Benign Breast Pathology

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Reactive, Inflammatory, and Infectious Lesions

Inflammation of the breast can have different etiologies such as infectious, systemic autoimmune, or unknown, also classified as idiopathic (Tables 34.1 and 34.2) [1]. One important aspect to keep in mind when dealing with an inflamed breast is to be aware of inflammatory breast carcinoma. In the latter, the entire breast may be erythematous and warm to the touch, with areas of skin thickening and the classic "peau d'orange" often associated with inflammatory breast cancer.

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Table 34.1 Pathological classification of benign breast diseases

Nonproliferative lesions
Cysts
Mild hyperplasia of the usual type
Epithelial-related calcifications
Fibroadenoma
Papillary apocrine change
Proliferative lesions without atypia
Sclerosing adenosis
Radial and complex sclerosing lesions
Moderate and florid hyperplasia of the usual type
Intraductal papillomas
Atypical proliferative lesions
Atypical ductal hyperplasia
Atypical lobular hyperplasia

Based on Love et al. [1]

Table 34.2 Clinical classification of benign breast diseases

Physiologic swelling and tenderness
Nodularity
Breast pain
Palpable lumps
Nipple discharge
Breast infections and inflammation

Based on Love et al. [1]

Inflammation of the breast can present in a similar fashion [2]. Failure to respond to antibiotic or anti-inflammatory treatment should raise the suspicion for an underlying malignancy, and biopsies should be performed of the skin and subcutaneous tissue

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(punch biopsy) or possibly a core of any suspicious underlying mass lesion. Similarly, pure squamous cell carcinoma (SCC) of the breast, although a rare entity, can also present with signs and symptoms of mastitis, as it can undergo central cystic changes (in approximately 50 % of cases) that is filled with keratin and necrotic debris eliciting an inflammatory response [3]. In such cases the clinical and radiologic findings might not discriminate benign from malignant lesions; therefore failure to respond to antibiotic therapy and identification of an underlying mass should prompt a core biopsy to clarify the diagnosis.

Most commonly encountered lesions in this segment are (a) lactation-related inflammation (acute mastitis), (b) non-puerperal periareolar inflammatory entities (periductal mastitis, Zuska's disease, and mammary duct ectasia), (c) fat necrosis, (d) sclerosing lymphocytic lobulitis, and (e) granulomatous mastitis. Those entities will be discussed below.

Lactation-Related Inflammation (Acute Mastitis)

Lactation-related inflammation is frequently seen during the first few months of breastfeeding. This is in contrast with inflammatory breast carcinoma, which is usually not associated with pregnancy [2]. The abscess appears as a red mass filled with pus and sometimes can mimic cancer. Biopsy procedures are rarely performed for this disorder, since it is usually managed by nonoperative means [4]. Synonyms are puerperal or acute mastitis, most usually presenting with the classical signs and symptoms of inflammation, such as localized pain, erythema, and associated fevers (Fig. 34.1). This is an inflammation of the breast stroma usually composed of neutrophils and plasma cells, which can lead to abscess formation and septicemia if left untreated [5]. *Staphylococcus aureus* is the most commonly identified infectious agent followed by *Staphylococcus epidermidis* and streptococci. Special stains can sometimes highlight the offending microorganism. It is thought that sleep deprivation, stress, and improper nursing techniques result in milk stasis and cracks of the nipple that lead to inflammation and infection [6]. Early diagnosis and treatment with antibiotics can lower the incidence of abscess formation. One should show due diligence in avoiding the use of antibiotics such as tetracycline that pass into breast milk and have harmful effects on the infant. Once an abscess is formed, aspiration or incision and drainage should be performed. Despite antibiotic therapy and drainage, if there

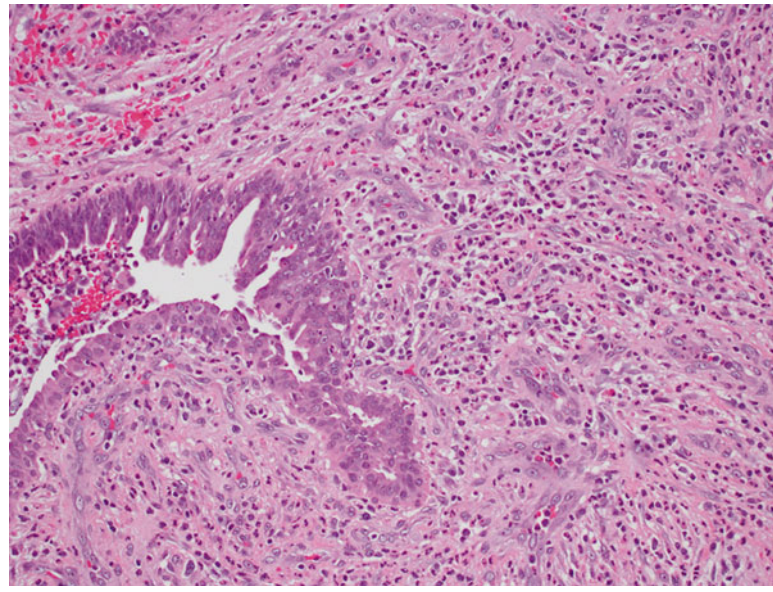

Fig. 34.1 Acute mastitis. Hematoxylin and eosin stain at 200× magnification

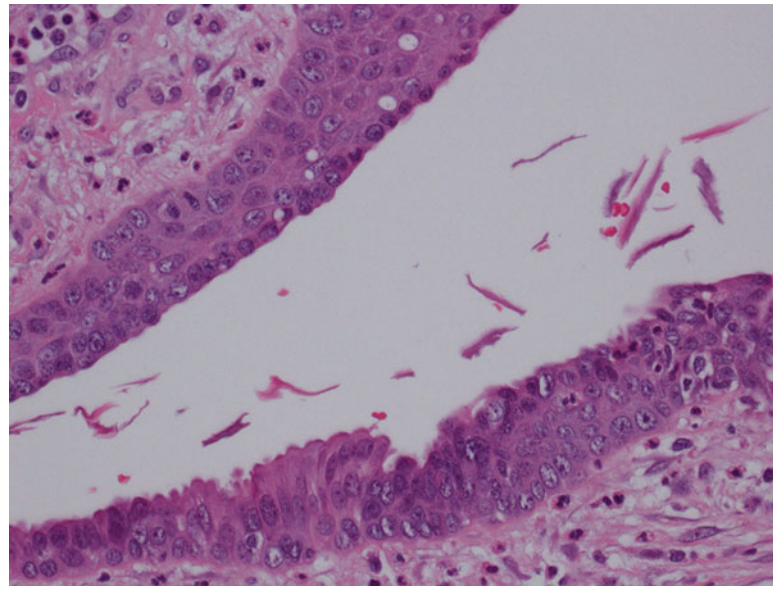

Fig. 34.2 Recurring subareolar abscess: squamous metaplasia. Hematoxylin and eosin stain at 400× magnification

is no response or if solid areas are identified, a tissue biopsy should be obtained to rule out the possibility of carcinoma.

Non-puerperal Periareolar Inflammatory Entities (Periductal Mastitis, Zuska's Disease, and Mammary Duct Ectasia)

The main difference between periductal mastitis and Zuska's disease or recurring subareolar abscess is that the latter occurs due to squamous metaplasia of the lactiferous ducts of the nipple, with secondary keratin plug formation that obstructs the proximal duct causing dilation and infection [5] (Figs. 34.2 and 34.3). This leads to abscess and fistula formation that drains at the margin of the areola [7]. Therefore Zuska's disease is also called SMOLDering (squamous metaplasia of lactiferous ducts) and can present with an inflamed and indurated nipple, nipple retraction, and painful nodules thus potentially mimicking cancer. Abscess drainage and excision of the affected ducts and fistula is the preferred treatment. In one series of 67 cases, half of the patients were successfully managed medically and the other half required surgical intervention [8]. In the same study, it was shown that radial elliptical incision with primary closure gave excellent long-term results. However, another study that looked at 24 women with a subareolar abscess suggests that the abscess together with the plugged duct has to be excised in order to prevent a recurrence [9]. The microbiologic studies performed on the material obtained from the lesions usually identify staphylococcus as the main infectious agent. Recurrent abscesses usually yield a mixed flora.

In a series of 60 patients suffering from recurrent subareolar breast abscess, heavy smoking was found at an unusually high frequency compared to a control group. The authors of the study postulated that cigarette smoking could have either a direct toxic effect on the retroareolar lactiferous ducts or an indirect effect via hormonal stimulation of the breast secretion [10]. Periductal mastitis on the other hand does not show squamous metaplasia, and the ducts are not dilated. It can occur centrally (periareolar) or peripherally. Periductal mastitis affects younger patients and should not be confused with mammary duct ectasia, which is a condition of the perimenopausal and postmenopausal women. Mammary duct ectasia characteristically shows dilation of the major ducts of the nipple with periductal fibrosis and inflammation (Fig. 34.4). The ducts may contain eosinophilic, granular, or inspissated material and sometimes

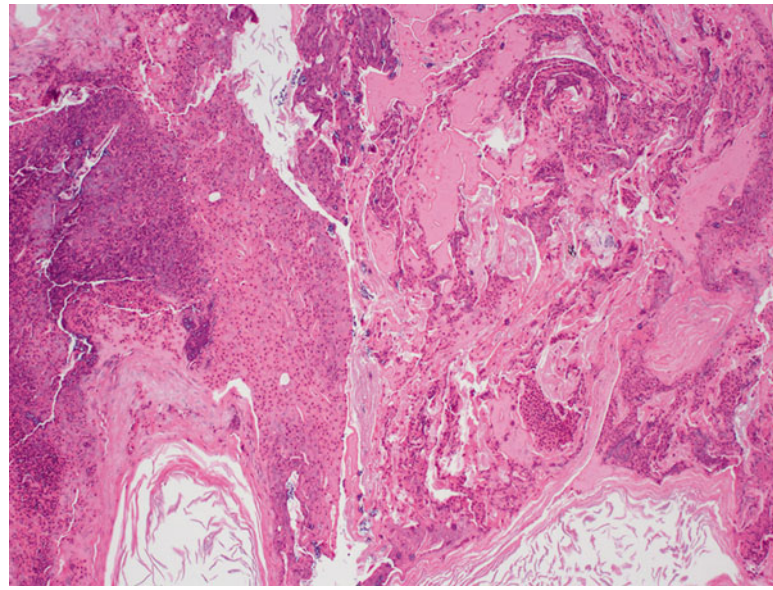

Fig. 34.3 Recurring subareolar abscess: keratin plug with secondary infection. Hematoxylin and eosin stain at 100× magnification

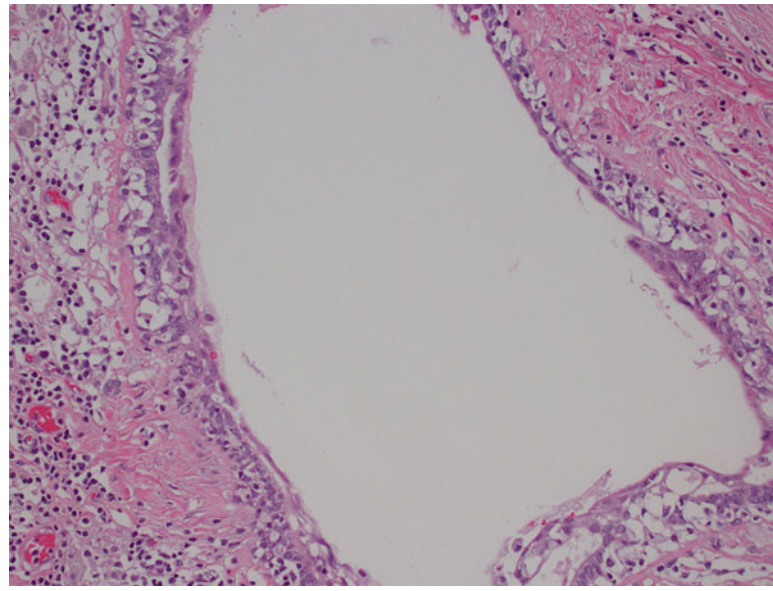

Fig. 34.4 Duct ectasia. Hematoxylin and eosin stain at 200× magnification

may become calcified. On gross examination, the inspissated material may mimic comedo necrosis that is associated with ductal carcinoma in situ. Some suggest that it is also related to smoking [11]. The disease usually affects the middle aged to older women and is usually asymptomatic. Occasionally, patients may present with nipple inversion, retraction, discharge, or a subareolar mass that may mimic a breast cancer [4]. Therefore, some patients with duct ectasia are biopsied to exclude malignancy; otherwise, most can be safely managed with mainly conservative measures [5]. Recurrence is uncommon.

Fat Necrosis

This is another entity that can be clinically confused with cancer, as it may present as an ill-defined, spiculated mass with associated skin retraction. Small areas of fat necrosis are probably not uncommon, but clinically significant

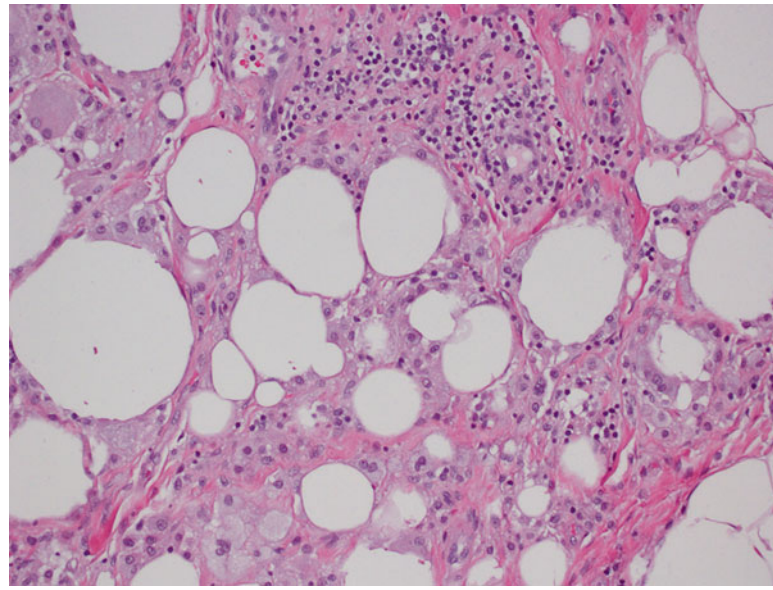

Fig. 34.5 Fat necrosis. Hematoxylin and eosin stain at 200× magnification

lesions are likely due to some sort of trauma, surgical procedure, biopsy, and radiation present in up to 50 % of patients; however the exact etiology is not always identified [12]. The lesion can also be associated with an adjacent malignancy [5]. Grossly, it may appear as a firm, ill-defined mass. Microscopically, the diagnosis is usually straightforward and is characterized by cystic spaces surrounded by lipid-laden histiocytes and foreign body-type giant cells (Fig. 34.5). Hemorrhage, a variable inflammatory infiltrate, and fibrosis can also be identified. When the lesion is fully evolved, it may have the appearance of a cystic cavity with calcified walls sometimes referred to as membranous fat necrosis [13].

Sclerosing Lymphocytic Lobulitis

This is a disorder usually occurring in patients with type 1, insulin-dependent diabetes mellitus. It can also be seen in nondiabetic patients that are affected by other autoimmune disorders such as Hashimoto's thyroiditis [14]. It is characterized by painless, immobile, discrete masses that are clinically suspicious for carcinoma. The lesions are usually bilateral but might also occur as a single mass. Radiologic findings can also be suspicious and usually require a biopsy to rule out a malignant proliferation. The majority of diabetic mastopathy lesions occur in the upper outer quadrant and are irregularly demarcated from the surrounding breast tissue.

Histologically, one usually finds a keloid-like fibrotic stroma; periductal, lobular, or perivascular lymphocytic infiltration by B cells; lobular atrophy; and fibroblasts embedded in fibrous stroma. Some point out that those findings are not specific as they may also be identified in patients with diabetes mellitus type 2 and nondiabetic patients [15]. It is postulated that this represents an immune reaction to hyperglycemia on connective tissue. Others suggest vascular changes as possible factors in the pathogenesis of diabetic mastopathy [16]. Microscopically sclerosing lymphocytic lobulitis shows small lymphocytes extending into epithelial cells, thus potentially mimicking a primary low-grade B cell lymphoma of the breast. Follow-up of patients with diabetic mastopathy is generally recommended.

Granulomatous Mastitis

As in other parts of the body, granulomatous inflammation (Fig. 34.6) of the breast can be infectious, idiopathic, due to foreign material or secondary to a systemic autoimmune disease such as sarcoidosis. The latter rarely involves

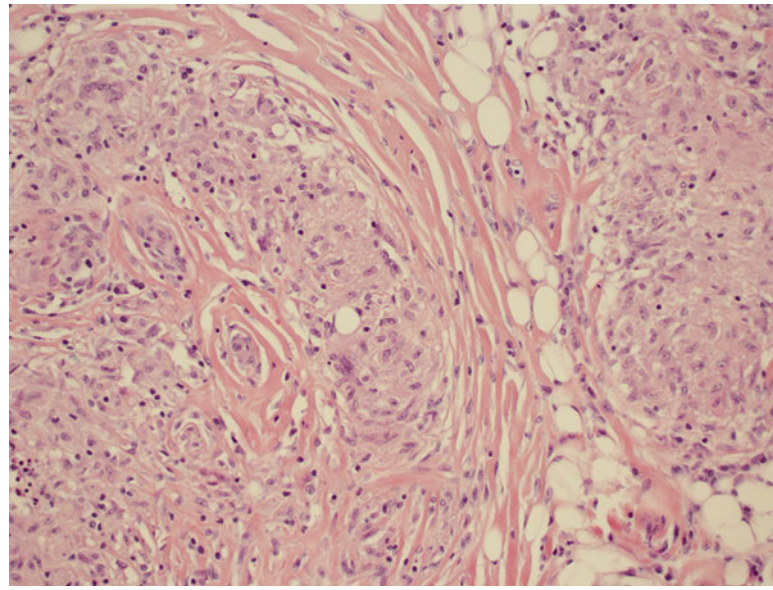

Fig. 34.6 Non-necrotizing granulomatous mastitis. Hematoxylin and eosin stain at 200× magnification

the breast, but it can simulate a neoplasm [17]. It is a diagnosis of exclusion and characterized by non-necrotizing granulomatous inflammation. Idiopathic granulomatous mastitis is an entity without an identifiable cause, thus also a diagnosis of exclusion. It may present as a mass simulating carcinoma, and it usually occurs in young women, often related to a recent pregnancy [18]. The management of this entity requires surgical excision, but sometimes it responds to corticosteroid therapy [4]. Management can be problematic, and despite treatment, recurrence and complications such as abscess and fistula formation are frequent [19]. The treatment sometimes spans over several years. Microscopically there are three neoplastic conditions in the differential diagnosis: histiocytic subtype of lobular carcinoma, carcinoma with osteoclastic giant cells, and granular cell tumor. In cases with abundant histiocytic cells, the inflammation can be confused with a rare variant of invasive lobular carcinoma called histiocytic type, where the neoplastic cells have ample cytoplasm and are disguised as histiocytes. In difficult cases immunohistochemical stains for keratin would confirm the diagnosis of carcinoma. The second tumor is invasive carcinoma with osteoclastic giant cells. In this condition malignant cells are accompanied by numerous reactive giant cells that are CD68 positive pointing to their histiocytic nature. Careful analysis of the surrounding carcinomatous cells should help in arriving at correct diagnosis. Granular cell tumor is another entity that might mimic an inflammatory condition composed of histiocytes. It is a rare neoplasm that usually occurs in other parts of the body, such as the head and neck, oral cavity, and digestive system [20]. It can also involve the breast in approximately 5 % of cases. This is a benign tumor that clinically may show fixation to the pectoral fascia, skin retraction, and ulceration, thus mimicking an invasive carcinoma. It may also occur in the male breast [21]. They are usually small lesions, measuring less than 3 cm, composed of polygonal cells with granular cytoplasm mimicking histiocytes (Fig. 34.7). They express the S100 protein and this is very useful in the confirmation of the diagnosis (Fig. 34.8). The tumor is believed to arise from peripheral nerve sheet cells, i.e., Schwann cells. Rarely, the tumors can be malignant, with the most useful characteristics of malignancy being large size (>5 cm), pleomorphic cells, prominent nucleoli, increased mitotic activity, necrosis, and local recurrence. Both benign and malignant tumors are treated with wide surgical excision. Incomplete excision may result in recurrence. Adjuvant treatment is only reserved for malignant tumors.

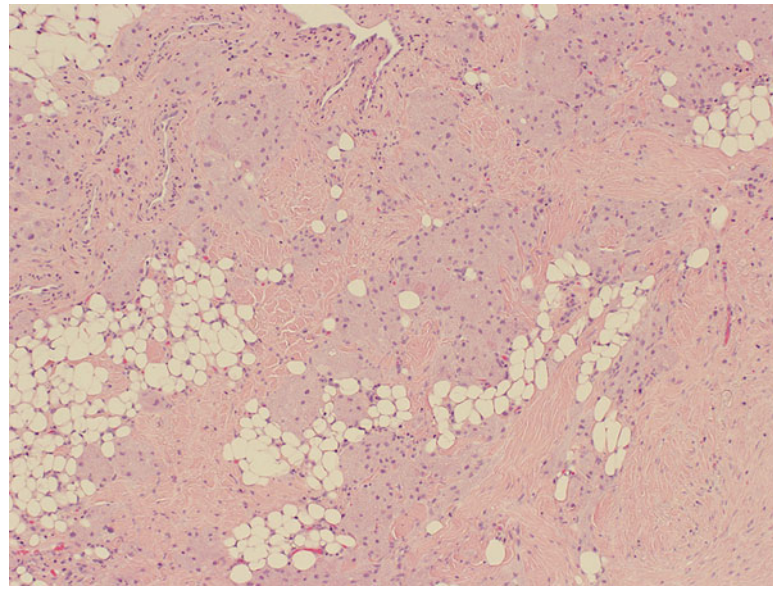

Fig. 34.7 Granular cell tumor. Hematoxylin and eosin stain at 40× magnification

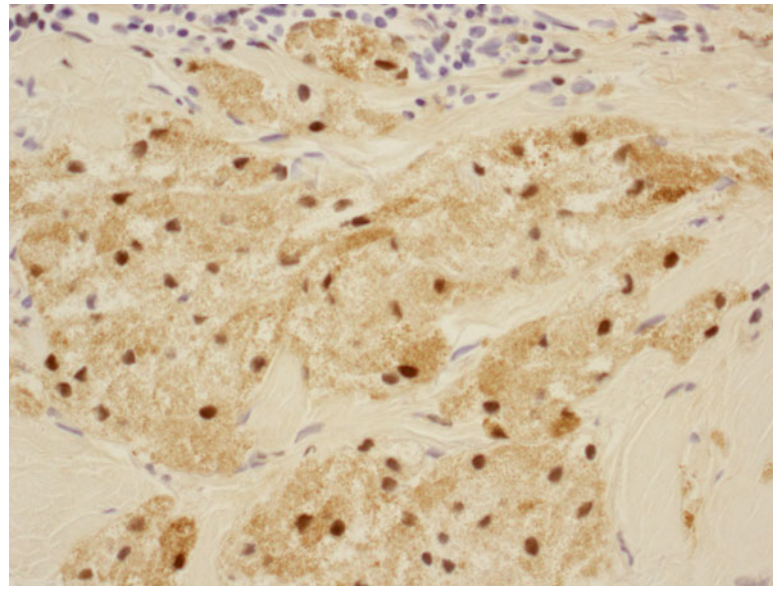

Fig. 34.8 Granular cell tumor: S100 stain at 400× magnification

Fibrocystic Changes (FCC) and Columnar Cell Changes (CCC)

Previously referred to as fibrocystic "disease" of the breast, the term "disease" has been dropped in favor of "changes." This is due to its very high prevalence and because it caused confusion between normal, physiologic changes and pathological ones [22]. Histologically, fibrocystic change can be identified in up to 90 % of all breast tissue examined in women. The most common presenting symptoms are breast pain and palpable nodules or lumps in the breast. It has been noted in a retrospective cohort study that only 6 % of patients between 40 and 70 years of age presenting with breast symptoms had cancer [23]. Cysts are the main component of fibrocystic changes and are characterized by fluid-filled structures that are mostly small and non-palpable, but approximately 20–25 %

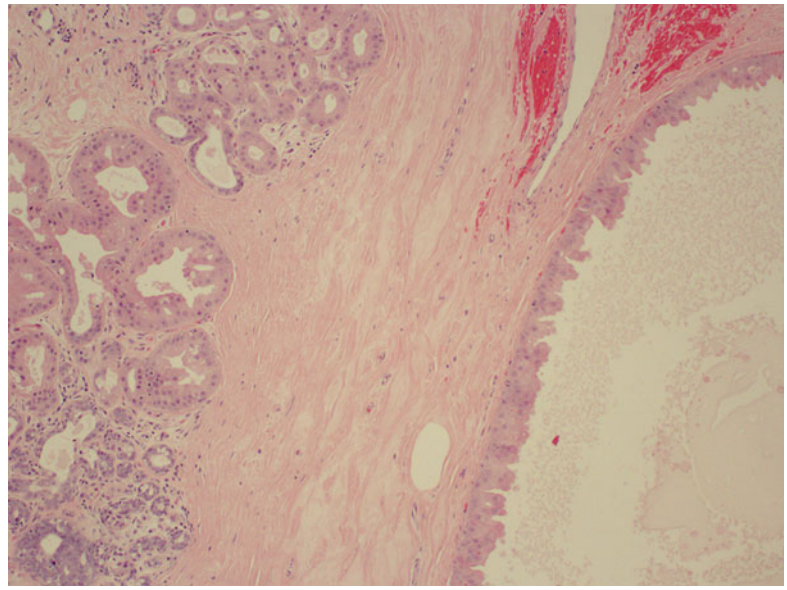

Fig. 34.9 Fibrocystic changes. Hematoxylin and eosin stain at 100× magnification

of them are large enough to present as masses [5, 24]. Mammography and physical examination are not reliable and cannot truly distinguish cysts from solid masses [25]. The utility of ultrasound can help to further define an abnormality identified on mammogram. Simple cysts are usually devoid of a lining or have a flat epithelium that sometimes may show apocrine metaplasia. Complex cysts have internal thin septations, thickened or irregular wall, and absent posterior acoustic enhancement on ultrasound. The malignancy rate in patients with complex cysts is very low, 0.3 % in one study, lower than that of lesions classified as probably benign [26]. If there is concern that the cyst is other than a simple cyst, possibly with internal wall thickening or complex septations, consideration should be given to further evaluation and possible biopsy of these areas in order to exclude a malignancy.

Besides cysts, FCC also comprises other lesions such as apocrine metaplasia (Fig. 34.9), epithelial hyperplasia both atypical and non-atypical, adenosis, radial scar, and papilloma. The most useful way to classify FCC is to divide it into three groups according to their risk of developing breast cancer: nonproliferative lesions (cysts, apocrine metaplasia, mild epithelial hyperplasia, non-sclerosing adenosis), proliferative lesions without atypia (moderate to florid epithelial hyperplasia, sclerosing adenosis, radial scar, papilloma, and papillomatosis), and proliferative lesions with atypia (atypical ductal hyperplasia and atypical lobular hyperplasia) [5] (Table 34.3). Relative to general population, women with nonproliferative lesions have no increased risk for developing breast cancer. On the other hand patients with non-atypical proliferative and atypical proliferative lesions have relative risks ranging from 1.3 to 1.9 and 3.9 to 13, respectively [27–30].

Table 34.3 Classification of fibrocystic changes

Nonproliferative lesions	Proliferative lesions without atypia	Proliferative lesions with atypia
Cysts	Moderate to florid epithelial hyperplasia	Atypical ductal hyperplasia
Apocrine metaplasia	Sclerosing adenosis	Atypical lobular hyperplasia
Mild epithelial hyperplasia	Radial scar	
Non-sclerosing adenosis	Papilloma and papillomatosis	

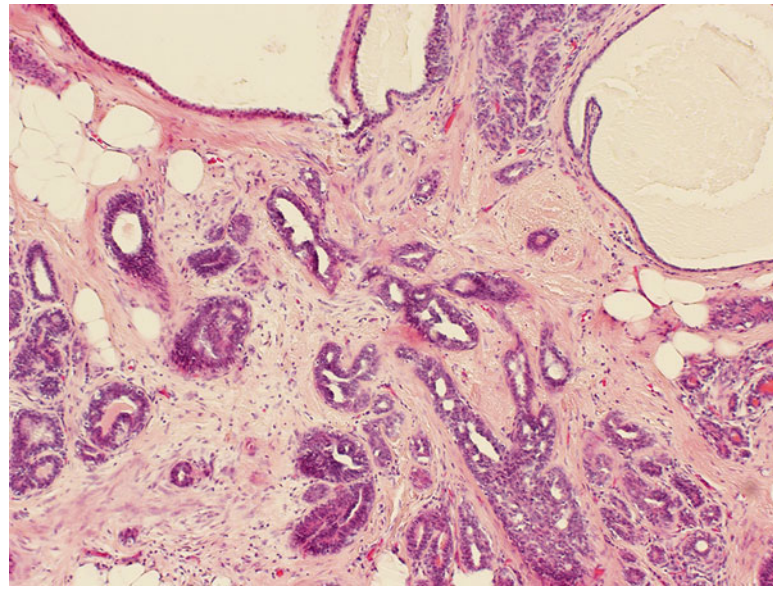

Fig. 34.10 Radial scar. Hematoxylin and eosin stain at 40× magnification

Adenosis and Microglandular Adenosis

Adenosis is defined as a glandular proliferation of the lobular units, with two subtypes that merit mentioning: sclerosing adenosis and microglandular adenosis. Sclerosing adenosis is a disordered proliferation of acini, myoepithelial cells and stromal elements that can be confused for invasive carcinoma both microscopically and grossly [5]. It can present as a mass or a radiologic abnormality such as an asymmetric opacity, cluster of microcalcifications, mass-like lesion, and architectural distortion [31]. In difficult lesions posing a diagnostic challenge, myoepithelial markers can be performed to rule out carcinoma.

On the other hand, microglandular adenosis is characterized by a proliferation of uniform small round glands haphazardly distributed within the breast parenchyma. The most important aspect of this lesion is that it lacks a myoepithelial layer; thus it can be easily confused with carcinoma. The presence of basal lamina encircling glandular structures, which can be confirmed by immunohistochemical stains, and overall round, rather than angulated, morphology of the glands are features that can be used in ruling out a malignant process. There is some evidence that microglandular adenosis can potentially progress to carcinoma, and it can recur if incompletely excised. Occasionally, microglandular adenosis presents as a palpable mass and may be associated with both in situ and invasive carcinoma [32].

Radial Scar and Complex Sclerosing Lesion

Radial scar is characterized by a fibroelastotic core with entrapped glandular structures, radiating ducts that become larger at the periphery of the lesion, and associated epithelial hyperplasia (Fig. 34.10). When larger than 1 cm, some refer to them as a "complex sclerosing lesion," while others require a less organized architecture to classify those as complex sclerosing lesions [4]. Mammographically, they may appear as a spiculated mass mimicking carcinoma [33]. Atypical epithelial proliferations as well as in situ and invasive carcinomas can be associated with radial scars. In general, a radial scar has an increased incidence of malignancy, whereas others found that radial scars are mainly associated with benign breast lesions. Based on its size, radial scars can be either excised or biopsied. Some but

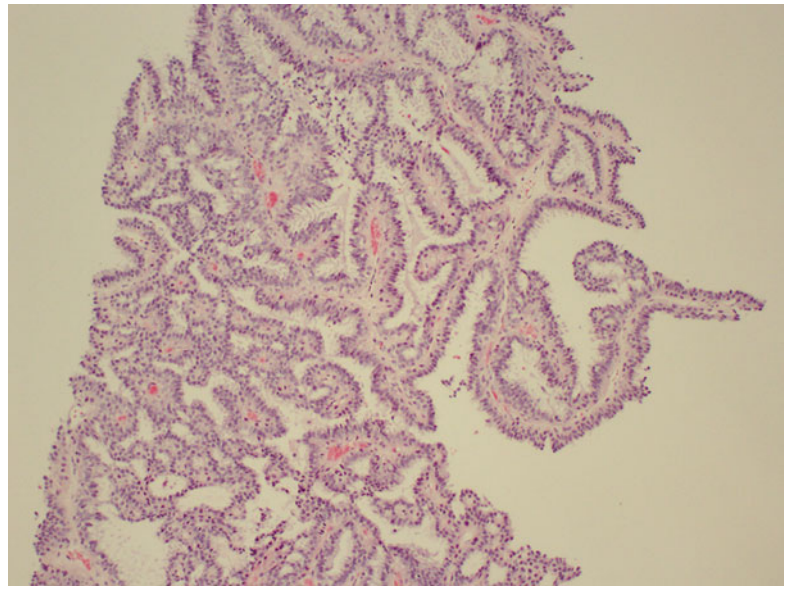

Fig. 34.11 Papilloma. Hematoxylin and eosin stain at 100× magnification

not all believe that radial scars identified on core needle biopsies should be excised due to their association with premalignant and malignant conditions [34]. Radial scars identified on excisional specimens need no further therapy [4].

Papillomas and Papillomatosis

Papillomas are frond-like intraductal proliferations of benign epithelial and myoepithelial cells (Fig. 34.11). They are usually encountered in two types: central and peripheral. Central ones are usually solitary and larger, whereas the peripheral ones tend to be smaller and multiple. Unless associated with atypical epithelial proliferations, central papillomas are not considered premalignant lesions. Certain studies confirm an increased incidence of in situ and invasive carcinoma on excisional specimens in patients with atypical ductal proliferation inside papillomas. On excisional biopsy samples, if the atypical epithelium is confined to the papilloma and the surrounding tissue is non-atypical, then the finding has no prognostic significance. In one study, 29 % of patients diagnosed with intraductal papilloma on core needle biopsy were upstaged to papilloma with atypia on excisional specimens, and 10 % were upstaged to carcinoma [35]. The authors concluded that surgical excision is recommended for benign papillary lesions diagnosed on core needle biopsies (Fig. 34.11).

However, other studies found an upstage rate of only 8.9 % to atypia or malignancy on the excision specimens [36]. Others report that only 3 % of cases diagnosed as benign papilloma on core biopsy are associated with malignancy and recommend follow-up instead of excision [37]. Furthermore, they show a high association with malignancy (67 %) when the diagnosis on biopsy was atypical papilloma and suggest prompt excision for definitive diagnosis. Papillomatosis or multiple papillomas, usually defined as having five or more peripheral papillomas, indicate a slightly elevated risk for subsequent carcinoma. Specimens containing multiple papillomas should be sampled extensively to rule out malignancy. Juvenile papillomatosis is another variant occurring in young patients younger than 30 years old. This is associated with a higher incidence of breast cancer and higher incidence of a family history of breast cancer. Therefore, those patients and their families require long-term follow-up.

Columnar Cell Changes

Columnar cell lesions are encountered with increasing frequency on breast biopsies due to associated microcalcifications detected on

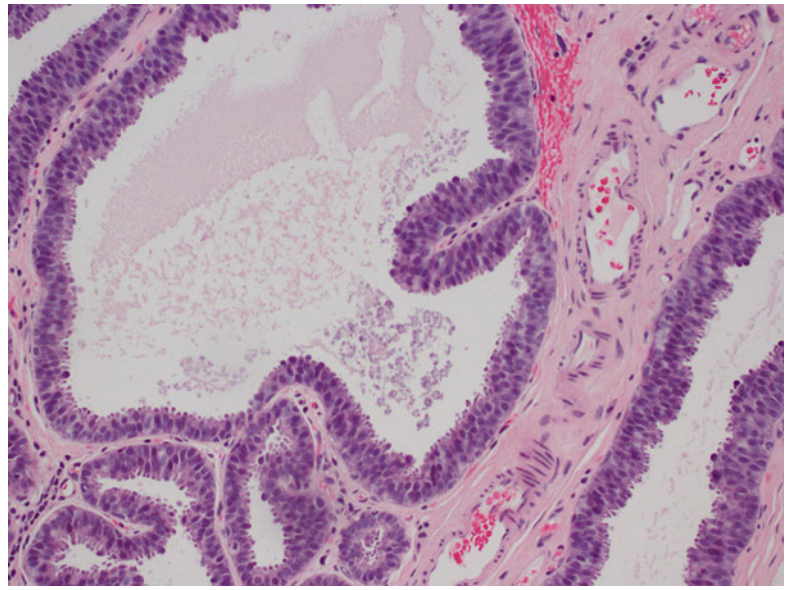

Fig. 34.12 Flat epithelial atypia. Hematoxylin and eosin stain at 200× magnification

screening mammograms [38]. When atypical, it is called "flat epithelial atypia" (FEA) with total excision of the area generally recommended, as there may be a more significant lesion in the surrounding breast tissue [39] (Fig. 34.12). Overall, its progression rate to invasive carcinoma is exceedingly low. However some suggest FEA should just be followed up and not surgically excised. It appears that more studies are needed to determine the significance of atypia in columnar cell alternations.

When flat epithelial atypia is diagnosed on core needle biopsy, the rate in upstaging to carcinoma on subsequent excision is 14 % [40]. The same study shows that the differences in upstaging in subsequent excisions in flat epithelial atypia and atypical ductal hyperplasia group were not statistically different. When FEA microscopically develops architectural changes such as micropapillary and cribriform patterns, the lesion is designated as atypical ductal hyperplasia. Some noted genetic alterations shared with low-grade ductal carcinoma in situ and tubular carcinoma suggesting that flat epithelial atypia might be a precursor of these lesions [41]. One interesting aspect of both atypical and non-atypical columnar cell changes is the diffuse and strong nuclear estrogen and progesterone receptor expression [41]. This is in contrast with normal breast epithelium that is usually only sparsely positive for the same receptors. Nevertheless, when columnar cell changes without atypia are encountered on breast biopsies, patient follow-up is considered sufficient.

Neoplasms

Fibroadenoma and Adenoma

As the most common mass lesion of the breast, fibroadenoma can be identified in up to 25 % of asymptomatic women [42]. This is a hormone-dependent lesion that occurs in young women, during lactational phases of pregnancy, and involutes at menopause. Oral contraceptive use before 20 years of age appears to increase the risk of developing fibroadenoma. It is usually unilateral, but in 20 % of cases, the tumors are multiple and can be bilateral [42]. It develops from the specialized stroma of the lobules. Grossly, the lesions are well-circumscribed, resilient lesions, showing a bulging cut surface and usually measuring less than 3 cm. Tumors reaching more than 10 cm in greatest dimension are often seen in younger patients and are called "giant fibroadenoma." Histologically, fibroadenomas are biphasic tumors that have both stromal and epithelial elements. Some studies suggest that both elements are neoplastic. Based on microscopic

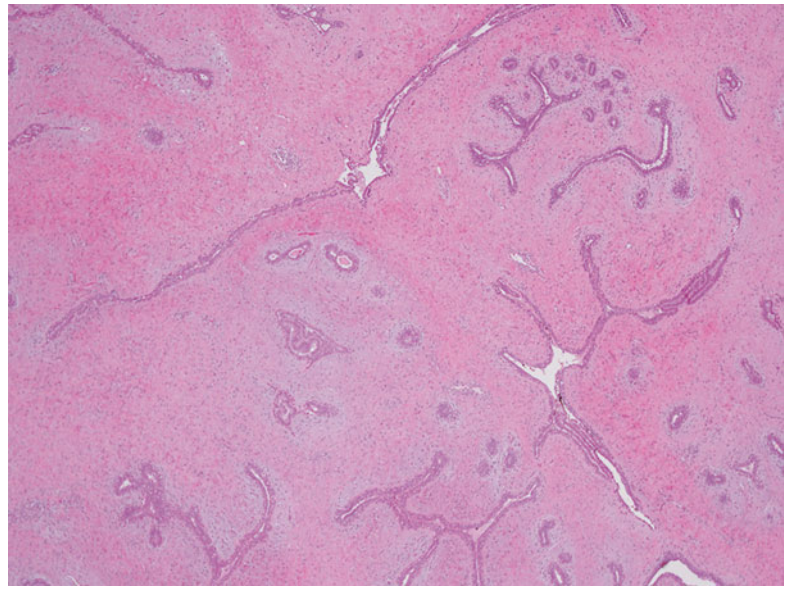

Fig. 34.13 Juvenile fibroadenoma. Hematoxylin and eosin stain at 40× magnification

appearance, the lesions can be divided into pericanalicular and intracanalicular types. The former is characterized by stromal growth around the glandular structures, whereas the latter shows compressed, cleft-like ducts. It is not uncommon that the two patterns occur together in the same tumor.

Histologically the main differential diagnosis for fibroadenomas is the phyllodes tumor, which is also a biphasic tumor. Benign phyllodes tumor can be difficult to distinguish from a fibroadenoma. Features such as stromal atypia, infiltrative margins, increased mitotic activity, and stromal cellularity favor a diagnosis of phyllodes tumor. The importance of distinguishing between the two lesions is that a phyllodes tumor needs to be excised with clear margins. Approximately 50 % of fibroadenomas contain epithelial proliferations such as sclerosing adenosis and epithelial hyperplasia. Those are classified as "complex fibroadenoma." While regular fibroadenoma is not associated with increased risk of developing cancer, patients with complex fibroadenoma have a slightly higher risk of developing breast cancer. Likewise, fibroadenomas in older women or in patients with a family history of breast cancer have a higher incidence of breast cancer.

Management of patients with fibroadenoma varies depending on the treating physicians. Some prefer to excise the tumors, while others will conservatively manage patients without operative removal. One study showed that an expectant management policy of fibroadenomas has not resulted in misdiagnosis of carcinomas. The same study claims that since a significant proportion of fibroadenomas remain static or reduce in size over a 5-year period, many women can avoid excision [43]. In general, there are three reasons to remove a fibroadenoma: persistent pain, rapid growth over a short period of time and cosmetic deformity related to a fibroadenoma just underneath the skin of the breast. A thorough conversation is important in determining the optimal approach to management, discussing both the risks and benefits of operative removal. However, it should be made clear that there is little, if any, risk of malignant degeneration or transformational risk to carcinoma associated with a fibroadenoma.

Some phyllodes tumors show areas compatible with a fibroadenoma on histologic evaluation. In such cases, undersampling of the lesion might result in underestimation of the lesion, i.e., a phyllodes tumor can be misdiagnosed as fibroadenoma on a core needle biopsy. Juvenile fibroadenoma is a rare variant that occurs in patients between the ages of 10 and 18. It is usually a larger mass, with an alarming rapid growth and gross disfigurement, measuring more than 5 cm, and is usually unilateral and painless (Fig. 34.13). Although it is a benign lesion, excision is usually recommended [44].

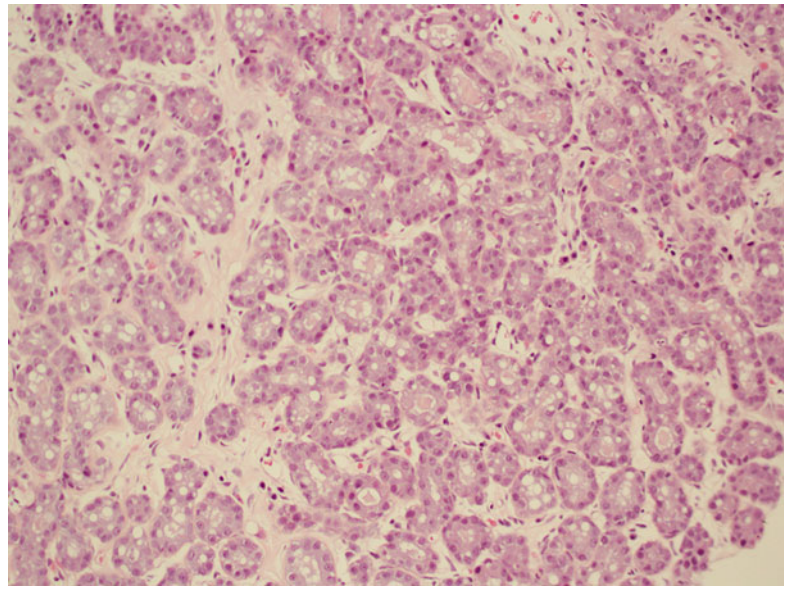

Fig. 34.14 Lactating adenoma. Hematoxylin and eosin stain at 200× magnification

Unlike biphasic fibroadenoma, adenoma is a pure benign epithelial lesion. Several variants exist such as tubular, lactating, apocrine, ductal, and pleomorphic (a lesion similar to a mixed tumor of the salivary glands). Except tubular and lactating adenomas, the remaining lesions are exceedingly rare; therefore, only those two lesions will be discussed. Lactating adenoma is a benign lesion with no malignant potential (Fig. 34.14). It is composed of hyperplastic lobules showing active secretion. It is thought to represent a variant of preexisting tubular adenoma or fibroadenoma [45]. It is usually a small lesion, less than 3 cm in overall diameter, and sometimes involutes post-pregnancy. In certain situations, it is resected due to the mass effect it produces. The lesion does not tend to recur. Tubular adenoma is also characterized by packed tubular and acinar structures with very scant stroma. Clinically and radiographically, such lesions can easily be confused with a fibroadenoma, sometimes showing calcifications. It is a benign lesion usually occurring in patients younger than 35 years old [46].

Nipple Adenoma and Syringomatous Adenoma

Nipple adenoma is an infrequent type of benign breast neoplasm that can show various histologic pictures. Those lesions usually present with nipple discharge and erosion, sometimes mimicking Paget's disease [47]. Histologically, it shows proliferating epithelial structures that might be confused with carcinoma (Fig. 34.15). Identifying a myoepithelial layer usually confirms the diagnosis. The lesions are treated with excision and they may recur if incompletely excised. Nipple adenoma is a benign tumor; however, some describe malignant changes within or adjacent to the lesions [48]. Syringomatous adenoma of the skin can also involve the nipple and is in the differential diagnosis. This is a more infiltrative lesion that requires excision and can recur but does not metastasize. It is characterized by bland infiltrative glands, some showing keratin cyst formation. It resembles the peripherally located low-grade adenosquamous carcinoma of the breast.

Hamartoma

Hamartoma, also known as a fibroadenolipoma, lipofibroadenoma, or adenolipoma, is composed of a mixture of glandular, adipose, and fibrous tissue (Fig. 34.16). Clinically, hamartomas present as a painless mass. It is considered to be a developmental abnormality, rather than a true neoplastic process. Some cases are associated with Cowden's syndrome [49], an autosomal dominant disorder

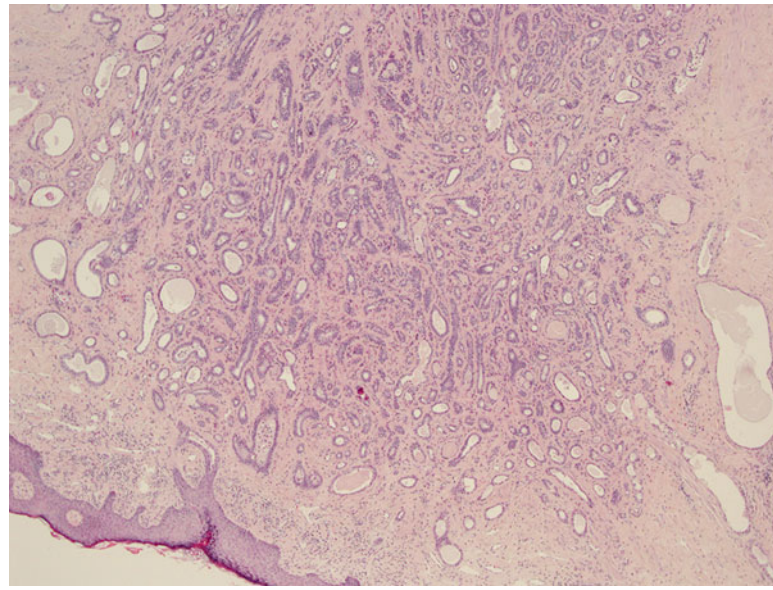

Fig. 34.15 Nipple adenoma. Hematoxylin and eosin stain at 20× magnification

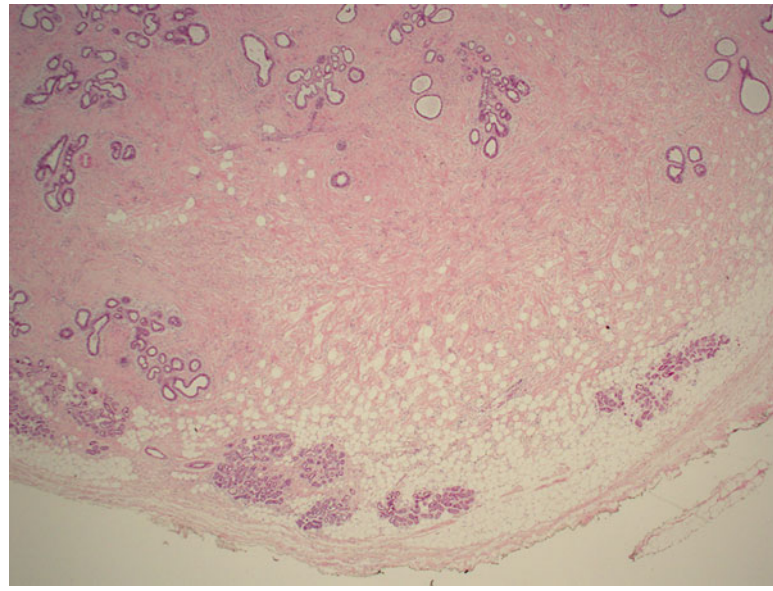

Fig. 34.16 Hamartoma. Hematoxylin and eosin stain at 20× magnification

that is characterized by macrocephaly, hamartomatous intestinal polyps, benign skin tumors, and dysplastic gangliocytoma of the cerebellum. Patients with this syndrome have a predisposition to develop breast, thyroid, and endometrial carcinoma. Macroscopically, those lesions are well-circumscribed tumors. Microscopically one sees normal breast and adipose tissue distributed in a nodular fashion. These lesions may go unrecognized by the pathologists because they show all the constituents of normal breast tissue and maybe reported as "no pathological diagnosis"

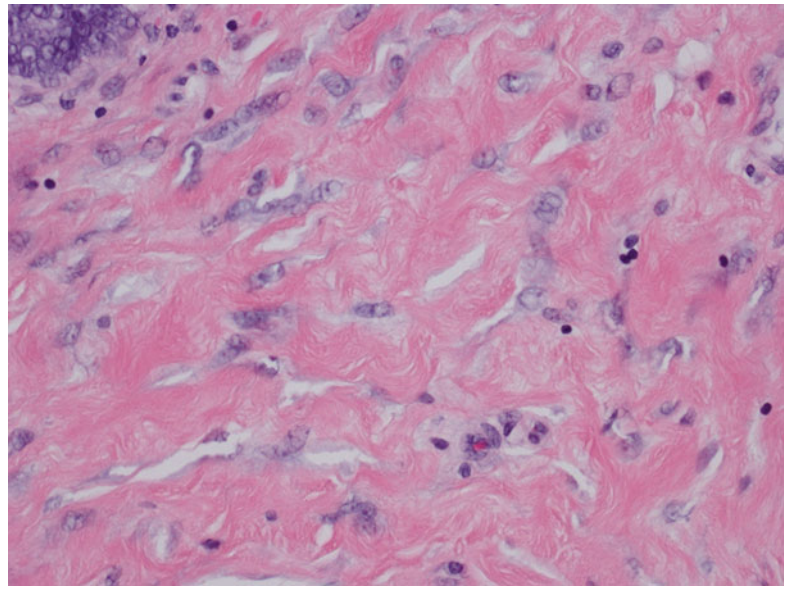

Fig. 34.17 Pseudoangiomatous stromal hyperplasia. Hematoxylin and eosin stain at 400× magnification

or "normal breast tissue" [50]. The treatment of hamartoma is surgical excision.

Pseudoangiomatous Stromal Hyperplasia (PASH) and Myofibroblastoma

Although not considered a true neoplasm, this benign proliferation of myofibroblasts in the breast stroma can present as a clinically palpable mass. It is however mostly an incidental finding on biopsies and excisions performed for other conditions. It may be identified in up to 23 % of breast specimens [51]. Its etiology is unknown; however hormonal stimulation, especially progesterone, is stipulated as a factor for the development of PASH lesions. PASH cells show expression of progesterone receptor and are positive for vimentin and CD34. Smooth muscle actin and desmin are variably expressed [4]. In rare cases where PASH forms a mass, it is usually well circumscribed and mimics a fibroadenoma or a phyllodes tumor. Microscopically, the lesions show anastomosing slit-like spaces within a collagenous stroma (Fig. 34.17). Due to this histologic appearance, one can easily mistake those benign lesions for angiosarcomas (Fig. 34.18). In difficult cases, immunohistochemical stains can be used to confirm the diagnosis. PASH can recur when treated with excision. However, so far malignant transformation has not been described [5].

Myofibroblastoma is a benign tumor that is well circumscribed, slow growing, and mobile. It is frequently mistaken for a fibroadenoma both on physical examination and radiologically [4]. The cells are bland and admixed with a collagenized stroma. Some have abundant stromal collagen and some are more cellular. The cells sometimes appear epithelioid and can form aggregates, thus microscopically mimicking carcinoma. As the lesional cells are also estrogen and progesterone positive, this may further complicate the diagnosis. In difficult cases, a lack of staining with keratin immunohistochemical stains and positivity with CD34 and desmin stains confirm the diagnosis. Some cases of PASH may show areas resembling myofibroblastoma, suggesting that the two entities are related. The treatment of myofibroblastoma is excision, which is considered curative.

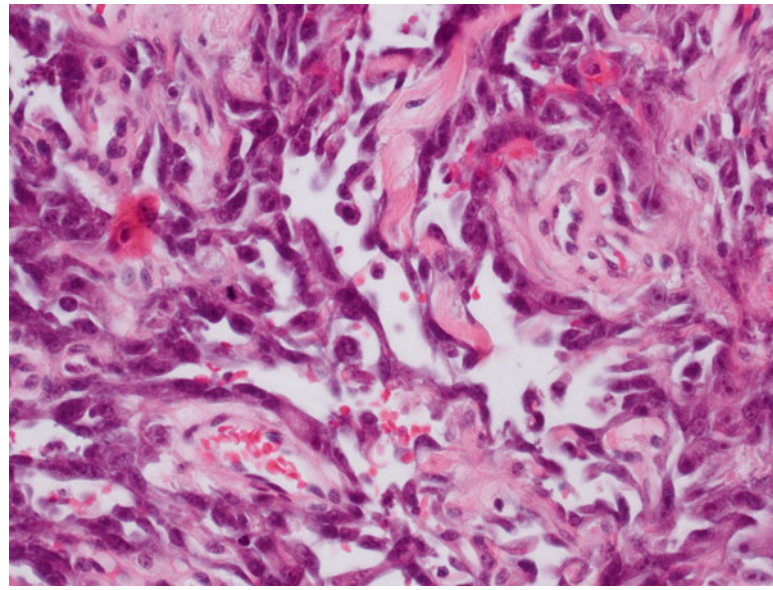

Fig. 34.18 Angiosarcoma. Hematoxylin and eosin stain at 100× magnification

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