Benign Lesions (Proliferations) and Tumors of the Breast

7

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Most of the lesions included in this chapter are frequently encountered in breast pathology and easy to diagnose. Some of them, however, may mimic radiologically, clinically, and pathologically an invasive carcinoma (the so-called pseudoinfiltrative lesions of the breast). Especially in these cases, the experience of the pathologist together with ancillary studies allow a correct diagnosis, while management requires a breast tumor board approach. Also, some of these lesions increase the risk of developing a malignancy, and closer follow-up should be considered in these patients.

7.1 Fibrocystic Changes

Fibrocystic changes are an extremely important finding in breast pathology, due to their high frequency, their ability to mimic carcinoma clinically, radiologically, and morphologically, and the possible relationships between some of their forms and the development of a breast carcinoma. Currently, it is considered that fibrocystic changes are represented by a very heterogeneous spectrum of processes, some physiologic and some pathologic, with widely varying cancer risks [1–3]. It originates in the terminal duct/lobular unit (TDLU). Several names have been proposed for this lesion (fibrous mastopathy, mammary dysplasia, etc.), but the terms fibrocystic disease or fibrocystic changes are currently in use (in the latter case, the histopathological report should specify and describe all the changes detected within the biopsy or surgical specimen).

Fibrocystic changes occur more frequently during the reproductive period (ages 20–45); more than one-third of women aged between these two limits develop fibrocystic disease [4]. Its emergence is favored by hormonal disorders (change in the estradiol-progesterone ratio), while prolonged treatment with oral contraceptives or methylxanthines (coffee, tea, chocolate) have not been proved to be definitively involved in the pathogenesis of fibrocystic changes.

Clinically, the lesion is frequently multifocal and bilateral, and especially occurs in the upper-outer quadrant of the breast. Associated symptoms are the following: breast discomfort; and a feeling of heaviness or pain that is sometimes associated with nipple discharge. About 20% of the patients present axillary adenopathy associated with sensitivity (due to axillary lymph node reaction to the inflammatory process of the breast, as a result of a cyst rupture). After menopause, the lesions gradually regress (excluding patients who either receive estrogen replacement therapy or are obese). The changes can be detected by ultrasound examination,

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especially because of the presence of the cysts, or by mammography (which detects microcalcifications associated with cysts, but characteristically a diffuse density secondary to the extensive stromal fibrosis can be detected). Tru-Cut Biopsy replaced fine-needle aspiration (FNA) as the method to diagnose palpable and non-palpable fibrocystic changes, and in most of the cases a portion of the cyst together with other associated lesions can be detected on microscopic examination.

Macroscopically, the lesion has ill-defined margins and it is usually represented by a gray-white fibrous tissue with elastic consistency, which on the cut surface has numerous cysts with a variable diameter of 2–20 mm, filled with clear or blue, yellow, sometimes hemorrhagic fluid (Figs. 7.1, 7.2, 7.3, and 7.4). However, in cases with small cysts identified on ultrasound or mammography, the macroscopic examination may disclose only an area of fibrosis and the microscopic examination will be necessary to reveal additional findings.

Microscopically, fibrocystic changes are characterized by a series of changes that are usually associated with one another:

- Hyperplasia of mammary ducts and acini, which retain their round shape and are lined by two characteristic cell layers (epithelial and myoepithelial cells).
- Cystic dilatation of the ducts and acini, forming micro- and macrocysts containing an acellular eosinophilic material in the lumina (Figs. 7.5, 7.6, 7.7, and 7.8); the lumina may also contain exfoliated epithelial cells or histiocytes with vacuolated cytoplasm (due to lipid content) and a small round nucleus, centrally located, called lamprocytes which, due to the hemorrhage, may contain hemosiderin pigment (Figs. 7.9 and 7.10); the migration of these cells from the lumina into epithelial layer can mimic a pseudo-pagetoid appearance (Fig. 7.11) that should not be mistaken for a precursor or a malignant lesion (immunohistochemical positivity of lamprocytes for CD-68 as well as negativity for pan-Cytokeratin can help to differentiate the two lesions); the cysts are lined by a cuboidal, cylindrical, or flattened epithelium (the latter condition occurs due to the containing contents of the cyst) (Figs. 7.12 and 7.13); if only one single cyst is identified in the breast tissue, it is called a *solitary cyst*; if more cysts are identified, fibrocystic changes diagnosis is preferable; the solitary cyst is usually unique with a diameter of over 10 mm; some of the cysts may contain calcifications of varying types including calcium, calcium phosphate, apatite, or calcium oxalate (Fig. 7.14).
- Apocrine metaplasia, which involves both acini and intralobular ducts (but sometimes also the extralobular ones); it represents a transformation of the cells of normal cuboidal/cylindrical epithelium into apocrine cells, which are characterized by a larger size, rounded or cylindrical shape, with abundant eosinophilic granular cytoplasm, a round nucleus, and a centrally located prominent nucleolus (Fig. 7.15); apocrine metaplasia may involve the epithelium of acini or ducts, without their cystic dilatation (in this case the term *apocrine adenosis* can be used), or it can involve cystically dilated ducts or acini; also, apocrine metaplasia can occur in the absence of any other changes, within normal acini or ducts, without any clinical/pathological significance (Fig. 7.16); the epithelium of apocrine metaplasia may sometimes be flat or may present a complex proliferation with small papillae centered around a fibro-vascular axis or forming arches and bridges (Figs. 7.17, 7.18, and 7.19); apocrine metaplasia cells may sometimes exhibit atypia represented by nuclear enlargement (more than threefold nuclear size variation), nuclear pleomorphism, prominent nucleolus, and mitotic figures; also, apocrine metaplastic cells may sometimes show intracytoplasmic microvacuoles, cells which are similar to the sebaceous cells (sebocrine metaplasia); immunohistochemically, apocrine cells are usually negative for estrogen receptors (ER) and progesterone receptors (PR) while they are positive for androgen receptors (AR) [5].
- Chronic inflammatory process due to the rupture of cysts and release of their contents into the surrounding stroma; the inflammatory infiltrate is usually composed of lymphocytes, plasma cells, and histiocytes (Figs. 7.20 and 7.21).
- Fibrosis of the stroma, which varies quantitatively from one lesion to the other and also from one field to another within the same lesion; the intralobular stroma is sclerotic, sometimes indistinguishable from the interlobular stroma; myxoid changes or microcalfications may occur (Figs. 7.22 and 7.23).
- Fibroadenomatoid changes similar to those that occur in fibroadenomas, but being diffuse and not circumscribed, forming a mass in fibrocystic changes (Fig. 7.24).
- Epithelial hyperplasia, which occurs only in some fibrocystic changes and which is the most important component because its presence increases the relative risk to the development of breast carcinoma. Therefore, in 1986, the College of American Pathologists [2] distinguished between *functional fibrocystic changes*, with no epithelial hyperplasia associated, and *proliferative fibrocystic changes*, with epithelial hyperplasia prone to carcinoma development (Figs. 7.25, 7.26, 7.27, 7.28, 7.29, 7.30, 7.31, 7.32, and 7.33). The two entities should be separated from a pathological point of view and treated differently. If the epithelium of apocrine metaplasia is accompanied by hyperplasia, the lesion is designated as proliferative fibrocystic changes and reported accordingly. The same rule applies to the solitary cyst if it is accompanied by epithelial hyperplasia.

Differential diagnosis is made with the following:

- Ductal ectasia (which has a different location and affects extralobular ducts, and a chronic inflammatory infiltrate can be observed periductally, as well as the presence of elastic tissue).
- Galactocele (a cavity beneath the areola filled with milk, due to the abrupt suppression of lactation; the cavity is usually lined by a secretory epithelium and the surrounding tissue may present areas of lipogranuloma due to the leakage of the cyst content consisting especially of a collection of foamy histocytes containing milk intracytoplasmatically) (Fig. 7.34).
- Hydatic cyst (produced by Echinococcus, very rare in the breast, presenting as usually unilocular cyst fluid filled but also containing daughter cysts and microscopically lined by three layers: germinal internal layer, laminated membrane beneath the germinal layer, and outer layer of dense fibrovascular tissue with chronic inflammatory infiltrate and variable calcifications) (Fig. 7.35).
- Pseudocyst cavity after surgical removal of breast lesions (the cavity is not lined by an epithelium and is surrounded by inflammatory infiltrate and numerous histiocytes) (Fig. 7.36).
- Cystic atrophy in postmenopausal patients (originating in intralobular acini and ducts, which are lined by an atrophic epithelium and surrounded by intralobular stroma while there is no association with the other conditions of fibrocystic changes).
- Flat atypia (the ducts and acini involved in such a lesion are usually distended, have a smooth contour, and may contain secretory material and microcalcifications mimicking fibrocystic changes at low-power; however, at high-power, they are lined by one-to-several epithelial cells lacking polarity with round nuclei presenting low atypicality and sometimes apical snouts while the myoepithelial cells are present but attenuated and barely visible at the periphery) (Figs. 7.37 and 7.38).
- Cystic hypersecretory hyperplasia or ductal carcinoma *in situ* (represented by cysts filled with secretory material which on microscopic examination resemble the thyroid colloid; the cysts are lined by epithelium showing various degrees of hyperplasia and/or ductal carcinoma *in situ*, with areas showing evidence of secretory activity resembling the lactating breast) (Figs. 7.39, 7.40, and 7.41).
- Blunt duct adenosis (distension of acini and ducts, with rounded or irregular contour, lined by both epithelial cells with columnar features and prominent myoepithelial cells, with various secretions within the lumina; some authors consider blunt duct adenosis as part of the spectrum of fibrocystic changes since the TDLU expands without ductal and/or lobular proliferation) (Figs. 7.42 and 7.43).
- Fibroadenoma (a nodular mass of more than 10 mm in diameter, surrounded by a capsule at the periphery and not associated with cysts or inflammation).
- *In situ* breast carcinoma of ductal or lobular type or atypical ductal or lobular hyperplasia (in the presence of atypical epithelial hyperplasia); as well as with Swiss-cheese tumor (also called juvenile papillomatosis, typically occurring in children—unlike fibrocystic changes—as a grossly distinct multinodular mass with clustering of cystic formations; microscopically, multiple cysts are associated with epithelial hyperplasia and papillomatosis usually without atypia) as well as multiple papillomatosis (multiple cysts involved by a papillary proliferation of fibro-vascular axes lined both epithelial and myoepithelial cells without atypia; other microscopic findings of fibrocystic changes are missing) (Figs. 7.44, 7.45, and 7.46) [6].

Changes such as fibrosis, dilatation of acini and ducts (only visible microscopically), involution or enlargement of lobules, when unaccompanied by other changes characteristic for fibrocystic changes, should be reported as normal changes because they are not considered benign pathological changes. In the final histopathological report, one must list all the changes or lesions found within the specimen, in the descending order of importance with regard to their potential level of breast cancer risk, including microcalcifications (even if these were associated with normal breast tissue).

If the fibrocystic changes are not associated with epithelial proliferation, the risk of subsequent development of invasive carcinoma is extremely low (0.89 relative risk), increasing with a positive family history (1.2 relative risk) and presence of larger cysts (1.3 relative risk); therefore, no specific follow-up is recommended for these patients other than for the normal population [6, 7]. Prognosis of fibrocystic changes without proliferation is excellent whether the prognosis of the proliferative lesion depends to the degree of the proliferation and/or atypia. No surgical treatment is indicated for patients with non-proliferative disease while hormonal treatment for providing symptomatic relief may be of use. For patients with large cysts, evaluation of the cysts using fine-needle aspiration (FNA) guided by ultrasound may be an option. The cytological assessment of the fluid is generally performed when the appearance of the fluid is bloody or turbid, or in cases in which the cyst does not collapse completely after aspiration; in some centers, however, the fluid is routinely cytologically examined. Also, when the lesion is associated with epithelial hyperplasia without atypia, a good radiological-pathological correlation is needed, and radiological follow-up is recommended. However, when proliferative changes are associated with atypia, surgical excision is indicated, and further treatment is based on the type and extent of the atypical proliferation.

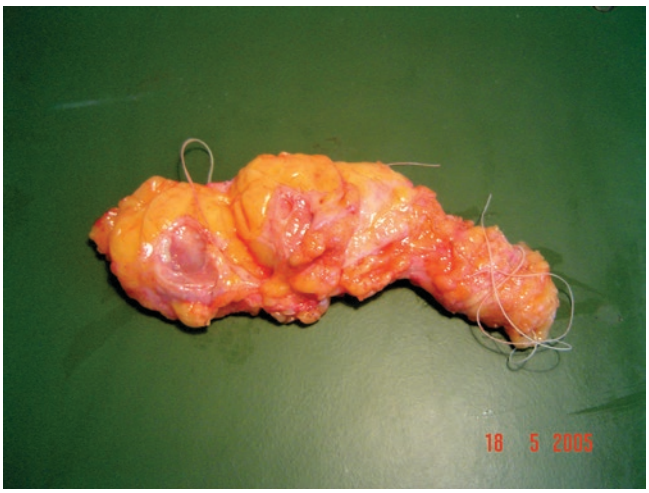

Fig. 7.1 Fibrocystic changes: surgically removed breast quadrant presenting an area of fibrosis and multiple cysts of various sizes

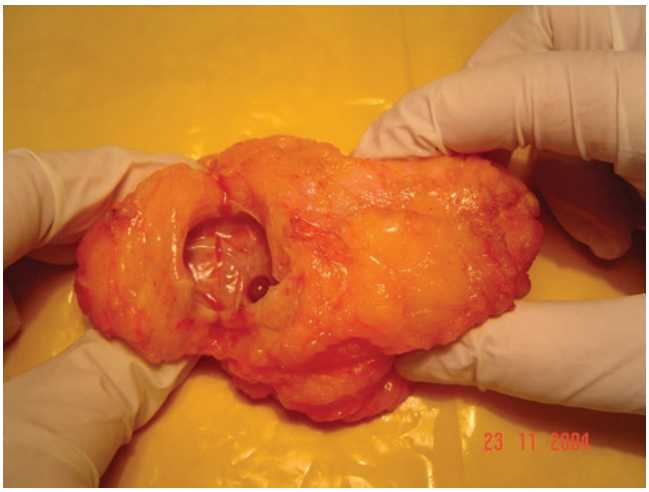

Fig. 7.2 Fibrocystic changes: on the cut surface, one of the cysts has smooth internal wall and the content is partially hemorrhagic

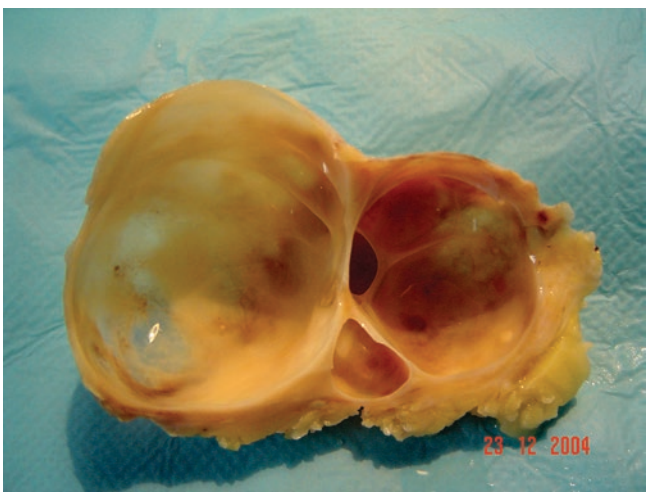

Fig. 7.3 Fibrocystic changes: surgical specimen with multiple cysts of various sizes with smooth contour

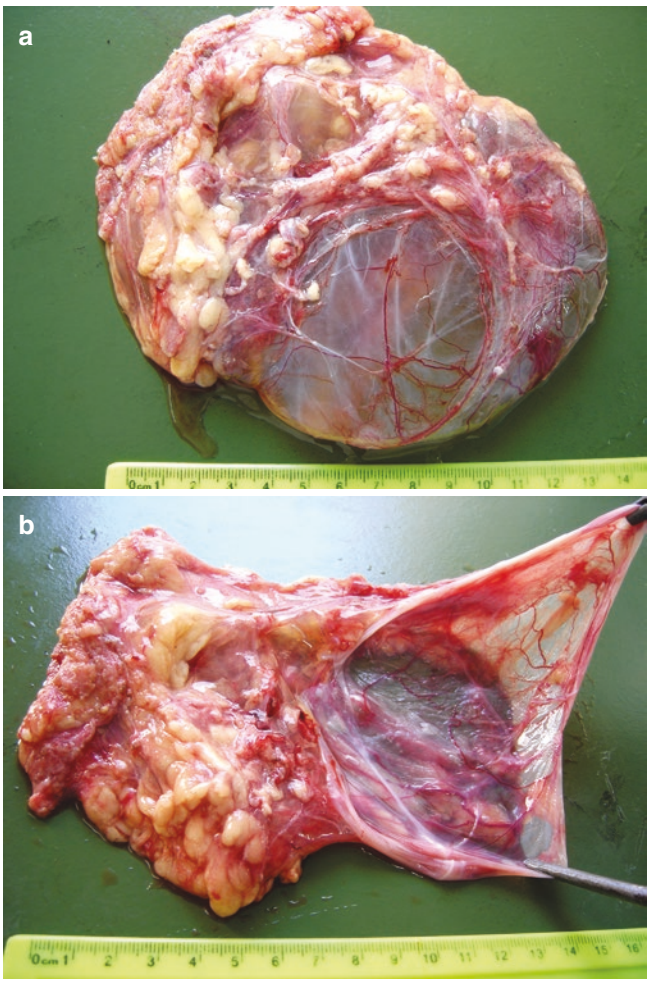

Fig. 7.4 Fibrocystic changes: (**a**) Surgical specimen with multiple cysts, one of which is large size. (**b**) On the cut surface, the largest cyst has smooth and thin wall due to the large amount of content

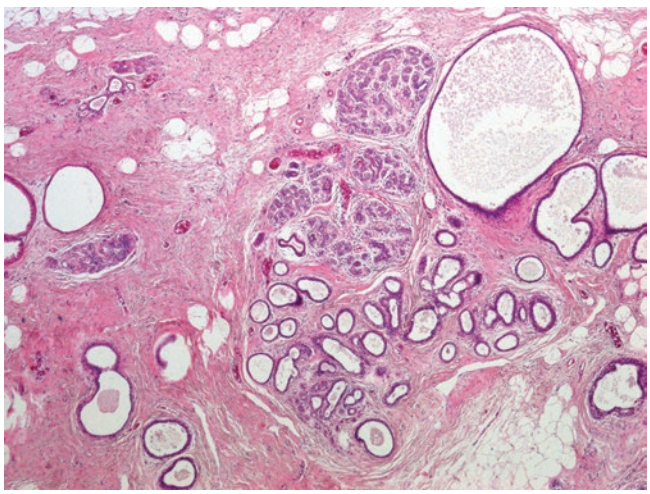

Fig. 7.5 Functional fibrocystic changes: hyperplasia of mammary ducts and acini, some of them cystically dilated

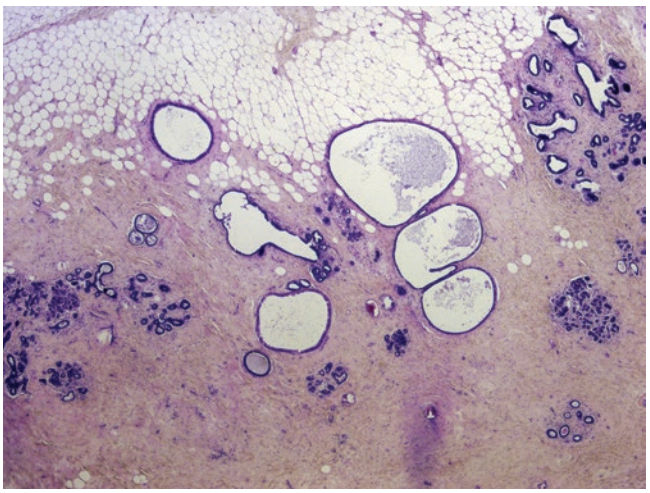

Fig. 7.6 Functional fibrocystic changes: hyperplasia of mammary ducts and acini, some of them cystically dilated

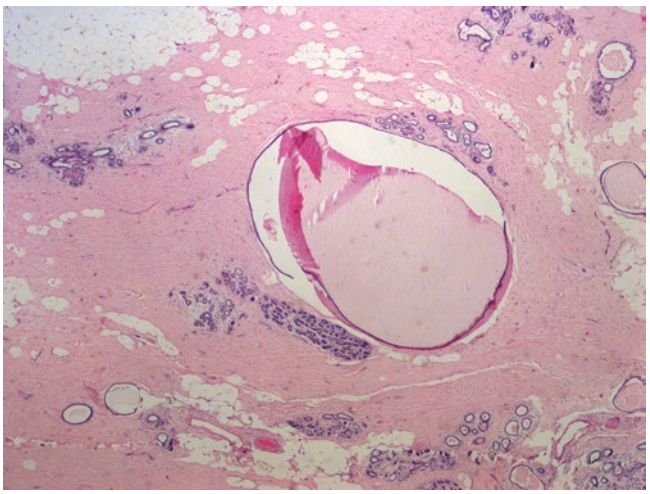

Fig. 7.7 Functional fibrocystic changes: multiple cysts containing an acellular eosinophilic material in the lumina

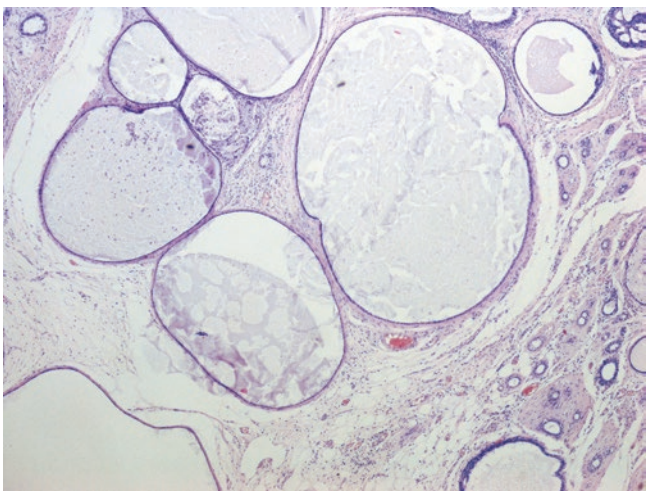

Fig. 7.8 Fibrocystic changes: multiple cysts, most of them containing an acellular eosinophilic material in the lumina

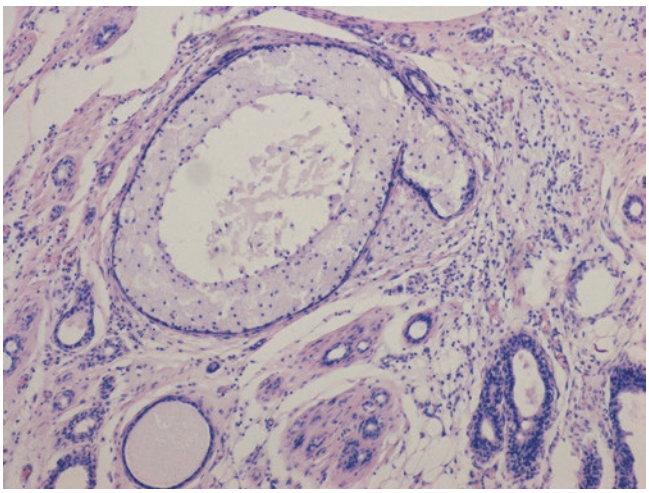

Fig. 7.9 Fibrocystic changes: the lumina of the cysts contain exfoliated epithelial cells and histiocytes with vacuolated cytoplasm (due to lipid content) and a small round nucleus, centrally located (called lamprocytes)

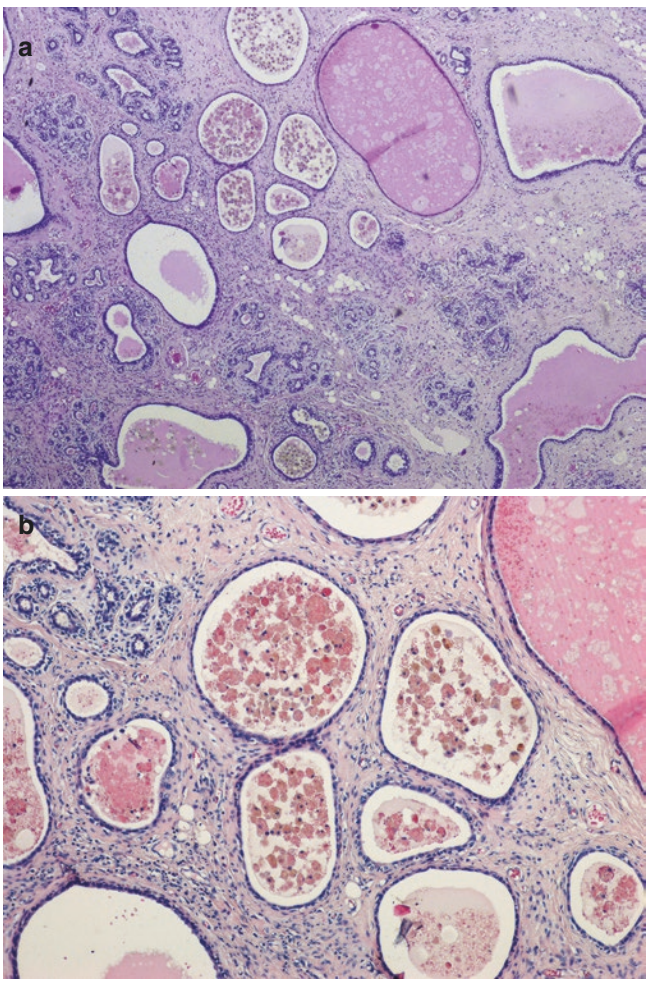

Fig. 7.10 Fibrocystic changes: (**a**) The lumina of the cysts contains numerous lamprocytes, (**b**) which due to the hemorrhage contain hemosiderin pigment intracytoplasmatically

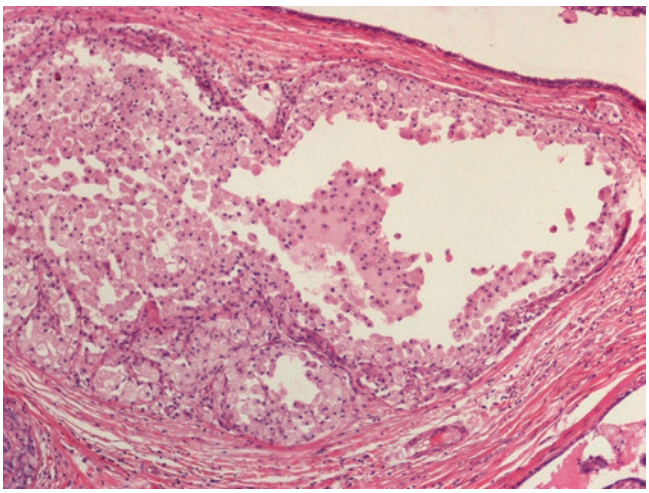

Fig. 7.11 Fibrocystic changes: the migration of lamprocytes from the lumina into epithelial layer can mimic a pseudo-pagetoid appearance

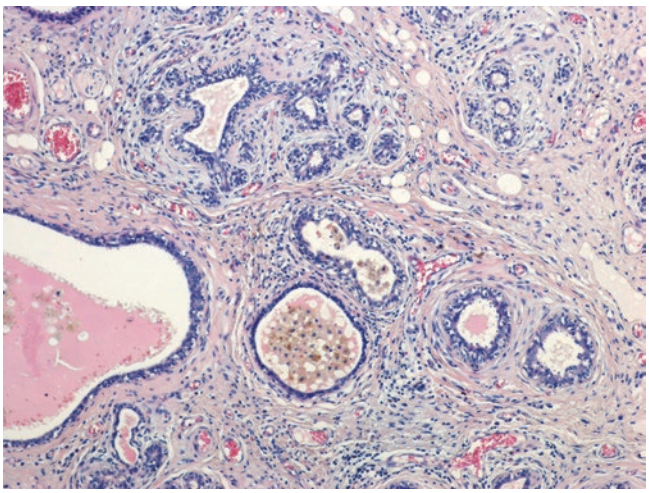

Fig. 7.12 Functional fibrocystic changes: hyperplasia of mammary ducts and acini, which retain their round shape and are lined by two characteristic cell layers (inner epithelial and outer myoepithelial cells)

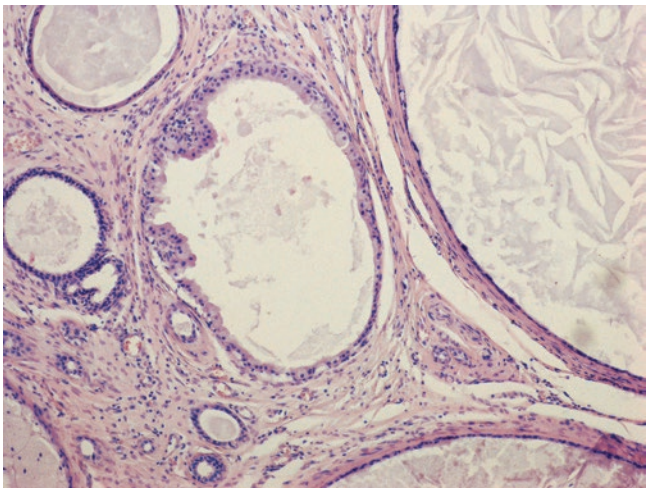

Fig. 7.13 Functional fibrocystic changes: some of the cysts have cuboidal epithelium, some have flattened epithelium, and some have epithelium with apocrine metaplasia

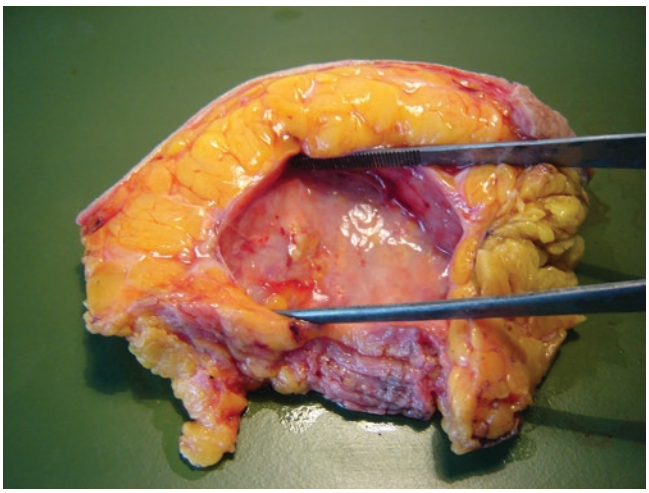

Fig. 7.14 Surgical specimen with one single cyst, called solitary cyst

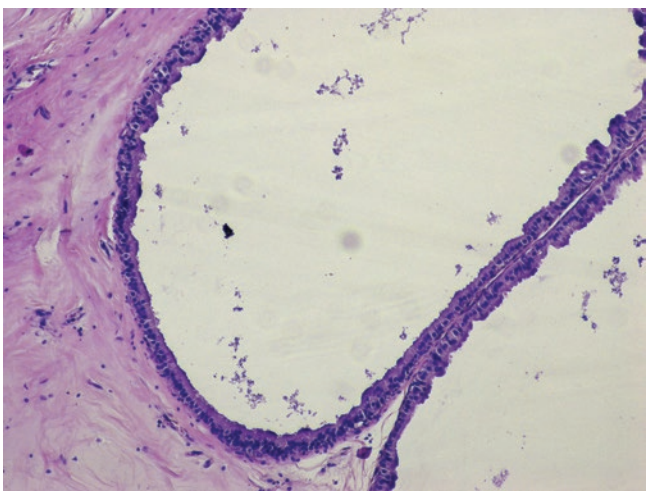

Fig. 7.15 Functional fibrocystic changes: two cysts lined by cylindrical epithelium with apocrine metaplasia

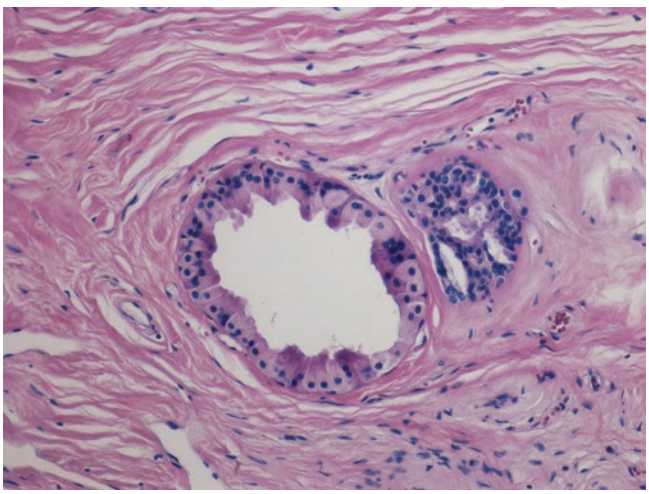

Fig. 7.16 Apocrine metaplasia involves the epithelium of acini, without their cystic dilatation; the cells are of larger size, rounded or cylindrical shape, with abundant eosinophilic granular cytoplasm and a round nucleus

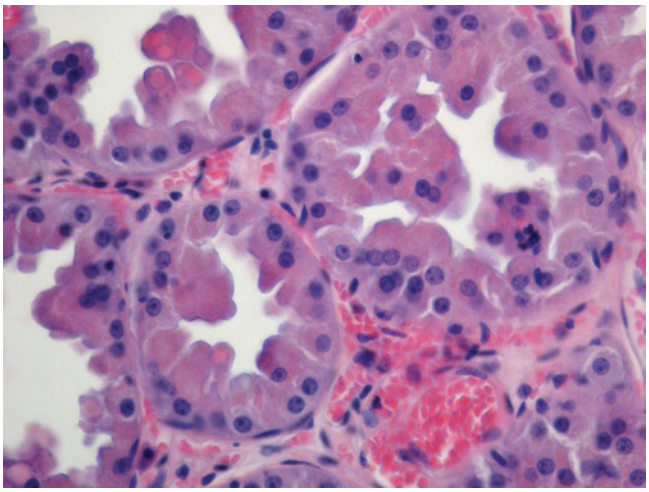

Fig. 7.17 Apocrine metaplasia; cylindrical cells with abundant eosinophilic granular cytoplasm and nuclei with prominent nucleoli

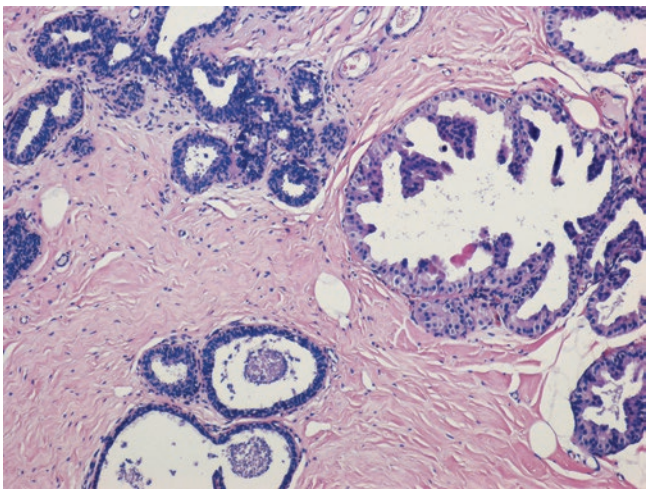

Fig. 7.18 Apocrine metaplasia with complex proliferation without atypia: cysts lined by metaplastic apocrine epithelium forming papillae and micropapillae

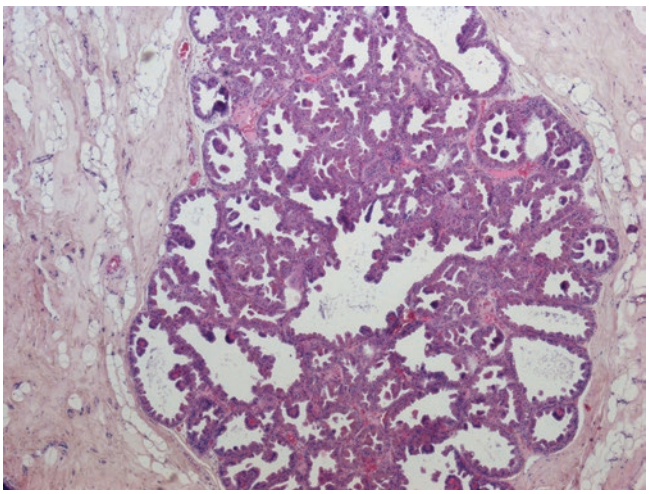

Fig. 7.19 Apocrine metaplasia with complex proliferation without atypia: cysts lined by metaplastic apocrine epithelium forming papillae (with a fibro-vascular axis) and micropapillae (without a fibro-vascular axis)

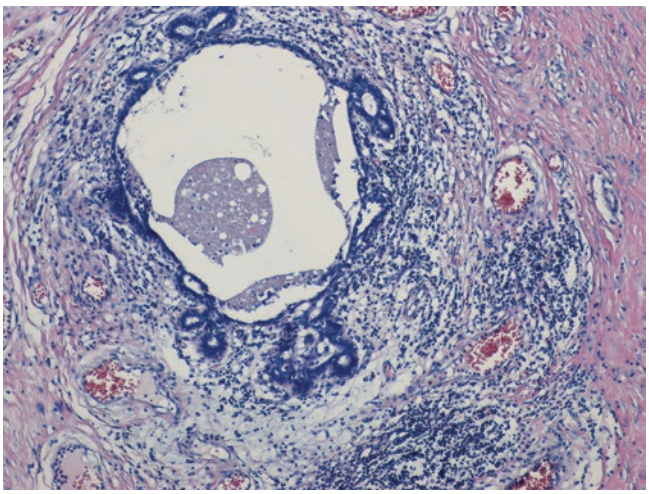

Fig. 7.20 Functional fibrocystic changes: chronic inflammatory process around the cyst

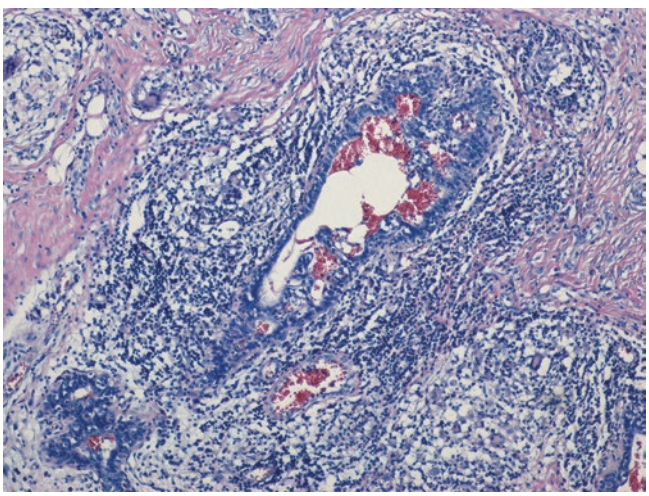

Fig. 7.21 Fibrocystic changes: chronic inflammatory process around the cyst represented by lymphocytes, plasma cells, and histiocytes, some of them multinucleated

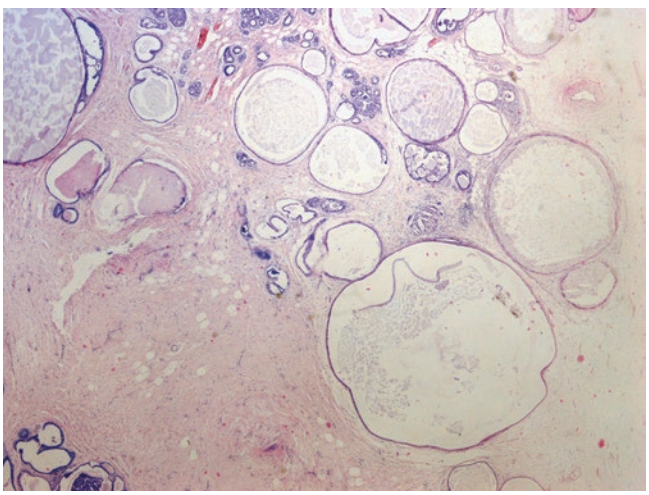

Fig. 7.22 Fibrocystic changes with fibrosis with a sclerotic appearance

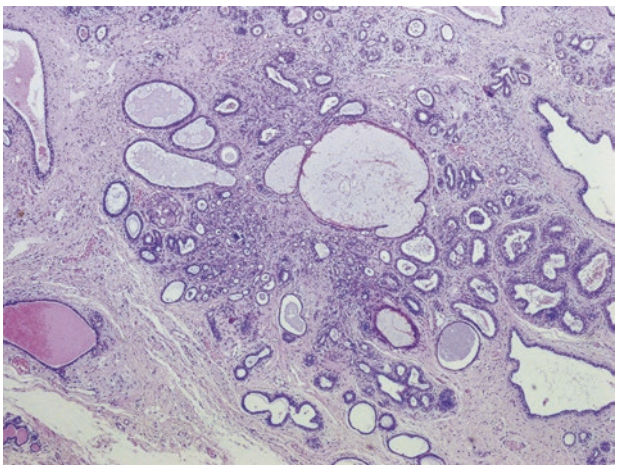

Fig. 7.23 Fibrocystic changes: microcalcifications into the stroma adjacent to the cysts

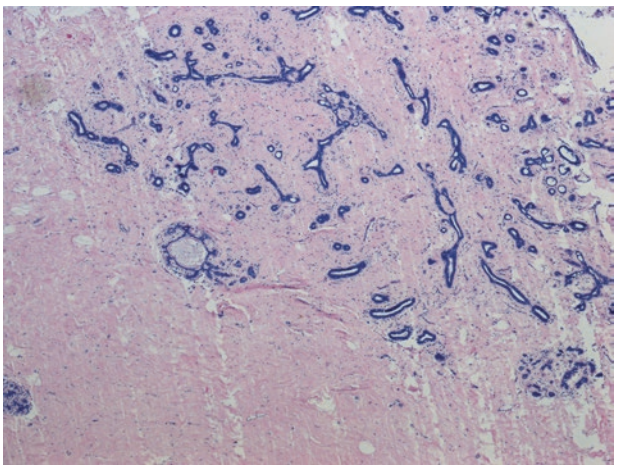

Fig. 7.24 Fibrocystic changes with fibroadenomatoid changes: they are similar in morphologic appearance to fibroadenoma, but have a diffuse character

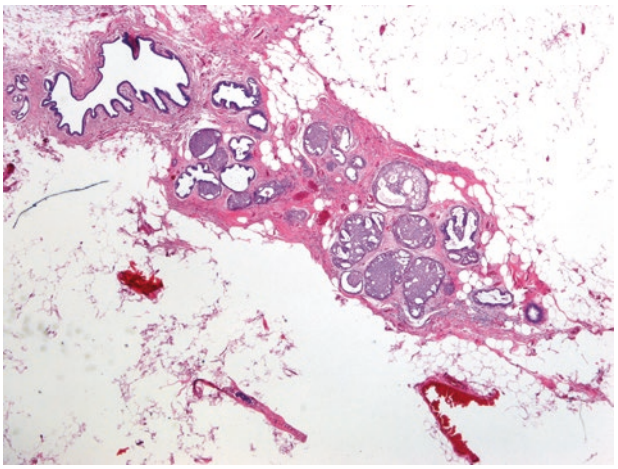

Fig. 7.25 Proliferative fibrocystic changes: multiple acini of the TDLU involved by a luminal proliferation without atypia while the duct is not affected

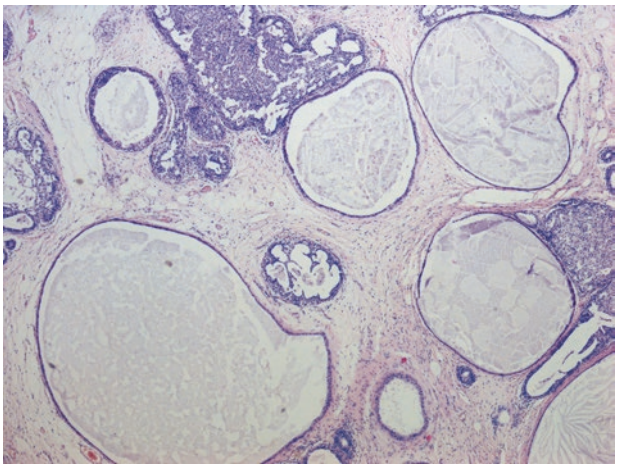

Fig. 7.26 Proliferative fibrocystic changes: some of the cysts are lined by a double layer of cells while others have intraluminal proliferation without atypia

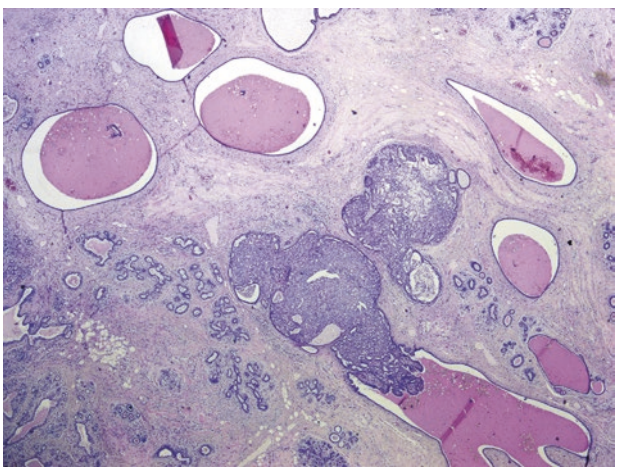

Fig. 7.27 Proliferative fibrocystic changes: some of the cysts are lined by a double layer of cells while others have intraluminal proliferation without atypia which involves partially or entirely the cysts

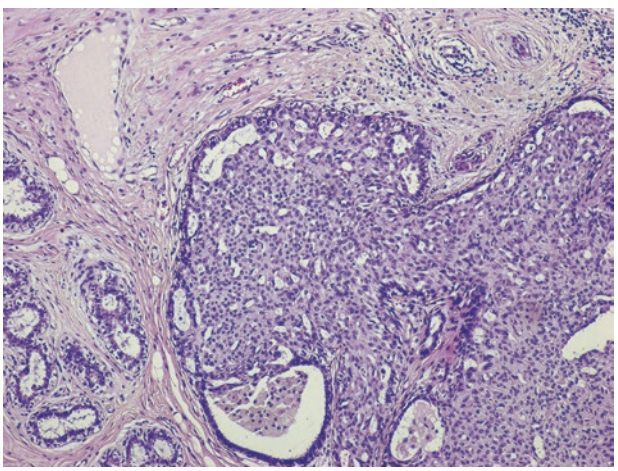

Fig. 7.28 Proliferative fibrocystic changes: high-power examination reveals that intraluminal proliferation is represented by a mixed population of cells with spindle shaped overlapping nuclei, syncytial appearance of the cytoplasm, and secondary lumina at the periphery of the cyst (usual ductal hyperplasia, without atypia)

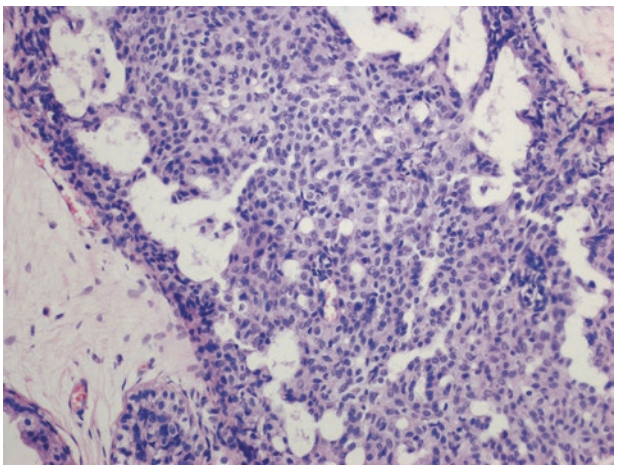

Fig. 7.29 Proliferative fibrocystic changes with usual ductal hyperplasia without atypia: most of the secondary lumina are located at the periphery of the cyst

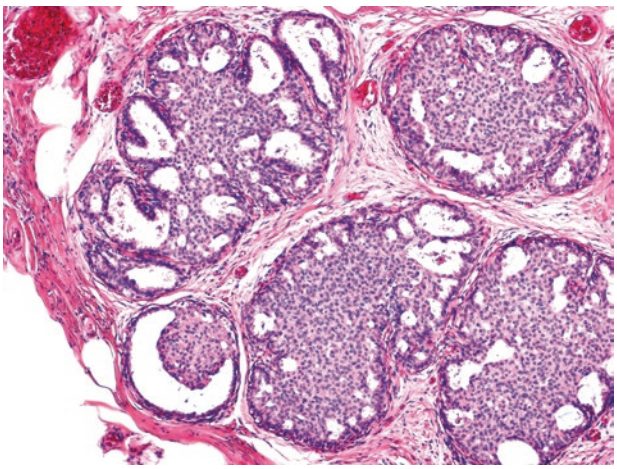

Fig. 7.30 Proliferative fibrocystic changes with usual ductal hyperplasia without atypia displaying various architecture appearance, including glomeruloid-type

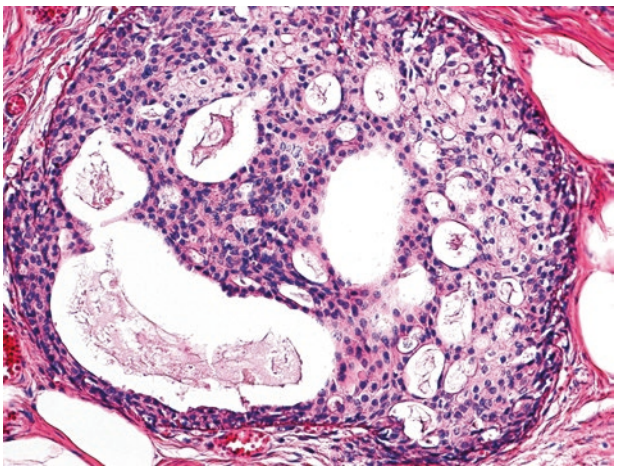

Fig. 7.31 Proliferative fibrocystic changes with usual ductal hyperplasia without atypia: high-power examination reveals a mixed population of epithelial, myoepithelial, and apocrine cells

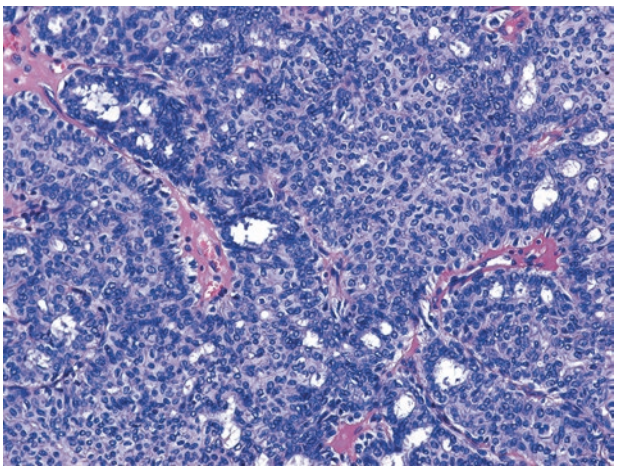

Fig. 7.32 Proliferative fibrocystic changes with usual ductal hyperplasia without atypia: high-power examination reveals a mixed population of epithelial and myoepithelial cells

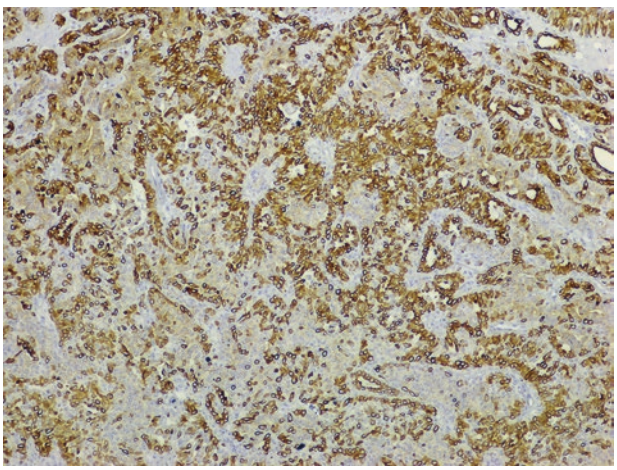

Fig. 7.33 Proliferative fibrocystic changes with usual ductal hyperplasia without atypia: the cells are Cytokeratin 18-positive (which is not helpful for differential diagnosis with atypical ductal hyperplasia since the later lesion is also positive for this marker)

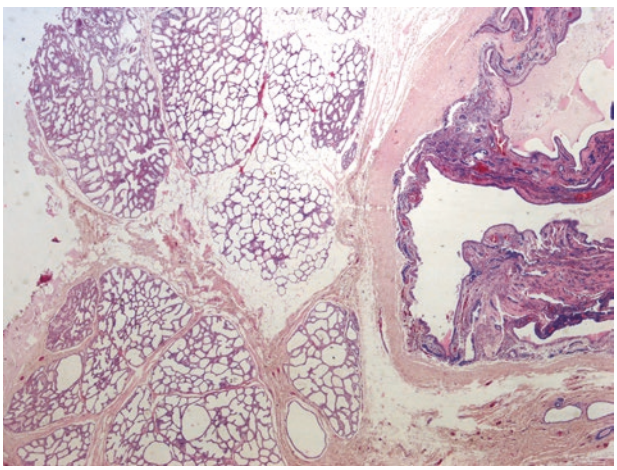

Fig. 7.34 Galactocele: a cavity lined by a cuboidal to flattened epithelium, surrounded by inflammatory infiltrate and breast parenchyma with secretory features (lactational changes)

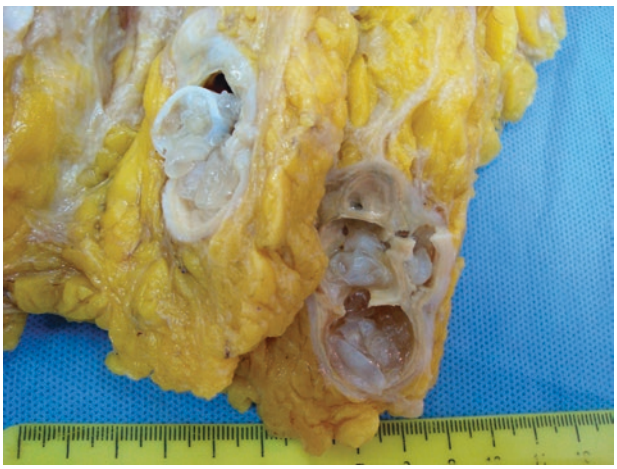

Fig. 7.35 Hydatic cysts within breast parenchyma: especially when this lesion is represented by multiple cysts it can be confused with fibrocystic changes; on cut surface one can appreciate the presence of the daughter cysts

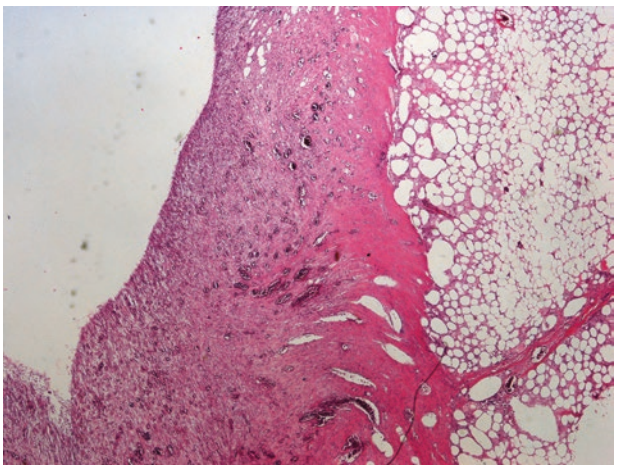

Fig. 7.36 Pseudocyst: the cavity is not lined by an epithelium and it is surrounded by granulation tissue and fat necrosis areas

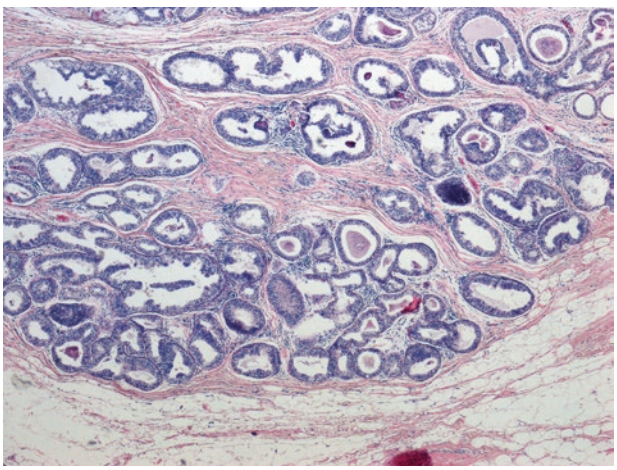

Fig. 7.37 Flat atypia: distended ducts and acini with smooth contour mimicking fibrocystic changes at low-power examination

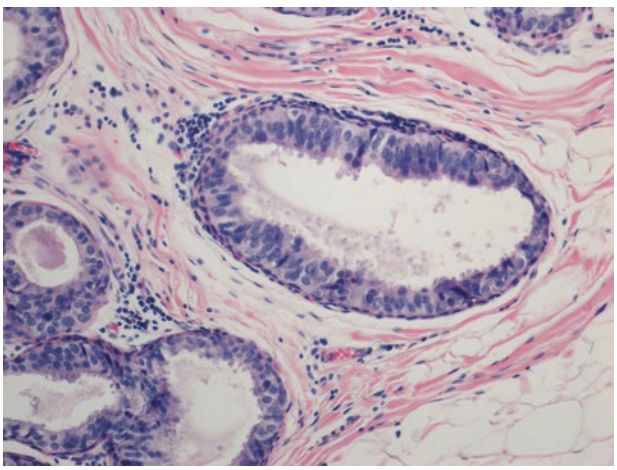

Fig. 7.38 Flat atypia: at high-power examination, the ducts and acini are lined by one to several epithelial cells lacking polarity, with round nuclei presenting low-atypicallity, apical snouts while the myoepithelial cells are present but attenuated and barely visible at the periphery

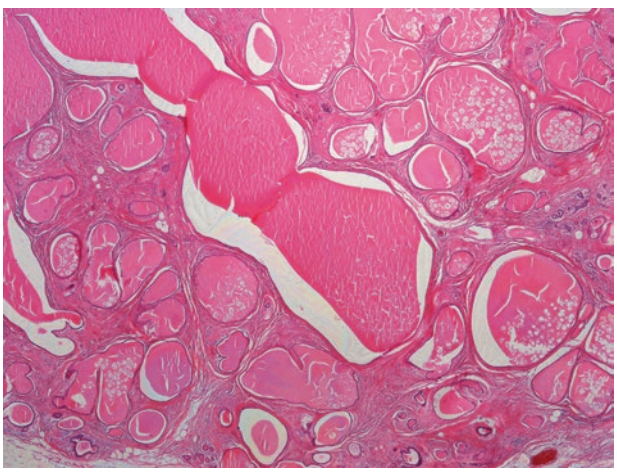

Fig. 7.39 Cystic hypersecretory hyperplasia: multiple cysts filled with secretory material which on microscopic examination, unlike in fibrocystic changes, resemble the thyroid colloid

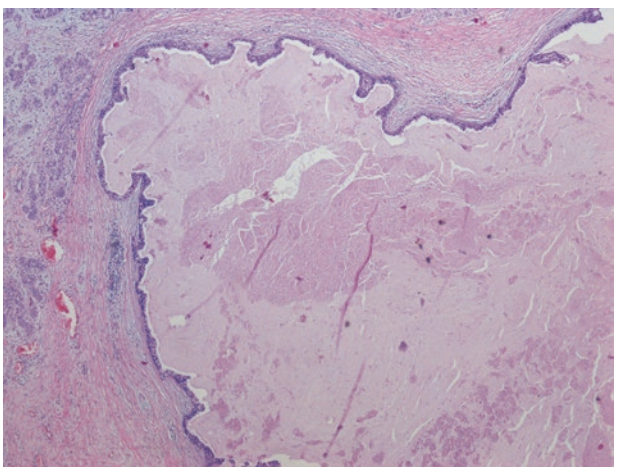

Fig. 7.40 Cystic hypersecretory hyperplasia with atypia: cysts filled with secretory material and lined by mostly flat atypical epithelium

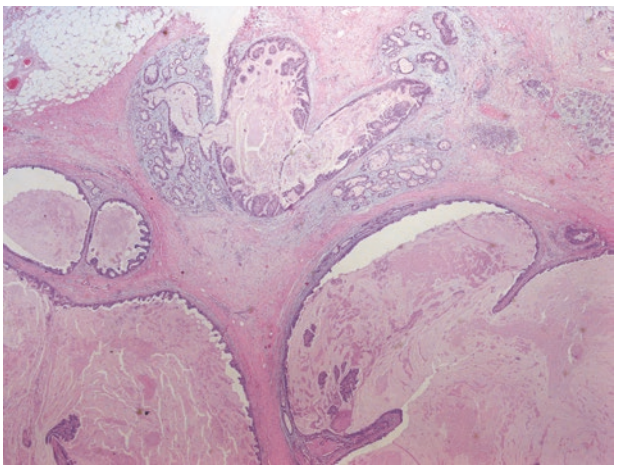

Fig. 7.41 Cystic hypersecretory hyperplasia with atypia: multiple cysts lined by atypical epithelium with various architecture like flat, papillary, micropapillary; areas of microinvasion can be detected as well in the upper part of the picture

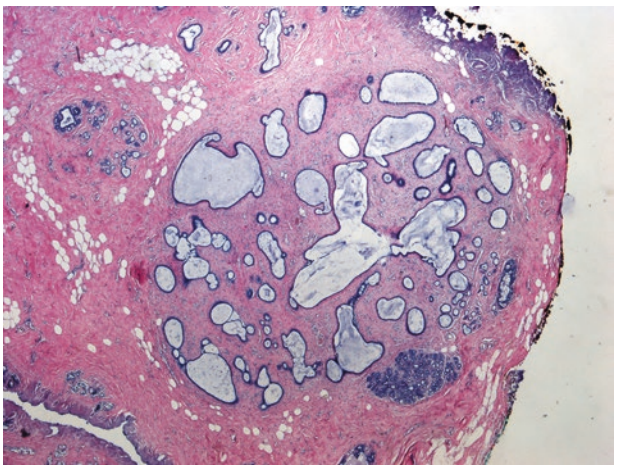

Fig. 7.42 Blunt duct adenosis: distension of acini and ducts, with rounded or irregular contour, lined by both epithelial cells and prominent myoepithelial cells

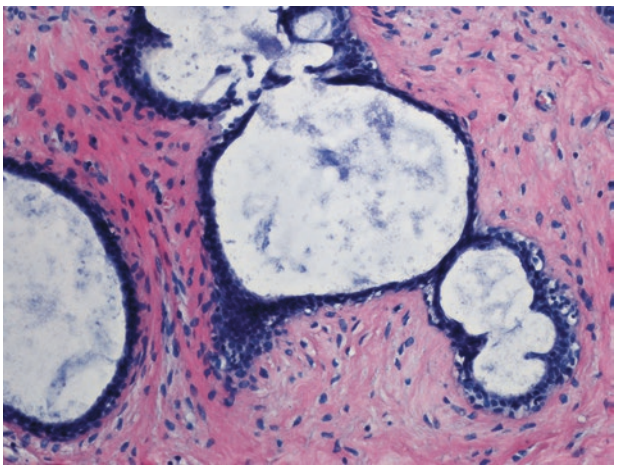

Fig. 7.43 Blunt duct adenosis: characteristically, the epithelial cells have columnar features and the myoepithelial cells are visible and prominent

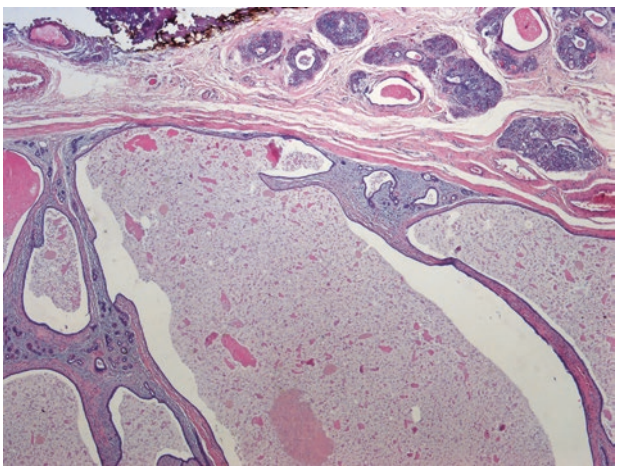

Fig. 7.44 Juvenile papillomatosis: distinct nodular mass within breast parenchyma, with smooth contour at the periphery

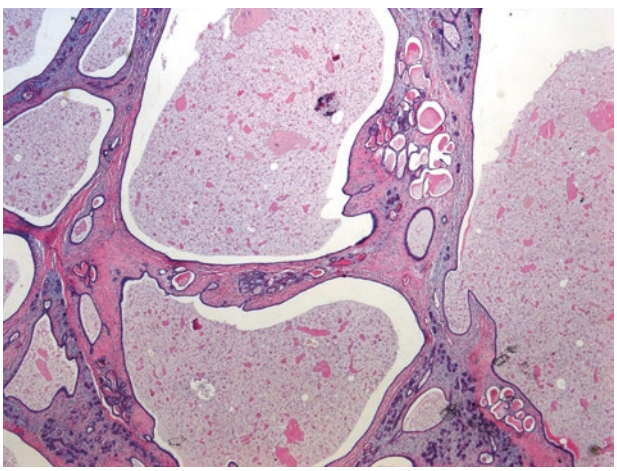

Fig. 7.45 Juvenile papillomatosis: multiple cystic spaces containing a secretory eosinophilic material within the lumina; no areas of intraepithelial proliferation can be detected in this picture

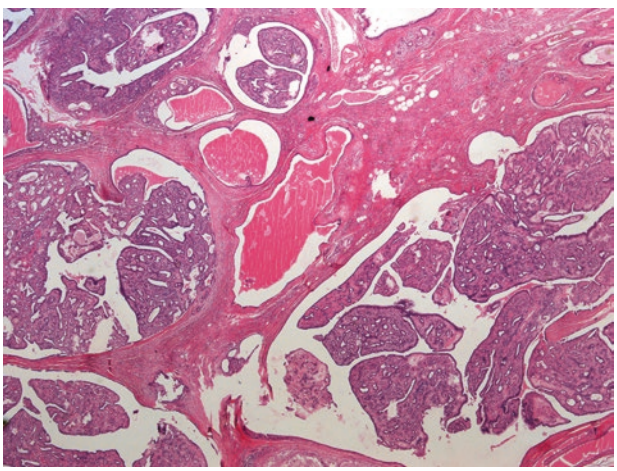

Fig. 7.46 Multiple papillomatosis: multiple cysts involved by a papillary proliferation of fibro-vascular axes lined both epithelial and myoepithelial cells without atypia

7.2 Radial Scar

First described by Semb in 1928, radial scar is a benign breast lesion which consists of a central area of fibro-elastosis surrounded by radially oriented ducts and acini [8]. The average age of occurrence is 55 years and the lesion can be multicentric (especially when it is small) and bilateral, and is often associated with fibrocystic changes or other lesions like adenosis, microcalcifications, apocrine metaplasia, collagenous sferulosis, papilloma, usual or atypical ductal hyperplasia, or *in situ* carcinoma of ductal or lobular type, invasive carcinoma. Regarding the pathogenesis of the lesion, some authors argue that it forms due to the obliteration of ducts within ductal ectasia, while others argue that it is due to a reactive process resulting from fine-needle biopsies performed for diagnostic purposes or from any other trauma through the breast parenchyma that may lead to a scar. The incidence is very variable (1.7–43% of cases) in relation with the sampling method and the type of the associated lesion. The radial scar may mimic an invasive carcinoma clinically, radiologically, and morphologically, especially for inexperienced pathologists. Radiologically, the lobular normal architecture is distorted and usually one can appreciate a stellate lesion with irregular configuration on mammography (like a "star in the sky"), simulating an invasive carcinoma; microcalcifications are, however, an uncommon finding (Fig. 7.47). Clinically, if it is larger in size, it can be confused, on palpation, with a carcinoma. Grossly, its diameter is typically under 1 cm and is not evident, being identified only microscopically (Fig. 7.48). When it is larger, it has a stellate, rarely nodular appearance, with a hard-white core, whitish, resembling a scar from which fibrous bands originate in the surrounding tissues. Radial scar is the most frequent, represented by a small lesion, less than 10 mm in diameter, usually with no hyperplasia associated. However, complex sclerosing lesion (also called infiltrative epitheliosis, a term that is not encouraged because it is very confusing for the clinicians) is a similar lesion but with a diameter of more than 10 mm, associated with hyperplasia (without atypia, or *in situ* ductal or lobular type); being larger, this lesion is less organized than the radial scar [9]. In routine practice, both lesions (radial scar and complex sclerosing lesion) can be misinterpreted on gross examination as an infiltrating carcinoma, and especially on frozen sections and pathologists are advised to wait for the permanent sections whenever a correct diagnosis cannot be established with confidence.

Microscopically, the central area is composed of fibrous and collagenous tissue, in a small quantity or which can be extended, in some cases covering the entire lesion. Also, massive areas of elastosis can be identified within the central area. Around it, within the midzone, radially arranged acini and ducts can be observed. Those in the central area are more compressed and distorted (raising concern for an invasive carcinoma), while those located in the peripheral area are round. They are bordered by two layers of cells (epithelial and myoepithelial) and can exhibit epithelial hyperplasia. Sometimes, ducts and acini can display apocrine metaplastic epithelium (a situation in which the diagnosis is very difficult even for more experienced pathologists). Another characteristic feature is that the epithelial cells seem to be retracted from the myoepithelial cells and the surrounding stroma, due to real retraction of the stroma but also to vacuolization of the cytoplasm of the myoepithelial cell. When this phenomenon occurs, a slit-like space is identified next to the epithelial cells and only small picnotic nuclei of the myoepithelial cells can be observed at the periphery of the distorted ducts. Especially in these cases, the use of ancillary stains for myoepithelial cells is of great help. Of interest, pathologists should use nuclear myoepithelial markers (such as p63) since cytoplasmic markers or membrane markers would not highlight the myoepithelial cells. At the periphery of the lesion, distended ducts forming cysts are highly characteristic (Figs. 7.49, 7.50, 7.51, 7.52, 7.53, 7.54, 7.55, 7.56, 7.57, 7.58, 7.59, 7.60, 7.61, 7.62, and 7.63). Less characteristic features are the following: presence of necrosis in the lumina of the tubules; presence of massive, usually ductal, hyperplasia in the center of the lesion rather than in the midzone; presence of vascular or perineural invasion (not clinically significant); presence of a malignant transformation (especially at the periphery of the lesion; this phenomenon may alter the symmetry of the scar, and is associated with reactive desmoplastic stroma and the myoepithelial cells are absent) (Figs. 7.64, 7.65, 7.66, 7.67, 7.68, 7.69, 7.70, 7.71, 7.72, 7.73, 7.74, 7.75, and 7.76).

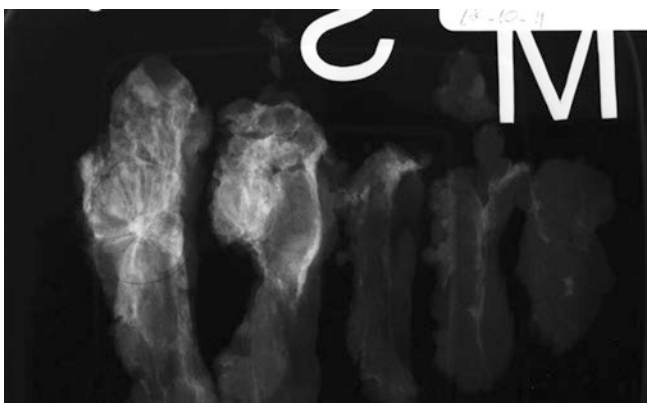

Fig. 7.47 Radial scar: lobular normal architecture is distorted on mammography and the lesion has a stellate shape, simulating an invasive carcinoma

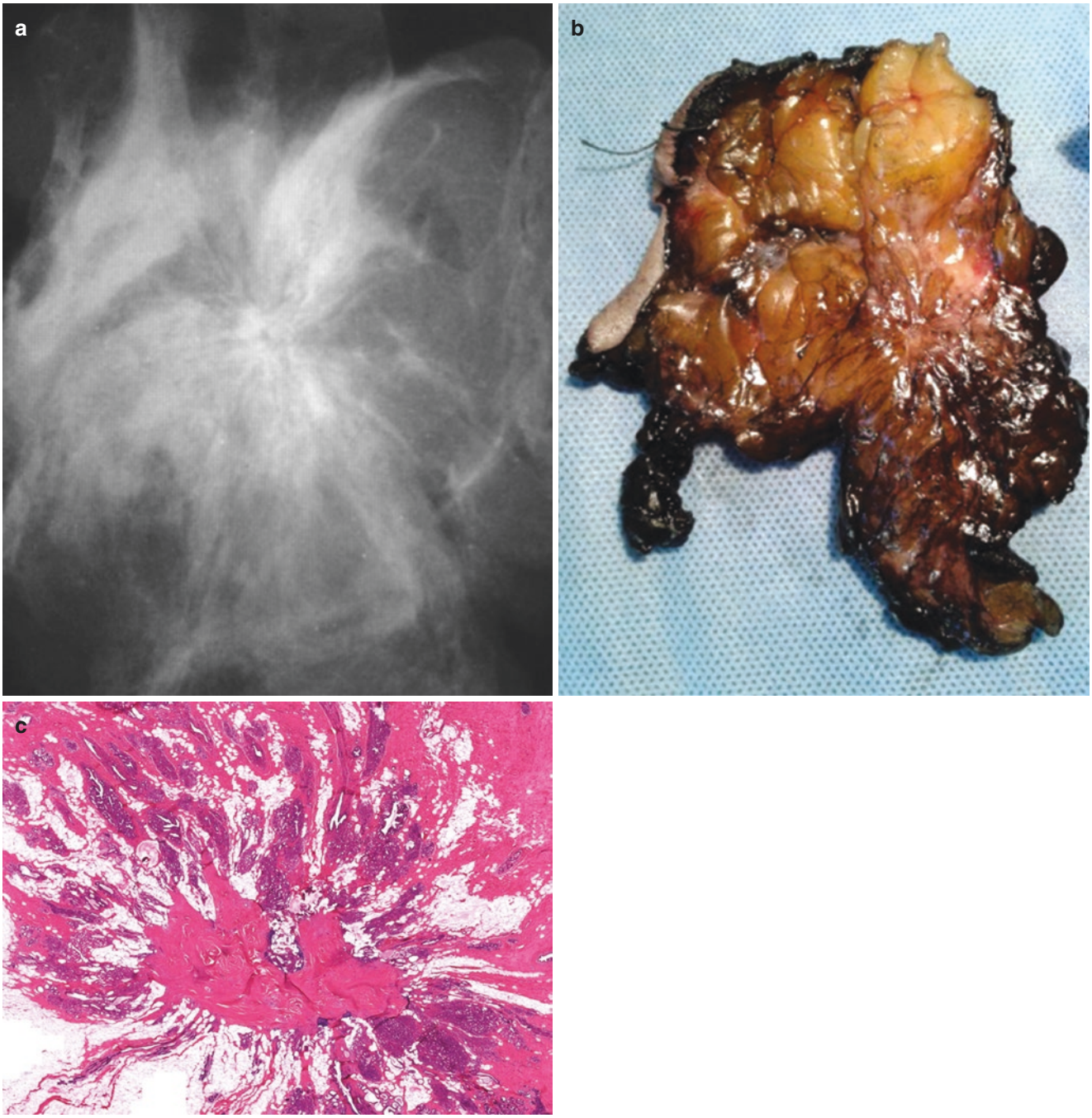

Fig. 7.48 Radial scar: (**a**) 53-year-old patient with a suspicious stellate lesion on mammography and (**b**) macroscopically with (**c**), a diameter of 10 mm, which at microscopic examination was diagnosed as a radial scar

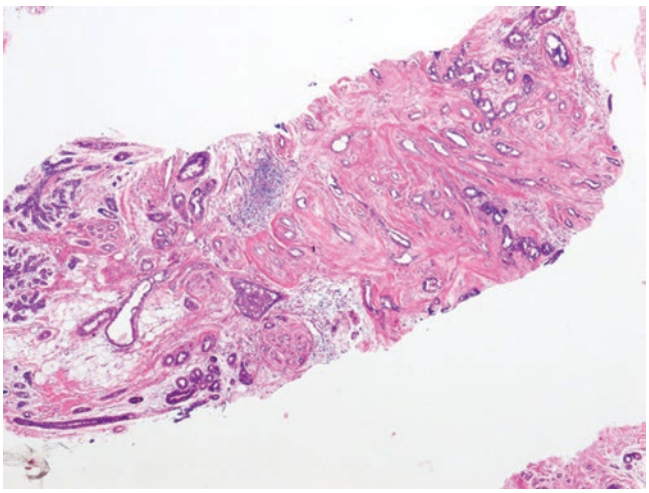

Fig. 7.49 Radial scar: on a biopsy one can appreciate three distinct areas—central area (right side), middle area and peripheral area (right side)

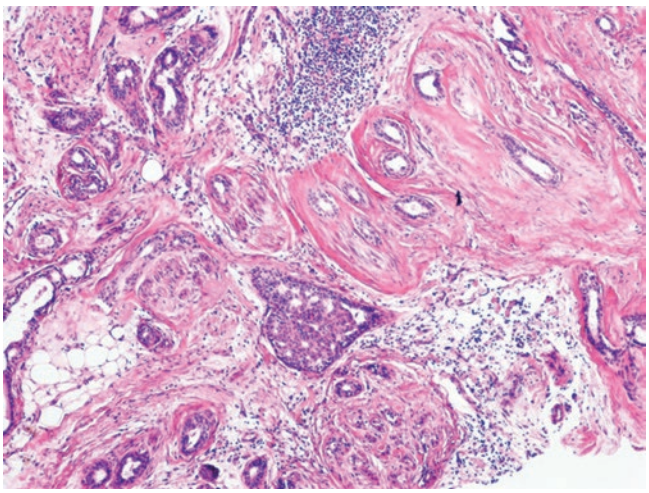

Fig. 7.50 Radial scar (high-power examination of the same lesion from Fig. 7.49): central area is characterized by entrapped tubular structure within a sclerotic tissue (left side), middle area is represented by inflammatory infiltrate and cysts with usual ductal hyperplasia, and at the periphery (right side) one can appreciate small round cysts

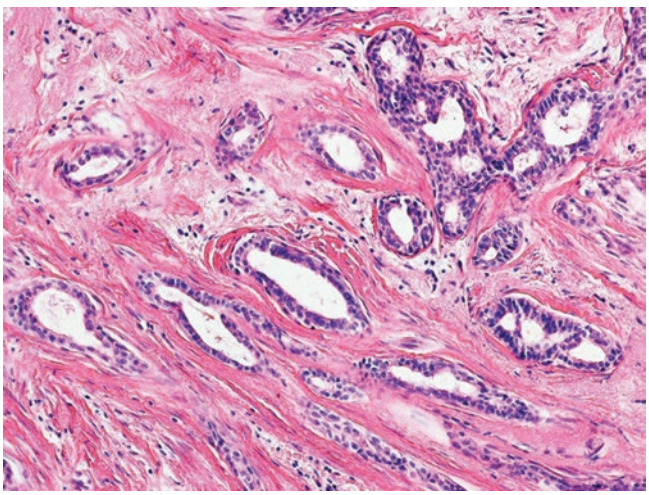

Fig. 7.51 Radial scar (high-power examination of the same lesion from Fig. 7.49): distorted angulated tubular structures lined by two layers of cells; areas of cribriform appearance raising concern of an infiltrative process can be appreciated

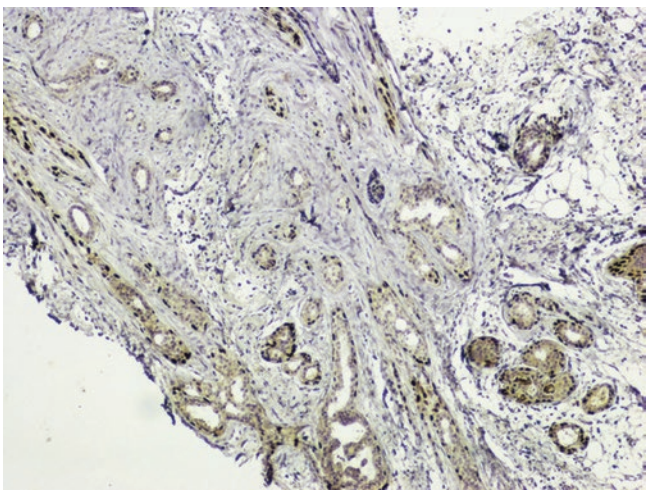

Fig. 7.52 Radial scar (high-power examination of the same lesion from Fig. 7.49): the presence of the myoepithelial layer is highlighted on p63 stain at the periphery of the angulated tubular structures

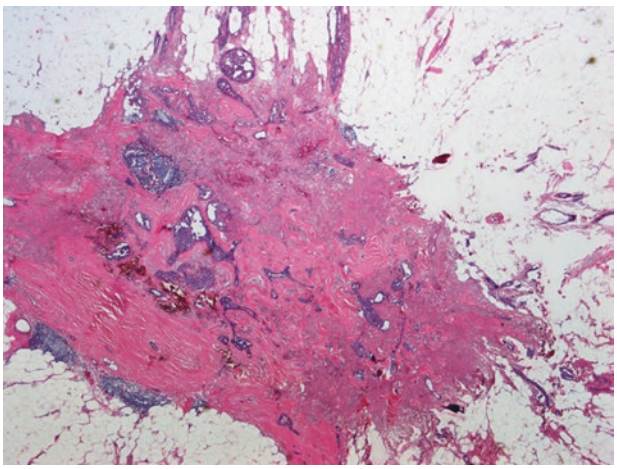

Fig. 7.53 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): a stellate-shape lesion with a central area of elastosis, midzone of inflammatory infiltrate and ducts with usual ductal hyperplasia and areas of hemorrhage due to the previous biopsy

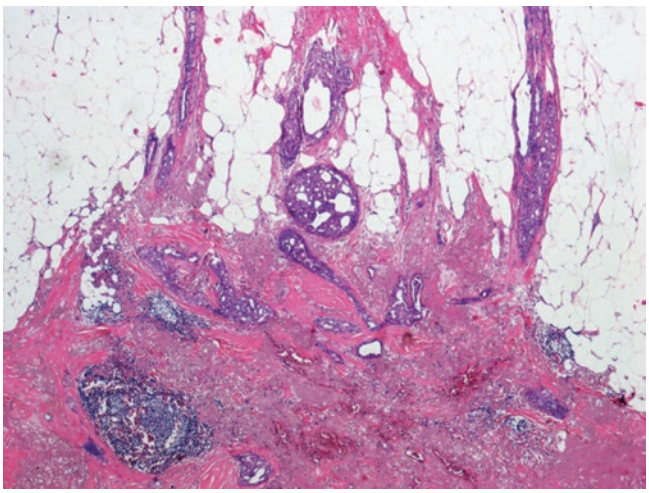

Fig. 7.54 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): high-power examination reveals usual ductal hyperplasia involving the midzone

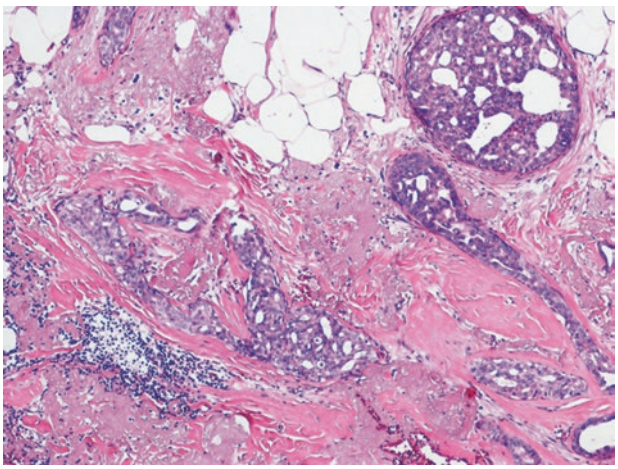

Fig. 7.55 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): high-power examination reveals central area of fibrosis and elastosis

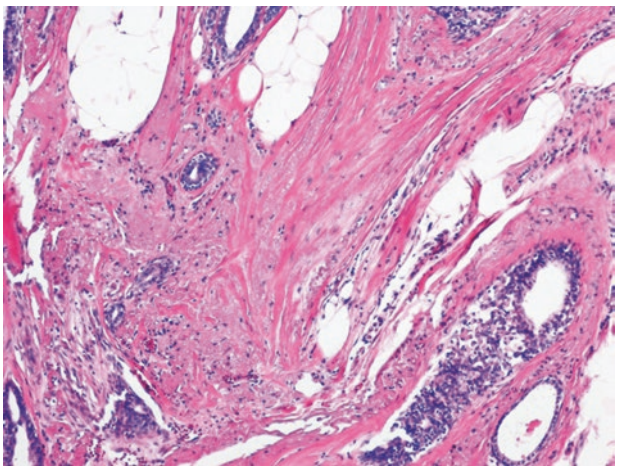

Fig. 7.56 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): entrapped tubules lined by epithelial and myoepithelial cells

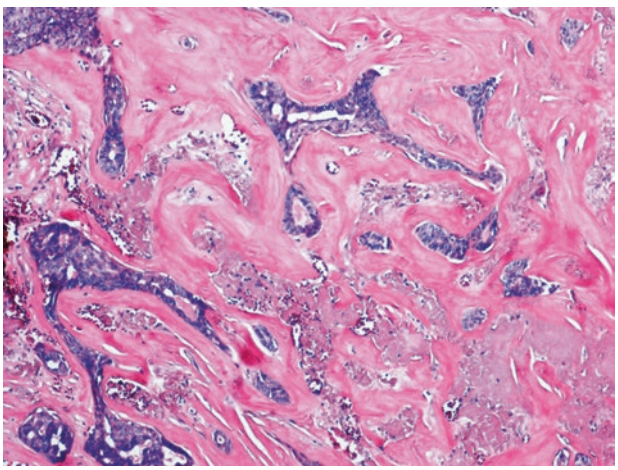

Fig. 7.57 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): high-power examination reveals that the epithelial cells seem to be retracted from the surrounding stroma; this phenomenon makes difficult the identification of the myoepithelial cells

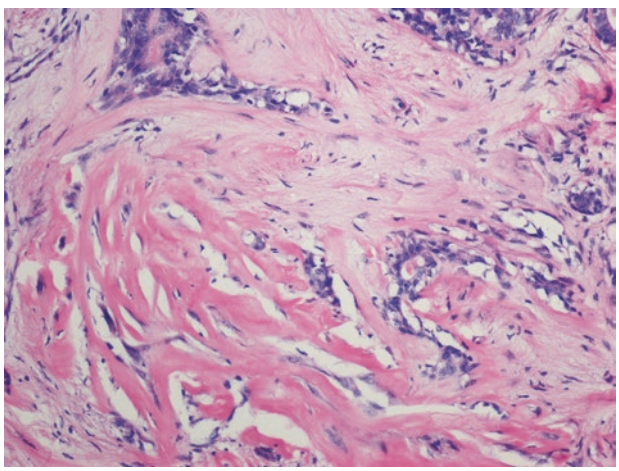

Fig. 7.58 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): high-power examination reveals that the epithelial cells seem to be retracted from the myoepithelial cells and the surrounding stroma and a slit-like space is identified next to the epithelial cells; only small picnotic nuclei of the myoepithelial cells can be observed at the peryphery of the dirtorted ducts

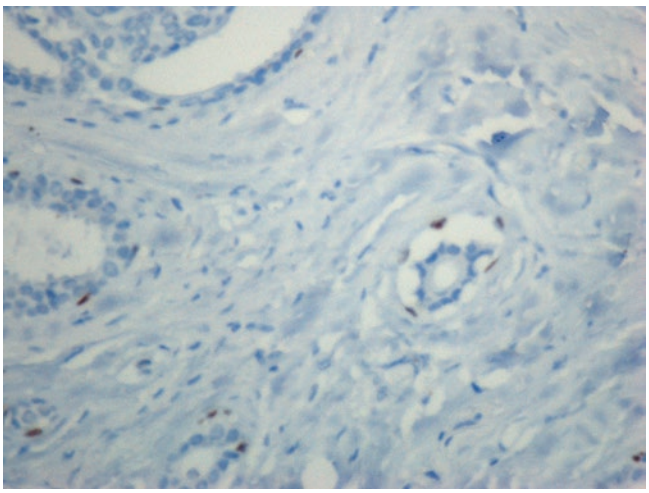

Fig. 7.59 Radial scar (surgical specimen followed the Tru-Cut biopsy from Fig. 7.49): the presence of the myoepithelial cells is highlighted with p63, a myoepithelial nuclear marker

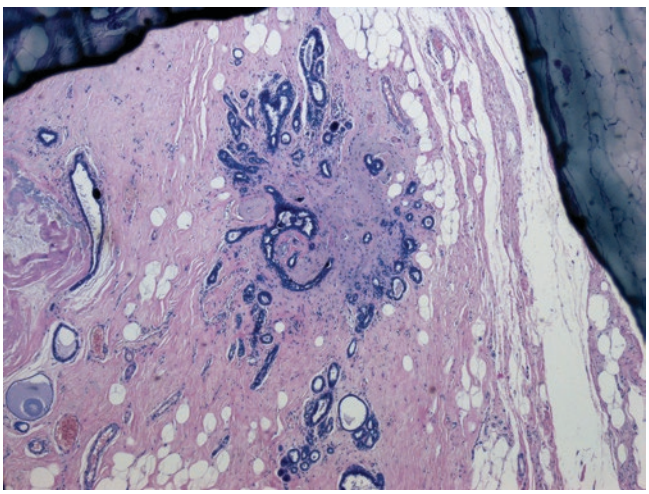

Fig. 7.61 Radial scar with a star-like shape and microcalcifications

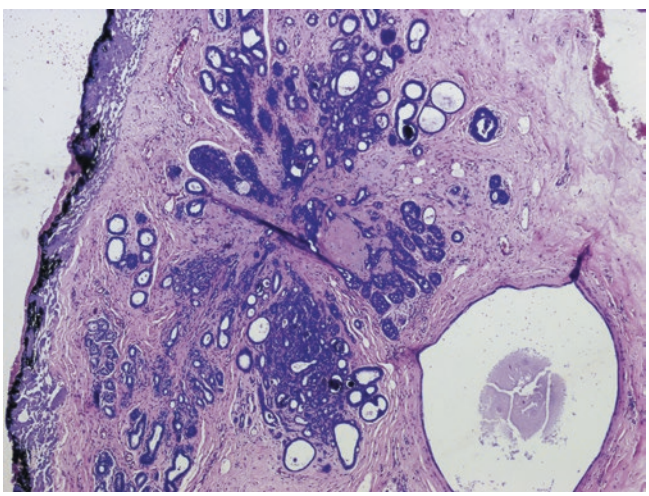

Fig. 7.63 Radial scar associated with microcalcifications and areas of adenosis

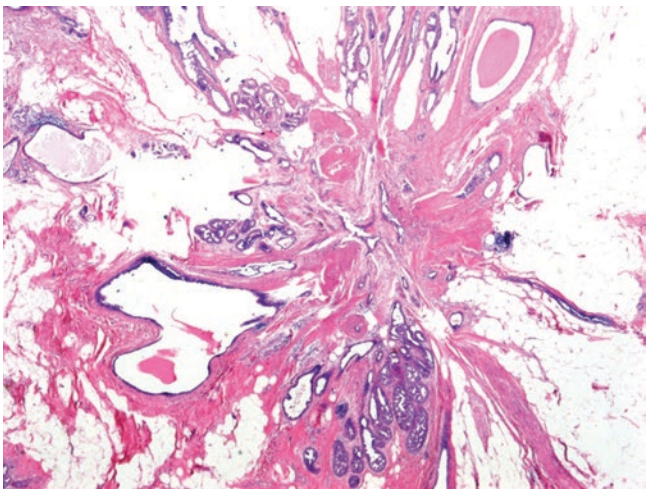

Fig. 7.60 Radial scar with a star-like shape at low power

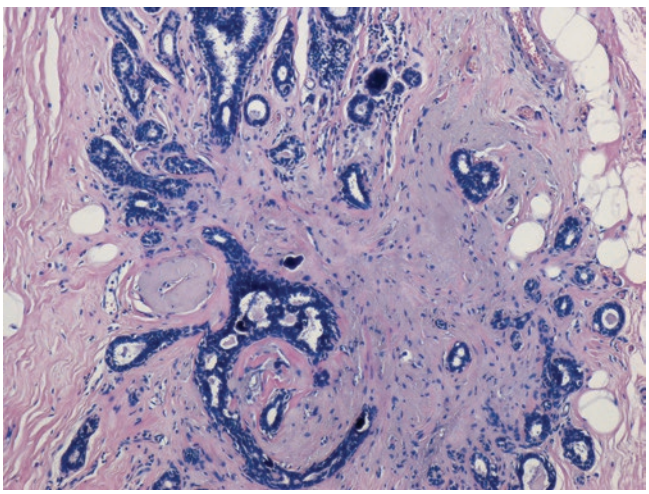

Fig. 7.62 Radial scar with a star-like shape and microcalcifications (same lesion as Fig. 7.62): high-power examination allows the detection of two cell layers

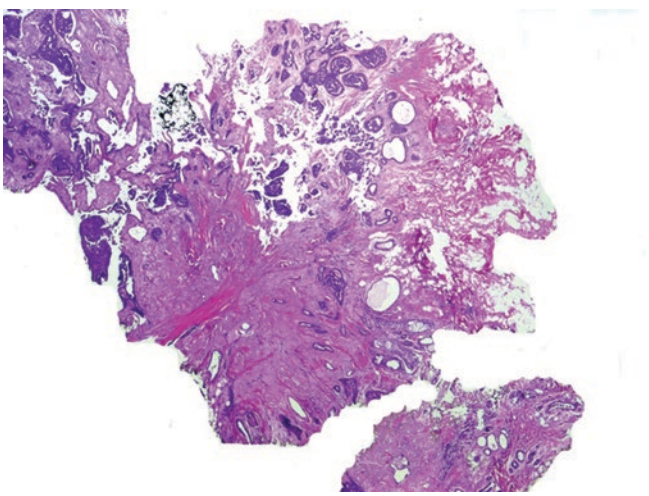

Fig. 7.64 Complex sclerosing lesion: 41-year-old patient with a palpable nodule for which frozen section examination was performed; at macroscopic examination a 21 mm stellate lesion was detected and two tissue fragments were sampled; first tissue fragment shows a central area of fibrosis with entrapped tubular structures and cysts with epithelial proliferation at the periphery

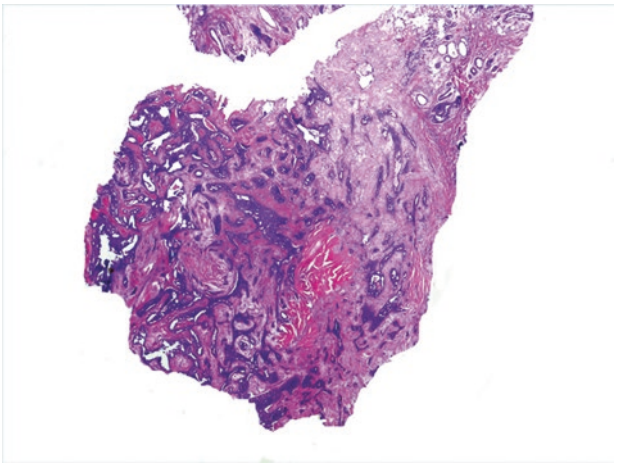

Fig. 7.65 Complex sclerosing lesion: lesion from Fig. 7.64 second tissue fragment at frozen section examination is more suspicious for a malignant process since it has only a small area of fibrosis in the center while the majority of the tissue presents nests of various sizes and shapes infiltrating the breast parenchyma

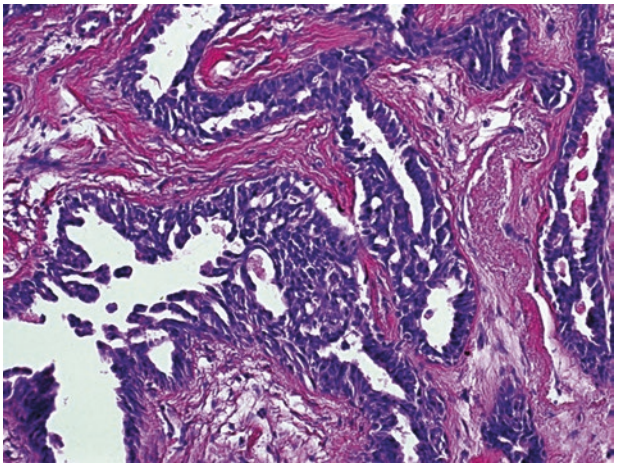

Fig. 7.66 Complex sclerosing lesion: lesion from Fig. 7.64 on high-power examination shows irregular and angulated nests of epithelial cells with secondary lumina and micropapillae; due to the dense stroma, the detection of the myoepithelial cells is difficult

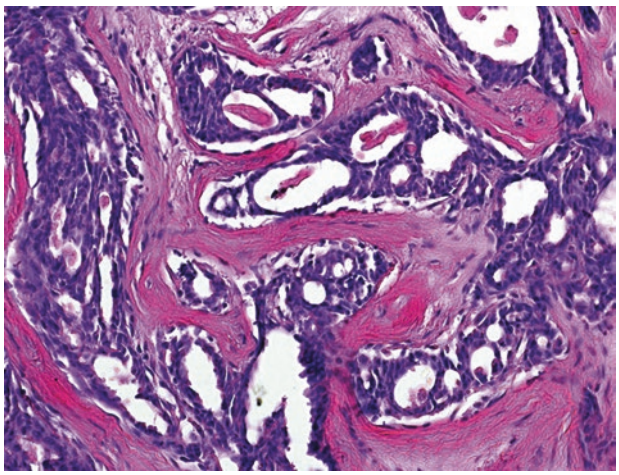

Fig. 7.67 Complex sclerosing lesion: lesion from Fig. 7.64 on high-power examination—other areas of epithelial cells with rounded contour and cribriform morphology; myoepithelial cells are difficult to detect

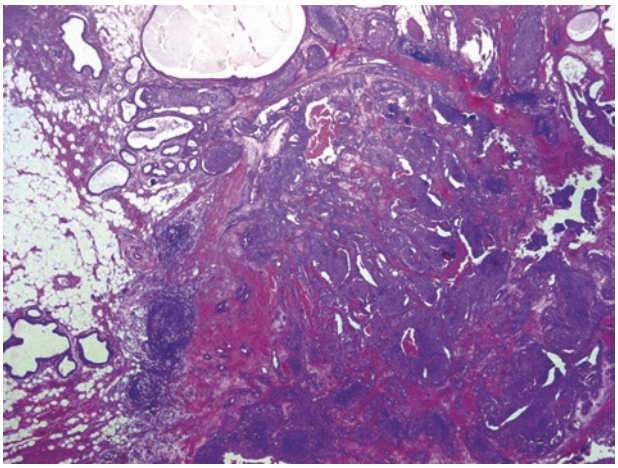

Fig. 7.68 Complex sclerosing lesion: lesion from Fig. 7.64 on permanent section examination has only a small area of fibrosis and elastosis, while the majority of the lesion is represented by nests of epithelial cells; cystic dilated ducts may be seen at the periphery of the lesion

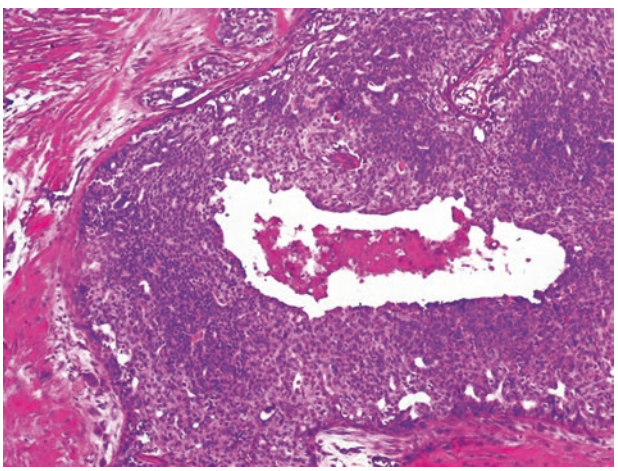

Fig. 7.69 Complex sclerosing lesion: lesion from Fig. 7.64 on permanent section examination with central area of necrosis involving some of the epithelial nests

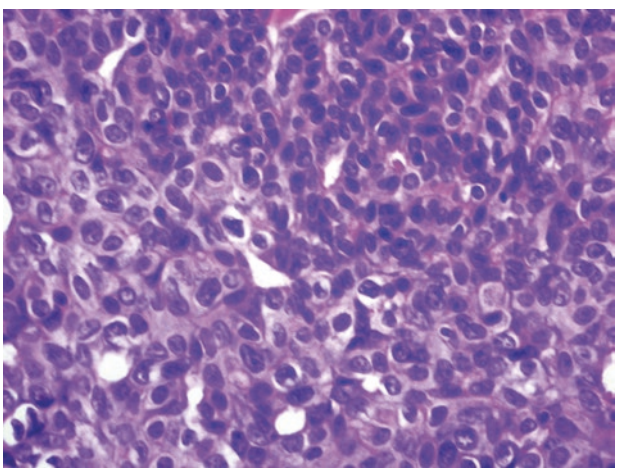

Fig. 7.70 Complex sclerosing lesion: lesion from Fig. 7.64 on permanent section. High-power examination detects a mixed population of epithelial and myoepithelial cells with ovoid nuclei and syncytial cytoplasm lacking atypical mitotic figures (usual ductal hyperplasia without atypia)

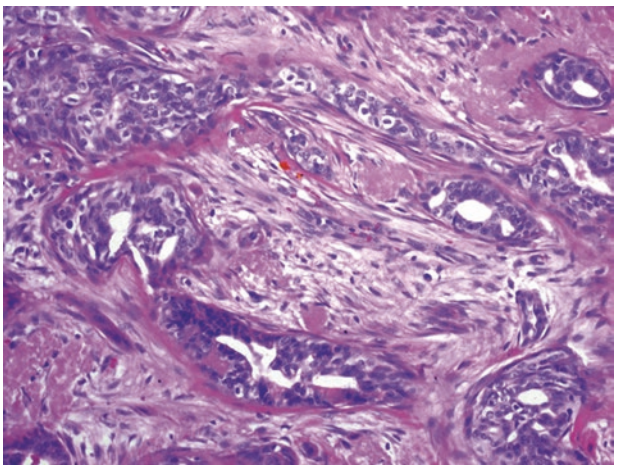

Fig. 7.71 Complex sclerosing lesion: lesion from Fig. 7.64 on permanent section examination—due to the fibrosis, one cannot easily appreciate the presence of the myoepithelial cells

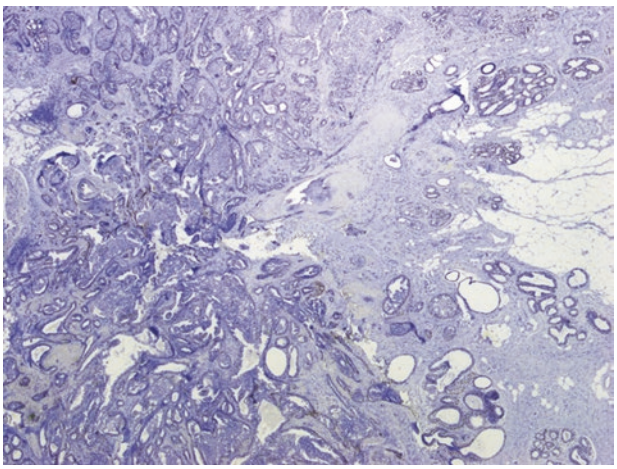

Fig. 7.72 Complex sclerosing lesion: lesion from Fig. 7.64—p63 is the best marker since the myoepithelial cells are attenuated by the fibrosis

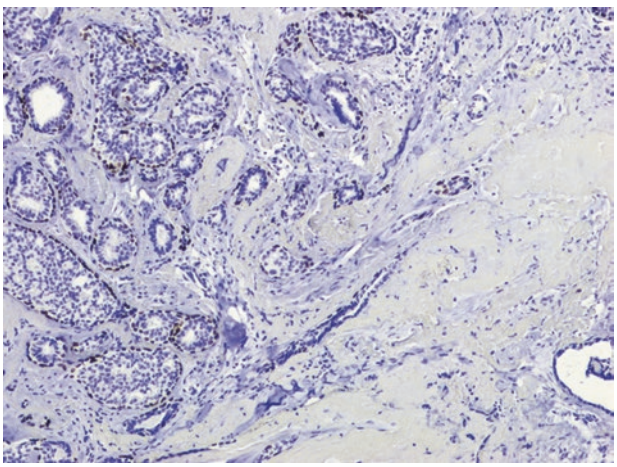

Fig. 7.73 Complex sclerosing lesion: lesion from Fig. 7.64—p63 marks a myoepithelial cell layer at the periphery of all the tubular structures and epithelial nests, including those with central necrosis

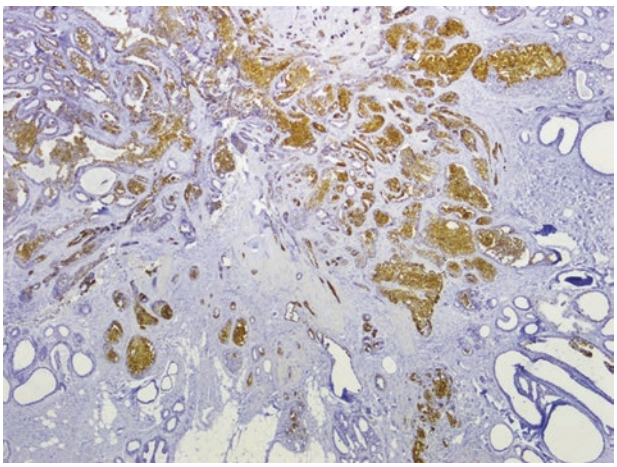

Fig. 7.74 Complex sclerosing lesion: lesion from Fig. 7.64—Cytokeratin 5/6 is mosaic-like positive distinguishing the usual ductal hyperplasia from atypical ductal hyperplasia or DCIS; final diagnosis was complex sclerosing lesion with usual ductal hyperplasia and areas of necrosis (due to the large size of the lesion—more than 10 mm—the complexity and its lack of classic organization like in a radial scar); no further treatment was indicated

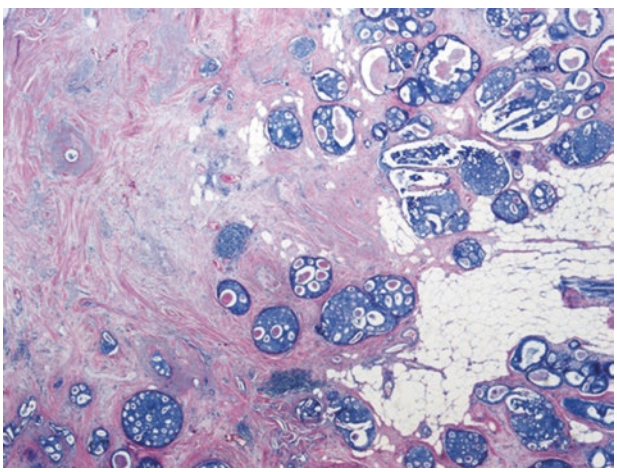

Fig. 7.75 Radial scar with areas of extensive grade 1 DCIS at the periphery (ER was positive in 100% of the epithelial cells in the areas of DCIS—not shown)

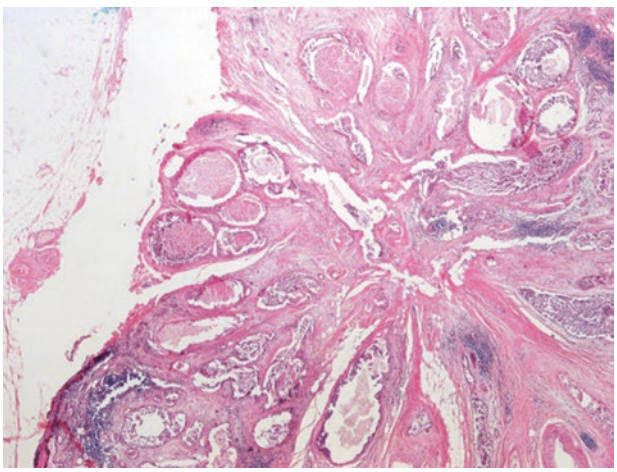

Fig. 7.76 Radial scar with areas of extensive grade 3 DCIS of comedonecrosis type at the periphery

Differential diagnosis is made with malignant lesions (tubular carcinoma, grade 1 invasive carcinoma of NST—no special type and invasive tubulo-lobular carcinoma) or benign lesions (microglandular adenosis, sclerosing adenosis, syringomatous adenoma and sclerosing papilloma). The most important differential diagnosis, however, is made with tubular carcinoma (Table 7.1). Radial scar has a stellate configuration while tubular carcinoma is represented by a nodule with infiltrative margins. Radial scar has a fibro-elastotic central part while tubular carcinoma has desmoplastic stroma throughout the lesion (central area with fibro-elastosis is not present). The ducts and acini that form the scar are distorted and entrapped in the central part of the lesion and lined by epithelial and myoepithelial cells, surrounded by a distinct basal membrane, elements that can be observed in both routine staining and through immunohistochemical analysis. In tubular carcinoma, tubules are angulated, lined only by epithelial cells, sometimes with apical snouts, and are located peripherally and/or centrally (Figs. 7.77, 7.78, 7.79, 7.80, 7.81, 7.82, and 7.83). To detect the presence of the myoepithelial cells in the radial scar, a panel of myoepithelial markers may be used such as p63, Calponin, SMA (smooth muscle actin), SMMHC (smooth muscle myosin heavy chain) [10] and, to confirm the presence of the basal membrane, Collagen IV and Laminin are of great help. Recall that myoepithelial antigens are often attenuated in sclerosing lesions (similar to DCIS), and one should not change the diagnosis if myoepithelial cells can be identified on H-E sections; but if the immunohistochemical stain is negative, one should try to perform immunohistochemical stains with other myoepithelial markers (the best would be a panel of markers) and one should examine the whole lesion.

Table 7.1 Differential diagnosis between radial scar and tubular carcinoma

	Radial scar	Tubular carcinoma
Origin	TDLU	TDLU
Size	Usually less than 10 mm	Usually less than 20 mm
Shape	Stellate	Infiltrative/stellate
Stroma	Fibroelastotic within the central area	Desmoplastic throughout the lesion
Tubules	Entrapped, distorted, centrally located, open lumina	Proliferative, angulated, throughout the lesion, open lumina
Apical snouts	Absent	Present
Myoepithelial cells	Present	Absent
Basal membrane	Present	Absent
Associated lesions	UDH, very rare ADH or DCIS, LN	DCIS or ADH common
Detection method	Incidental finding usually	Screening programme in most of the cases

ADH atypical ductal hyperplasia, *DCIS* ductal carcinoma *in situ*, *LN* lobular neoplasia, *TDLU* terminal duct-lobular unit, *UDH* usual ductal hyperplasia

Moreover, radial scar is associated with epithelial proliferation usually without atypia (rarely with *in situ* ductal or lobular carcinoma), while in the tubular carcinoma, the association with atypical ductal hyperplasia or low-grade ductal carcinoma *in situ* is common. Grade 1 NST infiltrating carcinoma can also display tubular structures with open lumina of round and/or angulated shape. However, the proliferation of the atypical epithelial cells in grade 1 NST infiltrating carcinoma tend to be more florid, with more than one cell layer lining the tubular structures and associated with micropapillae, transluminal bridging forming secondary microglandular structures (features not characteristic for tubular carcinoma). Also, the other characteristics of the radial scar are not found within a grade 1 NST infiltrating carcinoma. In the tubulo-lobular infiltrating carcinoma (a subtype of lobular infiltrating carcinoma) small and rounded glands with open lumina are admixed with the classic "Indian-file" pattern and the tumor cells are more uniform, less cohesive than in the tubular carcinoma or grade 1 NST type carcinoma, while E-Cadherin is usually negative. Also, the characteristic central hyalinized area, entrapped tubular structures and other characteristics of the radial scar are absent (Fig. 7.84 and 7.85).

Another differential diagnosis is made with adenosis, especially with sclerosing adenosis and microglandular adenosis. These have a pseudoinfiltrative pattern. Sclerosing adenosis does not have a stellate appearance. The lesion is round and lobulo-centric, this being the most important microscopic parameter. In contrast to the radial scar, the lesion is composed of a proliferation of (rather than entrapped) tubular structures, which are compressed by a fibrous stroma (rather than collagenized and associated with elastosis). Also, the tubular structures are lined by two types of cells (similar to the radial scar) and there are dilated cysts at the periphery of the lesions. Microglandular adenosis is a rare lesion characterized by a haphazardly infiltrative pattern of round and small tubules in which the myoepithelial cells are lacking. Also, the lesion does not have a stellate configuration and the center of the lesion lacks fibrosis and elastosis. The morphology together with the myoepithelial markers may help in differentiating from a radial scar. The syringomatous adenoma is a benign tumor always located within the nipple and with a nodular appearance, although with infiltrative margins. Syringomatous adenoma does not have a characteristic central area with hyaline and elastotic appearance. Sclerosing papilloma may resemble a radial scar (and some radial scars may represent the late stage of development of a sclerosing papilloma, according to some authors), both sharing the fibrotic center and dilated ducts at the periphery. At low power, however, the sclerosing papilloma does not have a stellate configuration.

Data suggesting that the radial scar is a premalignant lesion that should be surgically excised derive from the radiological literature, while pathological publications demonstrated contradictory results and that the risk of malignant transformation is low unless the lesion is associated with atypical ductal hyperplasia or ductal carcinoma *in situ* or lobular neoplasia [6, 11–13]. Also, some data showed that the presence of multiple radial scars increases the risk of malignant transformation [12]. Radial scars without epithelial atypia can be managed by vacuum-assisted core-needle biopsy and follow-up with meticulous radiological-pathological correlation, although some centers still recommend surgical excision [14–16]. Radial scars with epithelial atypia need to be excised. The final pathological report should contain data about the number of radial scar-type lesions and associated lesions.

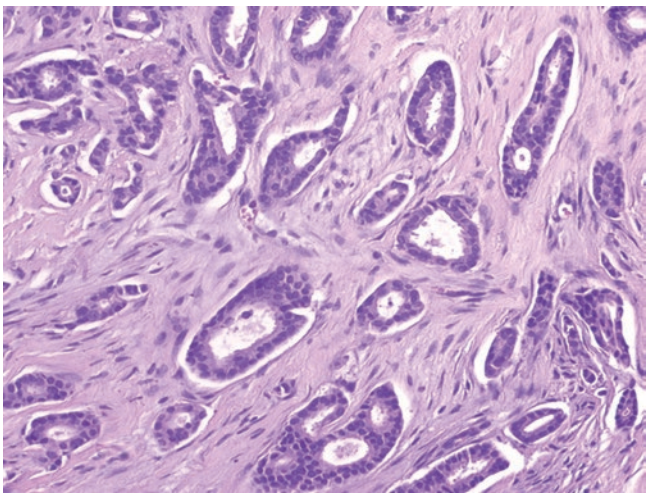

Fig. 7.79 Tubular carcinoma is represented by angulated tubular structures lined by only low-grade atypical epithelial cells with apical snouts

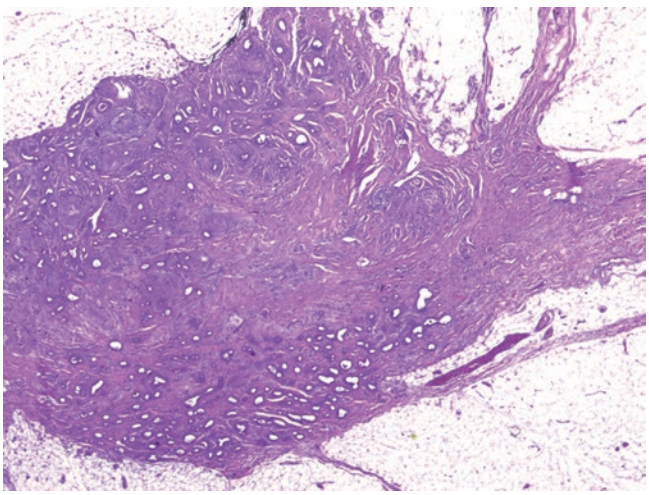

Fig. 7.77 Tubular carcinoma may present a stellate shape as in the radial scar

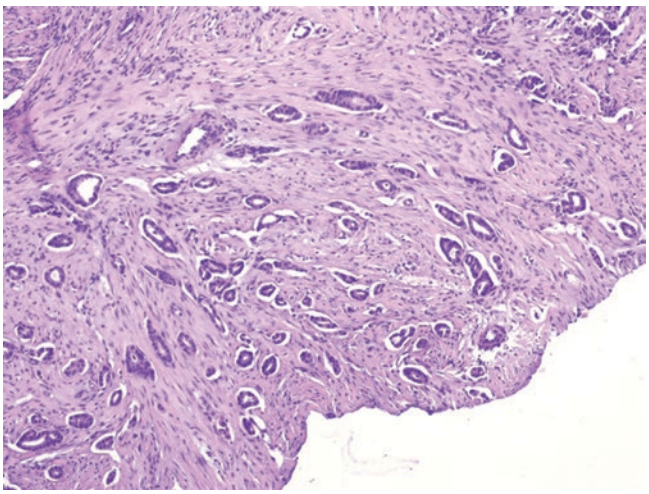

Fig. 7.80 Tubular carcinoma: desmoplastic stroma is present

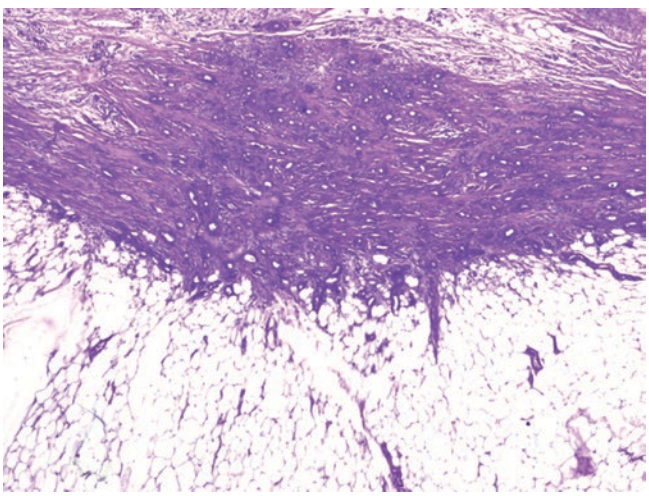

Fig. 7.78 Tubular carcinoma: tubular structures are infiltrating the fat tissue at the periphery of the lesion

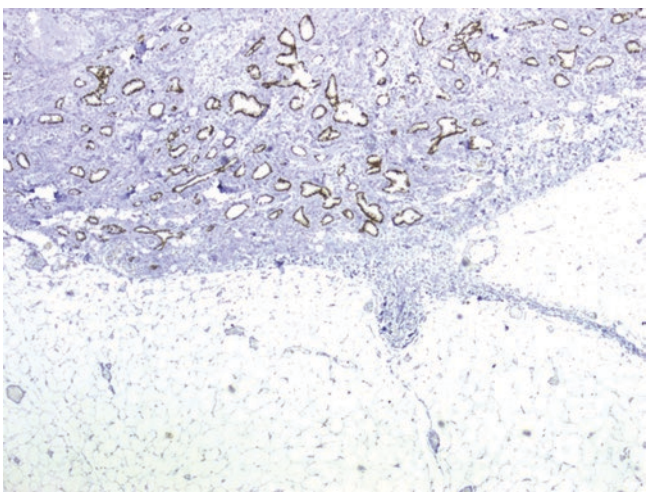

Fig. 7.81 Tubular carcinoma: most of the epithelial cells are positive for ER

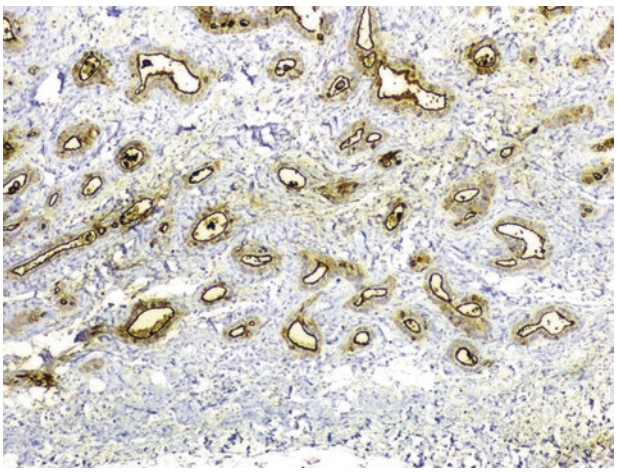

Fig. 7.82 Tubular carcinoma: atypical epithelial cells are positive for EMA

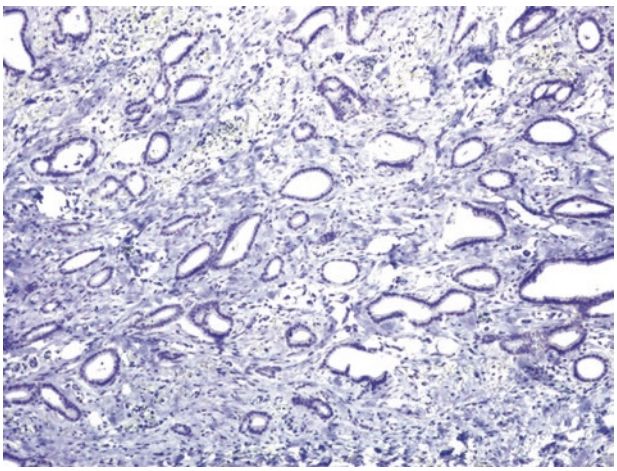

Fig. 7.83 Tubular carcinoma: p63 is negative as myoepithelial cells are absent

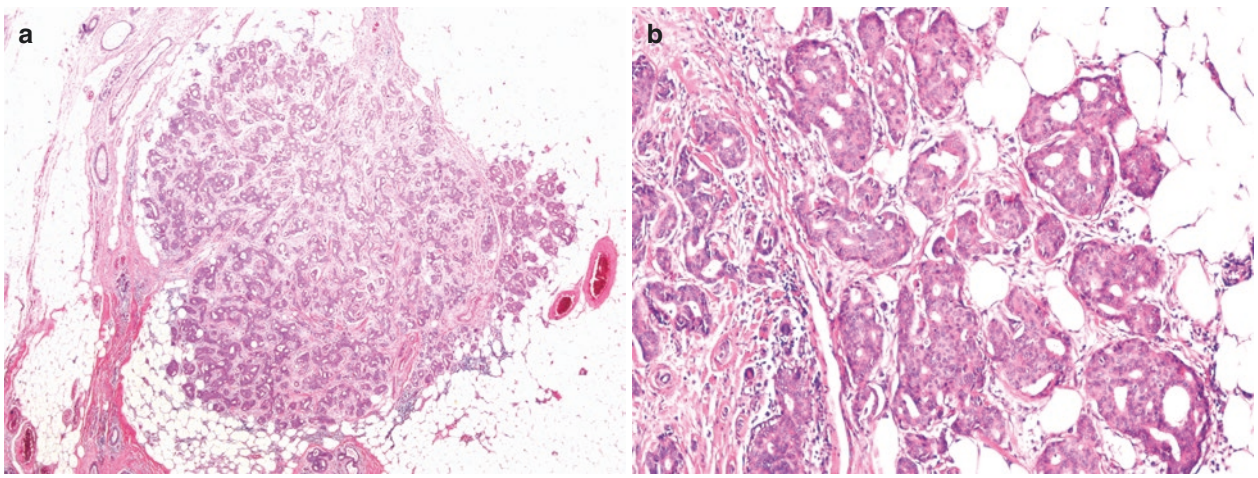

Fig. 7.84 Grade 1 infiltrating carcinoma of no special type: (**a**) The tumor displays tubular structures with open lumina, of round and/or angulated shape, together with more cribriform rounded shape areas; (**b**) the proliferation of the atypical epithelial cells in grade 1 NST infiltrating carcinoma is more florid, with more than one cell layer lining the tubular structures associated with bridges and secondary lumina; the other characteristics of the radial scar are not found

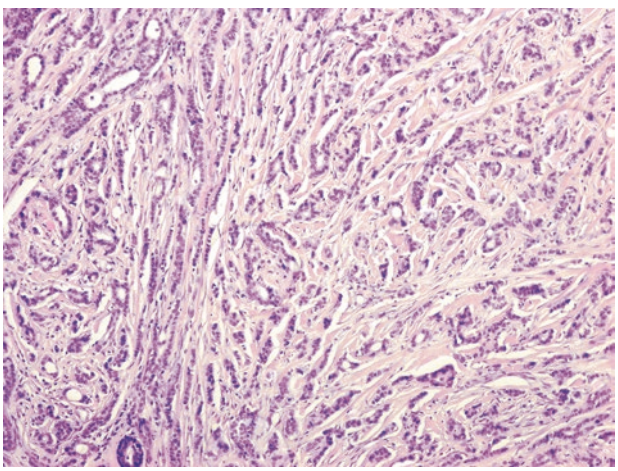

Fig. 7.85 Tubulo-lobular carcinoma: small and rounded glands with open lumina are admixed with the classic "Indian-file" pattern; the tumor cells are uniform; E-Cadherin is usually negative (not shown); the characteristic central hyalinized area, entrapped tubular structures and other characteristics of the radial scar are absent

7.3 Adenosis

Adenosis is represented by a proliferation of the acini resulting in enlargement of the lobules. It is a relatively common lesion that can have several microscopic versions with different clinical-pathological significance. The multiplication of the acini is accompanied by a process of fibrosis in most cases. The lesion can be detected microscopically, but it may sometimes appear as a palpable tumor mass, causing confusion with carcinoma (especially when it is also associated with microcalcifications). Adenoses occur mainly in the third and fourth decades of life, most often in association with fibrocystic changes.

7.3.1 Simple Adenosis

Simple adenosis is a multiplication of the acini that leads to enlargement of the lobules. It is rarely associated with a fibrosis process, so there is no distortion of lobular architecture. The acini are bound by two layers of typical cells exhibiting no atypia (Figs 7.86 and 7.87). This subtype is detected in most cases on microscopic examination, and does not form a visible mass. Sometimes the epithelial cells may undergo apocrine metaplasia, the lesion being diagnosed as *apocrine simple adenosis* (Fig. 7.88). When examining at low power, one can appreciate two main characteristics of the lesion: the rounded contour of the lobules and the uniformity of the appearance. In most cases, the diagnosis is easy and does not require ancillary examinations. Simple adenosis can be associated with various benign conditions of the breast, and if there is no atypia, the lesion does not require surgical excision.

Secretory adenosis is a variant of simple adenosis, represented by a proliferation of round acini, containing an eosinophilic secretory material (similar to the thyroid colloid, but with a more granular appearance). The structures are lined by both epithelial cells (which may have vacuolated cytoplasm) and flattened myoepithelial cells, surrounded by basement membrane. The presence of myoepithelial cells can be highlighted by immunohistochemical examination for Actin or p63, which differentiates it from microglandular adenosis. The epithelial cells are positive for S-100 Protein. Another differential diagnosis is made with secretory carcinoma (a very rare subtype of invasive carcinoma, usually developed in children, in which signs of atypia and stromal invasion are present). Finally, cystic hypersecretory hyperplasia is characterized by similar colloid-like material within the lumina, but the structures forming the lesion are cystically dilated.

Blunt duct adenosis is a controversial variant of simple adenosis. Some authors consider it as a minor alteration of lobular architecture, which develops within physiological limits. Some other authors call it *columnar cell change.* The lobular architecture is usually preserved, as is the intralobular specialized stroma, but the acini are dilated, with rounded ends and bordered by cylindrical epithelial cells with apical snouts, but lacking atypia. The epithelial cells are usually single-layered, but can sometimes be multilayered. The lumen of the acini frequently comprises round calcifications, resembling psammoma bodies. The myoepithelial cell layer is present and hypertrophic, so that these cells are easily identified during the microscopic examination at high power, as well as the basement membrane (Figs. 7.89, 7.90, 7.91, 7.92, 7.93, 7.94, 7.95, and 7.96). Differential diagnosis is made with fibrocystic changes, in which the architecture of the normal lobule is missing (but other changes are present) as well as with flat atypia in which the dilated acini are lined by several layers of low atypical epithelial cells, while the myoepithelial cells are present but attenuated. Also, blunt duct adenosis must be differentiated from columnar cell hyperplasia, a lesion with preserved architecture similar to that of blunt duct adenosis but in which the distended acini are lined by more than four layers of epithelial cells with elongated nuclei, oriented perpendicular to the basement membrane; cellular crowding, however, may give the impression of nuclear hypercromasia, the hyperplastic epithelial cells may form small tufts, and apical snouts may be present.

7.3.2 Sclerosing Adenosis

Sclerosing adenosis is the most frequent type of adenosis and is represented by the multiplication of acini associated with proliferation of a dense fibrous connective tissue (different from the normal intralobular connective tissue) that compresses the acini. It usually represents an incidental microscopic finding since the lesion is microscopic in size, but may also appear as a palpable gray nodule of varying sizes, increased consistency, with lobular or imprecisely defined edges. If the lesion has the appearance of a nodule, it can be called nodular sclerosing adenosis, a term that has been used incorrectly for other types of adenoses. Also, such a lesion can be termed *adenosis tumor*, which refers to the fact that the lesion becomes palpable, resembling a tumor formation (Fig. 7.97). Microscopic diagnosis is sometimes difficult, as the lesion can be confused with a malignant lesion owing to its pseudoinfiltrative pattern. Microscopic appearance is characteristic of a more cellular lesion in the center than on the periphery. One of the most important characteristics is the lobulo-centric appearance of the lesion when examined at low power (Figs. 7.98 and 7.99). It is round or oval and is constituted by a multiplication of acini, which are round or cystically dilated on the edge, but elongated or compressed in the center of the lesion due to the fibrosis. Therefore, sometimes the center of the lesion looks

pseudoinvasive and very cellular. When compressed, the acini lose the lumina and transform into cords or solid structures (Figs. 7.100 and 7.101). Some areas may display confluent growth of these structures, with cribriform areas, very suspicious for invasion (of great help in these areas is the identification of myoepithelial cells together with the examination at low power) (Figs. 7.102 and 7.103). Often it is notable that the proliferation of acini is arranged around the intralobular duct, sometimes extending into its lumen, thus, the focus of sclerosing adenosis appears intracystically (Fig. 7.104). The acini are bound by a basement membrane and the two characteristic layers (epithelial and myoepithelial) with no evidence of atypia. These acini structures may sometimes contain an eosinophilic secretion. The stroma is dense, fibrous, and can present foci of elastosis. Also, rarely, the lesion may have an infiltrative pattern at the periphery, with benign-looking proliferative acini infiltrating the fat tissue, which can be mistaken for an invasive carcinoma. In some of the lesions, especially in late stage of evolution, massive fibrosis and spindle-shaped myoepithelial cells may also lead to a pseudoinfiltrative area in the center of the lesion (Figs. 7.105 and 7.106). In these situations, it is essential to look at the lesion at low power. Sometimes calcification foci may appear, as well as apocrine metaplasia (Figs. 7.107 and 7.108). Apocrine cells may display various features, from conventional abundant granular pink cytoplasm with round nuclei and prominent nucleoli, but they may also have more enlarged and atypical nuclei, which should not be confused with a carcinoma (Figs. 7.109 and 7.110). When all or almost all the acinic structures are involved by apocrine metaplasia, the lesion is called *sclerosing apocrine adenosis* (Figs. 7.111 and 7.112). Only significant atypia should be considered for a diagnosis of atypical apocrine adenosis or DCIS involving sclerosing adenosis (the distinction between these two lesions is not clear cut yet) (Fig. 7.113). It is important, however, not to over-diagnose these lesions, but, on the other hand, to recognize them properly since atypical apocrine adenosis with severe atypia has a significant increased relative risk for malignant transformation. Some sclerosing adenosis may display intraductal or intralobular epithelial hyperplasia with or without atypia; more rarely, acini may be arranged perineurally or perivascularly with no clinical significance [17]. Therefore, these two latter elements should not be regarded as indicators of malignancy. In some cases, intralobular or intraductal carcinoma may occur in a sclerosing adenosis (in these cases, looking at low power would prompt a correct diagnosis due to the lobulo-centric appearance of the lesion; also, immunohistochemical stains with E-Cadherin and Cytokeratin 5/6 would be of much help to differentiate between these lesions and usual ductal hyperplasia) (Fig. 7.114). Of interest, sclerosing adenosis can be very florid and cellular in pregnant patients (when mitoses are more numerous, degenerative cells and areas of geographic necrosis may occur).

In all these difficult situations, ancillary stains are of great help, particularly the use of p63. Since the acini are compressed by the sclerosing process and the myoepithelial cells are compressed and attenuated, a nuclear marker is better than a cellular marker or a membrane marker (Fig. 7.115). The presence of a continuous or discontinuous myoepithelial layer at the periphery of acinary structures is in favor of a diagnosis of sclerosing adenosis.

The variant called *tubular adenosis* is a form of sclerosing adenosis in which the acini multiply, branch, and extend into the surrounding adipose tissue (Fig. 7.116). Due to the peculiar arrangement of the acini, in which most of them are cut longitudinally in the plane of the section and the branching phenomenon, they have pointed or rounded ends and compressed lumina. The lumina sometimes contain eosinophilic or basophilic secretion, occasionally with calcification foci. They are bordered by two characteristic layers and a basement membrane at the periphery, which may sometimes be thickened. The epithelial layer is represented by cuboid cells with round or oval nuclei, fine chromatin, eosinophilic cytoplasm and lacking apical snouts. The outer layer consists of flattened myoepithelial cells with small and hyperchromatic nuclei. The surrounding stroma may be sclerosing or hypocellular. However, tubular adenosis lacks the circumscription of sclerosing adenosis and its cellularity in the center of the lesion.

The differential diagnosis of sclerosing adenosis is made with other types of adenosis (microglandular adenosis in particular), as well as with radial scar, tubular adenoma, ductal adenoma, and, especially tubular carcinoma. Within microglandular adenosis, the acini are disposed irregularly, they are small, have a round shape, with an eosinophilic secretion into the lumen. They are bordered by a single layer of epithelial cells and basement membrane, the myoepithelial layer being absent. The epithelial cells are positive for Cytokeratin, S-100 protein, and the basement membrane is positive for laminin in PAS staining. The stroma is hypocellular and composed mainly of collagen fibers. The radial scar has a stellate appearance (in contrast to the rounded appearance of sclerosing adenosis), with a central area of fibrosis and elastosis, and it is sometimes associated with epithelial hyperplasia at the periphery. Tubular adenoma consists of small uniform, tubular structures, with reduced stroma, but the lesion has a circumscribed character, sometimes a capsule at the periphery, and a diameter over 1 cm. Ductal adenoma is also well-circumscribed, sometimes growing into a ductal lumen. In tubular carcinoma, the tubules are distributed irregularly and infiltrate the fat tissue, in association with a desmoplastic stroma. The neoplastic tubules are angulated, with open lumina, sometimes with apical snouts, and are delimited by a single layer of epithelial cells with minimal atypia. The myoepithelial layer and basement membrane are absent (Fig. 7.117). The most important

characteristics of the two lesions are shown in Table 7.2. A difficult differential diagnosis is between sclerosing adenosis associated with intraductal or intralobular carcinoma and invasive carcinoma. In this case, the lesion should be initially examined at low power because a process of fibrosis and elastosis often appears in the center of a sclerosing adenosis, which compresses the acini, while the acini are cystically dilated on the edge. In an invasive carcinoma, the stroma is desmoplastic (with the exception of tubular carcinoma, in which the stroma may also be hyalinized in some cases). On the other hand, immunohistochemical examinations for Actin or p63 differentiate the two lesions, because myoepithelial cells are missing in the invasive carcinoma.

The risk of malignant transformation in a sclerosing adenosis is slightly increased compared to normal population, similar to the risk in usual ductal hyperplasia [18]. The presence of sclerosing adenosis in a core biopsy does not require surgical excision unless there is radiological suspicion, association with microcalcifications, a spiculated contour, or presence of atypia. In the absence of suspicion, clinical-radiological follow-up may be advisable for the patient. Pathologists, especially those with limited experience, should be very careful with this type of lesion when a frozen section examination is required by the clinician; and when all the criteria for a positive diagnosis are lacking, one should wait for permanent sections.

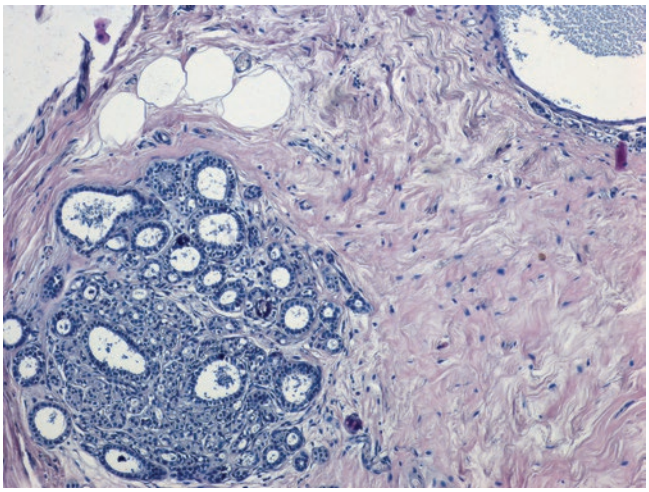

Fig. 7.86 Simple adenosis: multiplication of the acini and enlargement of the lobules without an associated process of fibrosis and no distortion of the lobular architecture

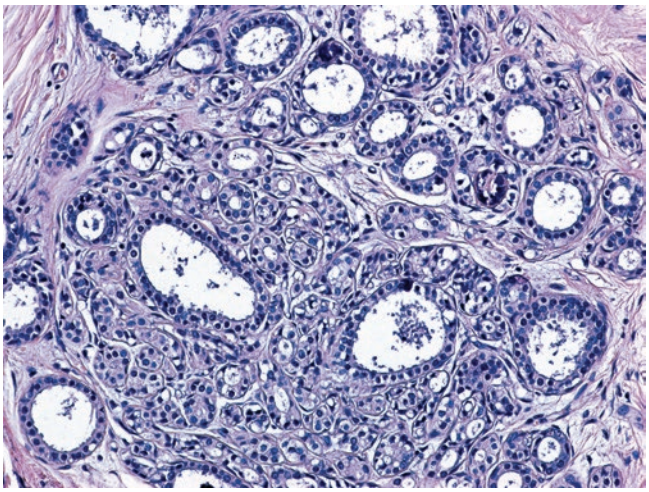

Fig. 7.87 Simple adenosis: the acini are lined by two characteristic cell layers and are associated with microcalcifications

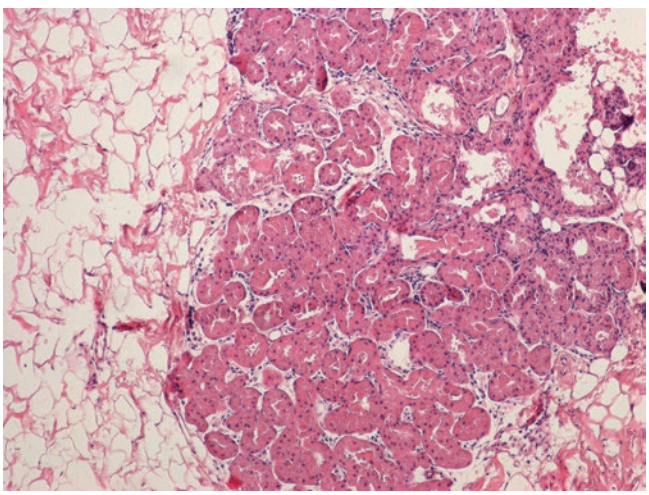

Fig. 7.88 Apocrine simple adenosis: characteristic lobular architecture preserved with multiplication of the acini which undergone apocrine metaplasia without atypia

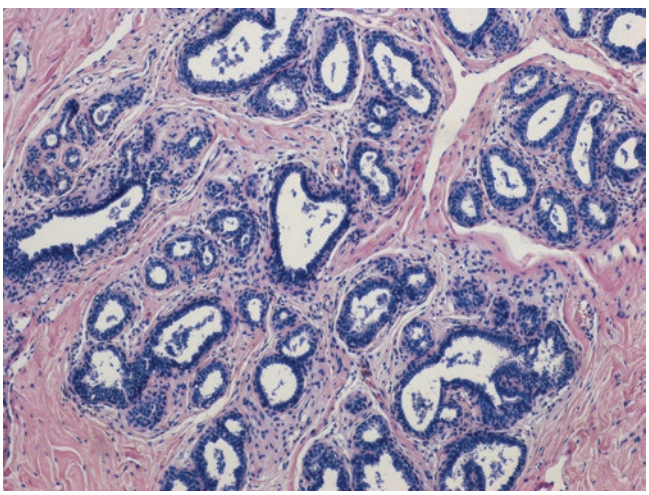

Fig. 7.89 Blunt duct adenosis: the lobular architecture is usually preserved, as well as the intralobular specialized stroma

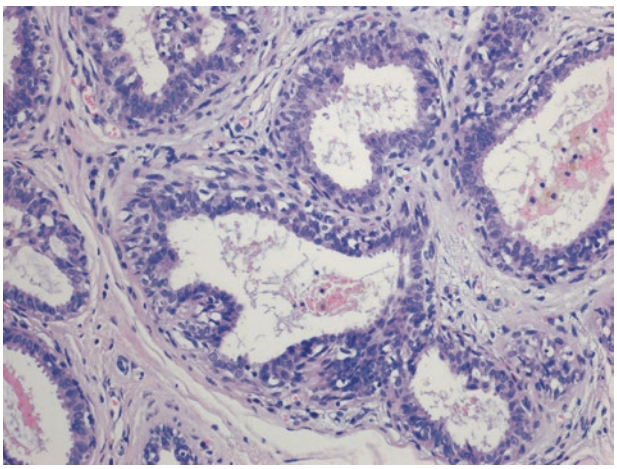

Fig. 7.90 Blunt duct adenosis: the acini are dilated, with rounded ends

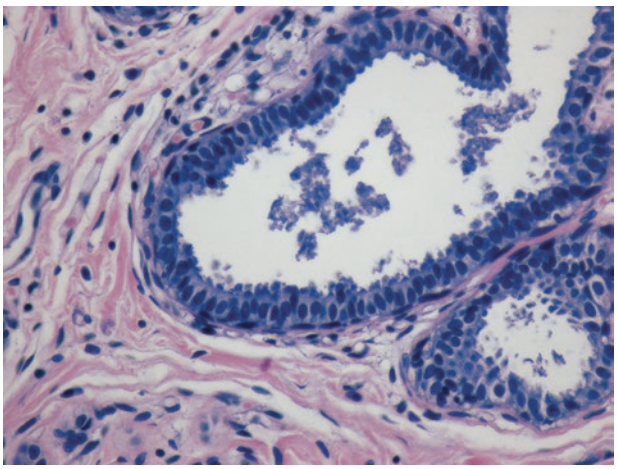

Fig. 7.92 Blunt duct adenosis: another example with distended acini and preserved architecture

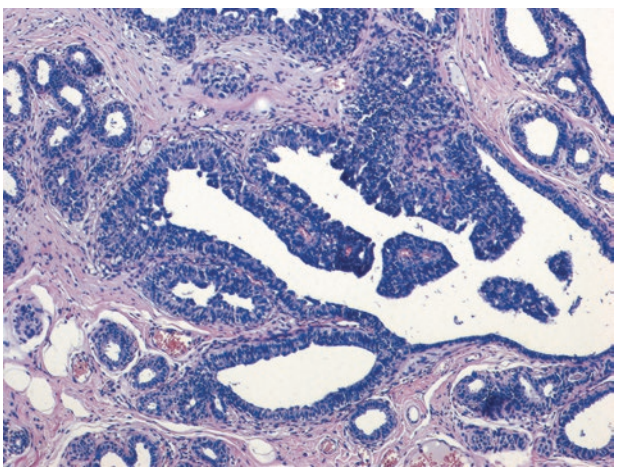

Fig. 7.94 Columnar cell hyperplasia: similar preserved architecture as in blunt duct adenosis but the distended acini are lined by several layers of epithelial cells with elongated nuclei, oriented perpendicular to the basement membrane; cellular crowding may, however, give the impression of nuclear hypercromasia and the hyperplastic epithelial cells may form small tufts; apical snouts may be present

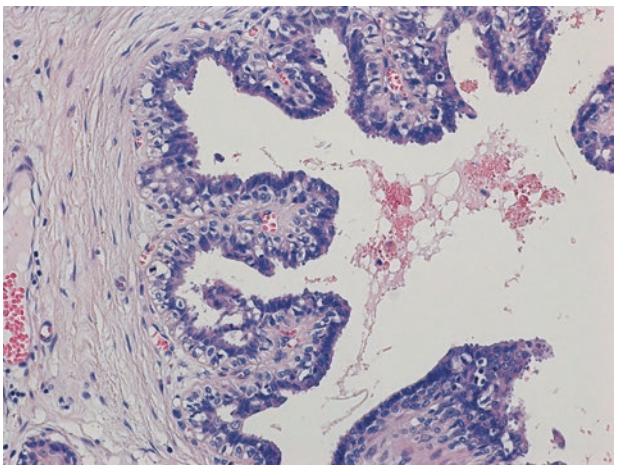

Fig. 7.91 Blunt duct adenosis: the acini are lined by cylindrical epithelial cells with ovoid-to-elongated nuclei, oriented in perpendicular fashion to the basement membrane, with evenly dispersed chromatin and rare mitotic figure, with apical snouts, lacking atypia; hypertrophic myoepithelial cells are visible even at low-power magnification

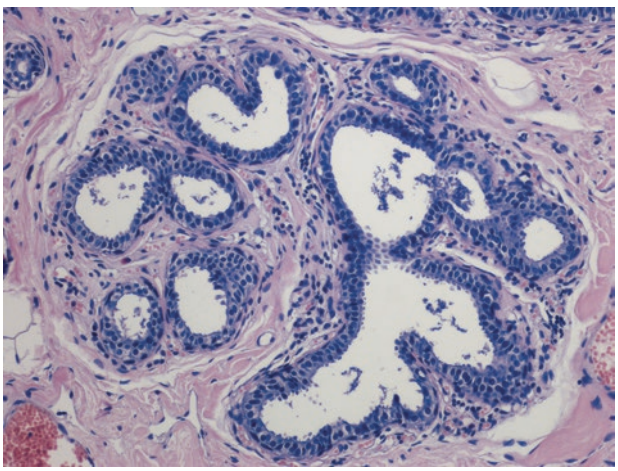

Fig. 7.93 Blunt duct adenosis: in this case (similar to Fig. 7.92), some of the acini have attenuated myoepithelial cells, but still present

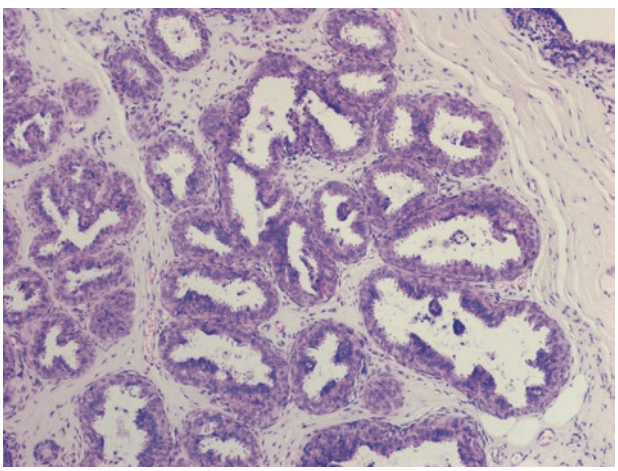

Fig. 7.95 Flat atypia: lobular architecture is preserved like in blunt duct adenosis and acini are dilated

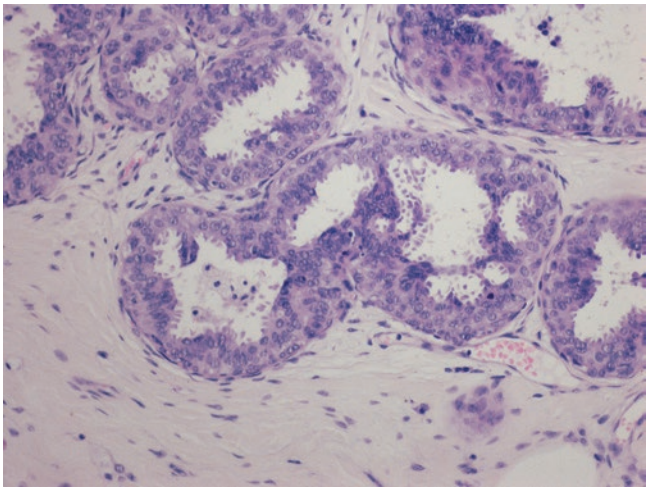

Fig. 7.96 Flat atypia (similar to lesion in Fig. 7.95): acini are lined by several layers of low atypical epithelial cells with rather rounded nuclei (as opposed to elongated) and visible nucleoli; the nuclei are not perpendicular to the basement membrane; myoepithelial cells are present but attenuated

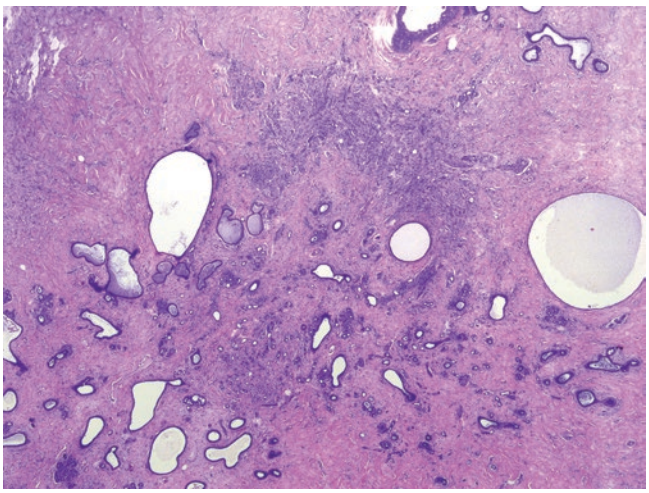

Fig. 7.98 Sclerosing adenosis: lobulo-centric appearance of the lesion at low-power examination; at the periphery, the acini are cystic-dilated

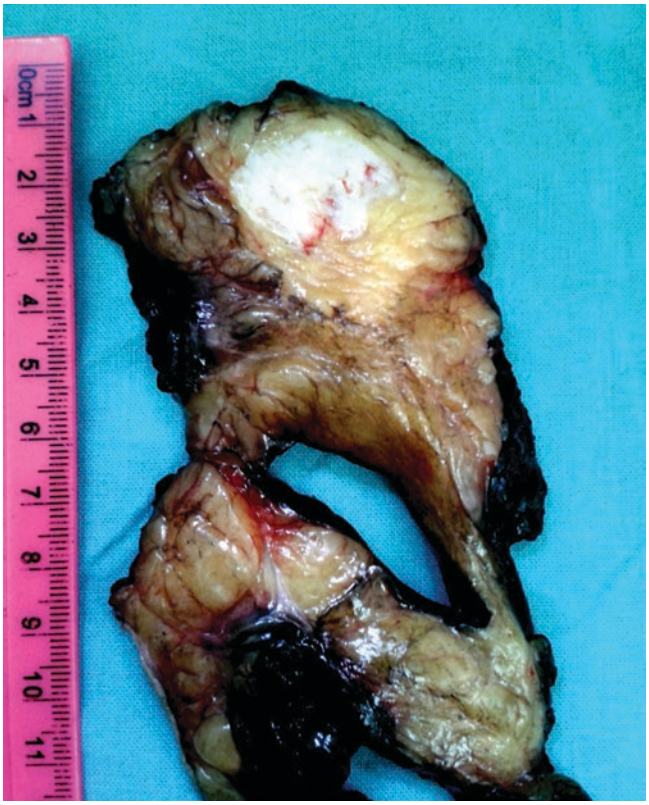

Fig. 7.97 Adenosis tumor: a sclerosing adenosis with large size, forming a palpable tumor-like mass within the breast parenchyma

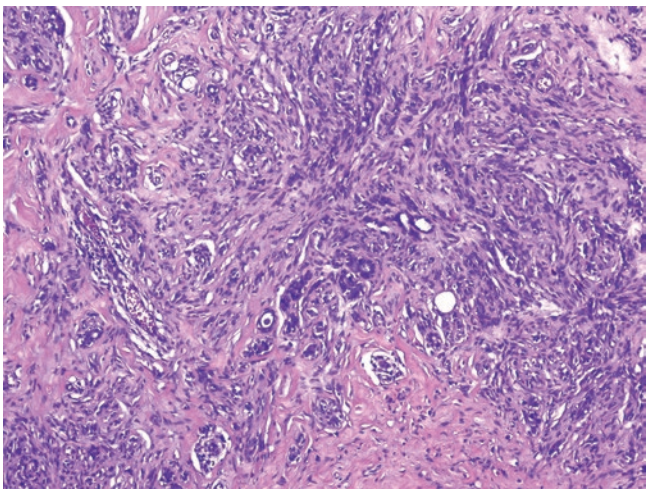

Fig. 7.99 Sclerosing adenosis: the lesion is characteristically more cellular in the center (elongated or compressed acini in the center of the lesion due to the fibrosis) than on the periphery—pseudoinvasive pattern mimicking an infiltrating carcinoma

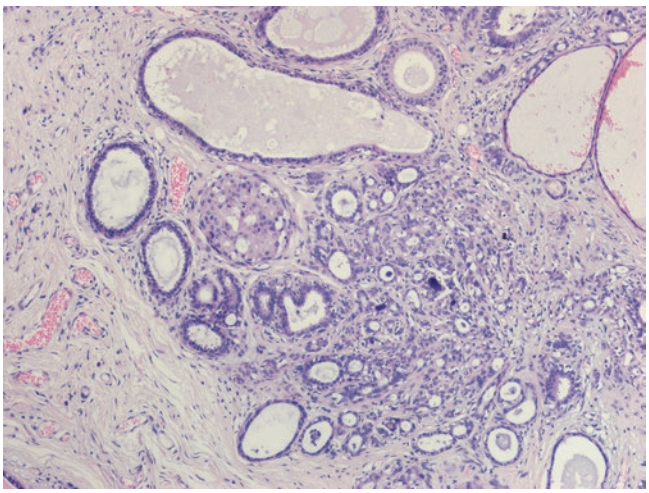

Fig. 7.100 Sclerosing adenosis: hyperplastic and compressed acini in the center of the lesion, forming cords, while at the periphery, they are dilated forming cysts, associated with apocrine metaplasia, inflammatory infiltrate into the stroma and microcalcifications

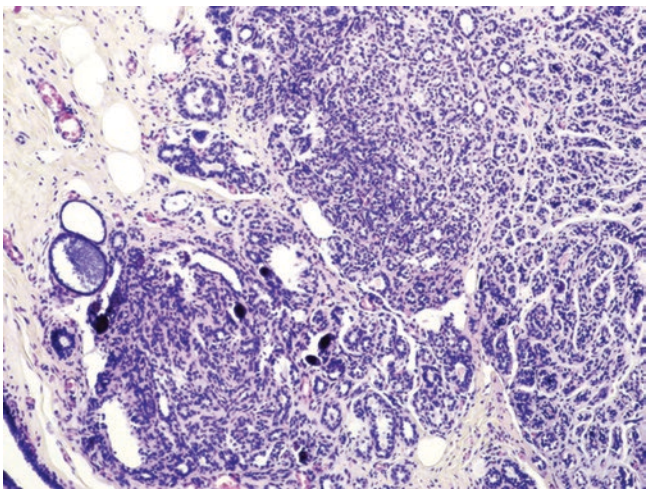

Fig. 7.101 Sclerosing adenosis: the lesion is more cellular in the middle zone than at the periphery and is associated with microcalcifications

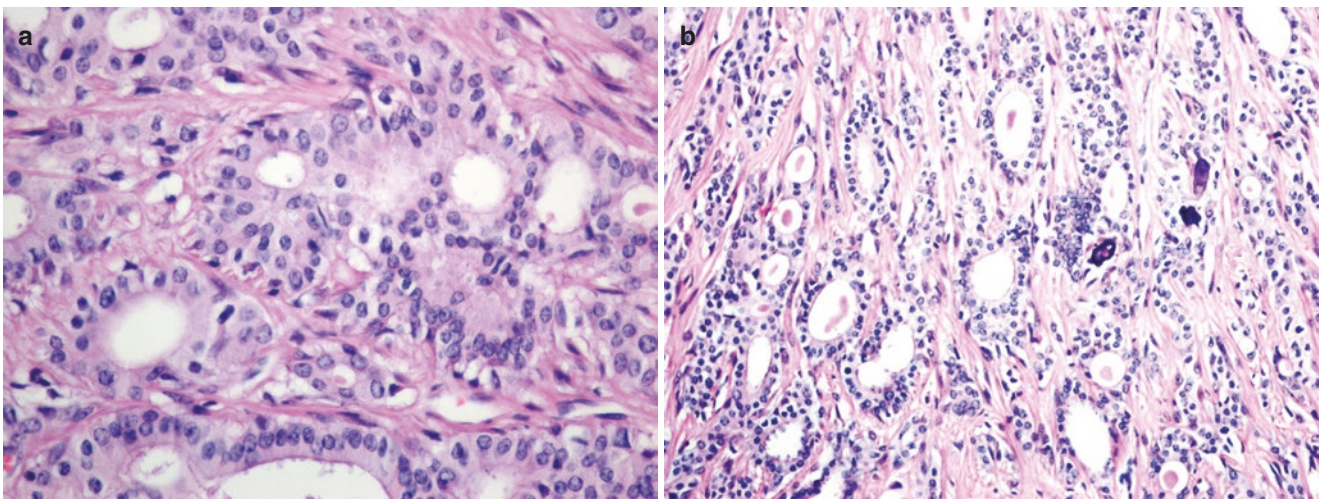

Fig. 7.102 Sclerosing adenosis: some areas may display confluent growth of these structures, with **a**, tubular and **b**, cribriform areas, very suspicious for invasive

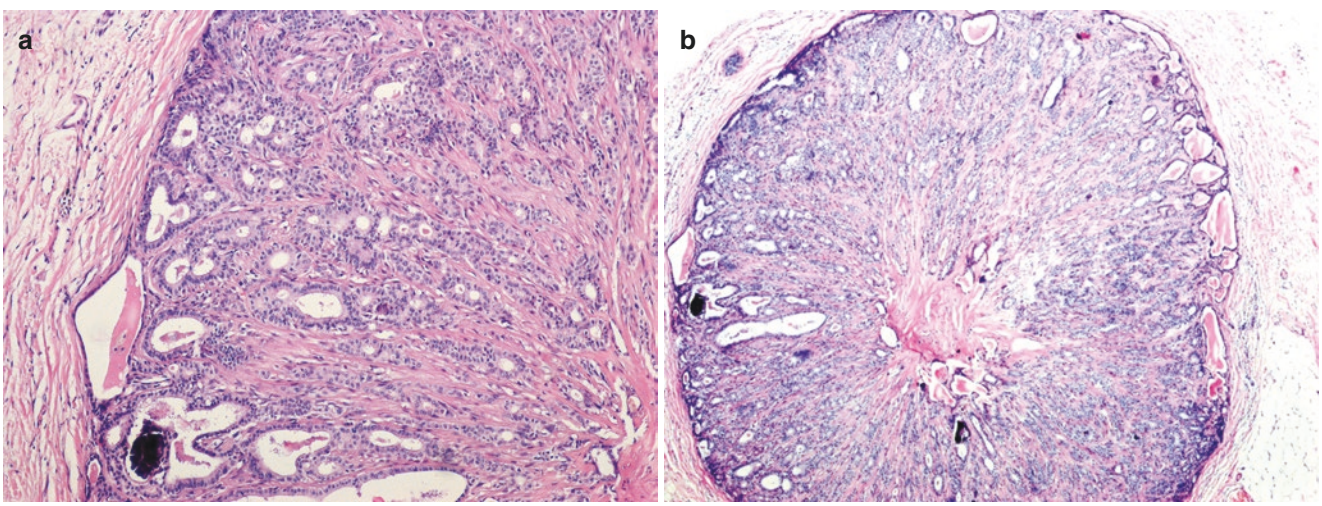

Fig. 7.103 Sclerosing adenosis: (**a**, **b**) Of great help in these areas is the identification of myoepithelial cells together with the examination at low power

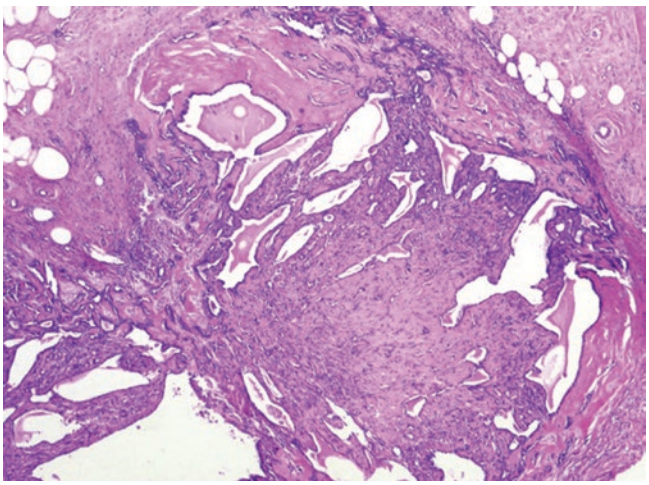

Fig. 7.104 Sclerosing adenosis: the proliferation of acini is arranged around the intralobular duct, sometimes extending into its lumen, thus, the focus of sclerosing adenosis appears intracystically

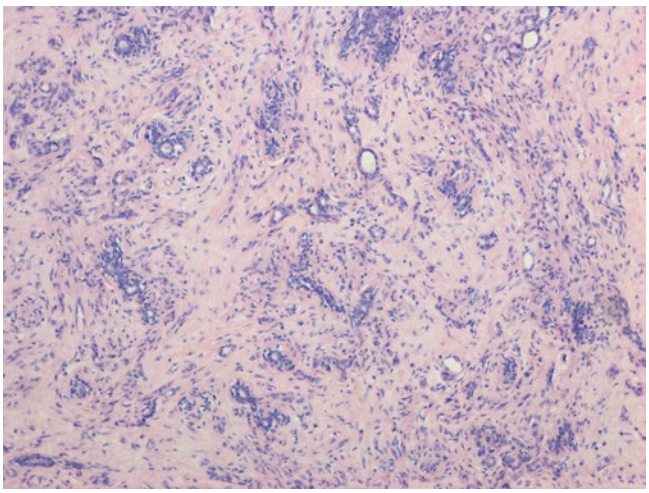

Fig. 7.105 Sclerosing adenosis: in late stage of evolution, massive fibrosis and spindle-shape myoepithelial cells may also lead to a pseudoinfiltrative area in the center of the lesion

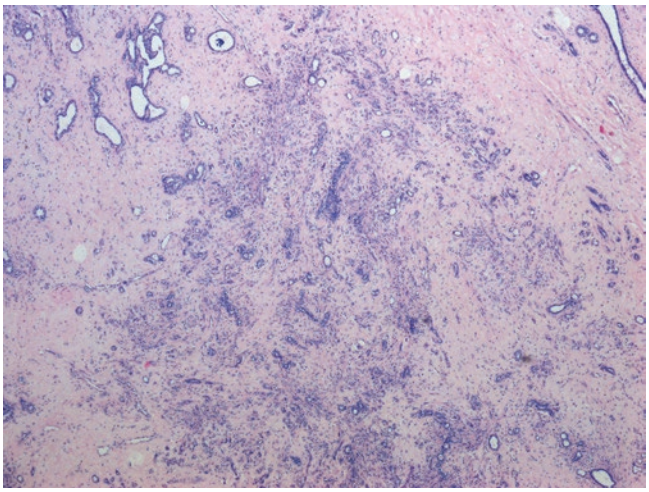

Fig. 7.106 Sclerosing adenosis: for this type of lesion (like in Fig. 7.105), it is advisable to examine the lesion at low power

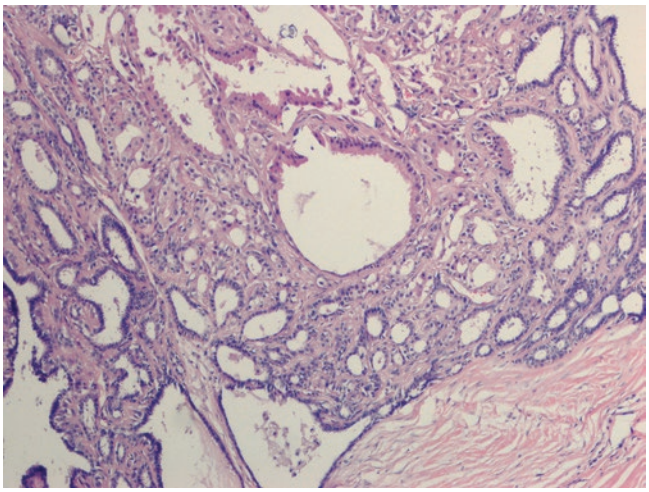

Fig. 7.107 Sclerosing adenosis with focus of apocrine metaplasia

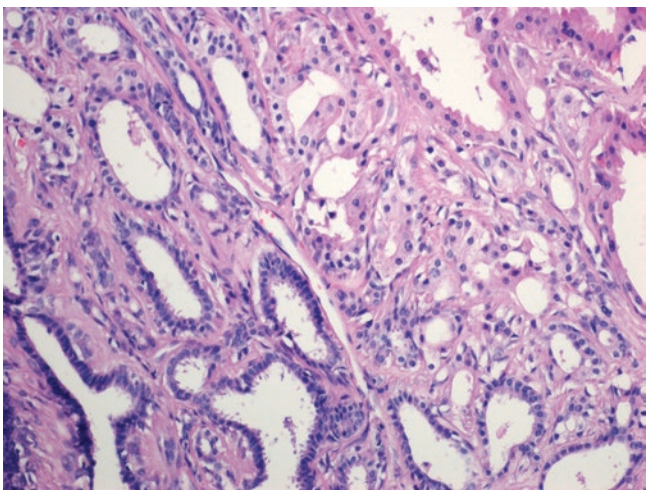

Fig. 7.108 Sclerosing adenosis: high-power examination of the same lesion as in Fig. 7.107 reveals lack of atypia within the apocrine metaplasia; the cells have round nuclei and prominent nucleoli (not enough features to diagnose the lesion as atypical)

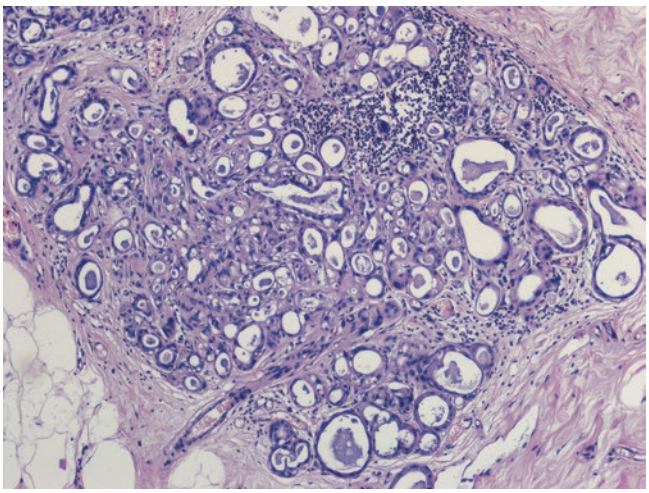

Fig. 7.109 Sclerosing adenosis with areas of apocrine metaplasia displaying more enlarged and atypical nuclei

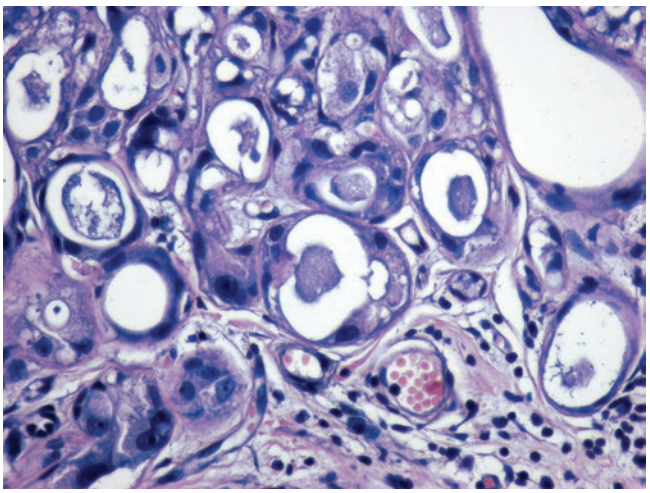

Fig. 7.110 Sclerosing adenosis with areas of apocrine metaplasia displaying more enlarged and atypical nuclei, which should not be confused with a carcinoma

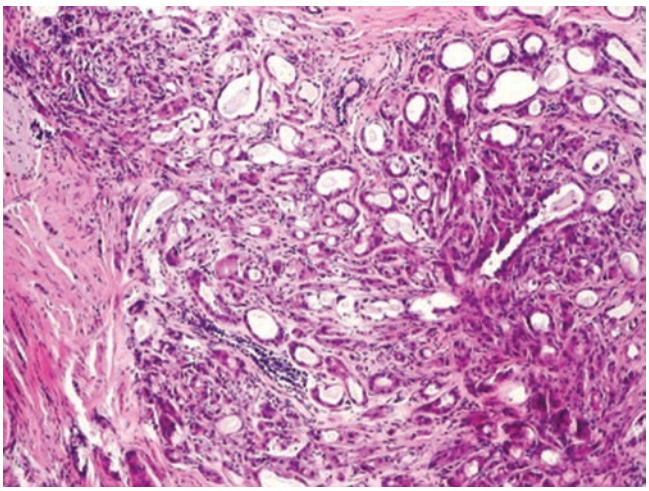

Fig. 7.111 Sclerosing apocrine adenosis: a sclerosing adenosis in which almost all the acinic structures are involved by apocrine metaplasia

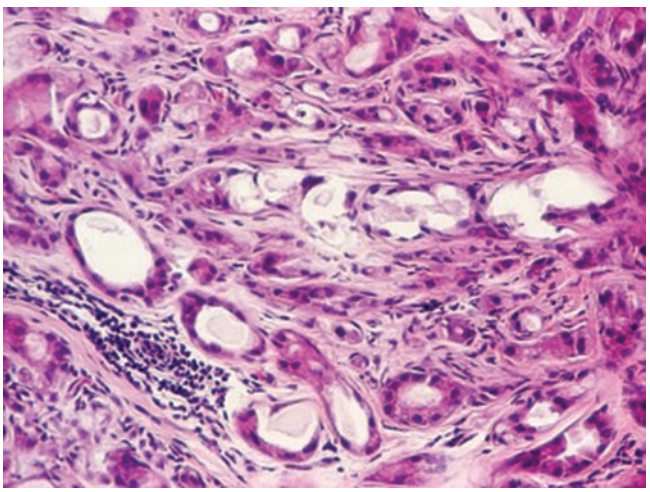

Fig. 7.112 Sclerosing apocrine adenosis: even if the apocrine metaplasia displays slightly more pleomorphic cells, it is advisable not to over-diagnose these type of lesions as atypical apocrine adenosis or DCIS unless there is significant atypia

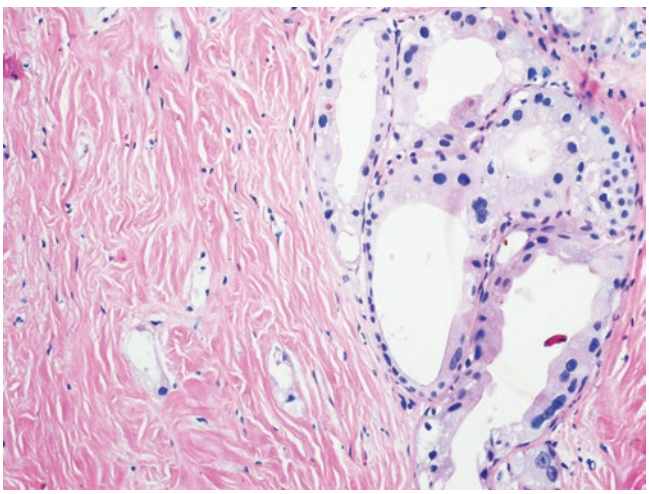

Fig. 7.113 Acini with significant apocrine atypia: the nuclei are four times more enlarged as the normal apocrine cells and are hyperchromatic

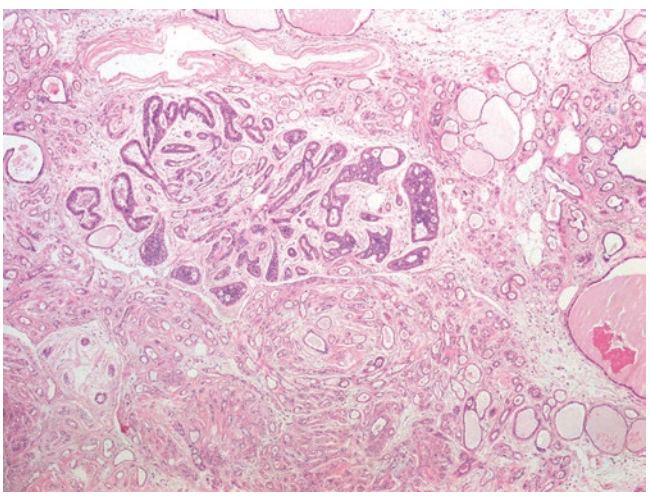

Fig. 7.114 Sclerosing adenosis with focus of DCIS of low-grade: examination at low power would prompt a correct diagnosis due to the lobulo-centric appearance of the lesion

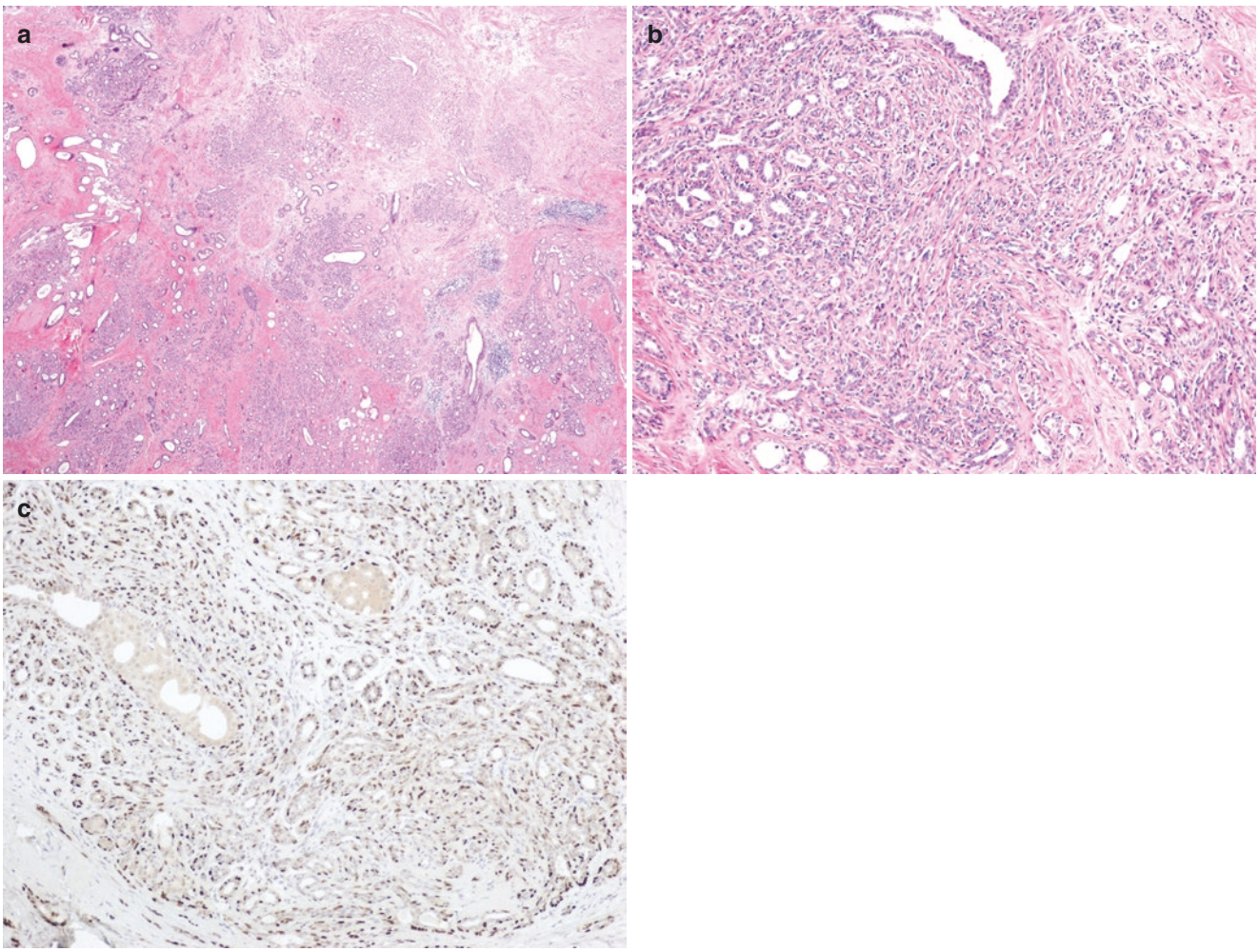

Fig. 7.115 Sclerosing adenosis: (**a**) Low-power examination reveals a lobulo-centric lesion in which (**b**), all the acini are lined by two cells layers; however, (**c**) more cellular areas and areas with compressed acini are difficult to diagnose and myoepithelial cells are not easy not be identified; their presence can be demonstrated with p63 stain

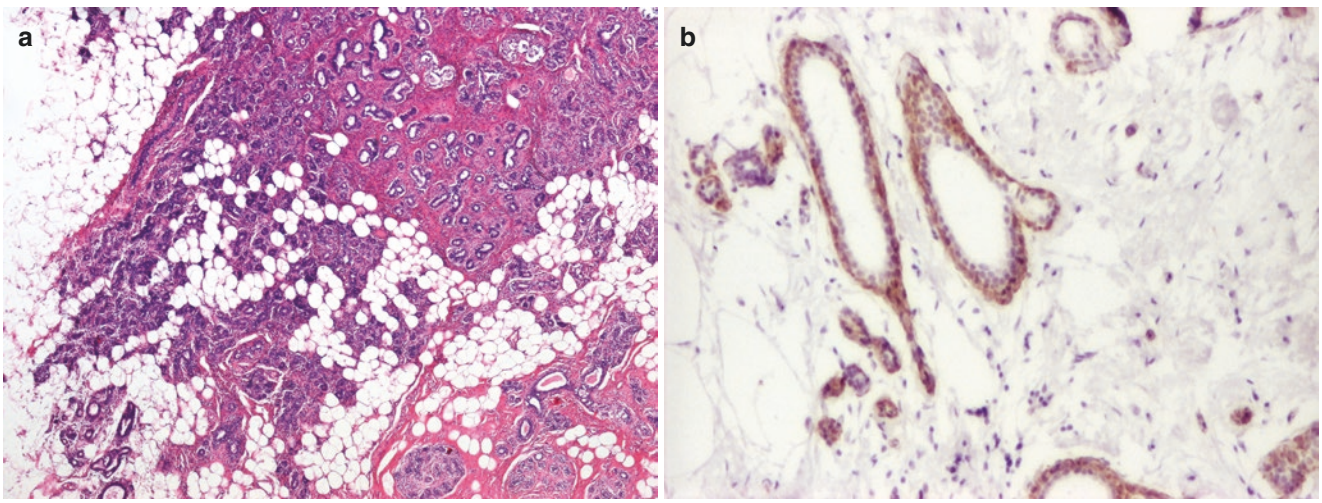

Fig. 7.116 Tubular adenosis: (**a**) Hyperplastic acini multiply, branch, and extend into the surrounding adipose tissue; this lesion lacks the circumscription of sclerosing adenosis and its cellularity in the center; however, the acini are lined by two cell layers. (**b**) Smooth Muscle Actin stain demonstrates that a layer of myoepithelial cells is present

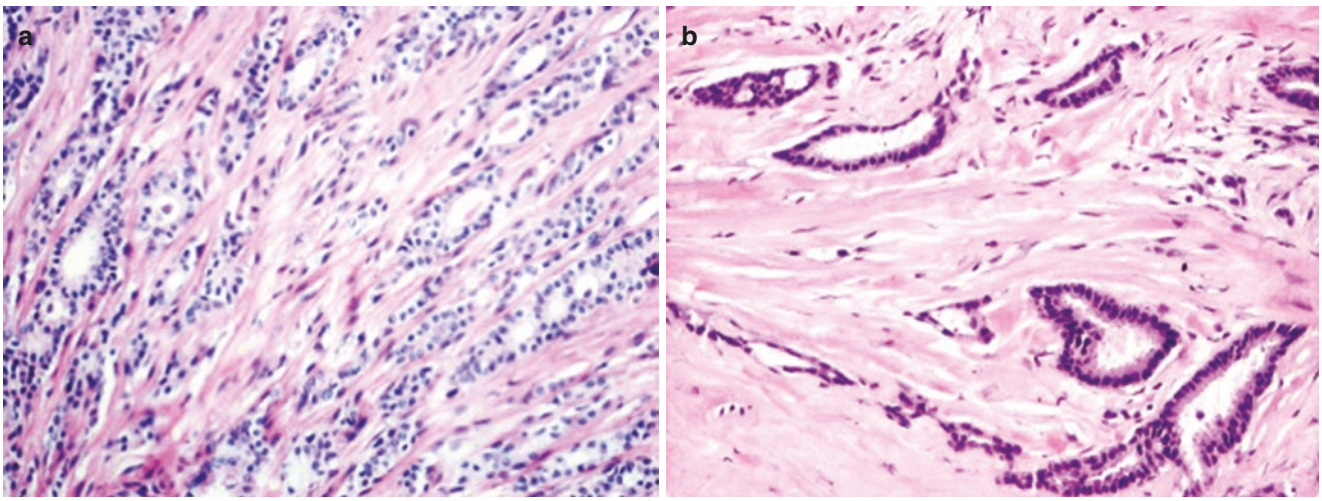

Fig. 7.117 (**a**) Differential diagnosis between compressed tubular structures in sclerosing adenosis lined by two cell types and (**b**) angulated tubules lined by one cell type in tubular carcinoma

Table 7.2 Main differences between sclerosing adenosis and tubular carcinoma

	Sclerosing adenosis	Tubular carcinoma
Shape	Lobulocentric	Infiltrative, stelate
Relation with adipose tissue	Respects adipose tissue	Infiltrates adipose tissue
Stroma	Sclerotic	Desmoplastic
Tubular structures	Compressed in the center, obliterated lumina, cystically dilated at periphery	Open lumina, angulated shape
Myoepithelial cells	Present	Absent
Basal membrane	Present	Absent
In situ component	Absent	Present

7.3.3 Microglandular Adenosis

Microglandular adenosis is a rare lesion characterized by irregular proliferation of small tubular structures arranged in a hypocellular hyalinized stroma [19–21]. The mean age of occurrence is 50 years, but it can occur at any age. Grossly, the lesion can be very small or can form a palpable firm and gray nodular mass with a mean diameter of 3–4 cm and ill-defined margins. No specific radiological findings are associated with microglandular adenosis. Microscopically, tubular structures haphazardly infiltrate the surrounding tissue (no lobulo-centric pattern is present), mimicking a low-grade infiltrating carcinoma. However, no stromal desmoplasia is present. The tubular structures are round, open, and their lumen contains a PAS-positive (sometimes Alcian-positive) eosinophilic secretory material (similar to the colloid material found within the thyroid gland), and are lined by a layer of cuboidal or flat epithelial cells without nuclear atypia. The cells have round nuclei with indistinct nucleoli, whereas the cytoplasm may be clear, eosinophilic, or granular. The epithelial cells are positive for Cytokeratin 8, 18, 7, HMW-CK (such as CK 34beta E12), EGFR, and S-100 protein. The epithelial cells are, however, negative for ER, PR, HER2, EMA, CK20, CK 5/6, and p63 [22, 23]. The myoepithelial cell layer is absent, microglandular adenosis being the only benign breast lesion in which myoepithelial cells are lacking. Therefore, the myoepithelial markers are negative. However, the basement membrane is present (demonstrable by immunohistochemical examination for Laminin and Collagen IV, or electron microscopy examination). The basement membrane in microglandular adenosis surrounding ductal type structures is thick and layered; it is therefore always obvious on special stains or immunostaining (Fig. 7.118). The lesion may present microcalcification foci or apocrine metaplasia. Perineural or vascular invasion has not been observed in any of these lesions. Differential diagnosis is made with tubular carcinoma (composed of tubular structures, lined by a layer of epithelial cells with mild atypia, but arranged in a desmoplastic stroma, without myoepithelial cells and basement membrane). The main differences between microglandular adenosis and tubular carcinoma are listed in Table 7.3. Another differential diagnosis is made with tubular adenosis, which has a myoepithelial layer (myoepithelial cells are positive for Actin and p63). Sometimes, microglandular adenosis can display atypia (*atypical microglandular adenosis,* in which the glands become more complex, with luminal bridges and cribriform areas, while atypia is present and cells are multilayered), and there are publications suggesting that these lesions represent a precursor and can transform into invasive carcinomas such as adenoid-cystic or

metaplastic carcinoma [23]. It is particularly difficult to differentiate between *in situ* carcinoma developed in a background of a microglandular adenosis and invasive carcinoma developed on microglandular adenosis, because both lack myoepithelial cells; the microglandular adenosis with *in situ* carcinoma, however, has a basal membrane surrounding the round tubular structures, and lacks coalescent and solid epithelial growth (Fig. 7.119).

Microglandular adenosis lacking atypia is treated with local excision. Incomplete excision may lead to recurrence and, in consequence, a complete surgical excision is required. In the cases with atypia present, negative surgical margins and performing sentinel lymph node excision is advisable together with a close correlation with the radiological settings, discussing the case in the tumor board and close follow-up of the patient.

7.3.4 Adenomyoepithelial Adenosis

Adenomyoepithelial adenosis is an extremely rare breast entity. Microscopically, the lesion is usually diffuse and infiltrative, composed of round tubular structures, arranged irregularly, containing eosinophilic secretion, and bordered by a layer of cuboidal or cylindrical epithelial cells, sometimes with apocrine or squamous metaplasia. The outer tubular structures are bordered by a layer of myoepithelial cells and basement membrane. The myoepithelial cells can be very prominent, with clear cytoplasm, and sometimes hyperplastic. The lesion shows no atypia. Differential diagnosis is made with microglandular adenosis (where the myoepithelial cells are absent) and adenomyoepithelioma (a benign tumor with the same microscopic appearance, but forming a nodule and with a diameter of more than 1 cm).

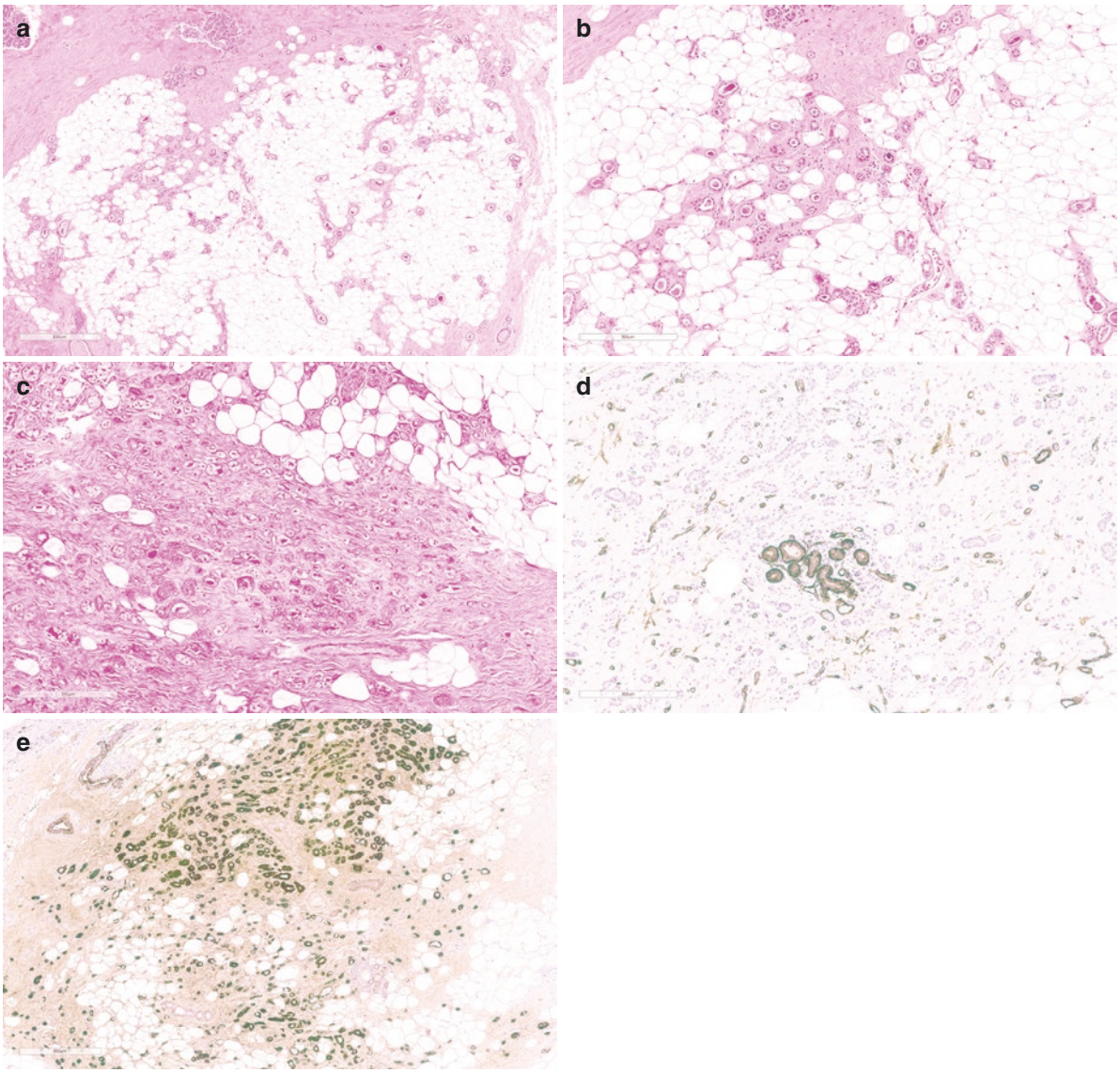

Fig. 7.118 Microglandular adenosis: (**a**) Tubular structures haphazardly infiltrate the breast tissue mimicking a low-grade infiltrating carcinoma; (**b**) the tubular structures are round, open, and their lumen contains an eosinophilic secretory material (**c**) which is PAS-positive. (**d**) Stain for Actin demonstrates that myoepithelial cell layer is absent compared to normal acini; (**e**) The tubular structures are lined by epithelial cells, positive for S-100 Protein and the basement membrane positive for PAS

Table 7.3 Major differences between microglandular adenosis and tubular carcinoma

	Microglandular adenosis	Tubular carcinoma
Pattern of growth	Infiltrative	Infiltrative, stellate
Tubules	Small and round	Angulated
Apical snouts	Absent	Present
Luminal secretion	Present	Absent
Epithelial cells	Present	Present and atypical
Myoepithelial cells	Absent	Absent
Basal membrane	Present	Absent
Stroma	No desmoplasia	Demoplastic
Immunohistochemical stains	ER, PR, EMA-; S 100 protein, Laminin, Colagen IV+	ER, PR, EMA+; S100 protein, Laminin,ColagenIV-
Associated DCIS	Not present	Present

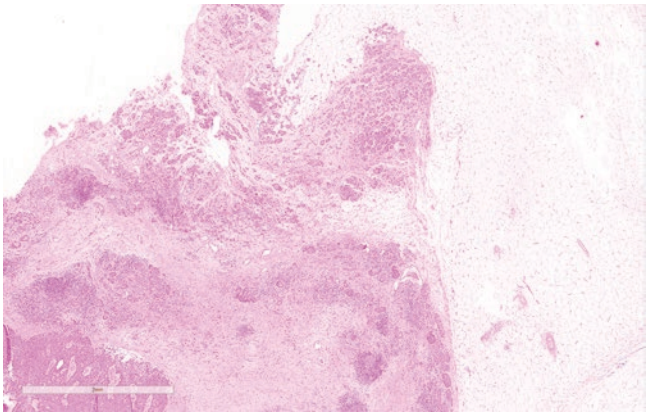

Fig. 7.119 Invasive carcinoma developed on microglandular adenosis is difficult to differentiate from *in situ* carcinoma developed in a background of a microglandular adenosis: both lack myoepithelial, but the former lesion illustrated in this picture has an obvious infiltrative component with coalescent and solid epithelial growth

7.4 Pregnancy-Like Changes

Pregnancy-like changes, also called pseudolactational changes (or pseudolactational metaplasia, pseudolactational hyperplasia) are similar to those which occur in the mammary gland during pregnancy or breastfeeding, but they occur in patients who are not pregnant or breastfeeding. The etiology is unknown. Some of the patients have never been pregnant and others are postmenopausal. Exceptionally, the lesion has also been described in men. The mechanism of development of this lesion is widely debated, in some cases considered a persistence of lactational changes from a previous pregnancy, but in most cases the lesion is considered to be caused by an exogenous hormonal intake or by the administration of other drugs such as antihypertensive or neuroleptic medication. Pseudolactational changes never form a palpable mass. The lesion is identified on microscopy and usually affects several lobules, but when it occurs within one lobule, only a few acini are affected. It can present in two microscopic forms, both associated with the preservation of the normal architecture of the lobule. The first form, called *classic type*, has dilated acini, with abundant secretory material in the lumen and lined by a cylindrical epithelium (Figs. 7.120 and 7.121). Epithelial cells have abundant, granular, or vacuolated cytoplasm, and small and round nuclei. The cytoplasm is positive for S-100 protein and α-lactalbumin. The second variant, called *hobnail-type*, has the same architecture and the cytoplasmic vacuolization is minimal, but the epithelial cells have different sizes and hyperchromatic, irregular nuclei, which are located in the apical part of the cell and create a "hobnail" appearance (Figs. 7.122, 7.123, and 7.124). The secretory material within the dilated structures is minimal. It may contain detached cells, some of which are multinucleated. This appearance is very similar to the changes called Arias-Stella in the endometrium or cervix. In both variants, the cells are negative for Mucicarmine and Alcian blue, but they contain PAS-positive intracytoplasmic granules, and the intraluminal secretion is positive for Mucicarmin and Alcian blue. In some cases, calcifications also appear in the lumen of the cysts. These changes can sometimes also affect the ducts.

Differential diagnosis is made with lactation and pregnancy changes (which affect all lobules and all the acini within a lobule; it is mandatory, however, to know the clinical history and age of the patients), with hypersecretory cystic hyperplasia (cystic cavities lined by a cylindrical or flat epithelium consisting of cells without atypia and containing an eosinophilic material in the lumen, of colloid-type), as well as various microscopic mammary carcinoma variants (all associated with cytological atypia). Of note, a rare lesion called *pregnancy-like hyperplasia* may occur. It is similar to pregnancy-like changes, but has a multilayered epithelium with papillary fronds composed entirely of epithelial cells lining the dilated acini. The secretion within the lumina may contain microcalcification; the lesion can therefore be detected radiologically. Also, hyperplasia can sometimes be associated with atypia, most of the cases occurring in association with cystic hypersecretory hyperplasia [24].

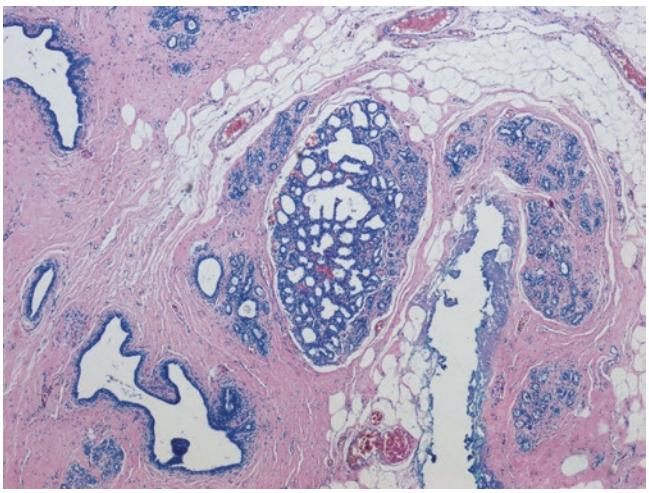

Fig. 7.120 Pregnancy-like changes: the lesion only affects several lobules and some but not all the acini within a lobule

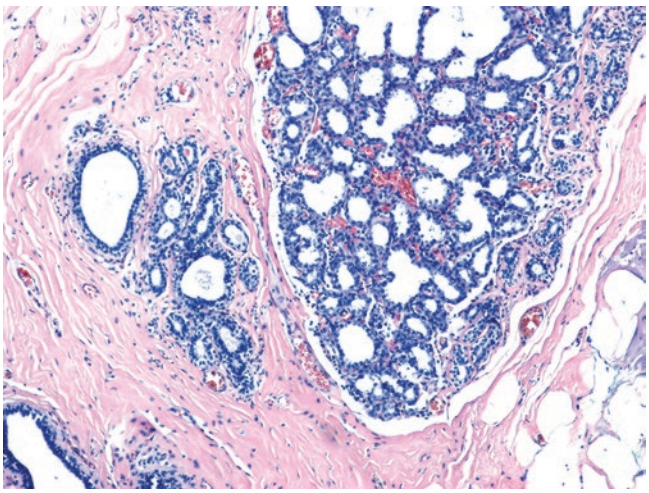

Fig. 7.121 Pregnancy-like changes: in the classic type, one can appreciate the preservation of the normal lobule, dilated acini lined by a cuboidal/cylindrical epithelium with vacuolated cytoplasm and small, round nuclei

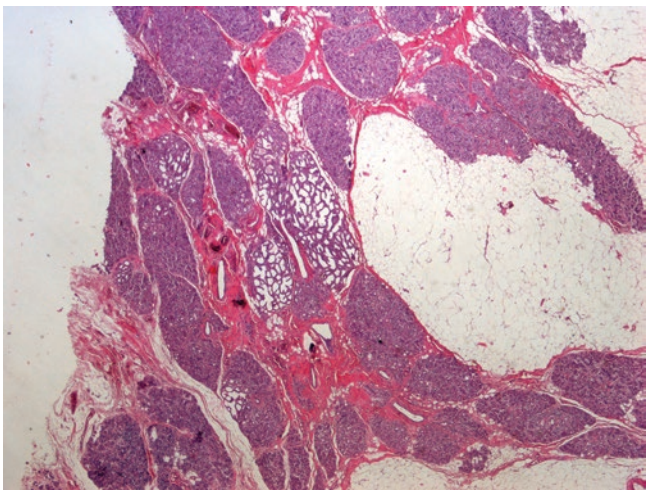

Fig. 7.122 Pregnancy-like changes: the lesion is represented by lactational metaplasia involving some but not all the lobules

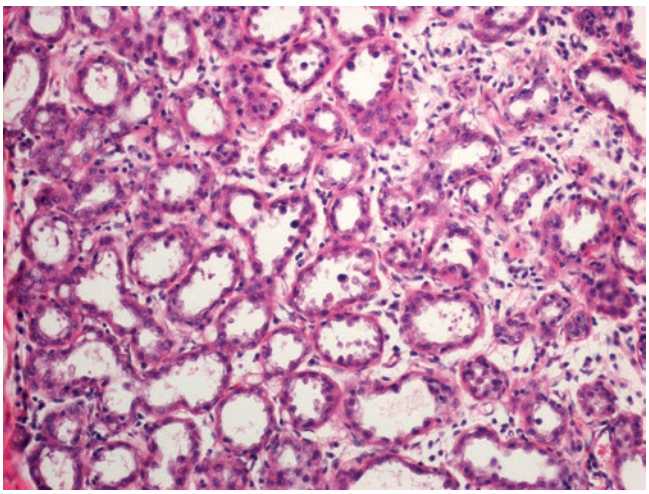

Fig. 7.123 Pregnancy-like changes: hobnail-type with epithelial cells having different sizes, hyperchromatic, irregular nuclei, which are located in the apical part of the cell

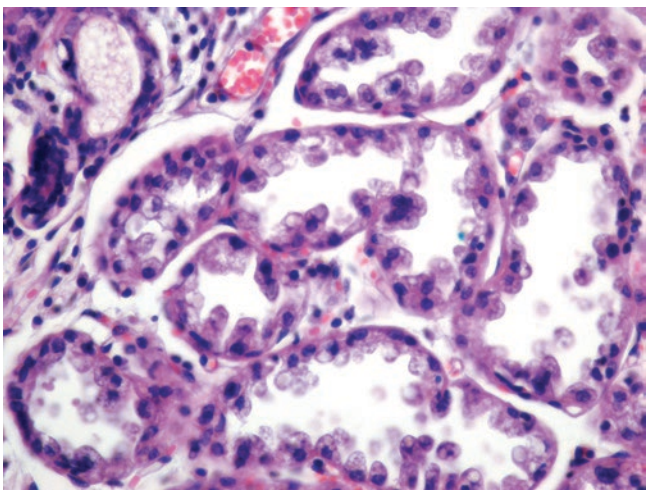

Fig. 7.124 Pregnancy-like changes: hobnail-type

7.5 Epithelial Metaplasia

7.5.1 Apocrine Metaplasia

Apocrine Metaplasia is the most frequent form of epithelial metaplasia encountered within the breast. It is represented by the transformation of the epithelial cells lining both ducts and acini into larger, cuboidal or columnar cells, with large amount of granular eosinophilic cytoplasm, apical snouts, round nuclei, and visible nucleoli. Lipofuscin granules and iron pigment can be seen intracytoplasmatically. It does not have a clinical significance itself unless associated with atypia and/or other pathological breast conditions. The most frequent association is with fibrocystic changes. Apocrine metaplasia is not detectable with radiological investigations and is not visible to the naked eye. It can be detected e only via microscopic examination, and in this particular case it may involve a few structures or sometimes may be more extensive.

Simple apocrine metaplasia (represented by a single layer of apocrine cells) has to be differentiated from *hyperplastic apocrine changes* (multiple layers of cells) and *atypical apocrine metaplasia* (nuclei enlarged more than three times than normal and pleomorphic) (Fig. 7.125).

7.5.2 Clear Cell Metaplasia

Clear cell metaplasia may occur in the acini and ducts and is occasionally detected under microscopic examination. It occurs, however, much less frequently than apocrine metaplasia. It is seen especially in patients in pre- and post-menopause, with no relation to the pregnancy or exogenous hormonal use. It is a focal lesion with partial or complete involvement of a lobule, but most often, multiple lobules are affected. The architecture of the lobule does not change, but it increases in size due to the increase in volume of metaplastic epithelial cells. The epithelial cells have clear, abundant cytoplasm, sometimes foamy or vacuolated (Fig. 7.126). The cytoplasm sometimes contains PAS-positive granules, but is negative for Alcian blue and Mucicarmin. The nuclei are located eccentrically and are small and round, with no obvious nucleolus. The lumen of the acini is usually open, but it can also be obliterated; however, the acini are never cystically dilated. Differential diagnosis should be made with pregnancy-like changes (presenting a typical secretion located at the luminal border of the cells), myoepithelial cell hyperplasia (metaplastic clear cells are not positive for S-100 protein, Actin or any other myoepithelial markers), as well as primary or metastatic clear cell carcinoma (clear cells show signs of atypia, infiltration of the stroma, and stromal response; in the metastases, the clinical history information is very helpful). Clear cell metaplasia is not associated with an increased risk for developing a breast carcinoma.

7.5.3 Squamous Metaplasia

Squamous metaplasia occurs mainly in infarction areas within an intraductal papilloma or on a previous biopsy site, sometimes within a fibroadenoma (Figs. 7.127, 7.128, 7.129, and 7.130). Also, the lactiferous ducts may undergo extensive squamous metaplasia, which may obliterate the duct and produce a cyst eventually associated with inflammation (subareolar abscess). Recent papers suggest however that the myoepithelial cell appears to be the cell of origin of metaplastic squamous epithelium. Differential diagnosis includes metaplastic carcinoma (especially low-grade adenosquamous carcinoma but in which, besides the areas of squamous cells with low atypicality, tubules embedded in a desmoplastic stroma with infiltrative margins are seen).

7.5.4 Mucinous Metaplasia

Mucinous metaplasia occurs either within a papilloma or associated with pregnancy-like changes [25]. Rarely, it can be seen in association with collagenous spherulosis (it is also called mucinous spherulosis, but there is an associated proliferation of myoepithelial cells within this lesion) (Fig. 7.131). It must be differentiated from a mucinous breast carcinoma (which has atypia and stromal invasion).

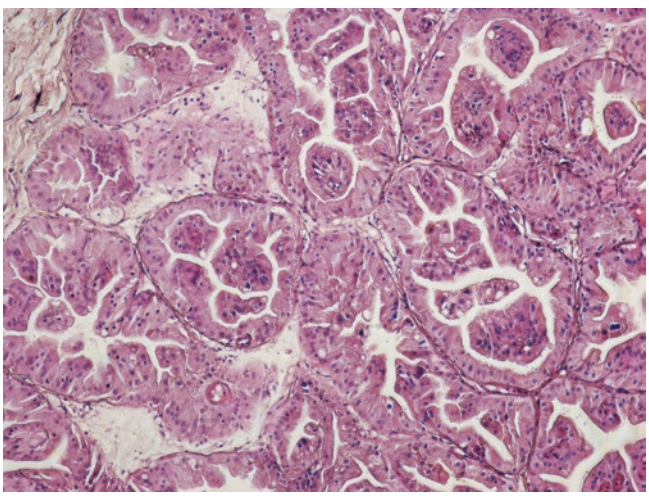

Fig. 7.125 Apocrine metaplasia: ducts and acini are distended, lined by a simple cylindrical apocrine epithelium in some of the areas but mostly by hyperplastic apocrine epithelium forming papillae and micropapillae; however, no atypia is detected

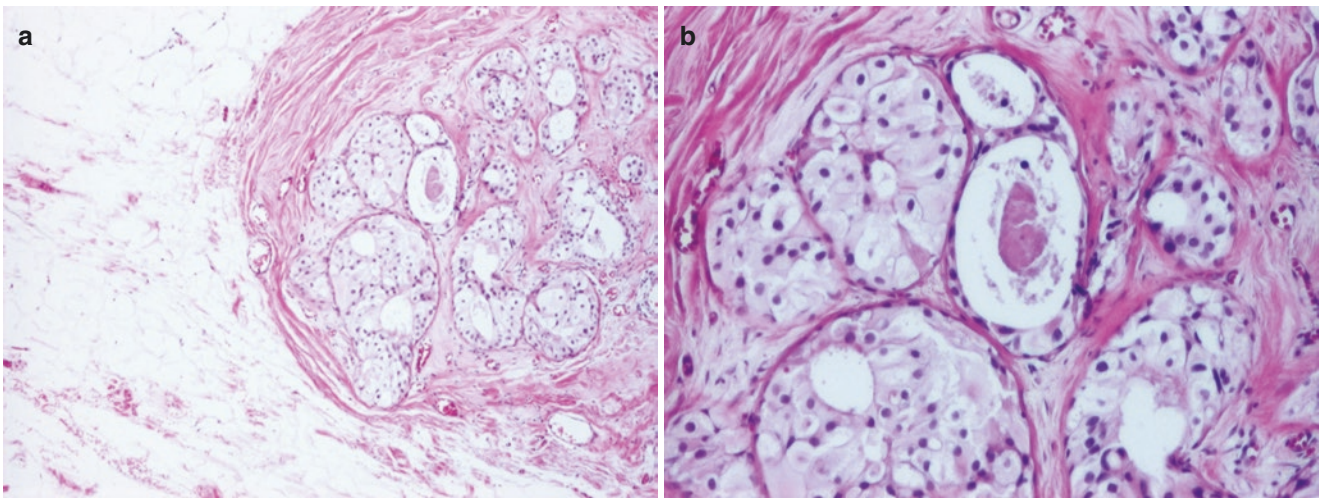

Fig. 7.126 Clear cell metaplasia: (**a**) The architecture of the lobule is not changed, but it increases in size due to the increase in volume of metaplastic epithelial cells: (**b**) the epithelial cells have clear, abundant cytoplasm, with small, round, nuclei located eccentrically

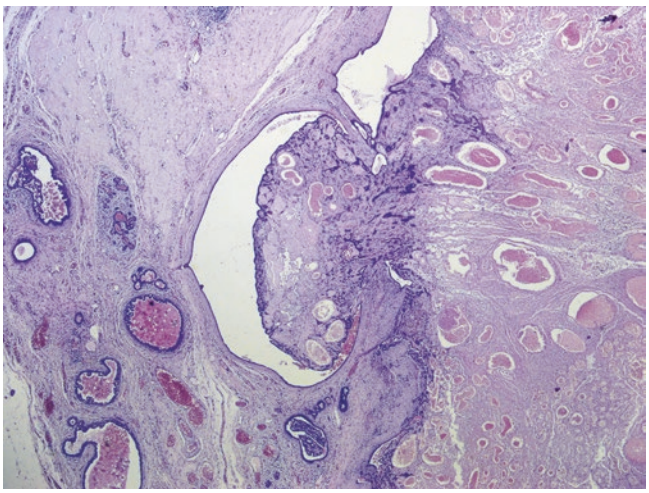

Fig. 7.127 Sclerosing papilloma with massive area of necrosis—consequently, foci of squamous metaplasia can be detected

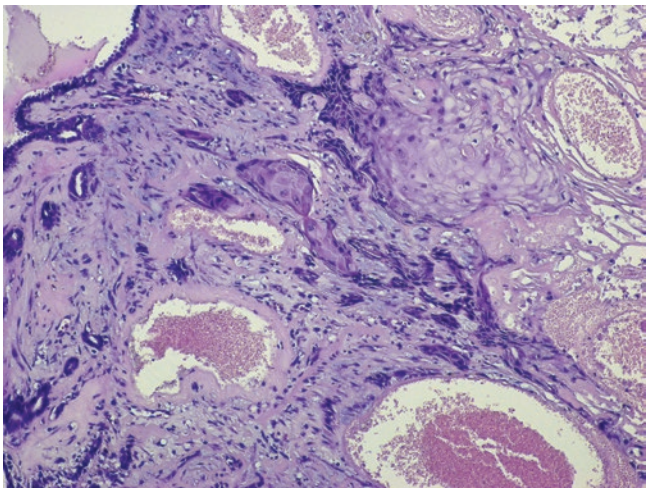

Fig. 7.128 Sclerosing papilloma with massive area of necrosis (same lesion as in Fig. 7.127)—high-power examination allows detection of benign foci of squamous metaplasia

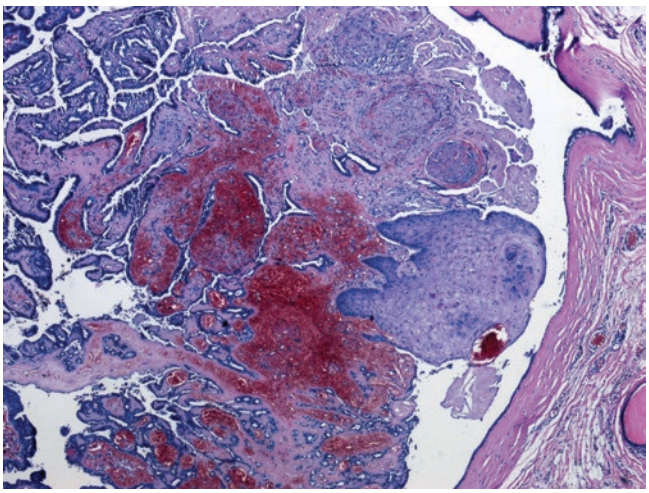

Fig. 7.129 Intraductal papilloma with areas of hemorrhage and squamous metaplasia

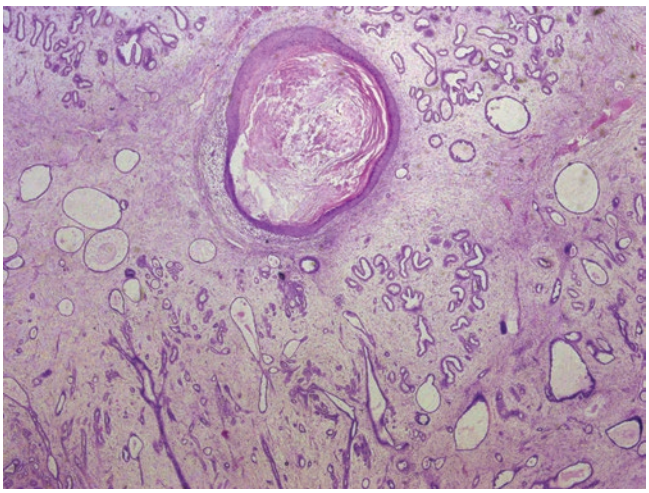

Fig. 7.130 Fibroadenoma with central area of squamous metaplasia

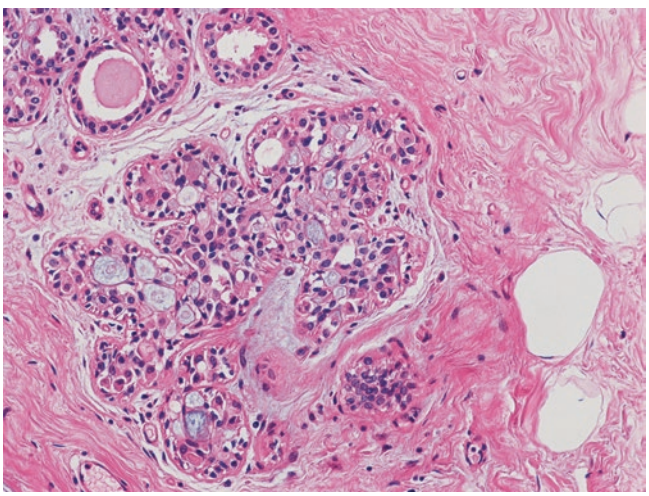

Fig. 7.131 Mucinous metaplasia can be seen in association with collagenous spherulosis (it is also called mucinous spherulosis)

7.6 Microcalcifications

Microcalcifications are calcium deposits that can occur in benign and malignant lesions, but also in association with normal breast tissue, especially in menopause or after lactation. In benign lesions, microcalcifications occur more frequently in sclerosing adenosis and fibrocystic changes. In malignant lesions, comedocarcinoma type of DCIS and NST-infiltrating carcinoma are the most frequent associations. The presence of microcalcifications is an important finding on mammography, because, depending on size, shape, number, and distribution, they allow the differentiation between benign and malignant lesions (Figs. 7.132 and 7.133). They occur due to either tumor necrosis or calcification of the secretion product from the mammary acini and ducts. The mammographic appearance of microcalcifications in benign lesions is round, punctuated, and regular, while in malignant ones microcalcifications are polymorphic, irregular, and branched. Since some forms of microcalcification are characteristic of both benign and malignant lesions, it is always advisable that mammographic diagnosis be followed by a biopsy and a microscopic diagnosis be established.

Sometimes, besides calcium, microcalcifications may also contain small amounts of aluminum, potassium, iron, silicon, titanium, and sulphides. Such layered deposits, usually occurring inside cysts and rarely in the adjacent stroma, are called Liesegang rings and should not be confused with the parasites on microscopy. Also, crystalline deposits with an eosinophilic appearance may occur within the cyst. These usually accompany benign lesions, but have also been recorded in atypical intraductal hyperplasia or *in situ* ductal carcinomas. Crystals can be few or extremely numerous inside a cyst or may involve several cysts. Their size is variable, and they can have various shapes: triangular, quadrangular, pentagonal, or hexagonal. The chemical composition and ultrastructural appearance suggest that they are made up of condensed protein material.

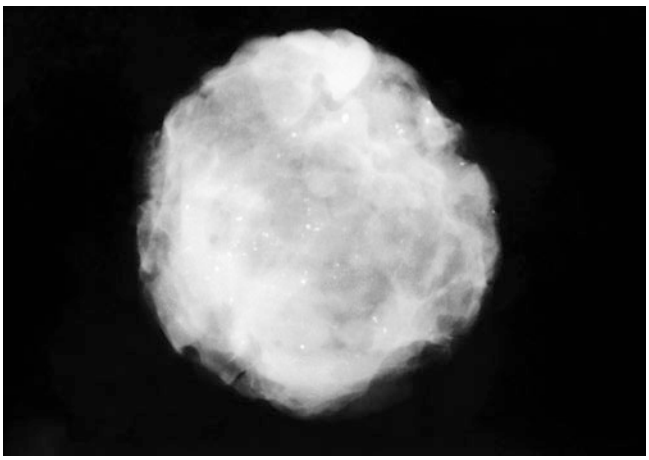

Fig. 7.132 Mammography in a 38-year-old patient reveals multiple benign-looking microcalcifications after a lactation period of 2 years

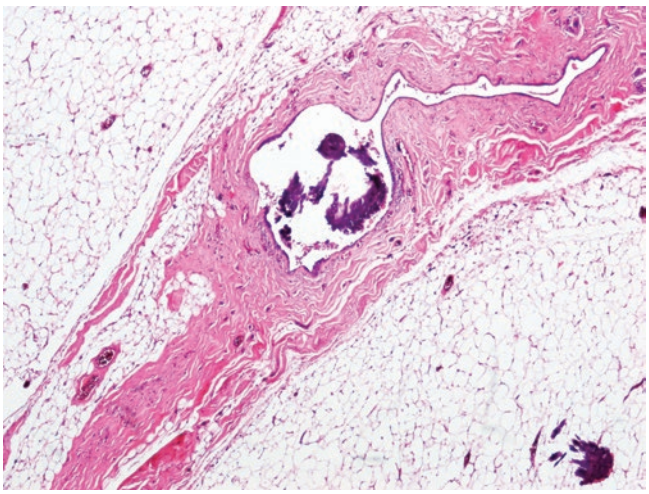

Fig. 7.133 Microscopic examination reveals multiple areas of microcalcifications associated with normal breast tissue (same patient as in Fig. 7.132)

7.7 Hypersecretory Cystic Hyperplasia

Hypersecretory cystic hyperplasia is a rare, macroscopically well-defined lesion that consists of a various number of cysts with a diameter between 0.5 and 2 cm, smooth wall, and a greenish jelly material inside. Microscopically, the lesion consists of numerous dilated cystic ducts, surrounded by a fibrous stroma. The ducts are delimited by a unilateral, cuboidal, or flattened epithelium. The epithelial cells have round, uniform nuclei and moderate eosinophilic cytoplasm (Fig. 7.134). Rarely, the epithelium may be layered or have papillary (arranged on a fibro-vascular axis) or micropapillary (lacking a fibro-vascular axis) growths. If there is a nuclear pleomorphism in these situations, the lesion is called *atypical hypersecretory cystic hyperplasia*. The cysts contain an eosinophilic, PAS-positive acellular material, retracted from the cyst walls, with smooth or scalloped margins and showing characteristic slits, folds, linear cracks, or small punched-out holes. The secretion is not associated with necrosis or microcalcifications. These elements are very similar to thyroid colloid. If one or more cysts rupture, the secretion that reaches the adjacent stroma produces a chronic inflammatory reaction. The lesion must be distinguished from fibrocystic changes (the cysts have a different content and are associated with other changes as well). In young patients, juvenile papillomatosis can occur, but it forms a macroscopic mass, while microscopically it is characterized by multiple cysts and ectatic ducts with intraluminal secretion and foamy histiocytes. Of note, in some cases, cystic hypersecretory hyperplasia may coexist with pregnancy-like hyperplasia [18]. Also, the lesion must be distinguished from secretory carcinoma (characterized by atypical features and invasion into the stroma) (Fig. 7.135).

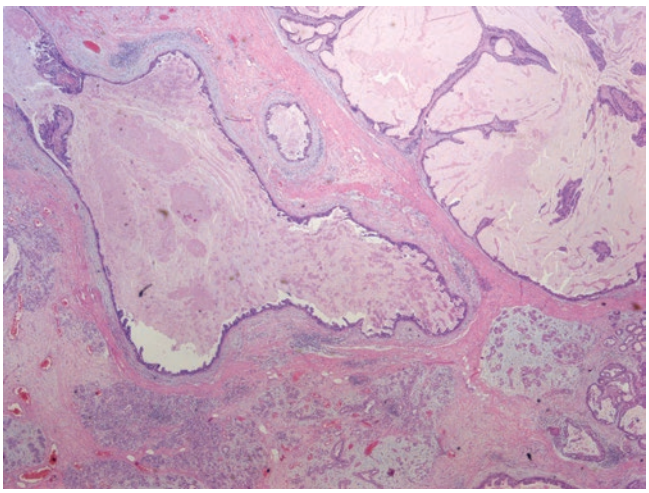

Fig. 7.134 Cystic hypersecretory hyperplasia: multiple cysts filled with secretory material resembling the colloid; cysts are line by atypical epithelium in this case

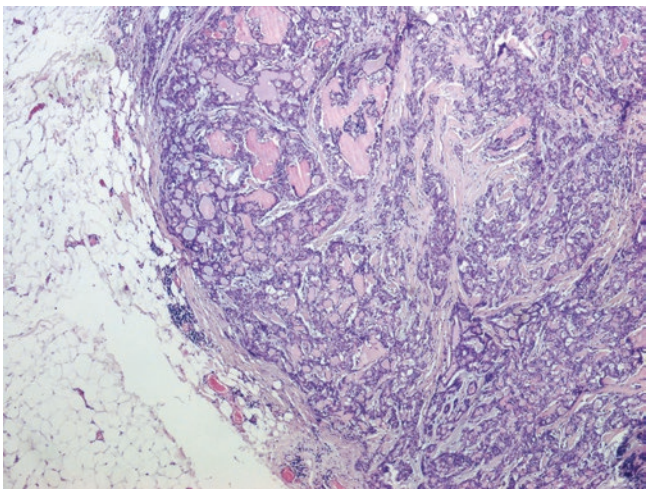

Fig. 7.135 Secretory carcinoma is characterized by atypical features and invasion into the stroma, unlike cystic hypersecretory hyperplasia

7.8 Mucocele-Like Tumor

The mucocele-like tumor is a benign rare lesion, usually microscopic in size; in some lesions, however, it may form a well-demarcated palpable mass identified on radiological examinations. Macroscopically, the lesion consists of many cysts of various sizes on the cut surface, containing a gelatinous material. Microscopically, it consists of cystic cavities lined by a single-layer cuboidal, cylindrical, or flattened epithelium, without signs of atypia and containing an abundant secretory material (Fig. 7.136). The epithelium may present papillary stratification or micropapillary growths. Some cavities are ruptured, and the mucinous material is extravasated into the adjacent stroma, forming mucin pools of different sizes, similar to the same lesion within the salivary glands. This material can lack epithelial cells, although sometimes they have epithelial cell groups that "float" in the mucus. These groups are the epithelial cells that delineate the cysts and which, by rupturing, reach the surrounding stroma. These cell groups *must* contain myoepithelial cells for a diagnosis for mucocele-like tumor. If it is difficult to identify them on Hematoxylin-Eosin stains, immunohistochemical examination for myoepithelial markers are of real use. The secretory material has the same histochemical characteristics as mucinous carcinoma (PAS- and Alcian blue-positive), suggesting the possibility of a continuous spectrum of alterations, including both mucocele-like tumor at one end of the spectrum, and mucinous carcinoma at the other end [6]. This theory suggests that the mucocele-like tumor is a precursor lesion of mucinous carcinoma. However, most invasive mucinous carcinomas derive from *in situ* ductal carcinoma, which sometimes can be detected at the periphery of the lesion. Mucocele-like tumor has also to be distinguished from hypocellular invasive mucinous carcinoma (the distinction is very challenging; however, in the latter, myoepithelial cells are lacking and also, coarse and granular microcalcifications are usually absent, while they are characteristically present in the former), mucinous cystadenocarcinoma (a mucin-producing type of invasive carcinoma) and from other lesions of the breast with a myxoid stroma (for example, myxoid fibroadenoma) (Figs. 7.137, 7.138, 7.139, and 7.140).

Excisional biopsy is recommended for mucocele-like tumor, especially if it was diagnosed on a Tru-Cut biopsy and/or it is associated with atypia or a breast mass.

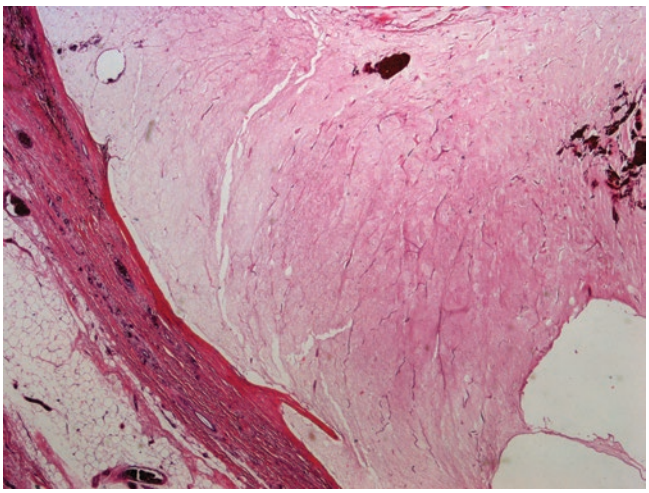

Fig. 7.136 Mucocele-like tumor: cystic cavity lined by a single layer of flattened epithelium, without signs of atypia and containing an abundant secretory material lacking epithelial or myoepithelial cells

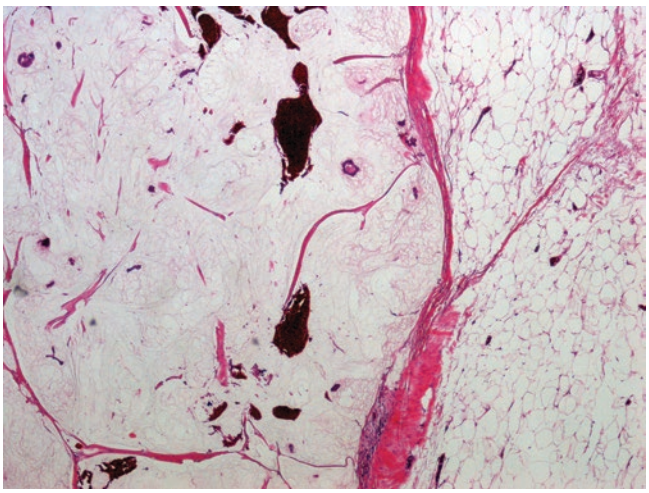

Fig. 7.137 Mucinous infiltrating carcinoma of hypocellular type: pools of mucin with rare groups of low-atypical epithelial cells in which myoepithelial cells are lacking

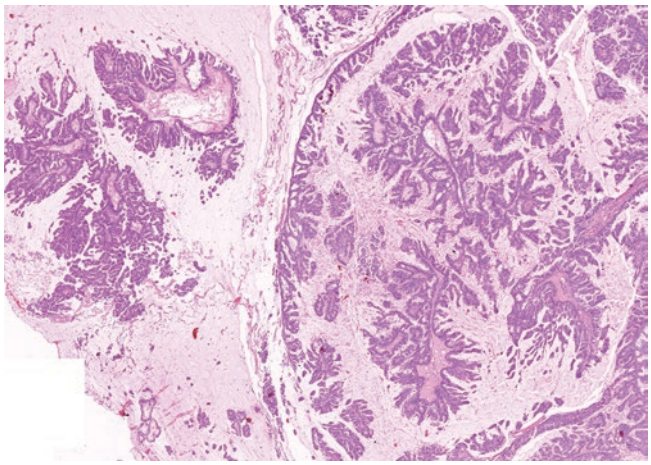

Fig. 7.138 Mucinous cystadenocarcinoma: cystic dilated spaces containing massive amounts of mucin, lined by stratified atypical cells; pools of mucin with floating papillae lined by atypical cells can be also detected at the left side of the picture; the myoepithelial cells are missing through the entire lesion

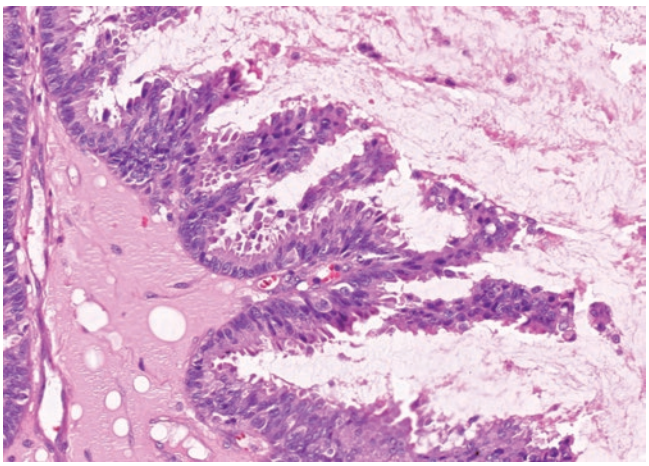

Fig. 7.139 Mucinous cystadenocarcinoma: the cysts are lined by several layers of atypical columnar cells producing mucin

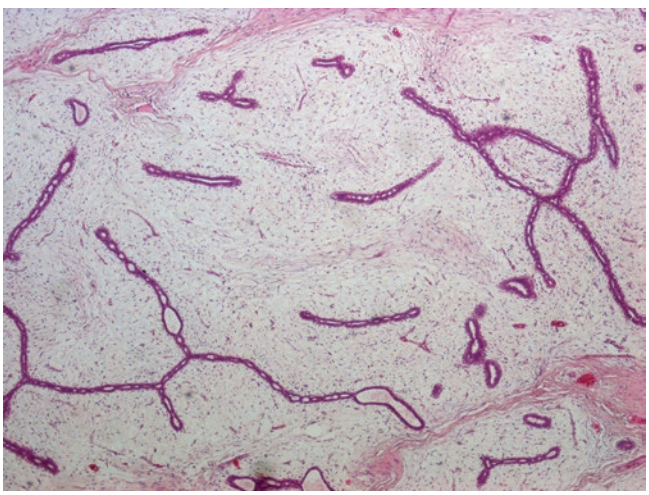

Fig. 7.140 Fibroadenoma with myxoid stroma

7.9 Benign Tumors of the Breast

7.9.1 Tubular Adenoma

Tubular adenoma is a rare benign breast tumor that occurs mainly in young patients (although it may occur at any age) in the form of a single, well-defined, firm, yellow-gray lesion. It has a mean diameter of 3 cm, mobile on superficial and deep planes. Rarely, the tumor may be bilateral or multiple. Radiologically, it resembles a fibroadenoma. Microscopically, it is composed of small tubular, rounded structures with little stoma between them, sometimes containing a minimal lymphocytic infiltrate (Figs. 7.141, 7.142, 7.143, 7.144, 7.145, and 7.146). These structures are lined by an internal epithelial layer represented by uniform cells (lacking atypia and presenting very few mitoses) and peripherally surrounded by a myoepithelial layer. The tubules have a small lumina that may be empty or may contain an eosinophilic proteinaceous material or mucin. The tubules are sometimes larger in size and may be branched. At the periphery, the tumor is surrounded by a fibrous capsule, but in some cases no capsule can be seen. Sometimes, a combined microscopic appearance of adenoma and fibroadenoma can be observed, suggesting that the two processes are related; some authors consequently consider that tubular adenoma should not be distinguished from fibroadenoma, although the latter is a biphasic tumor with a prominent mesenchymal component, while the former has little intervening stroma. There is no association with the development of tubular carcinoma with pregnancy (although some authors report the appearance of these tumors during pregnancy), or oral contraceptives. In a tubular adenoma, infarcted areas, apocrine metaplasia, atypical intraepithelial hyperplasia, atypical intralobular hyperplasia, secretory, and lactation changes may occur. Very rarely, cases of *in situ* or invasive carcinoma developed in a tubular adenoma have been described. Rarely, cases of stromal proliferation have been described in a tubular adenoma, the stromal component being formed of spindle cells with nuclear pleomorphism and mitotic activity. This is not surprising, given the link between a tubular adenoma, a fibroadenoma, and a phyllodes tumor. For the diagnosis of tubular adenoma, some authors request a size of more than 1 cm or presence of the capsule in lesions under 1 cm, since the tubular structures present within the tumor are identical to the acini in normal breast tissue or in adenosis [25].

Differential diagnosis is made with tubular adenosis (the lesion does not have the appearance of a nodule delimited by a capsule, being characterized by an infiltrating appearance) and tubular carcinoma (tubular structures infiltrate the surrounding tissue, are angulated, delimited by a layer of atypical epithelial cells without the presence of myoepithelial cells and basal membrane and are associated with a desmoplastic stroma).

Tubular adenoma does not increase the risk for developing a breast carcinoma, and surgical excision is curative.

7.9.2 Lactating Adenoma

Lactating adenoma is a benign tumor that develops in younger patients only during pregnancy or breastfeeding. It appears in the mammary gland and more rarely in ectopic mammary tissue of the axilla, thoracic wall, or vulva. Macroscopically, it is a well-defined nodular tumor with lobulated contour, a gray-yellow color, and soft consistency. Rarely, lactation adenoma may be multiple. Microscopically, the lesion is well-delimited by the adjacent tissue, but most often it does not have a proper capsule. It consists of multiple lobes surrounded by delicate fibrous bands. The lobes are formed by numerous round acini with varied secretory activity depending on the duration of pregnancy or breastfeeding. Thus, during pregnancy, the acini are only slightly distended, containing a small amount of secretion, while the epithelial cells have a small number of cytoplasmic vacuoles (Figs. 7.147, 7.148, 7.149, and 7.150). Tumors developed during lactation have distended acini containing abundant secretion, and the epithelial cells have many vacuoles intracytoplasmatically and hyperchromatic nuclei ("hobnail cells"), which have a similar appearance to the Arias-Stella changes. The secretory material contains lipids and is associated with degenerated cells or cellular debris. Myoepithelial cells are present but flattened. They can be identified by immunohistochemical examinations with myoepithelial markers. In a small number of cases, infarction areas may occur. Of interest, some tumors may contain a higher number of mitoses. The breast tissue adjacent to the tumor exhibits gestational or lactational hyperplasia. Differential diagnosis is made with gestational and lactational hyperplasia (both of which have a diffuse character) as well as fibroadenoma and tubular adenoma (which do not show lactation type secretion changes in the epithelium). Lactating adenoma is a benign tumor that does not increase the risk of developing a carcinoma and surgical excision is curative. However, lactating adenoma may occur simultaneously with a carcinoma during pregnancy or lactation.

7.9.3 Apocrine Adenoma

Apocrine adenoma is a benign, nodular, well-defined tumor, microscopically constituted by a proliferation of acini surrounded by a reduced stroma and exhibiting apocrine metaplasia of the epithelium. It appears in younger patients and is a rare lesion. Microscopically, the acini are lined by cylindrical metaplastic epithelial cells with abundant eosinophilic

granular cytoplasm and a round nucleus with prominent nucleolus. This epithelium is usually single-layered, but can also exhibit papillary or micropapillary hyperplasia without or with atypia. Differential diagnosis is made with tubular adenoma, lactating adenoma, and fibroadenoma, which may present focal apocrine metaplasia but does not involve the epithelial component entirely in most of the cases. Also, differential diagnosis is made with apocrine adenosis, which does not constitute a nodule but is rather a microscopic lesion. The lesion is benign and does not increase the risk for developing a carcinoma unless it is associated with atypia.

7.9.4 Pleomorphic Adenoma

Pleomorphic adenoma is a rare tumor, similar to that developing in the salivary glands. It may occur at any age (mean age 65 years), usually as a single tumor, rarely multifocal, with cases also reported in men. Some authors consider that pleomorphic adenoma is a variant of intraductal papilloma with extensive cartilaginous metaplasia or a variant of adenomyoepithelioma. Macroscopically, it has the appearance of a well-defined and lobulated nodule, with an average diameter of 2 cm, firm consistency, and alternating elastic or soft white-gray areas. It is usually located in the subareolar or juxta-areolar area and is sometimes associated with nipple discharge. Microscopically, the tumor is well-delimited, with expansive margins, and consists of epithelial and myoepithelial cell groups, arranged in a myxochondroid stroma, which frequently has osseous foci. Epithelial and myoepithelial cells form tubular structures, cords, or islands. Sometimes, myoepithelial cells have a spindle shape, but most of the time they are rounded. Immunohistochemical stains can highlight both epithelial and myoepithelial cell populations (Figs. 7.151, 7.152, 7.153, and 7.154). Differential diagnosis is made with intraductal papilloma (it can have a chondroid or bone component, but no myoepithelial cell islands, and it has a classic papillary architecture that is missing in the pleomorphic adenoma), carcinoma of NST type with small areas of chondroid or osseous differentiation (the carcinomatous component with atypia and invasive areas is obvious), metaplastic carcinoma (atypical cells and areas of invasive carcinoma), benign mesenchymal breast tumors or malignant such as osteosarcoma and chondrosarcoma (both represented by high atypical cells, lacking the epithelial and myoepithelial component) (Figs. 7.155, 7.156, and 7.157). Pleomorphic adenoma is a benign lesion, but which can cause local recurrences.

7.9.5 Ductal Adenoma

Ductal adenoma is a benign tumor that develops in the lumen of a cystically dilated duct (synonymous with *sclerosing papilloma*). The mean age of occurrence is 40 years. It is sometimes associated with pain and nipple discharge. Mammographically, it has well-defined margins and can present microcalcifications. Macroscopically, it appears as a single or multiple nodular formation of approximately 2 cm in diameter and located intracystically. Microscopically, glandular structures on the periphery are delimited by the two characteristic layers and may be distended, while in the center of the lesion there is a fibrotic and hyalinization area, which compresses the adjacent glandular structures, with a pseudoinfiltrating appearance. The wall of the duct where the lesion occurs may be thickened. At the periphery of the lesion, one can sometimes detect remnants of the cystic duct space in which the lesion developed. Areas of apocrine or squamous metaplasia may occur, and only through multiple sections can the presence of papillary axes within the lesion be determined (Figs. 7.158, 7.159, 7.160, and 7.161). When these can be highlighted, the term of sclerosing papilloma is preferred. Differential diagnosis is made with sclerosing adenosis (usually, it does not develop within a duct), central or peripheral papilloma (proliferation of fibro-vascular axes delimited by two atypical cell layers without the central areas of hyalinization), adenomyoepithelioma (when the myoepithelial cell proliferation is prominent), and infiltrating carcinoma of NST type (glandular structures delimited by atypical epithelial cells, without myoepithelial cells and which infiltrate the stroma) (Figs. 7.161, 7.162, 7.163, 7.164, and 7.165). Ductal adenoma does not increase the risk of developing a malignant lesion and does not lead to local recurrences after surgical excision.

7.9.6 Other Types of Benign Tumors

Salivary-gland and skin adnexal type of tumors, such as cylindroma and clear cell hidradenoma, may occur, very rarely, in the breast. They are morphologically identical to their counterparts that occur in the skin or salivary glands.

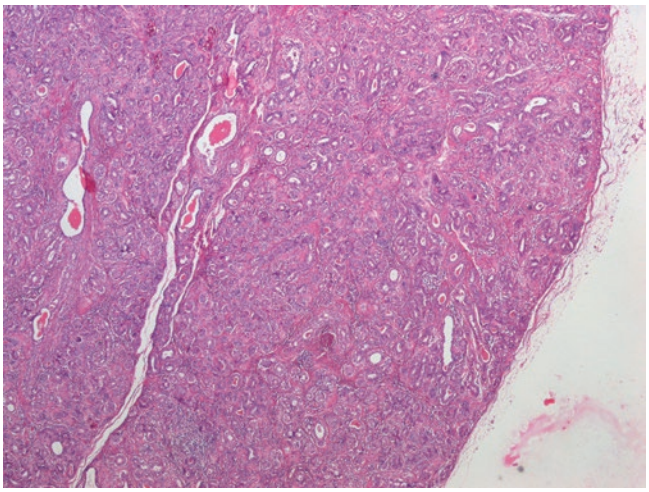

Fig. 7.141 Tubular adenoma: nodular tumor surrounded by a thin fibrous capsule at the periphery

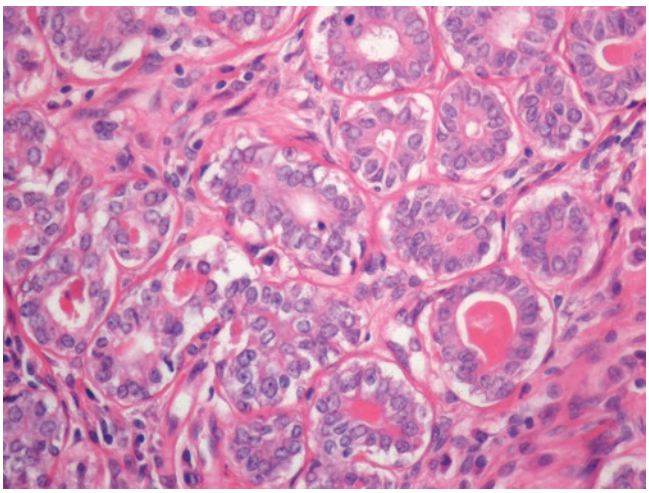

Fig. 7.142 Tubular adenoma: rounded structures, containing an eosinophilic proteinaceous material, lined by two cell layers, with little stoma between them

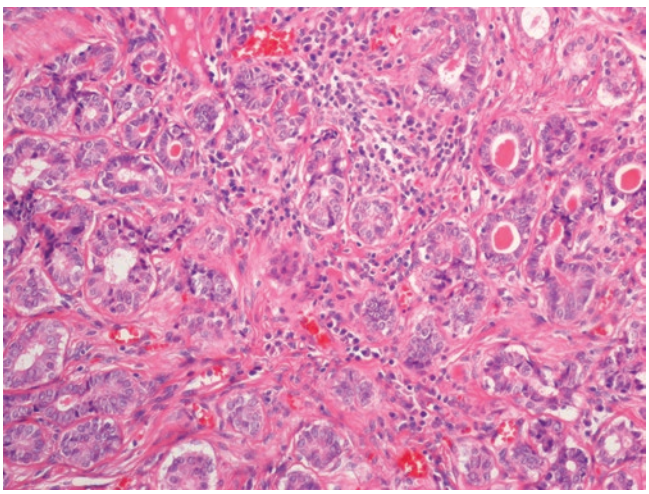

Fig. 7.143 Tubular adenoma: the stroma contains a minimal lymphocytic infiltrate

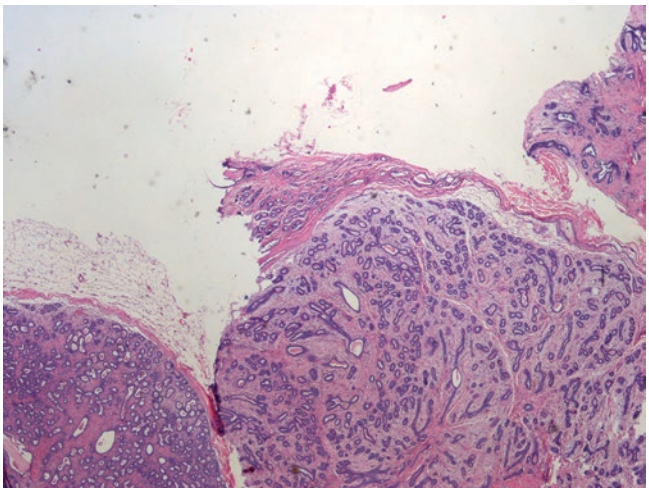

Fig. 7.144 Tubular adenoma: a combined microscopic appearance of adenoma and fibroadenoma can be observed in this lesion

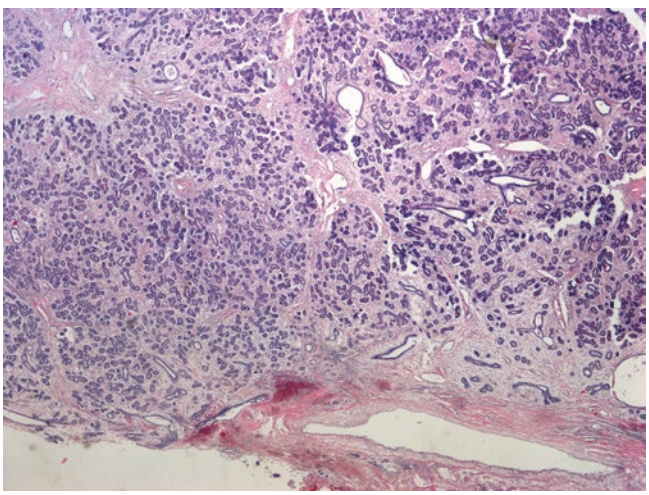

Fig. 7.145 Tubular adenoma: no capsule at the periphery of the tumor can be detected in this lesion

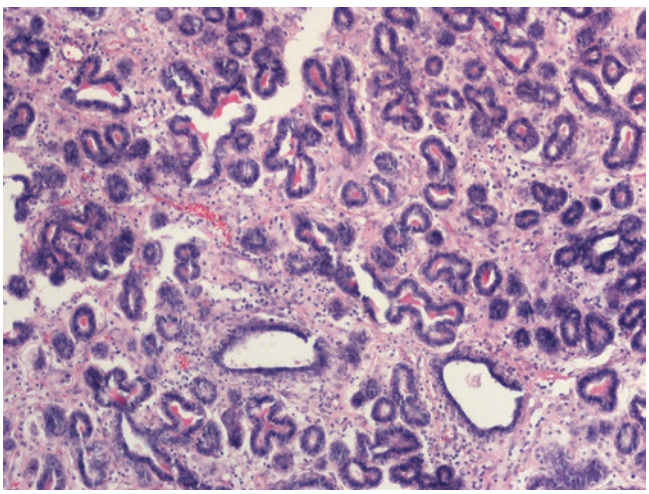

Fig. 7.146 Tubular adenoma: the round tubular structures are lined by an internal epithelial layer and peripherally surrounded by a myoepithelial layer

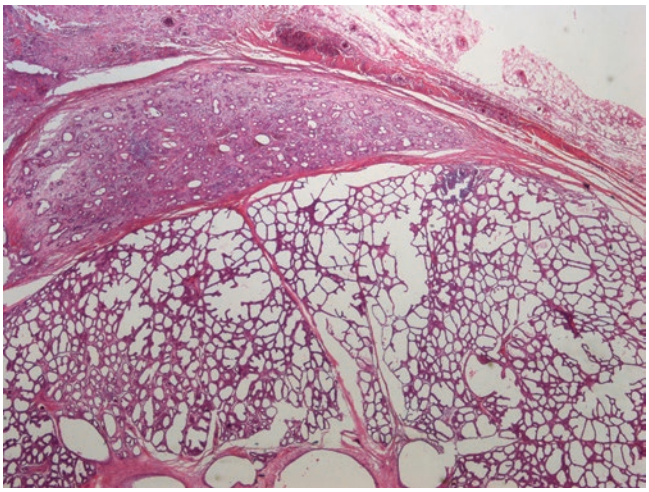

Fig. 7.147 Lactating adenoma: nodular tumor surrounded by a fibrous capsule at the periphery

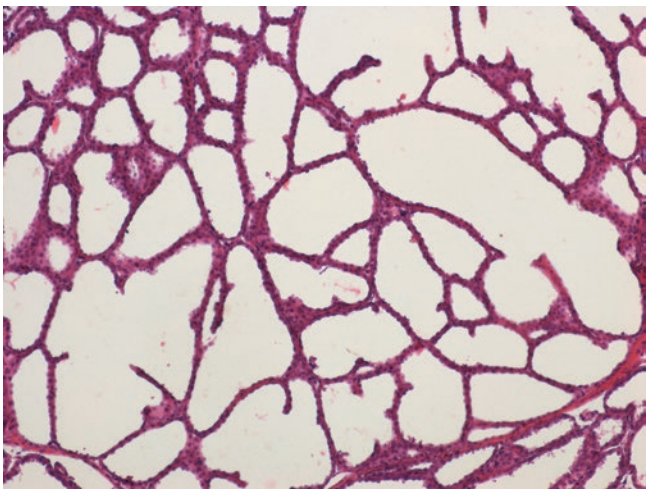

Fig. 7.148 Lactating adenoma: numerous round and distended acini lined by flattened epithelium

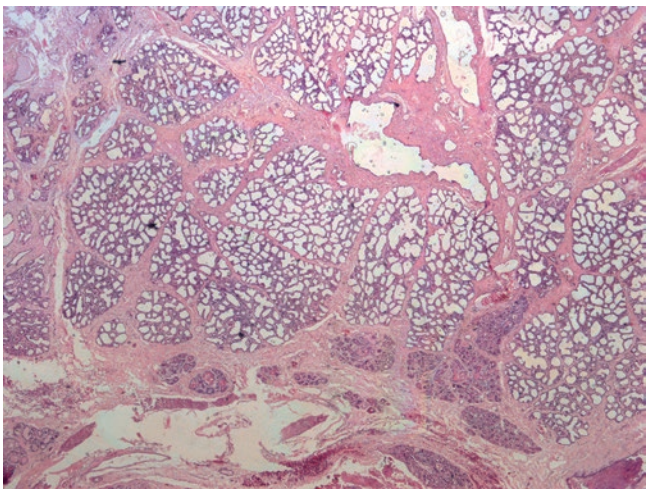

Fig. 7.149 Lactating adenoma: nodule without a capsule at the periphery, consisting of multiple lobes surrounded by delicate fibrous bands

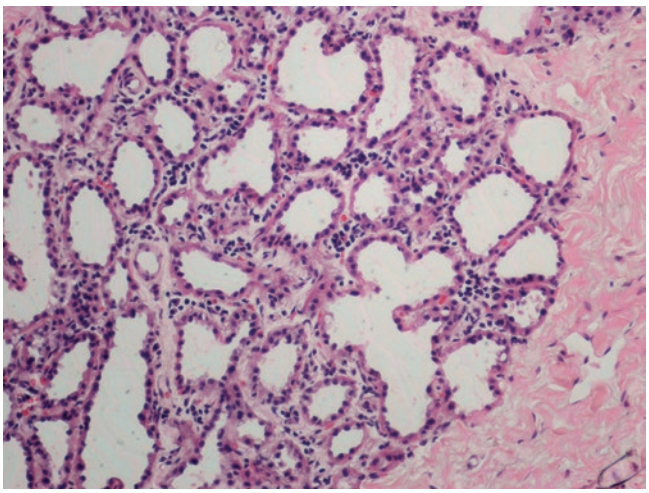

Fig. 7.150 Lactating adenoma developed during pregnancy: the acini are only slightly distended, lined by epithelial cuboidal cells with small number of cytoplasmic vacuoles

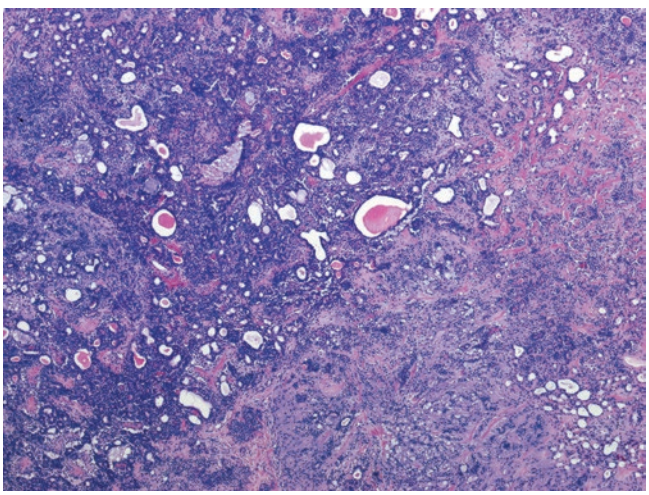

Fig. 7.151 Pleomorphic adenoma: mixed epithelial and myoepithelial proliferation

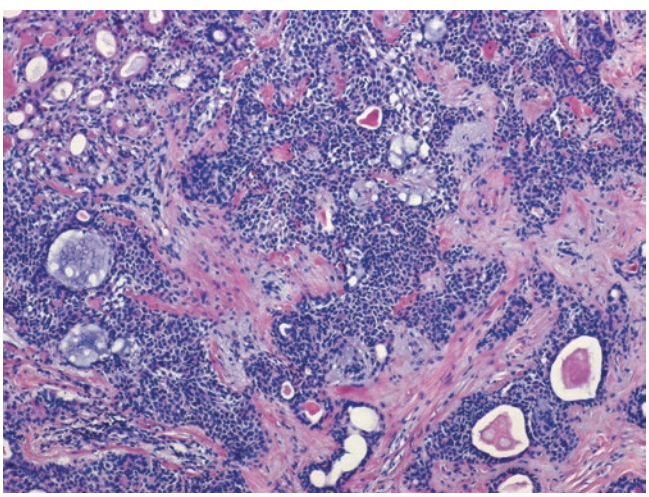

Fig. 7.152 Pleomorphic adenoma: epithelial and myoepithelial cells form tubular structures, cords, or islands

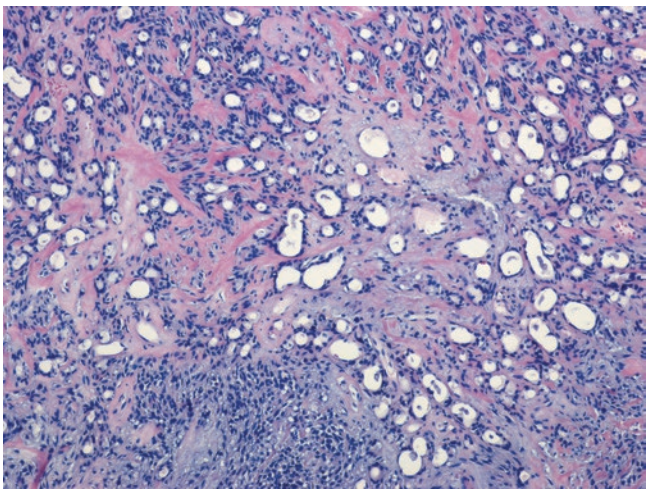

Fig. 7.153 Pleomorphic adenoma: tubular structures are predominant in this area of the tumor

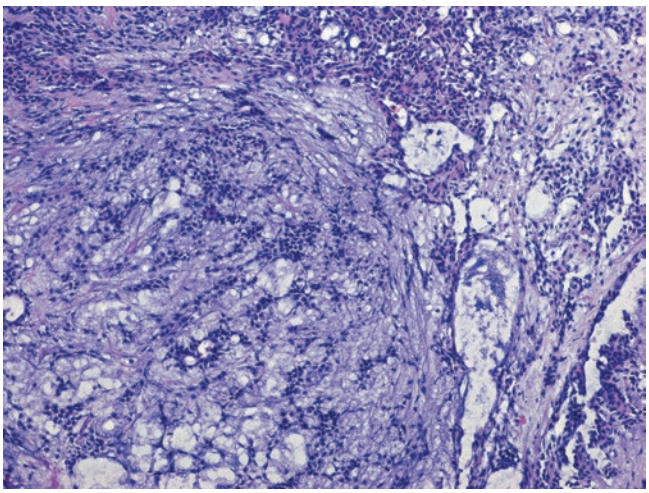

Fig. 7.154 Pleomorphic adenoma: the myxochondroid stroma is predominant in this area of the tumor; the myoepithelial cells have spindle shape

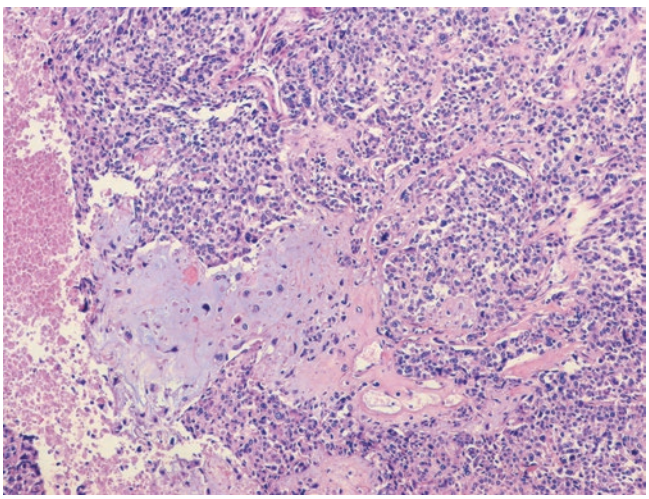

Fig. 7.155 Infiltrating carcinoma of no special (NST) type with small areas of chondroid differentiation (the carcinomatous component with atypia and invasive areas are obvious)

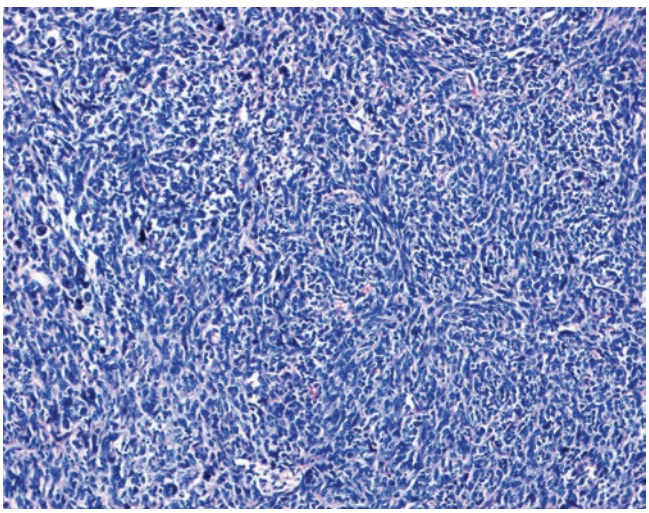

Fig. 7.156 Metaplastic carcinoma of spindle type: highly pleomorphic spindle atypical cells infiltrating the stroma

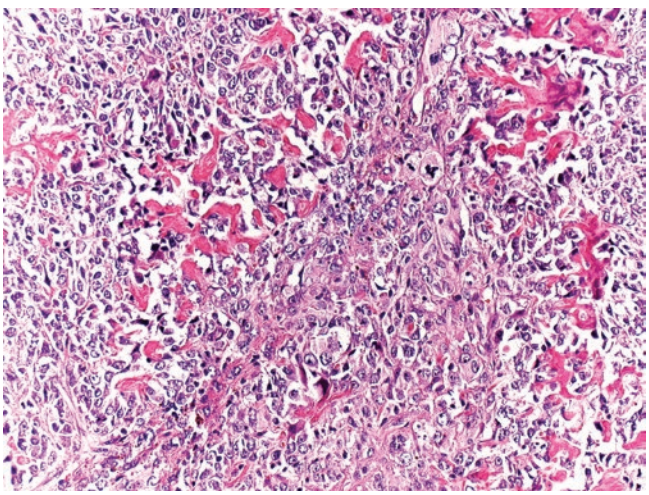

Fig. 7.157 Primary osteosarcoma of the breast represented by highly atypical cells with osteoid atypical areas, lacking the epithelial and myoepithelial component

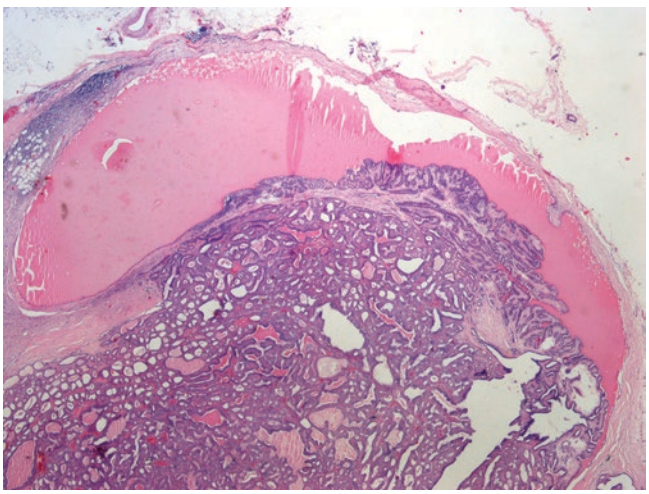

Fig. 7.158 Ductal adenoma: the tumor is located within a cystic duct space presenting a thickened wall

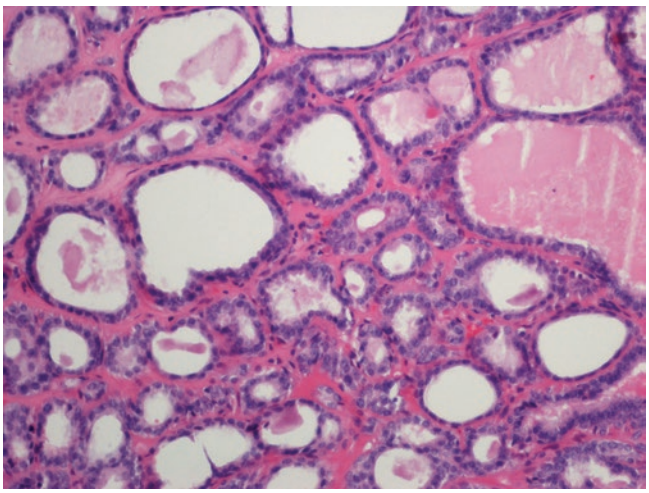

Fig. 7.159 Ductal adenoma: the tubular structures are delimited by the two characteristic layers

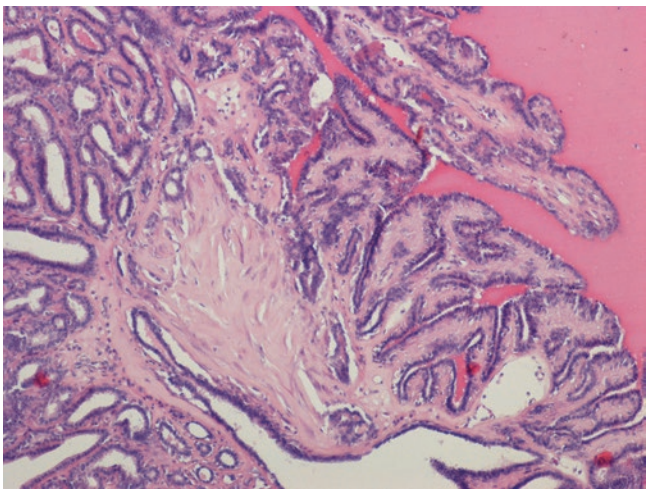

Fig. 7.160 Ductal adenoma: fibrotic and hyalinization area, which compresses the adjacent glandular structures, with a pseudoinfiltrating appearance

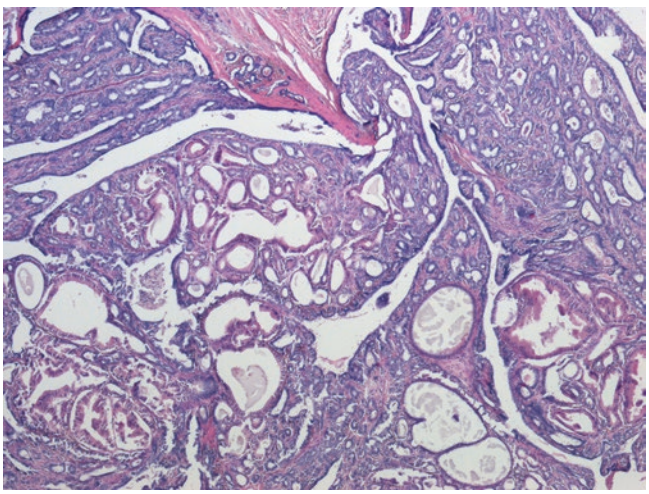

Fig. 7.161 Ductal adenoma: area of apocrine metaplasia

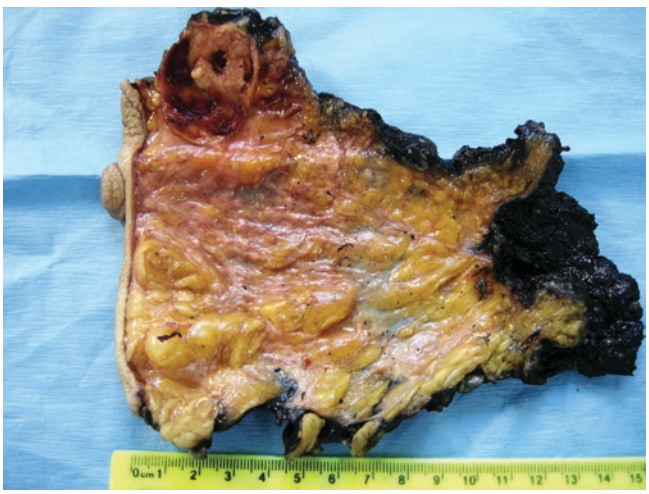

Fig. 7.162 Adenomyoepithelioma: macroscopic appearance of a nodular lesion developed within a cystic space; on the cut surface, the nodule has yellow color and soft consistency

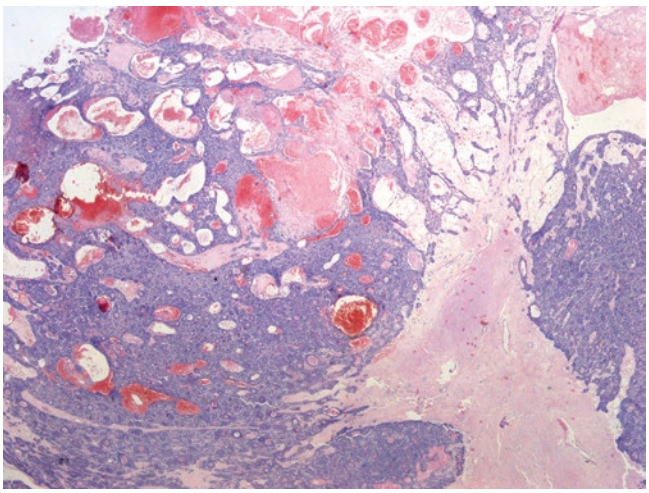

Fig. 7.163 Adenomyoepithelioma (same lesion as in Fig. 7.162): microscopic examination reveals proliferation of solid areas within a cystic space admixed with fibrosis and hemorrhage

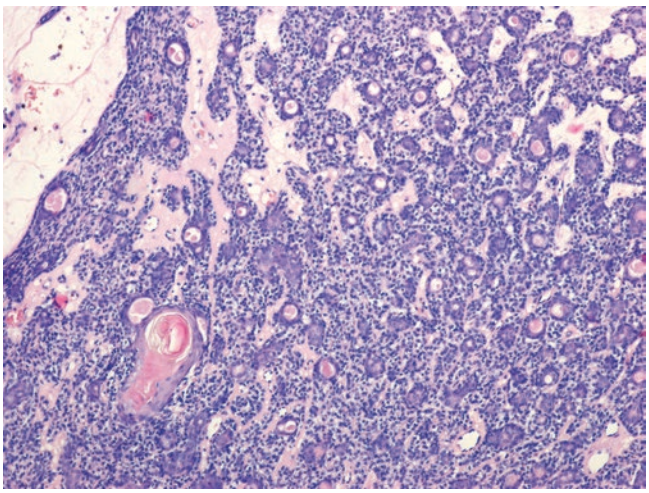

Fig. 7.164 Adenomyoepithelioma (same lesion as in Fig. 7.162): tubular structures lined by epithelial and myoepithelial cells; the myoepithelial component is more prominent, forming nests of clear cells surrounding the tubules

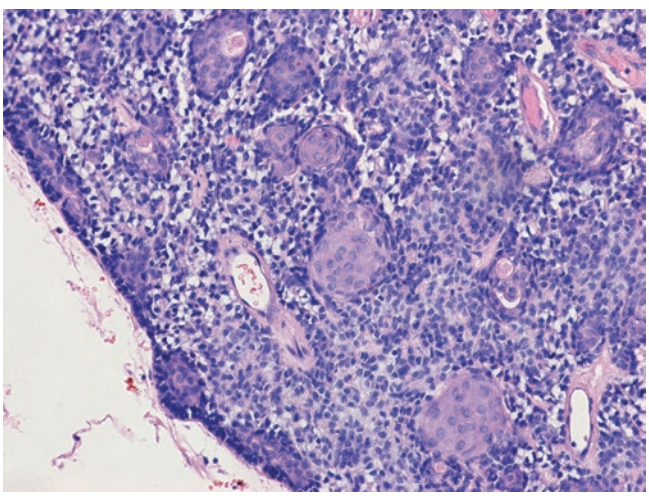

Fig. 7.165 Adenomyoepithelioma (same lesion as in Fig. 7.162): areas of benign squamous metaplasia

References

1. Moinfar F. Essentials of diagnostic breast pathology. New York, NY: Springer; 2007. p. 16.
2. Hutter RVP. Consensus meeting: is "fibrocystic disease" of the breast precancerous? Arch Pathol Lab Med. 1986;110:171–3.
3. Stolnicu S, Mocan S, Radulescu D, Podeanu MD. Diagnosticul morfologic al leziunilor mamare. Lanham, MD: University Press; 2005.
4. Leis HP Jr. Fibrocystic disease of the breast. J Med Assoc Alabama. 1962;32:97–104.
5. Tavassoli FA, Purcell CA, Bratthauer GL, Man Y-G. Androgen receptor expression along with loss of bcl-2, ER and PR expression in benign and malignant apocrine lesions of the breast: implications for therapy. Breast J. 1996;4:261–9.
6. Tavassoli FA, Eusebi V. Tumors of the mammary gland. AFIP Atlas of tumor pathology, series 4. Washington, DC: American Registry of Pathology; 2009.
7. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative disease. N Engl J Med. 1985;312:146–51.
8. Semb C. Pathologico-anatomical and clinical investigations of fibroadenomatosis cystica mammae and its relation to the other pathological conditions in mamma, especially cancer. Acta Chir Scand. 1928;64:1–484.
9. Anderson TJ, Battersby S. Radial scars and complex sclerosing lesions. Histopathology. 1994;24:296–7.
10. Hilson JB, Schnitt SJ, Collins LC. Phenotypic alterations in myoepithelial cells associated with benign sclerosing lesions of the breast. Am J Surg Pathol. 2010;34(6):896–900.
11. Lakhani SR, Schnitt SJ, Tan PH, van de Vijver MJ. WHO classification of tumors of the breast. IARC: Lyon; 2012.
12. Jacobs TW, Byrne C, Colditz G, Connolly JL, Schnitt SJ. Radial scar in benign breast-biopsy specimens and the risk of breast cancer. N Engl J Med. 1999;340(6):430–6.
13. Sanders ME, Page DL, Simpson JF, Schuyler PA, Dale Plummer W, Dupont WD. Interdependence of radial scar and proliferative disease with respect to invasive breast carcinoma risk in patients with benign breast biopsies. Cancer. 2006;106(7):1453–61.
14. Resetkova E, Edelweiss M, Albarracin CT, Yang WT. Management of radial sclerosing lesions of the breast diagnosed using percutaneous vacuum-assisted core needle biopsy: recommendations for excision based on seven years of experience at a single institution. Breast Cancer Res Treat. 2011;127(2):335–43.
15. Bianchi S, Giannotti E, Vanzi E, Marziali M, Abdulcadir D, Boeri C, et al. Radial scar without associated atypical epithelial proliferation on image-guided 14-gauge needle core biopsy: analysis of 49 cases from a single—center and review of the literature. Breast. 2012;21(2):159–64.
16. Ferreira AI, Borges S, Sousa A, Ribeiro C, Mesquita A, Martins PC, et al. Radial scar of the breast: is it possible to avoid surgery? Eur J Surg Oncol. 2017;43(7):1265–72.
17. Carter DJ, Rosen PP. Atypical apocrine metaplasia in sclerosing lesions of the breast. A study of 51 patients. Mod Pathol. 1991;4:1–5.
18. Rosen PP. Rosen's breast pathology. 3rd ed. Philadelphia, PA: Lippincott Williams and Wilkins; 2009.
19. Tavassoli FA, Norris HJ. Microglandular adenosis of the breast. A clinicopathologic study of 11 cases with ultrastructural observations. Am J Surg Pathol. 1983;7(8):731–7.
20. Clement PB, Azzopardi JG. Microglamdular adenosis of the breast—a lesion simulating tubular racinoma. Histopathology. 1983;7(2):169–80.
21. Rosen PP. Microglandular adenosis. A benign lesion simulating invasive mammary carcinoma. Am J Surg Pathol. 1983;7(2):137–44.

22. Geyer FC, Lacroix-Triki M, Colombo PE, Patani N, Gauthier A, Natrajan R, et al. Molecular evidence in support of the neoplastic and precursor nature of microglandular adenosis. Histopathology. 2012;60:E115–30.
23. Khalifeh IM, Albarracin C, Diaz LK, Symmans FW, Edgerton ME, Hwang RF, et al. Clinical, histopathologic and immunohistochemical features of mucroglandular adenosis and transition into in situ and invasive carcinoma. Am J Surg Pathol. 2008;32(2):544–52.
24. Shin SJ, Rosen PP. Pregnancy-like (pseudolactational) hyperplasia: a primary diagnosis in mammographically detected lesions of the breast and its relationship to cystic hypersecretory hyperplasia. Am J Surg Pathol. 2000;24:1670–4.
25. Tavassoli FA. Pathology of the breast. 2nd ed. Appleton and Lange: Stamford, CT; 1999.