (**b**) UDH can have more rounded spaces but they are not polarized and the cell population has a jumbled, polyclonal appearance. (**c**) ADH forming rigid arches that contain monotonous cells that have minimal overlap. (**d**) UDH with tapered, thin bridges containing cells with compressed nuclei. (**e**) ADH with partial involvement of a duct by elongated micropapillae containing monotonous cells with uniform nuclei. (**f**) UDH/columnar cell hyperplasia with formation of small micropapillae that contain jumbled nuclei that are smaller in size than those in the surrounding duct

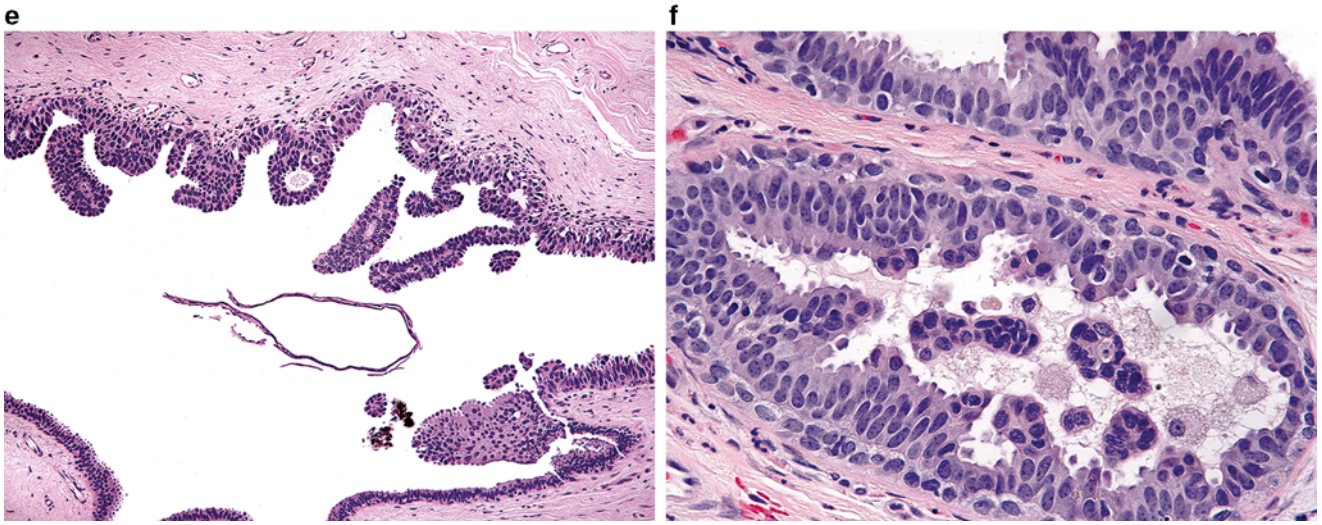

Fig. 9.37 (continued)

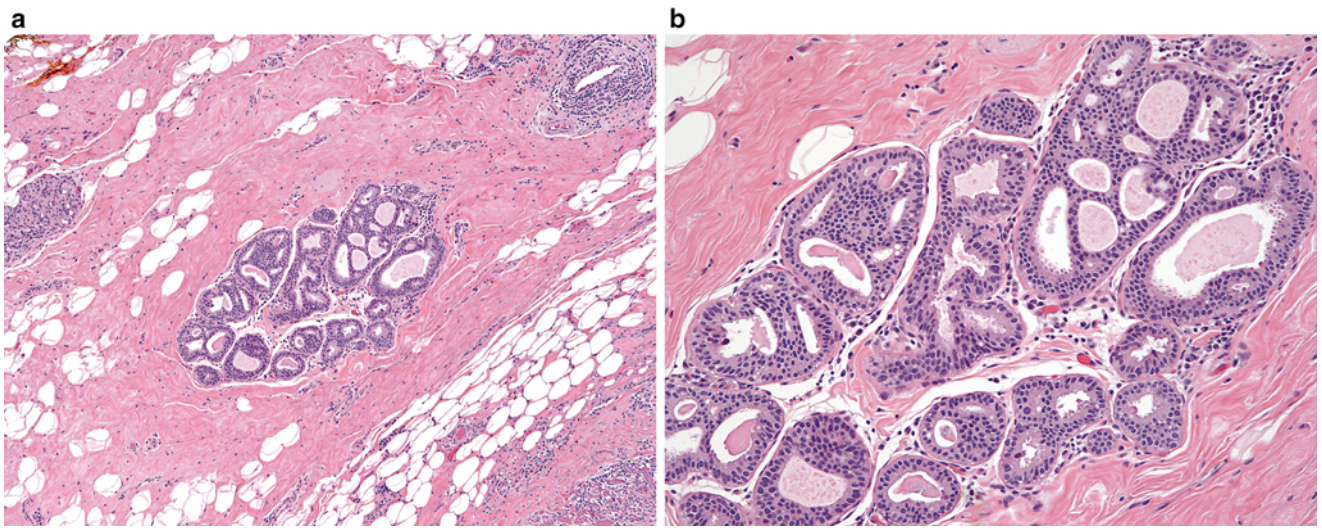

Fig. 9.38 (**a**, **b**) A core biopsy with a single focus <1 mm of an intraductal proliferation with enough cytologic monotony and early architectural changes to consider a diagnosis of minimal ADH

In cases such as these, it can be helpful to clinicians to describe the truly minimal extent of the ADH present in the core biopsy sampling, since these very focal, not-suspicious lesions are less likely to upgrade on excision and it may not be mandatory to perform excisional biopsies in all such patients [68, 69].

Immunohistochemistry

There is no clinically indicated reason to apply ER staining to ADH. In contrast to DCIS, which has a spectrum of ER expression in lesions of different nuclear grade, ADH should be uniformly ER positive. Although the majority of women with ADH only do not receive hormone-targeted therapies for risk reduction, this therapy has been shown to reduce their long-term risk of invasive cancer.

As mentioned in the differential diagnosis section, staining for basal cytokeratins CK5/6 can aid in the differential between UDH and ADH. There are additional antibody cocktail stains, such as the ADH-5 stain, which contains a combination of low and high molecular weight cytokeratins including CK5, 7, 14, 18, and p63. Some studies suggest that interobserver reproducibility can be improved when these stains are performed routinely [70].

Pathogenesis

It is crucial to understand that there are differences between what a lesion is considered from a biologic standpoint and how it is managed clinically. Risk lesions such as ADH were initially defined and classified based on results of long-term follow-up after excisional biopsy without the benefit of molecular data. If the increased risk of developing invasive cancer over time was bilateral, it was considered a risk lesion, and if it was unilateral, it was considered a precursor lesion. Today, we know much more about the biology of these lesions and understand that some risk lesions, such as ADH, can be neoplastic and non-obligate precursors to invasion. Studies of loss of heterozygosity (LOH) in low-grade DCIS and ADH have shown similar genetic lesions, providing evidence that these are clonal processes and both therefore fulfill the basic concept of neoplasia [71]. The bilateral risk associated with risk lesions is likely a result of a tendency for the lesion to be distributed in a patchy, scattered, and bilateral pattern as can occur with ADH.

The current model of the pathogenesis of breast cancer places many of the high-risk lesions, including ADH, in the low-grade pathway to "luminal"/estrogen receptor-positive invasive disease [37]. ADH is thought to be a very early neoplastic step in the pathway to low-intermediate grade DCIS and estrogen receptor-positive, low-grade invasive ductal carcinomas [36]. Allelic imbalances are seen with similar frequencies in ADH and low-grade DCIS and there are similar recurrent regions with LOH including loci on 1q, 16q, and 17p [40, 71, 72].

Outcomes

The identification of ADH as the clinically most significant lesion on a core needle biopsy will prompt most practices to offer a trip to the operating room for an excisional biopsy to rule out unsampled DCIS or invasive carcinoma. This is due to the upgrade rates for ADH on core biopsy, which range widely by study but in general are between 10 and 20% [60, 73–97].

Multiple studies have looked at ways to identify subgroups of ADH on core biopsy that are not at risk of upgrade and can avoid surgical excision. Lower upgrade rates can be achieved if cases are segregated by "low-risk features" such as complete removal of the targeted calcifications by core biopsy, very focal ADH without cytologic suspicion for an intermediate grade process, and no family or personal history of breast cancer, etc. But even using these risk stratification strategies, it is challenging to find a reproducible set of criteria that will give a risk of upgrade that is <3%.

However, in the few available prospective studies that have used criteria to avoid excision in some patients with ADH on core biopsy, there have been minimal events although follow-up was limited [98]. This suggests that upgrade rates may not be the best measure of outcome. The majority of these lesions will not invade and if they do it will be a favorable biology-invasive disease over many years. In fact, some studies looking at SEER data on excised versus not excised low-grade DCIS suggest that there is no overall survival benefit for surgical excision [46]. Because of this, most authorities agree that performing bilateral mastectomies would be overtreatment for ADH even though their risk for developing invasive disease is bilateral (although more recent studies suggest there is an increased ipsilateral risk) [99]. Some authorities argue that the increased risk of cancer should be managed medically with hormonal therapies [65]. However, most opt for high-risk screening protocols in these patients as the only risk prevention intervention.

Usual Ductal Hyperplasia

Overview

UDH is a benign proliferative lesion that can range from mild to florid. On a core needle biopsy, its presence can distract from other areas and raise concern for atypical processes. It carries a mildly increased risk of future development of breast cancer, estimated to be 1.5–2.0× [100].

Gross and Radiologic Features

UDH has no distinguishing gross or radiologic features. It can be found as an incidental background finding in core biopsies, or can be associated with the imaging abnormality of interest. Dense breasts more often have proliferative changes such as UDH on biopsy. UDH is most commonly identified in core biopsies performed for calcifications on mammography (often incidentally but sometimes also associated with calcifications) but can also be seen in biopsies for MRI enhancement or associated with mass lesions. Because UDH can involve lesions like radial scars, it can also present as an architecture distortion. Biopsies performed for a mass that contain UDH frequently contain papillary lesions, sclerosing adenosis, or fibroadenomas that explain the presence of a mass on imaging.

Microscopic Features

UDH is characterized by a polyclonal proliferation of cells that have indistinct cell borders, creating a "syncytial" appearance that is often streaming or windswept in appearance. The nuclei have bland chromatin patterns and vary in shape and size, consistent with a polyclonal process. When

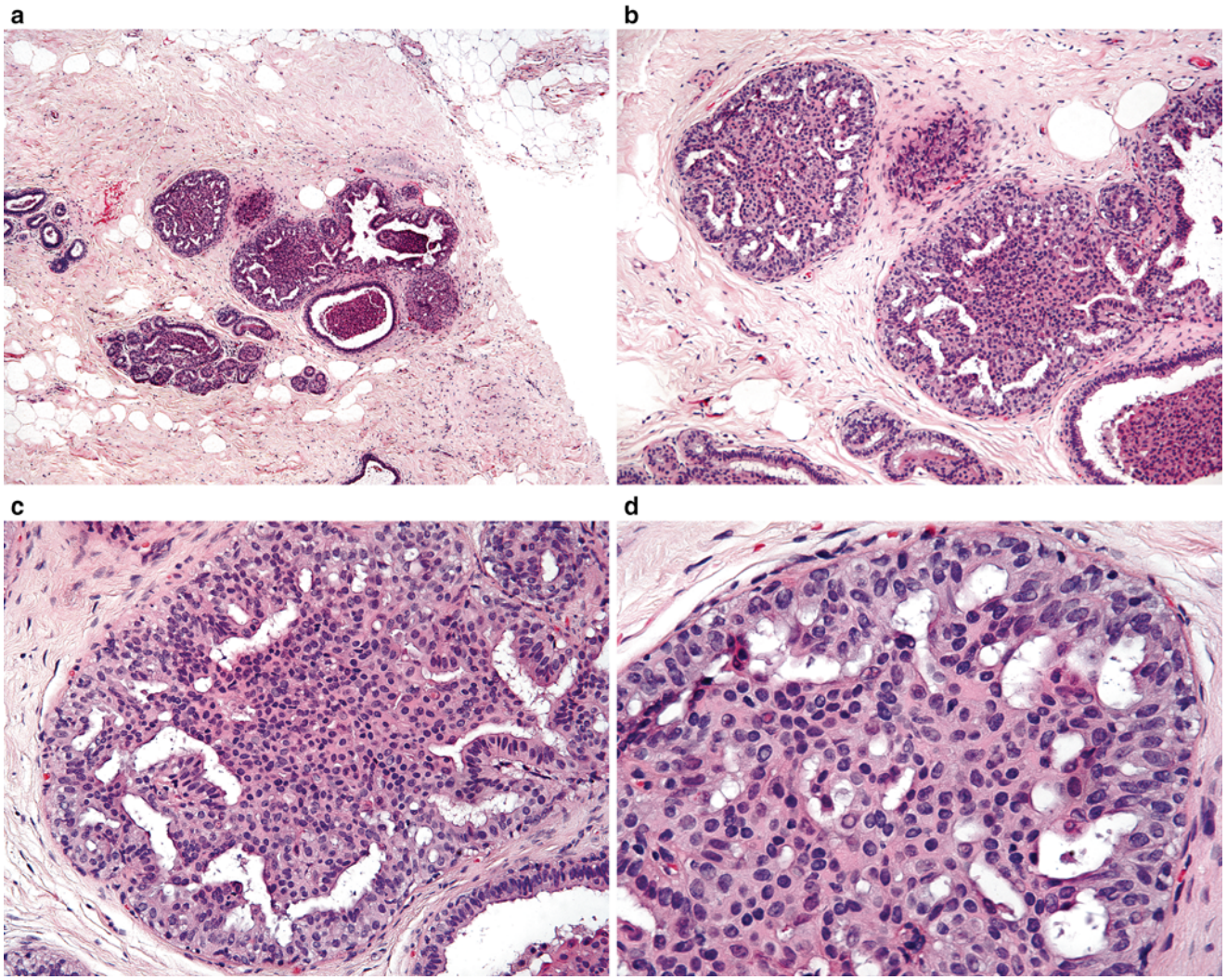

Fig. 9.39 (**a**–**d**) A core biopsy with an intraductal proliferation without cytologic monotony (cells are non-uniform, overlapping and of different sizes and shapes) and peripheral split-like spaces that are non-polarized. These features are diagnostic of usual ductal hyperplasia

spaces are formed within the proliferation, they are typically peripherally located within the duct and slit-like, without polarization of cells around these spaces (Fig. 9.39a–d). The compact form of hyperplasia has very dense collections of nuclei in the center of the duct, often with a spindled appearance. Micropapillary hyperplasia is characterized by tufts of columnar-type epithelium forming "pinched" or pyramid-shaped structures with smaller, crowded nuclei present toward the lumen aspect than the basal aspect (*see* Fig. 9.37f).

UDH that is more florid often contains collections of histiocytes and can rarely be so florid that there are areas of necrosis present (Fig. 9.40a–d). There are no well-defined criteria to distinguish florid from moderate to mild UDH. Florid UDH involving a papillary lesion, sclerosing lesions or radial scar can complicate diagnosis. Myoepithelial stains in conjunction with CK5/6 staining can help clarify these processes as UDH involving these lesions. Mitotic figures can be present in usual ductal hyperplasia, but atypical mitotic figures should warrant consideration of DCIS.

Differential Diagnosis

The differential diagnosis of UDH has been discussed in sections on DCIS and ADH. Florid UDH with a compact pattern can mimic spindled DCIS (see section on differential diagnosis of spindled DCIS versus UDH above). UDH and ADH can also be in the differential diagnosis of cases containing proliferations with features that overlap between these diagnoses (see section on differential diagnosis of ADH versus UDH above).

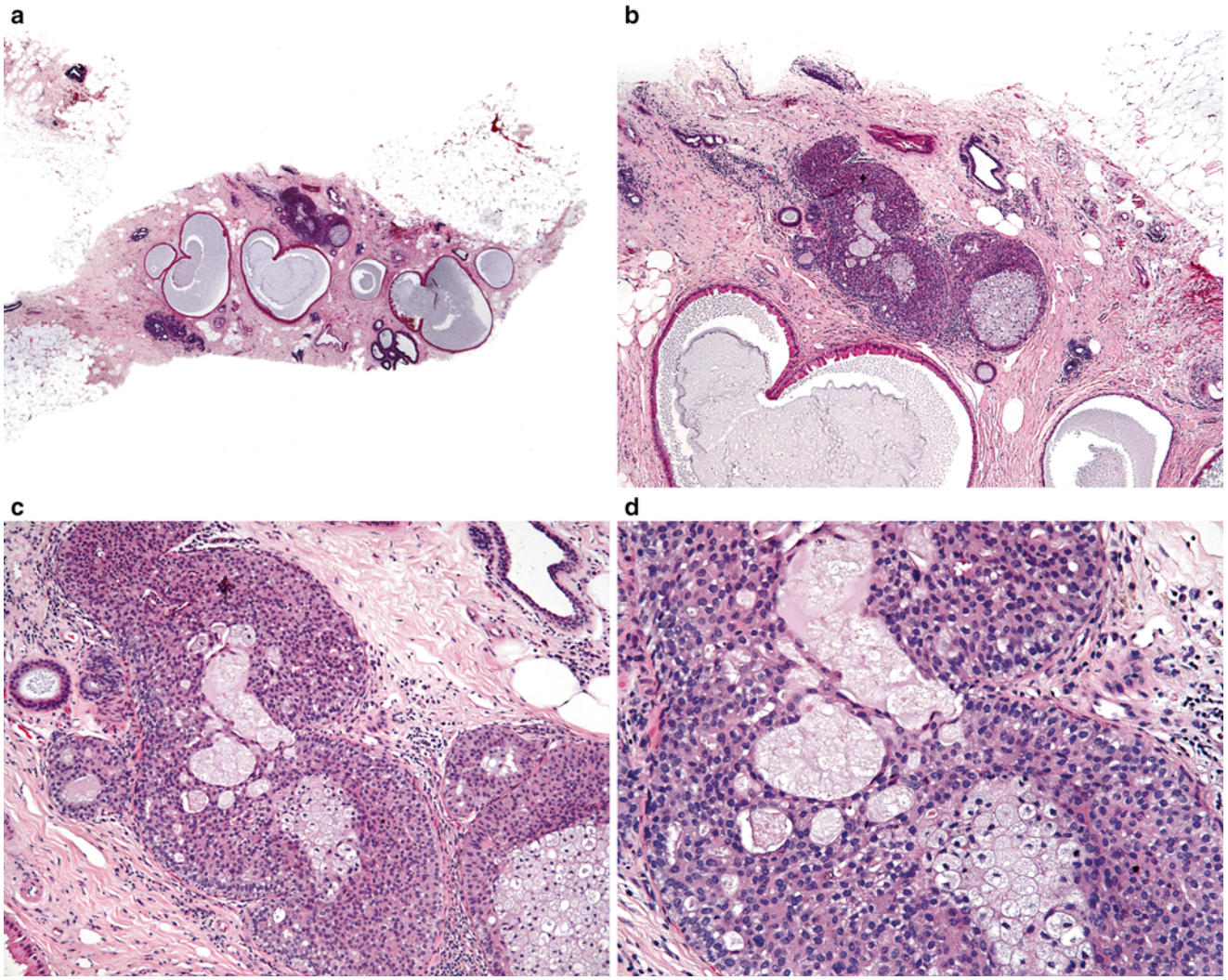

Fig. 9.40 (**a**–**d**) This core biopsy contains cysts as well as an intraductal proliferation that is filling some duct spaces. This proliferation contains polyclonal appearing cells with overlapping nuclei. There are collections of histiocytes and acellular secretions in the center of the proliferation. These features are most consistent with a diagnosis of usual ductal hyperplasia on core biopsy. If a diagnosis of forms of ADH or DCIS are being considered, a CK5/6 and ER stain can be helpful

Immunohistochemistry

There are no clinically relevant antibody stains to perform when a diagnosis of UDH is rendered. As discussed in the differential diagnosis sections, CK5/6 staining patterns in UDH are mixed or "mosaic" since UDH contains cells with both luminal and basal-type cytokeratins admixed (Fig. 9.41a, b). Estrogen receptor expression also tends to be in a similar, but inverse in pattern, with the luminal-type epithelial cells staining more often than the admixed basal-type cells (Fig. 9.41c, d).

Pathogenesis

UDH is a benign, proliferative intraductal process. The frequency of LOH in cases of usual hyperplasia is low and typically at random sites, suggesting that in contrast to ADH and DCIS, it is non-neoplastic [71, 101]. Therefore, while it is difficult to find genetic distinctions between low-grade DCIS and ADH, the border between ADH and UDH is better defined from the standpoint of molecular alterations [102].

The formation of UDH and other proliferative lesions may be related to hormonally regulated changes, since it is

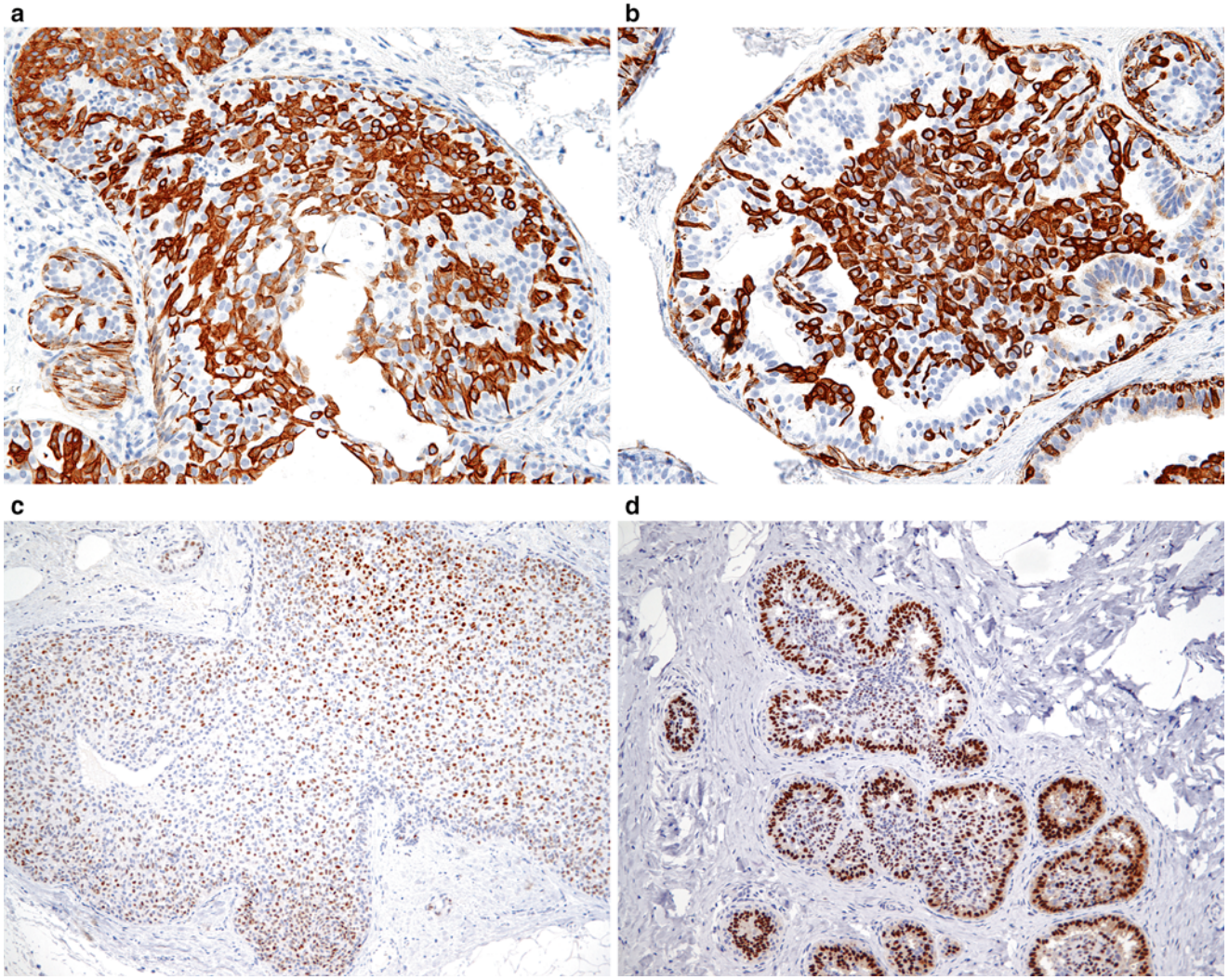

Fig. 9.41 (**a**, **b**) CK5/6 "mosaic" staining pattern seen in usual ductal hyperplasia (in contrast to the absent staining seen in low-grade DCIS/ADH). (**c**, **d**) Variable patterns of ER expression are seen in UDH (in contrast to the uniform strong expression expected throughout low-grade DCIS or ADH)

more frequently found in younger patients with dense breasts and during the menstrual cycle. While there is still some debate about whether UDH is a step in the pathway to ADH and low-grade carcinomas, UDH that shows higher levels of estrogen expression, higher Ki-67 proliferative rates, and is more frequently associated with patients who developed breast cancers [103–106].

Outcomes

UDH is not considered a lesion with a significant risk of upgrade to DCIS or invasive carcinoma on excision, so in general a diagnosis of UDH on a core biopsy has minimal impact. It can be important to describe the degree of the proliferative changes present on core biopsies with non-atypical

proliferations like UDH such that appropriate radiologic–pathologic correlation can occur.

Although women with florid UDH are slightly more likely to develop invasive breast cancer in either breast and more frequently have other associated proliferative lesions of the breast, there are currently no medical management implications from this diagnosis.

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