Inflammatory, Reactive, and Infectious Conditions of the Breast

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Fat Necrosis

Overview

Fat necrosis, a relatively common finding in breast core biopsy specimens, is most often seen in breast tissue that has undergone some type of trauma and is typically a component of post-surgical or post-biopsy reactive changes. Radiation therapy can induce the development of fat necrosis, and fat necrosis can develop following all types of radiation, including external beam, accelerated partial breast irradiation (Mammosite®), and intraoperative radiotherapy [1–3]. Less commonly, fat necrosis occurs when there is no history of prior trauma. Fat necrosis can present as a palpable abnormality in an area of prior surgery or trauma. In some cases, skin and/or nipple retraction may be present and can simulate invasive carcinoma [4]. Fat necrosis may also come to attention on screening mammography or follow-up imaging as a mass or calcifications and may be suspicious enough to warrant biopsy.

A histologic diagnosis of fat necrosis is relatively straightforward, especially in the appropriate clinical context. It is necessary for the pathologist to have information about the patient's clinical history (surgery, trauma, radiation) as well as imaging findings. If the patient has a history of carcinoma in the site being biopsied, information about the type of carcinoma should be known, either from prior reports or preferably from review of prior slides. Some uncommon types of mammary carcinoma show similar morphologic features to fat necrosis (discussed below) and should be kept in mind. Fat necrosis is benign and does not need to be excised when diagnosed in a core biopsy sample, provided there is radiologic-pathologic concordance.

Gross and Radiologic features

Grossly, fat necrosis is firm and shows a gritty or chalky yellow cut surface that may contain areas of cystic degeneration and hemorrhage. Calcifications can be grossly appreciated in some cases. Fat necrosis can be seen on mammography as a spiculated mass, asymmetric density, lipid or oil cyst, or due to the presence of calcifications [5, 6]. Lipid cysts are a pathognomonic finding of fat necrosis [5, 7, 8]. They appear as round radiolucent masses with a fibrous rim and frequently calcify (Fig. 4.1). In other instances, calcifications in fat necrosis appear clustered, pleomorphic, and linear and may simulate malignancy [5, 6]. On ultrasonography, fat necrosis has a variable appearance and may be identified as a solid well-circumscribed mass, a stellate mass with infiltrative margins, a complex cyst, or as lipid cysts [9–11]. Fat

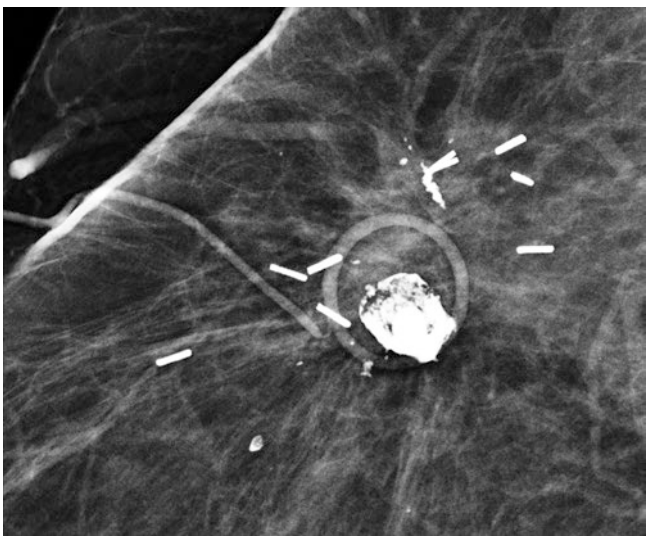

Fig. 4.1 Mammography of fat necrosis shows a lipid cyst with well-defined borders and coarse calcification. Surgical clips from a prior resection are present in the vicinity of fat necrosis. (*Courtesy of Janine Katzen, MD*, Weill Cornell Medicine, with permission)

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S. J. Shin et al. (eds.), *A Comprehensive Guide to Core Needle Biopsies of the Breast*,
https://doi.org/10.1007/978-3-031-05532-4_4

necrosis may show a variable pattern of enhancement on magnetic resonance imaging (MRI) and can mimic invasive carcinoma [6].

Microscopic Features

The appearance of fat necrosis is variable and depends on the degree of fibrosis and inflammation within the lesion. In areas of recent trauma, fat necrosis shows more inflammation and less fibrosis, while in older lesions, scarring and calcification are present and less inflammation is seen. Fat necrosis is easily recognized due to the presence of foamy histocytes and foreign body type giant cells surrounding lipid vacuoles and anucleate necrotic adipocytes (Fig. 4.2). Cysts are formed containing saponified lipids and are surrounded by foamy histiocytes and giant cells (Fig. 4.3). Lymphocytes, plasma cells, and in some cases eosinophils are present to a variable degree (Fig. 4.4). Neutrophils are seen in the first few days of the process and are not abundant. Evidence of prior hemorrhage is seen as hemosiderin-laden macrophages or hematoidin pigment (Fig. 4.5). Fibrosis progressively develops around necrotic fat and can form fibrous walled cysts that undergo calcification (Fig. 4.6). Breast glandular tissue is often not present in core biopsies of fat necrosis, particularly in prior surgical sites.

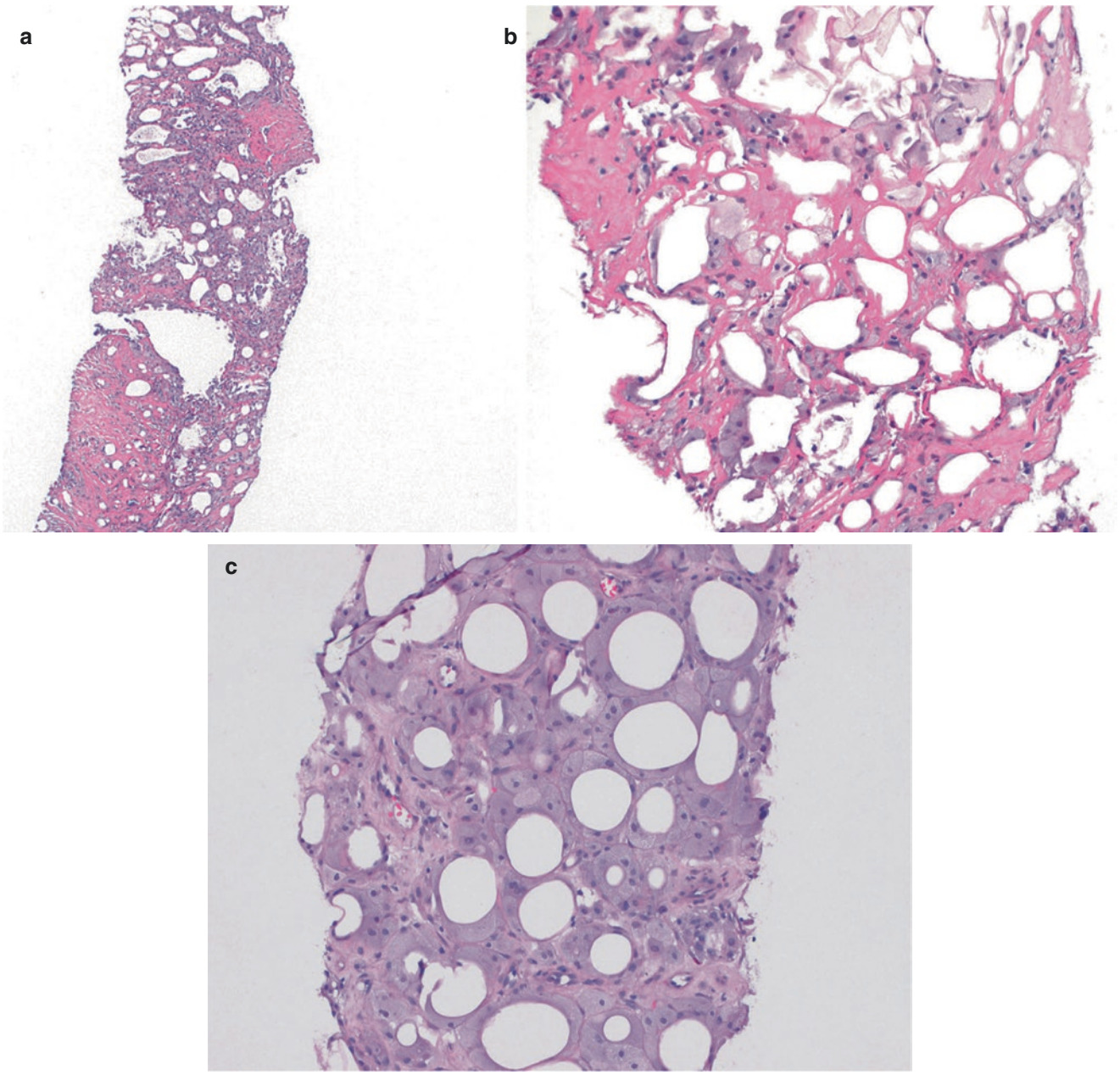

Fig. 4.2 Fat necrosis in core biopsy samples. (**a**, **b**) Core biopsy showing fibrosis and foamy histiocytes surrounding necrotic adipocytes. (**c**) Another case of fat necrosis in a core biopsy sample

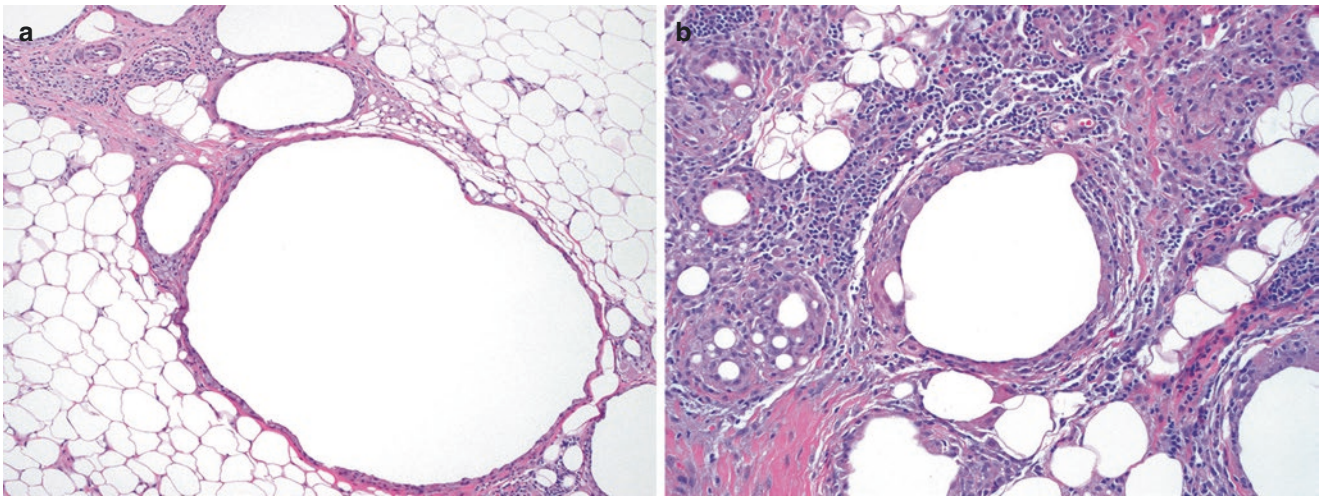

Fig. 4.3 Cysts formed by histiocytes lining lipid pools (**a**, **b**)

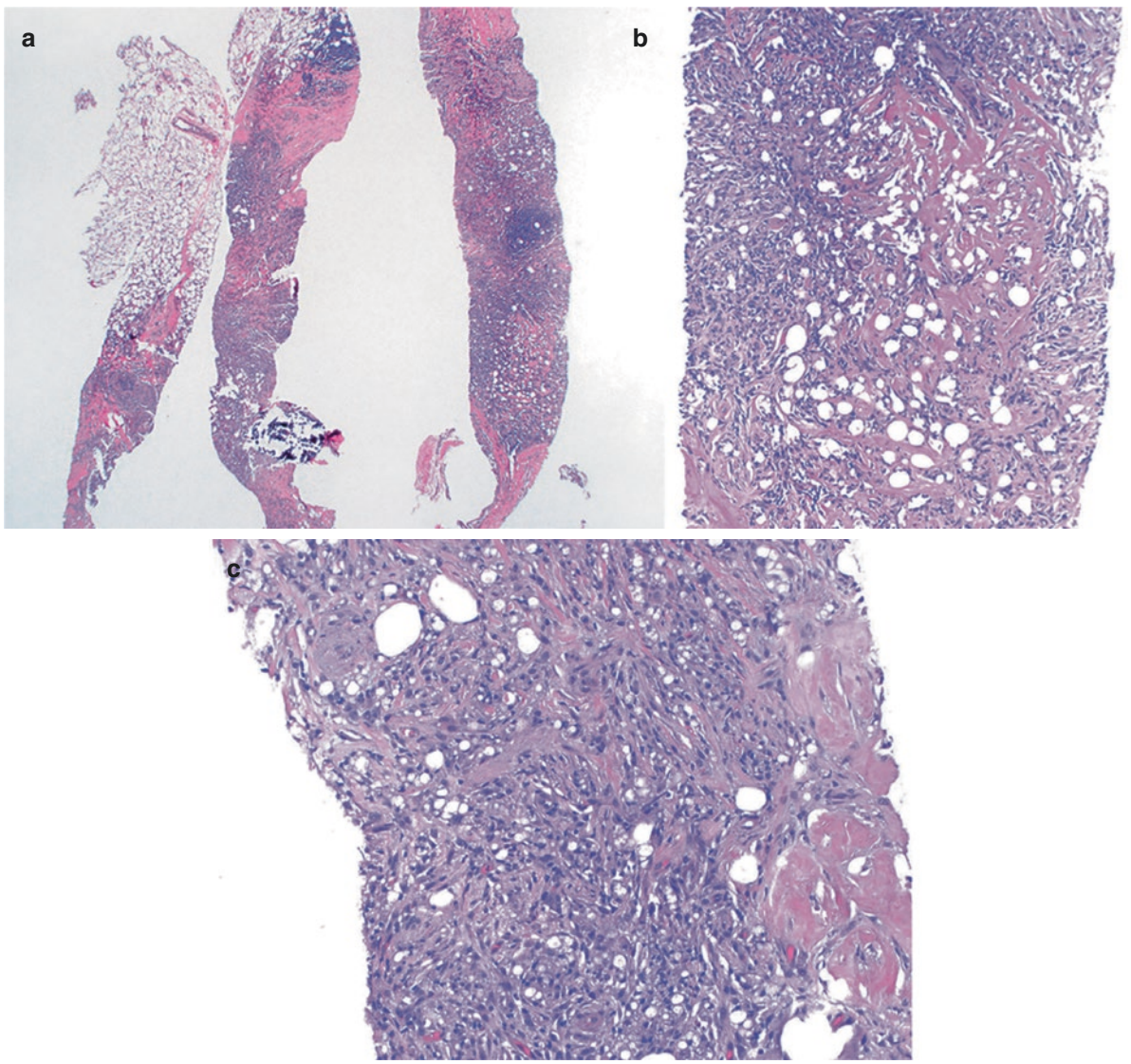

Fig. 4.4 Fat necrosis in a core biopsy performed for a mass in the site of prior lumpectomy. (**a**) A cellular proliferation of inflammatory cells is seen in fibroadipose tissue. (**b**) The inflammatory component is mostly composed of lymphocytes and histiocytes. (**c**) Cellular focus of spindled histiocytes. A cytokeratin (AE1/AE3) immunostain (not shown) was performed in this case to rule out recurrent carcinoma and was negative

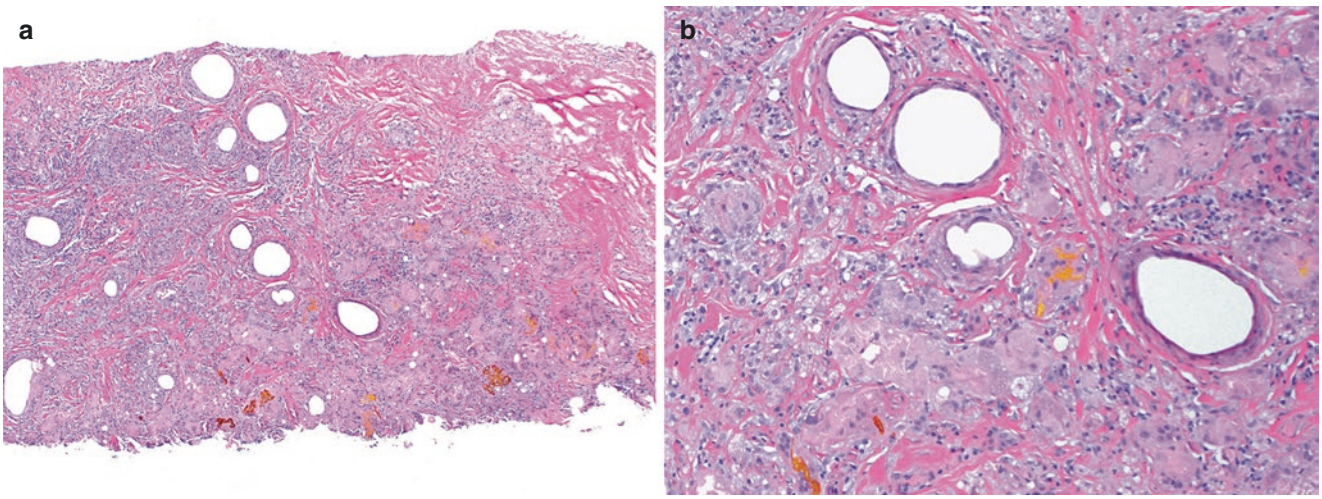

Fig. 4.5 (**a**) Fibrosis, mixed inflammation, and cysts lined by histiocytes are present. Yellow-brown hematoidin pigment is also seen (*bottom* of image). (**b**) The pigment is surrounded by foreign body type giant cells

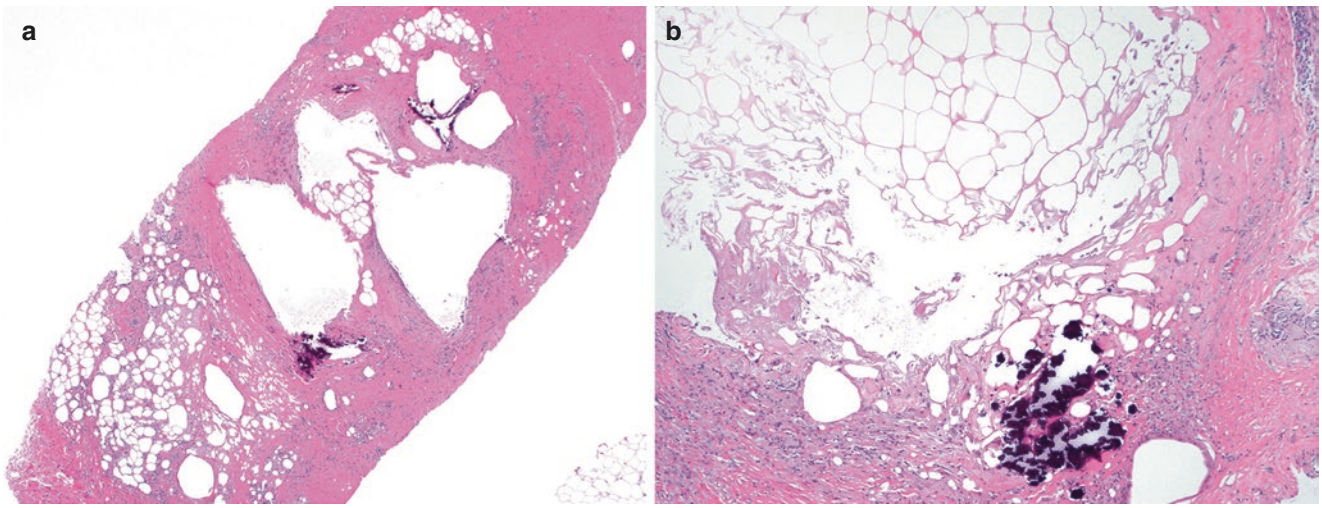

Fig. 4.6 Calcification can be identified in the fibrotic cyst walls surrounding necrotic fat, as seen in these two cases (**a**, **b**)

Differential Diagnosis

Fat necrosis is often biopsied in areas of prior surgery to rule out recurrent carcinoma. In most instances, fat necrosis is diagnosed based on its classic morphologic appearance. If there is a cellular inflammatory component, and there is any doubt to the diagnosis of fat necrosis, a broad-spectrum cytokeratin or CK7 immunostain may be performed to help rule out carcinoma. This is important if there is history of classical type invasive lobular carcinoma, in which the cells can mimic lymphocytes. Other less common types of invasive carcinoma show cells with abundant cytoplasm that can mimic histiocytes. These include "histiocytoid" invasive lobular carcinoma (Fig. 4.7), apocrine carcinoma with histiocytoid morphology, and lipid-rich carcinoma [12–14]. A cytokeratin immunostain will highlight these.

Less common histiocytic proliferations may also be included in the differential diagnosis of fat necrosis, provided the clinical and radiographic features support their consideration. Rosai–Dorfman disease, also known as sinus histiocytosis with massive lymphadenopathy, is a rare, self-limited histiocytic disorder that most commonly occurs in children and young adults. The disease can occur in nodal and extranodal sites, and virtually all sites in the body have been affected [15]. Involvement of the breast is uncommon but has been reported in both males and females. The disease

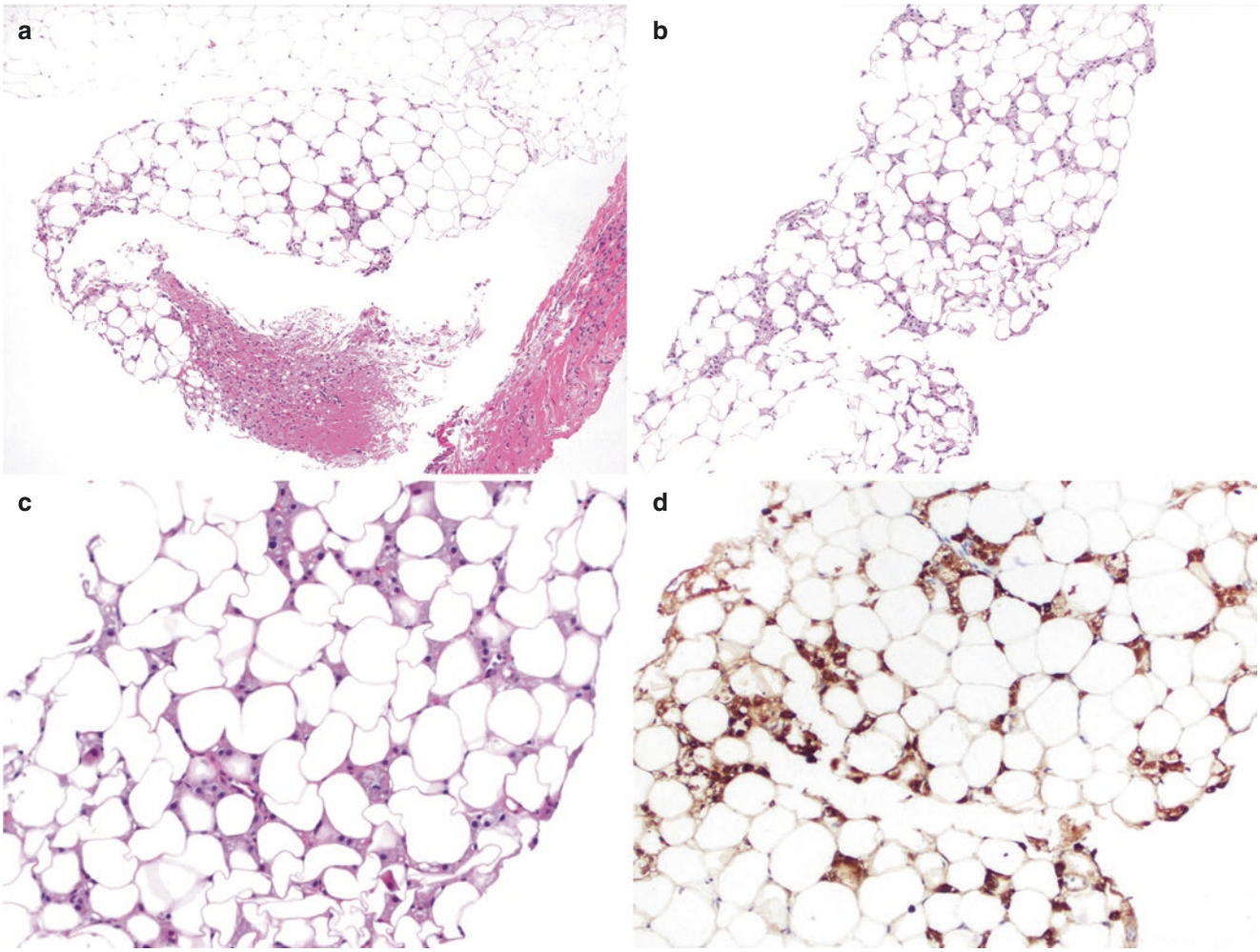

Fig. 4.7 Invasive lobular carcinoma with histiocytoid features in a core biopsy performed for a spiculated mass. (**a**, **b**) Carcinoma cells infiltrating fat mimic fat necrosis on low-power magnification. (**c**) Neoplastic cells have small uniform nuclei and abundant pink cytoplasm. (**d**) Carcinoma cells are highlighted by cytokeratin (AE1/AE3). E-cadherin (not shown) was negative, supporting lobular differentiation. (*Courtesy of Paula Ginter*, *MD*, Weill Cornell Medicine, with permission)

presents in the breast as a mass that is either palpable or detected on screening imaging [15–17]. Axillary lymph nodes may also be involved, leading to the clinical impression of malignancy. Microscopically, a diffuse multinodular infiltrate composed of histiocytes and accompanying lymphocytes and plasma cells is seen in the breast tissue or deep dermis/subcutaneous tissue (Fig. 4.8). Histiocytes have abundant eosinophilic cytoplasm and round nuclei with a single central nucleolus. A diagnostic feature seen in Rosai–Dorfman disease is emperipolesis, in which histiocytes contain lymphocytes in their cytoplasm, and occasionally, plasma cells, neutrophils, and erythrocytes. Emperipolesis may be more difficult to identify in extranodal locations such as the breast. Histiocytes in Rosai–Dorfman disease show positive immunostaining with S100 protein and macrophage-associated antigens (CD68, CD163), and are negative for CD1a and langerin.

Erdheim–Chester is an uncommon histiocytosis composed of foamy histiocytes that is extremely rare in the breast and occurs in the setting of multisystem disease in all cases [18]. Sheets of foamy histiocytes, lymphocytes, plasma cells, and Touton-type giant cells are seen in breast tissue. Histiocytes are positive for CD68 and negative for S100 protein and CD1a.

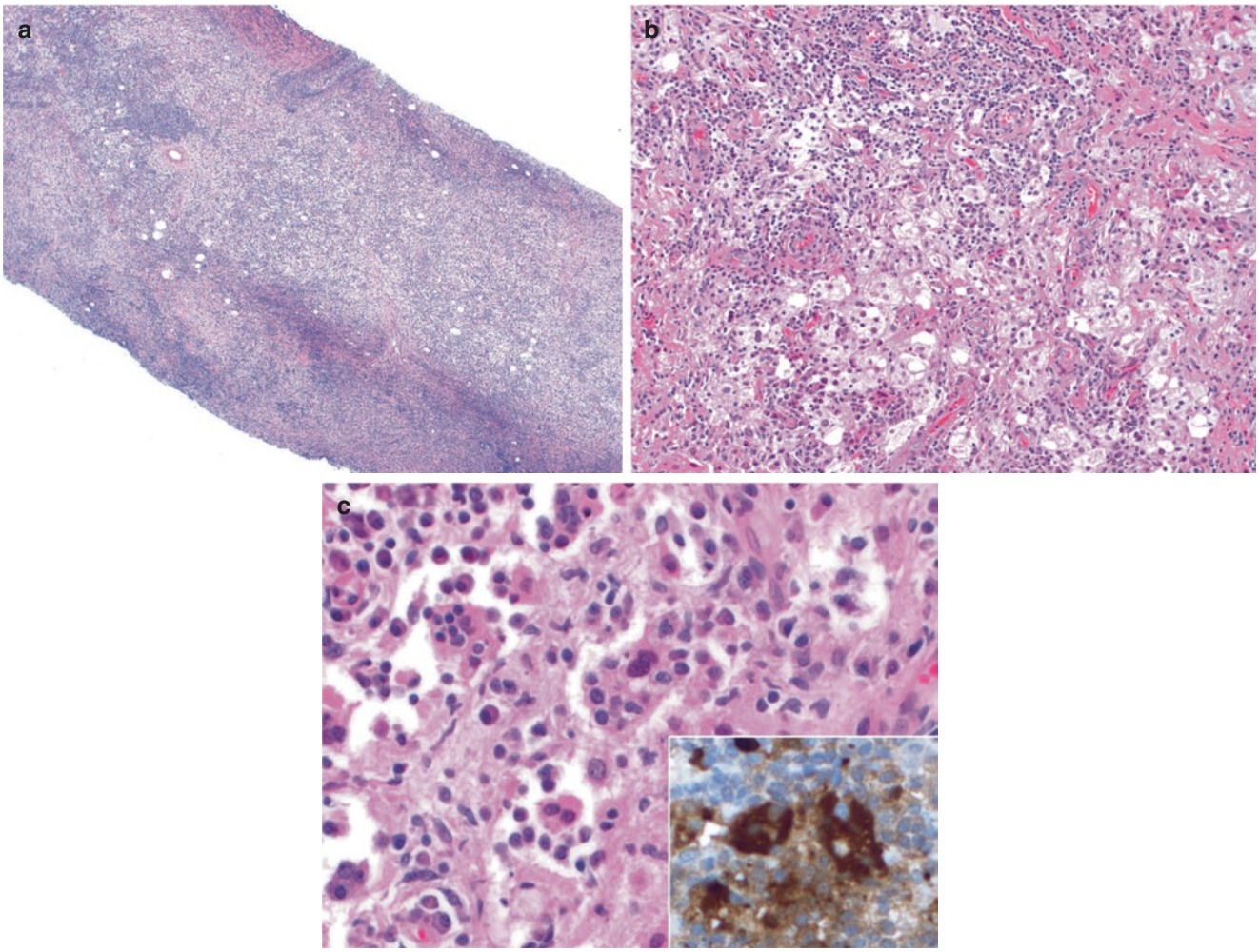

Fig. 4.8 Rosai–Dorfman disease involving the breast. (**a**) Core biopsy shows a diffuse infiltrate of histiocytes, lymphocytes, and plasma cells. (**b**, **c**) The lesion is composed of histiocytes with abundant eosinophilic cytoplasm that show emperipolesis of lymphocytes and plasma cells. Histiocytes are highlighted by an S100 protein immunostain (*inset*, **c**)

Prognosis

Fat necrosis is benign and does not need to be excised when diagnosed in a core biopsy.

Mammary Duct Ectasia

Overview

Mammary duct ectasia is an inflammatory process characterized by dilatation of the central ducts of the breast with variable degrees of fibrosis and inflammation. There are some overlapping clinical and pathologic features with periductal mastitis, squamous metaplasia of lactiferous ducts, and subareolar abscess and these processes can coexist. Minor degrees of ductal dilatation with associated inflammation are not uncommon and are often seen in breast surgical specimens as incidental findings. The discussion of duct ectasia in this chapter will focus on duct ectasia as the pathologic manifestation an inflammatory condition with characteristic clinical and radiographic features [19].

Duct ectasia occurs in adult women in their 30s–60s [20–22]. Rare cases have been reported in males and in children [23–25]. Duct ectasia can be unilateral or bilateral. Clinically, duct ectasia presents as nipple discharge, nipple or skin retraction, or as a subareolar mass. Pain is often present in association with these signs and symptoms or may be the only symptom [26]. Nipple discharge, when present, is yellow, brown, or green in color. Discharge can be spontaneous, intermittent, and can occur over long periods of time (months to years) [26]. Rare cases of duct ectasia reported in infants and children of both sexes have come to clinical attention due to bloody nipple discharge [23, 24]. It has been suggested that cigarette smoking is associated with the development of duct ectasia; however, smoking appears to be related

to periductal inflammation/mastitis, but not ductal dilatation [20, 27, 28]. Duct ectasia has been reported in patients with hyperprolactinemia secondary to pituitary adenomas and phenothiazine therapy [29].

Gross and Radiologic Features

Grossly, duct ectasia shows dilated ducts with thick fibrous walls. The dilated ducts may contain a pasty, yellow-brown secretion, similar to that seen in ductal carcinoma in situ (DCIS) with "comedonecrosis." Features of duct ectasia on imaging can mimic malignancy and are often suspicious enough to warrant a biopsy. On mammography, duct ectasia shows intraductal or periductal branching calcifications, ductal dilatation, or a stellate mass [30]. Periductal calcifications form rings of dense calcification with a central lucency and converge on the nipple [30]. In some cases of duct ectasia, there may be no mammographic findings and abnormalities are only seen on ultrasound. Ultrasound shows dilated subareolar ducts or a mass-like lesion filled with echogenic material [31].

Microscopic Features

Duct ectasia is characterized by dilated ducts with luminal foamy histiocytes and variable degrees of fibrosis and periductal chronic inflammation (Fig. 4.9). The morphology varies depending on the stage in evolution of the process. Early lesions show mild ductal dilatation with luminal histiocytes and minimal or no fibrosis of the ducts. The epithelium of involved ducts is either attenuated or absent and is not hyperplastic. Sloughed epithelium can be seen in duct lumens in

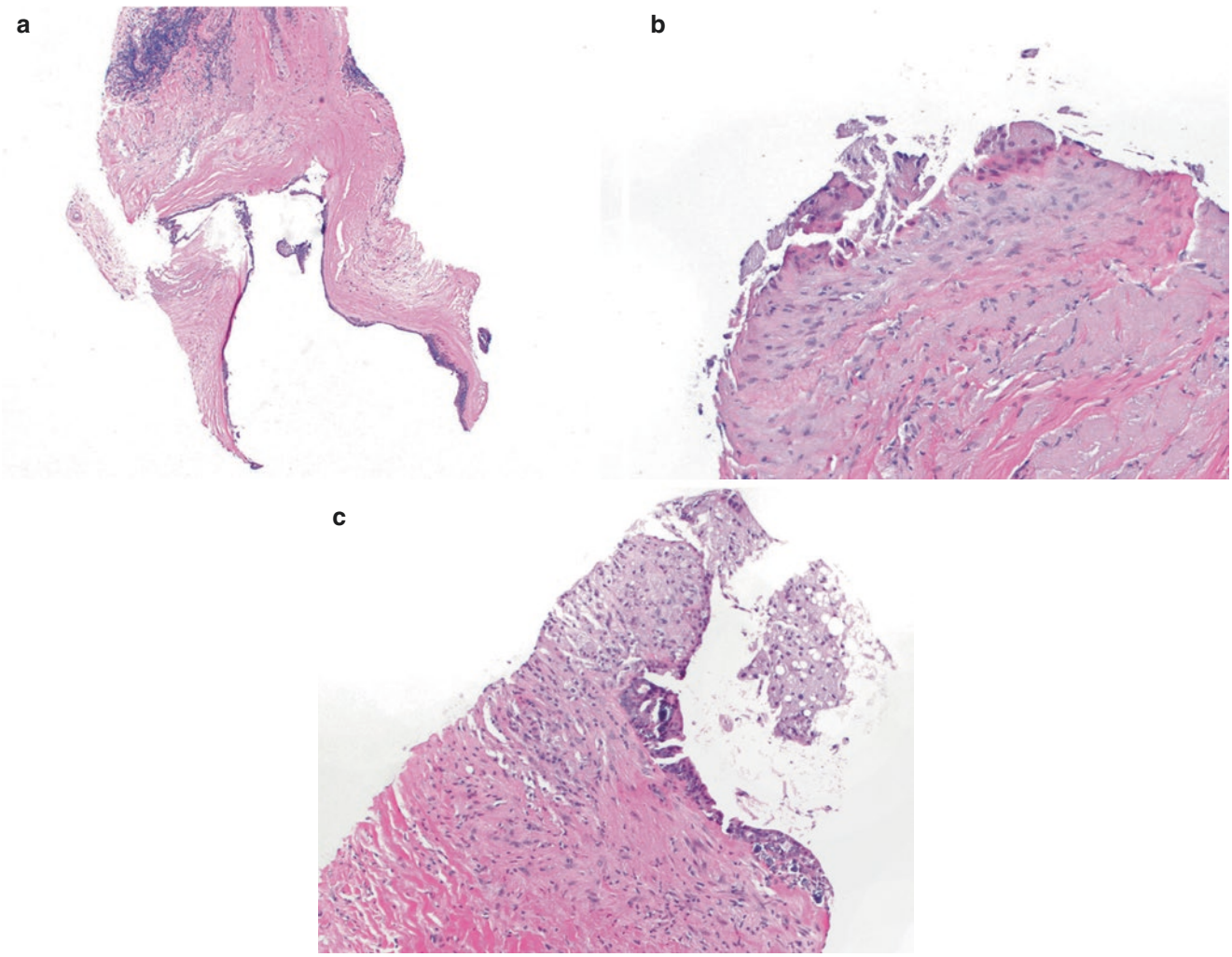

Fig. 4.9 Duct ectasia in core biopsy samples. (**a**) The duct is fibrotic with a flattened epithelial lining. Periductal lymphocytic inflammation is present. (**b**) The duct wall in this case is fibrotic and shows elastosis. The lining is composed of histiocytes only. (**c**) Flatted ductal epithelium and luminal foamy histiocytes are seen

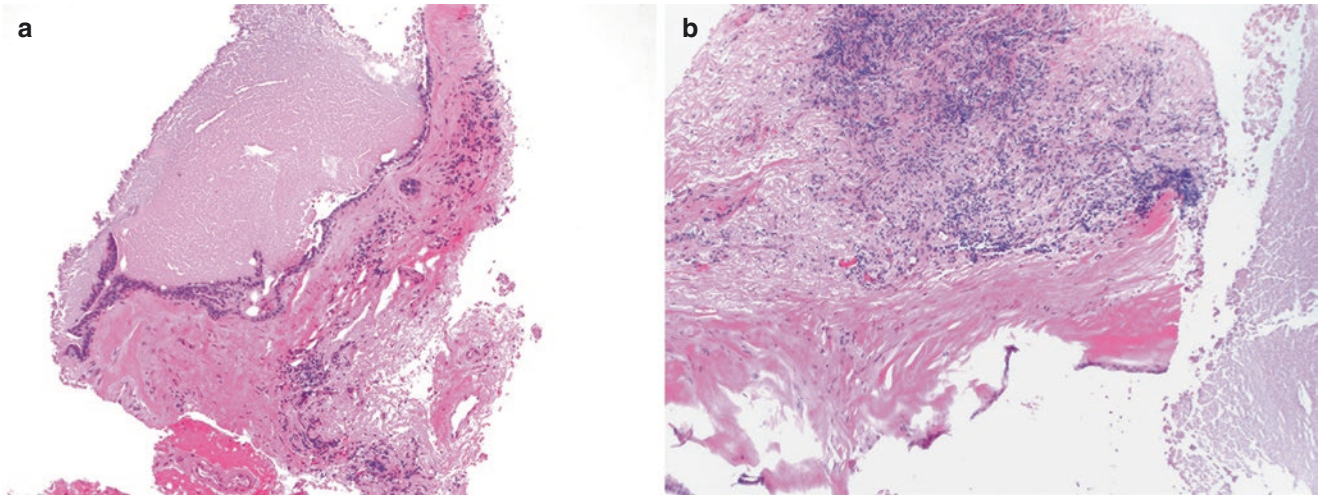

Fig. 4.10 Duct ectasia in a core biopsy sample. (**a**) Amorphous pink secretion is present in the lumen of a dilated duct. (**b**) The duct wall is fibrotic and is associated with periductal chronic inflammation

some cases. The luminal debris is composed of lipid-laden foamy histiocytes, amorphous pink secretion, and sometimes foreign body type giant cells (Fig. 4.10). Intraepithelial foamy histiocytes may be seen (Fig. 4.11). Histiocytes containing brown pigment, referred to as "ochrocytes," may be present in a periductal location (Fig. 4.12) [32]. Periductal chronic inflammation is composed mainly of lymphocytes and plasma cells.

As duct ectasia evolves, duct walls become thickened and fibrotic and are more likely to cause symptoms and become apparent on imaging. Fibrosis is often accompanied by elastosis in the duct walls. Calcification can be present in the lumen of the duct or within the duct wall (Fig. 4.13). A core biopsy of duct ectasia at this stage may only reveal a small portion of a fibrotic duct wall with minimal inflammation. In the late stages of duct ectasia, ducts may become ruptured and obliterated (Fig. 4.14). Rupture of the duct wall with spilling of contents into the surrounding breast tissue can lead to the formation of abscess. Cholesterol granulomas, "cholesterolomas," may form within fibrotic ducts and can manifest as a mass or calcifications on imaging (Fig. 4.15) [33]. "Mastitis obliterans" refers to the histologic finding of fibrosis completely filling the duct lumen that occurs in the later stages of duct ectasia (Fig. 4.16).

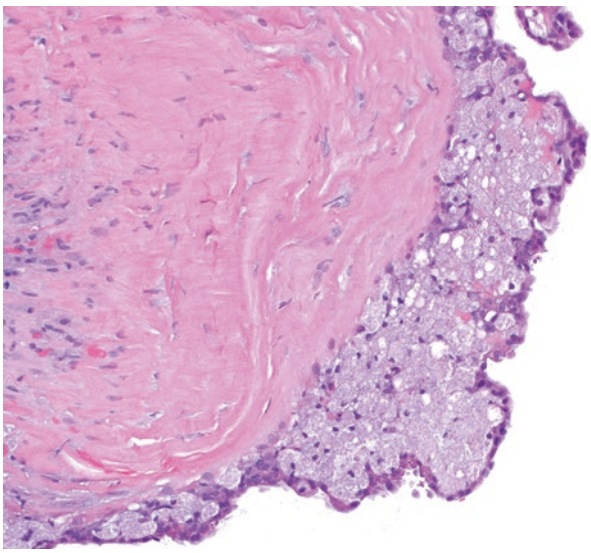

Fig. 4.11 Duct ectasia with intraepithelial histiocytes

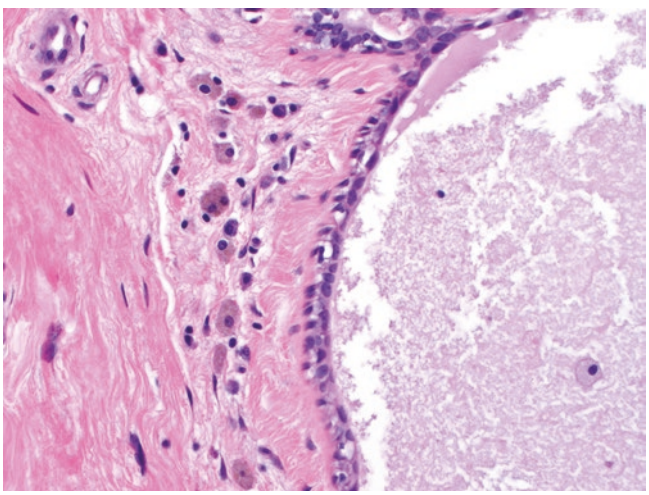

Fig. 4.12 Periductal histiocytes containing brown pigment, so-called "ochrocytes"

Differential Diagnosis

By clinical, imaging, and gross findings, duct ectasia mimics high-grade DCIS with central necrosis ("comedonecrosis"). In cases that show fibrotic ducts without epithelium, it is important to rule out the presence of DCIS. Clues to the presence of DCIS include necrosis and luminal calcifications. Periductal inflammation will be present in DCIS, but typically does not contain foamy histiocytes. Additional deeper hematoxylin and eosin (H&E) levels should be obtained in

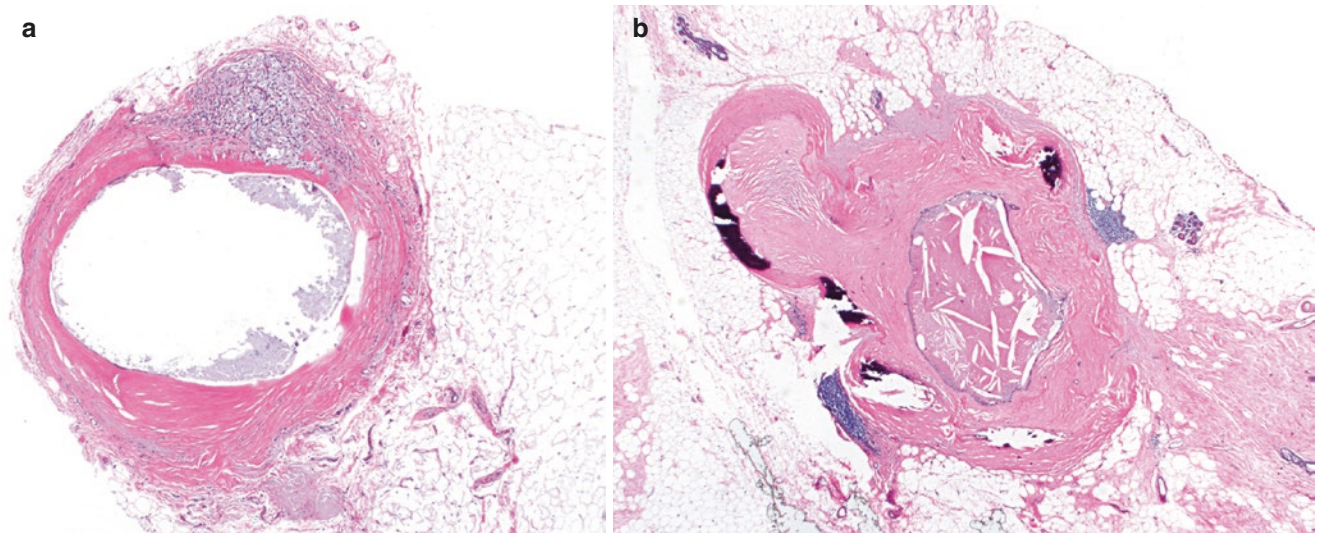

Fig. 4.13 Duct ectasia in stereotactic biopsies performed for mammographic calcifications. (**a**) Luminal calcifications are present in this biopsy. (**b**) Calcifications are present within the fibrotic duct wall

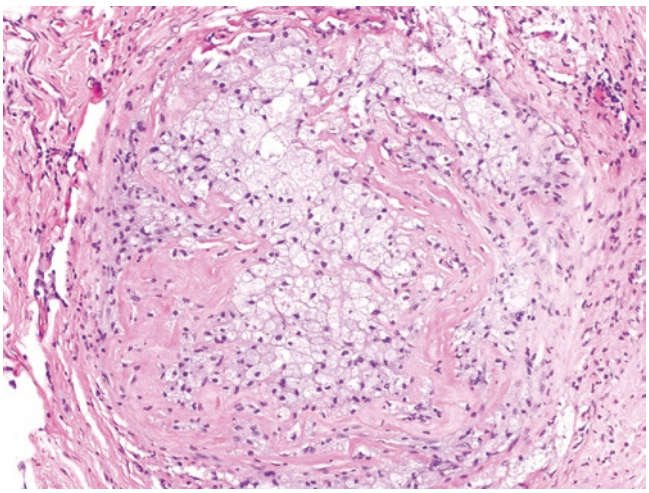

Fig. 4.14 Duct ectasia showing obliteration of duct wall

uncertain cases. Intraepithelial histiocytes can mimic pagetoid spread of carcinoma, either ductal or lobular. A broad-spectrum cytokeratin stain can be used to rule out carcinoma, if necessary. Ductal dilatation can occur distal to an intraductal lesion such as a papilloma. If dilated ducts are present in a core biopsy for an intraductal mass, correlation with imaging findings is necessary to determine whether the targeted lesion has been sampled.

Cysts associated with fibrocystic changes can show fibrosis and inflammation of the cyst wall. Cysts are formed in the terminal duct lobular units, while duct ectasia involves subareolar ducts. Proximity to the nipple favors duct ectasia. Making the distinction between cysts and duct ectasia in a core biopsy is not critically important as these are managed similarly.

Immunohistochemistry

Duct ectasia is usually diagnosed without immunohistochemical stains. CD68 may be used to highlight histiocytes in uncertain cases. A broad-spectrum cytokeratin stain can be used to rule out pagetoid spread of carcinoma when intraepithelial histiocytes appear atypical, especially in cases with coexisting DCIS in the breast.

Pathogenesis

Duct ectasia may be a result of stasis and accumulation of debris in ducts, which leads to an inflammatory response and duct fibrosis. Squamous metaplasia of lactiferous ducts is the cause of duct stasis in some cases. Alternatively, the process may begin with periductal inflammation which leads to fibrosis and duct dilatation [34].

Prognosis

Duct ectasia may be treated by excision of the involved duct(s) in symptomatic cases. Re-excision and/or incision and drainage may be necessary in cases complicated by abscess or sinus formation. In most cases, if duct ectasia is diagnosed in a core biopsy of a radiographically detected lesion in an asymptomatic patient, the lesion does not need to be excised, provided there is radiologic-pathologic concordance. Patients with duct ectasia are not at increased risk for the development of breast carcinoma.

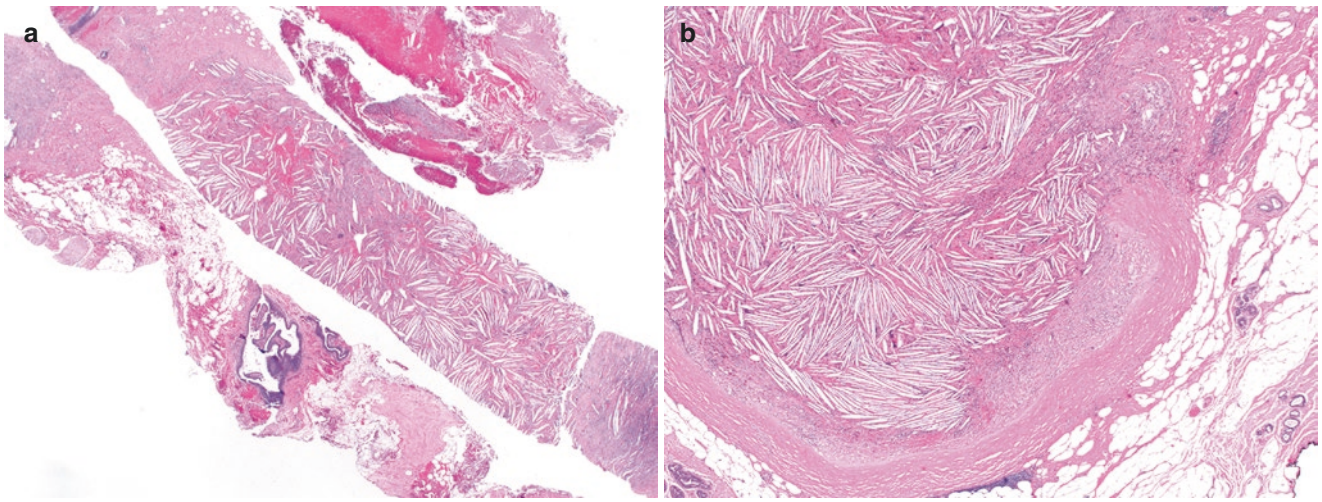

Fig. 4.15 "Cholesteroloma" in duct ectasia. (**a**) Core biopsy and (**b**) excision shows cholesterol clefts associated with histiocytes within a fibrotic duct

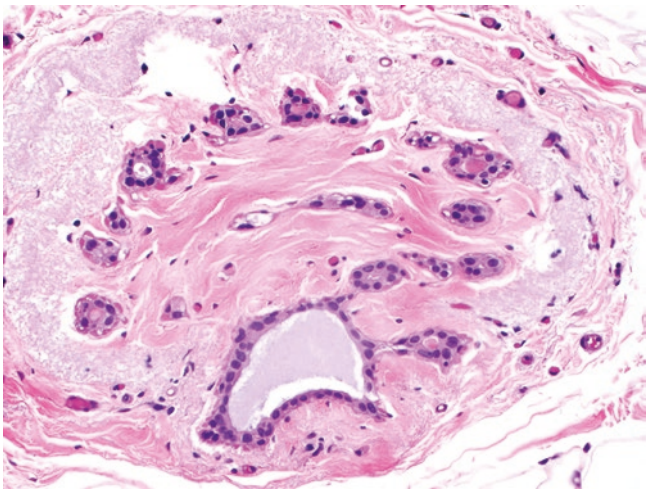

Fig. 4.16 Mastitis obliterans shows fibrosis completely filling the duct lumen and a garland pattern of epithelium at periphery of the duct

Granulomatous Lobular Mastitis

Overview

Granulomatous inflammation involving breast tissue is uncommon and can occur as a result of various infectious and inflammatory processes. Non-necrotizing granulomatous mastitis that is idiopathic is referred to as granulomatous lobular mastitis. The clinical and imaging features of granulomatous lobular mastitis are often suggestive of malignancy and core biopsy is necessary to rule out a malignant process.

Granulomatous lobular mastitis typically occurs in parous women of reproductive age (20s–40s) [35–38]. Some studies have noted a demographic trend of the development of granulomatous mastitis in Hispanic patients and patients born outside of the United States [38–40]. Clinical features can mimic malignancy or an inflammatory process. Most cases are unilateral. Less than 5% of patients present with bilateral disease [38, 41]. Patients present most often with a palpable mass or ill-defined firmness in the breast that may be accompanied by overlying skin erythema and nipple retraction. Masses are often large (over 3 cm in size) and may be associated with pain and tenderness. Nipple discharge can be the presenting symptom in some cases. Palpable ipsilateral axillary lymphadenopathy is reported in about one-quarter of cases [36, 37, 41]. Patients report a history of prior trauma to the affected breast in rare cases [42–44]. Many cases of granulomatous lobular mastitis become complicated by the development of abscesses and draining skin sinuses. Granulomatous lobular mastitis is difficult to treat, and patients often experience persistent and/or recurrent disease. In recent years, infection with *Corynebacterium* bacteria has been implicated in the development of granulomatous lobular mastitis. "Cystic neutrophilic granulomatous mastitis" is a distinctive histologic pattern of granulomatous mastitis characterized by suppurative lipogranulomas in which *Corynebacterium* bacteria may be identified on a Gram stain [44].

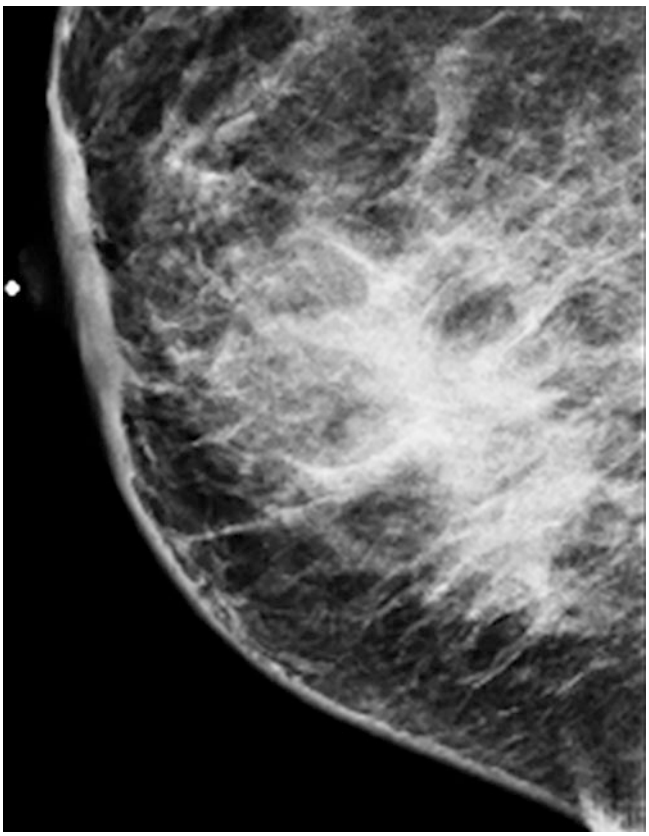

Fig. 4.17 Granulomatous lobular mastitis on mammography. Mammography shows an ill-defined spiculated mass in this case. (*Courtesy of Elizabeth Arleo*, *MD*, Weill Cornell Medicine, with permission)

When granulomatous lobular mastitis is identified in a core biopsy sample, obtaining clinical history is important to exclude other causes of granulomatous information. Special stains for fungi and acid-fast bacilli (AFB) should be performed to rule out these as infectious causes. Review of clinical, imaging, and pathologic findings in an interdisciplinary setting such as tumor board is helpful for establishing an effective treatment plan for these uncommon cases.

Gross and Radiologic Features

Grossly, granulomatous lobular mastitis is characterized by one or multiple ill-defined firm masses or nodules. Granulomatous lobular mastitis can appear on mammography as an ill-defined mass which with spiculated contours (Fig. 4.17) or heterogeneous parenchyma without a discrete mass [37, 45, 46]. Multiple masses or nodules may be identified. Microcalcifications are not a feature of granulomatous lobular mastitis. Ultrasound may show an irregular hypoechoic mass with shadowing, fluid collection, tubular structures, or parenchymal mixed echogenicity [36, 37, 45–47].

Microscopic Features

Granulomatous lobular mastitis is characterized by non-necrotizing granulomatous inflammation that is centered on lobules (Fig. 4.18). Granulomas are composed of epithelioid histiocytes, Langhans giant cells, and variable numbers of lymphocytes, plasma cells, and neutrophils. Eosinophils can be identified in some cases. Microabscesses can be present within or outside lobules (Fig. 4.19). Granulomatous inflammation can involve few lobules or can diffusely involve the breast. Lobules may appear confluent with destruction of the lobules by the granulomatous inflammation. Frank abscesses can develop in some cases. Core biopsy samples are often taken at the time an abscess develops. In these samples, rare breast glands may be present in the biopsy that show granulomatous lobular mastitis.

"Cystic neutrophilic granulomatous mastitis" refers to a histologic pattern of granulomatous lobular mastitis characterized by granulomas containing cystic vacuoles lined by neutrophils [42–44]. The empty vacuoles represent dissolved lipid and contain Gram-positive bacilli (described below) (Fig. 4.20). The cystic neutrophilic pattern may be identified within lobules and may also be formed within an abscess without any identified glands (Fig. 4.21).

Differential Diagnosis

The differential diagnosis includes other causes of lobular granulomatous inflammation. Granulomas seen in tuberculosis are necrotizing, while those of granulomatous lobular mastitis are non-necrotizing, suppurative granulomas containing neutrophils. Clinical and laboratory findings help to exclude sarcoidosis as a cause of granulomatous mastitis. Sarcoidosis rarely involves the breast without evidence of disease in other sites. Asteroid bodies and Schaumann bodies can be seen in sarcoidosis but are not seen in granulomatous lobular mastitis. Rosai–Dorfman disease (discussed above under differential diagnosis for fat necrosis) is characterized by sheets of large S100 protein-positive histiocytes accompanied by lymphocytes and plasma cells, which can mimic granulomatous lobular mastitis histologically. Langhans giant cells are not seen in Rosai–Dorfman disease.

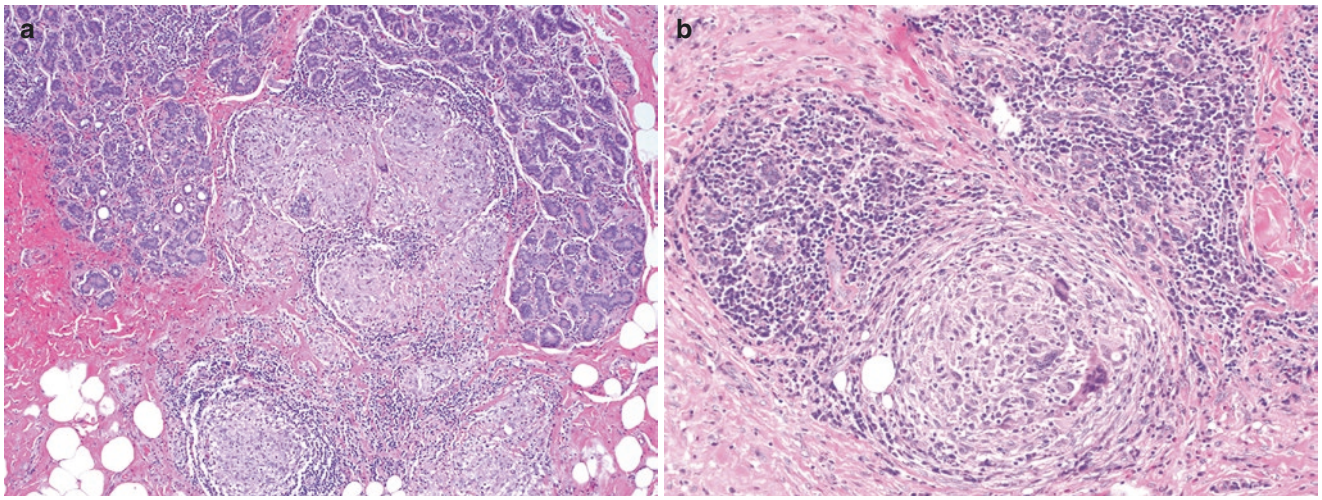

Fig. 4.18 Granulomatous lobular mastitis. (**a**) Non-necrotizing granulomatous inflammation centered on lobules. (**b**) Granulomas are composed of epithelioid histiocytes, Langhans giant cells, lymphocytes, and plasma cells

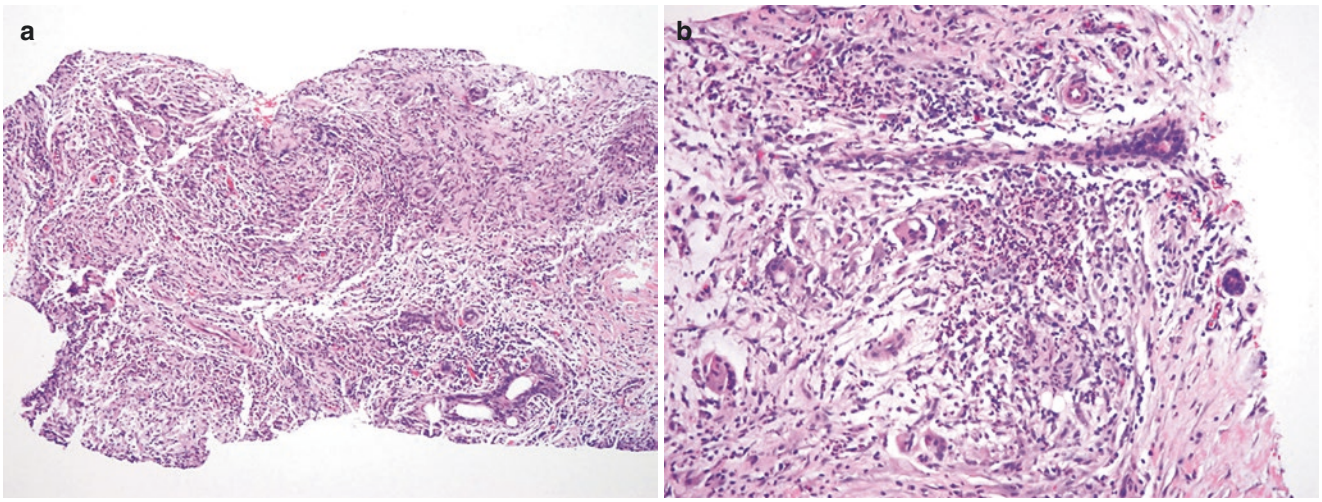

Fig. 4.19 Granulomatous lobular mastitis in a core biopsy. (**a**) Granulomas have destroyed the lobules. (**b**) Microabscesses are evident

Special Histochemical Stains and Methods to Identify Bacteria

Special stains for AFB and fungal organisms (Periodic acid–Schiff or Grocott-Gomori's [or Gömöri] methenamine silver) help to rule out mycobacterial and fungal infection as the cause of granulomatous mastitis. A Gram stain may allow identification of bacteria in cases that show cystic neutrophilic granulomatous mastitis (Fig. 4.19c, d). In most cases, only rare bacteria will be evident on the Gram-stained section and will only be present in 1–2 vacuoles. One study reported that performing Gram stains on 6 μm "thick sections" resulted in increased detection and easier identification of bacteria compared with 4 μm sections [48]. Coryneform features such as grouping of bacteria into "V" shapes and palisade arrangement may be seen in cases with more abundant bacteria. These bacteria are not usually evident on H&E examination.

Corynebacterium species can be difficult to isolate by routine culture and may require a special medium containing 1% polysorbate (Tween) 80 that may more easily grow lipophilic bacteria [42, 49]. Other methods such as matrix assisted later desorption ionization-time of flight mass spectrometry and 16S rRNA sequencing have been employed successfully to identify *Corynebacterium* in granulomatous mastitis specimens and these tests can be performed on paraffin-embedded tissue [39, 40, 50].

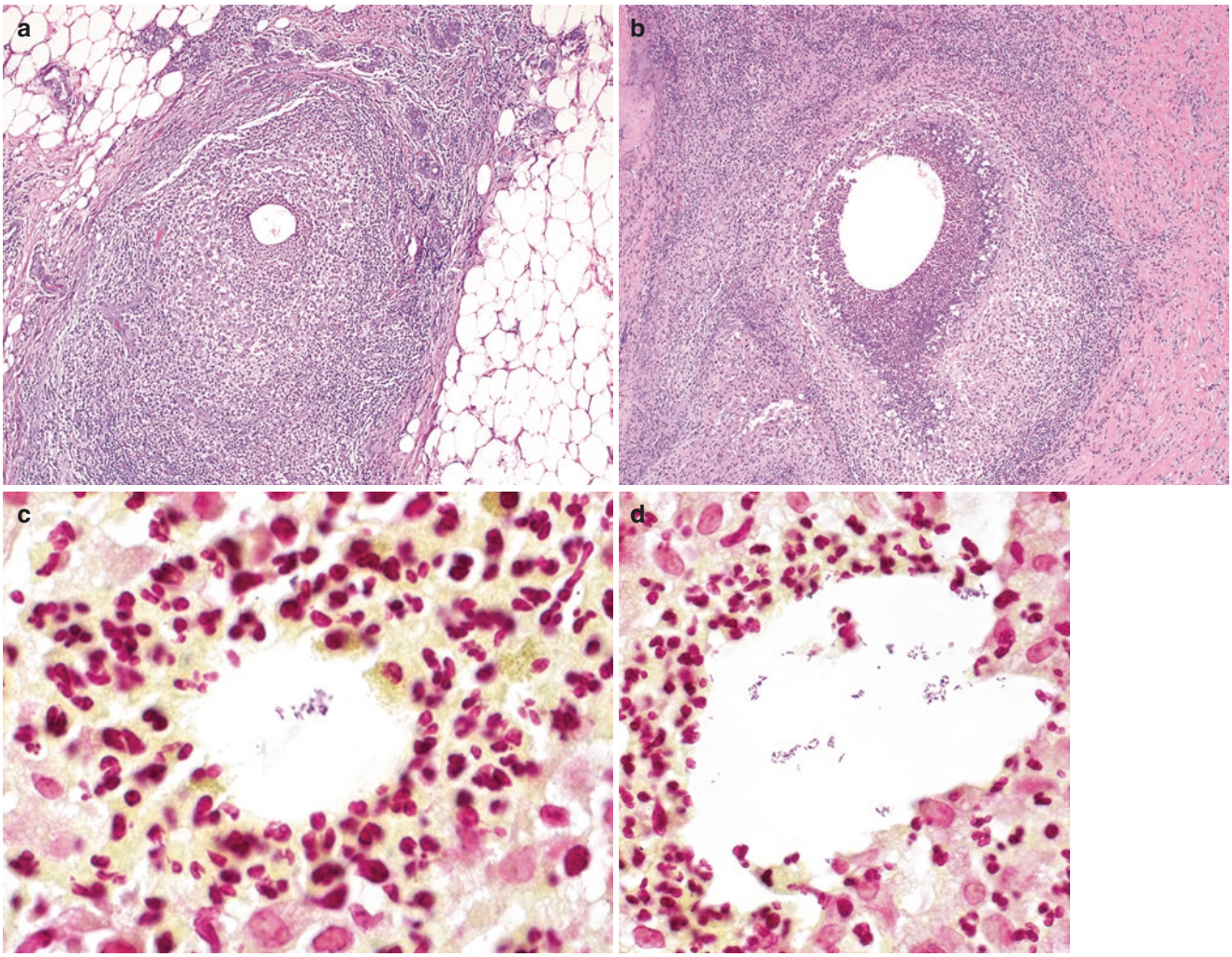

Fig. 4.20 Cystic neutrophilic granulomatous mastitis. (**a**) Suppurative granuloma centered on a lobule with a central clear vacuole surrounded by neutrophils. (**b**) Cystic neutrophilic granuloma showing more abundant neutrophils. (**c**, **d**) Gram-positive coryneform bacilli within cystic vacuoles

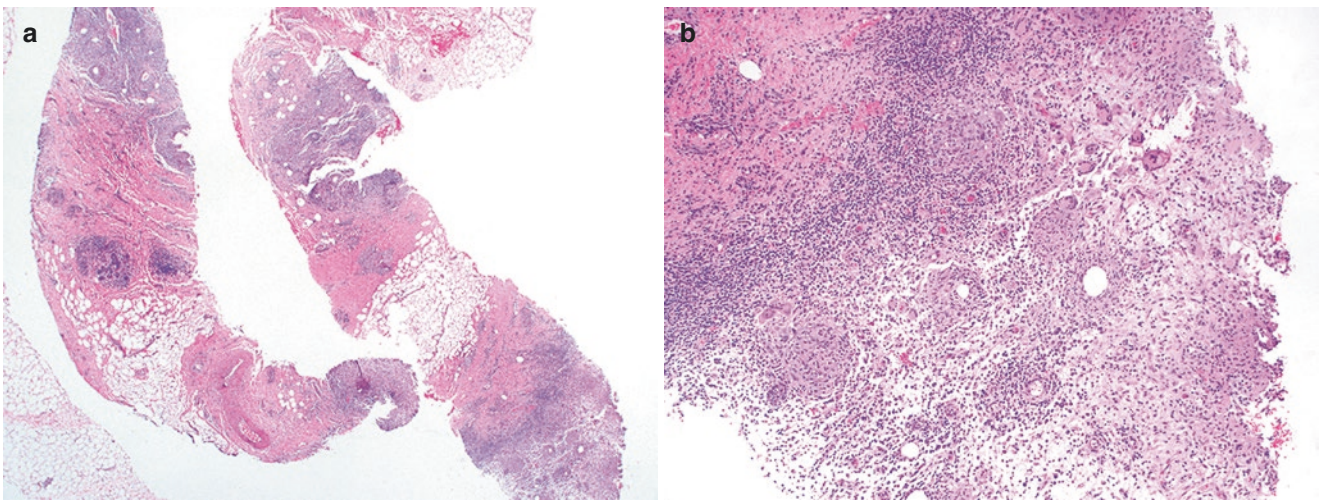

Fig. 4.21 Core biopsy of granulomatous lobular mastitis with abscess. (**a**, **b**) Core biopsy shows abscess containing non-necrotizing granulomas, some of which contain neutrophil-lined cystic vacuoles

Pathogenesis

The etiology of granulomatous lobular mastitis is unclear, which is why the disease is also called "idiopathic granulomatous mastitis." It is thought that prior pregnancy and breastfeeding leads to stasis of secretion and predisposes ducts rupture, which can lead to granulomatous lobular mastitis [36, 42]. There are some overlapping features with duct ectasia and these processes can coexist [42]. Oral contraceptive use, smoking, and autoimmune disease do not appear to be directly related to the development of granulomatous lobular mastitis [41].

Corynebacterium bacteria, which are typically non-pathogenic skin microbiota, are associated with cystic neutrophilic granulomatous mastitis and appear to be pathogenic in this disease. Evidence for pathogenicity include its pure growth in culture, association with acute inflammatory cells, and the presence of bacteria in clinical specimens (i.e., histologic slides) [42, 49, 51]. Species of *Corynebacterium* that are most frequently isolated are lipophilic bacteria, which is consistent with their presence in lipid vacuoles [42].

Prognosis

There is no standard approach for treating patients with granulomatous lobular mastitis. The use of steroids alone or in combination with surgery or antibiotics has been shown to be effective in multiple reports [37–39, 42, 52, 53]. Surgery includes wide excision or abscess drainage, and patients may require multiple procedures to manage persistent disease. Antibiotics appear to be less effective but may be beneficial if granulomatous mastitis is complicated by abscess formation. Tetracycline was effective in resolving the process in all 3 patients with cystic neutrophilic granulomatous mastitis in one study [44]. Microbial cultures should be taken to help guide therapy.

Sarcoidosis

Overview

Sarcoidosis is a systemic inflammatory condition that rarely involves the breast and can mimic malignancy based on clinical and imaging features. Women in their 20s–40s are most often affected. Breast sarcoidosis is not usually the primary manifestation of the disease and most patients have been diagnosed with sarcoidosis prior to the time of presentation. Patients present with a unilateral non-tender palpable mobile mass in most cases [54]. Rare patients have been reported to have bilateral disease [54]. In some cases, the mass can become fixed to the skin, clinically mimicking involvement by invasive carcinoma [55].

Gross and Radiologic Features

Sarcoidosis grossly shows firm nodules with well-defined or ill-defined borders. Mammography may show a spiculated mass, architectural distortion, or asymmetry, and can be suggestive of malignancy [54, 56, 57]. The most common finding on ultrasound is an ill-defined hypoechoic mass [58]. Enlarged axillary or intramammary lymph nodes may be seen if also involved by sarcoidosis. MRI shows an irregular enhancing mass, similar to an invasive carcinoma [58]. Core biopsy may be performed to rule out malignancy because of the worrisome imaging features.

Microscopic Features

Sarcoidosis is characterized by non-necrotizing granulomas with variable numbers of Langhans giant cells (Fig. 4.22). Schaumann bodies and asteroid bodies may be identified. Granulomas are present within lobules and are

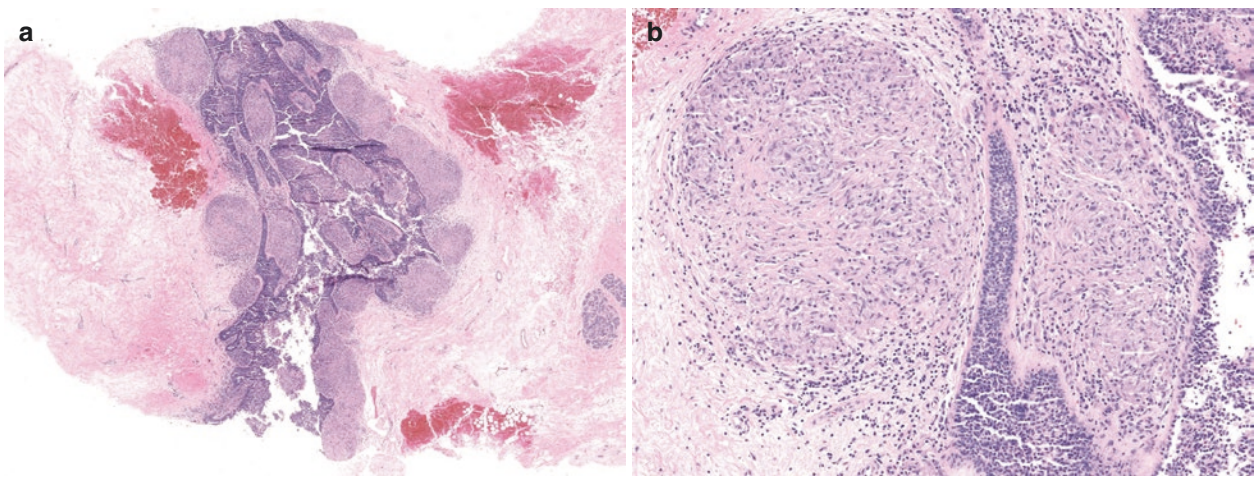

Fig. 4.22 Sarcoidosis in an MRI-guided biopsy for suspicious enhancement in a patient with known systemic sarcoidosis. (**a**) Low-power examination of the biopsy shows a duct extensively involved by granulomatous inflammation. (**b**) Higher power shows periductal non-necrotizing granulomas associated with minimal chronic inflammation

also seen in the interlobular stroma. Microabscess formation and suppurative granulomas are not typical features of sarcoidosis.

Differential Diagnosis

The differential diagnosis of sarcoidosis includes other causes of granulomatous inflammation such as granulomatous lobular mastitis and mycobacterial and fungal infections. As such special stains should be performed to rule out infectious processes. Sarcoid-like granulomas can be present in association with invasive carcinoma in rare cases [59]. Granulomas are present within the tumor and circumferentially around the tumor, so they are unlikely to be the sole finding in a core biopsy.

Prognosis

Treatment may include excisional biopsy of the lesion if imaging features are suspicious, and it is necessary to exclude the possibility of coexisting carcinoma. Recurrence of sarcoidosis can occur in the ipsilateral or contralateral breast following excision [54].

Diabetic Mastopathy

Overview

Diabetic mastopathy refers to a mass-forming fibrous proliferation of the breast occurring in patients with diabetes mellitus. The histologic changes of diabetic mastopathy are most often seen in patients with long-standing insulin-dependent (type 1) diabetes mellitus with secondary complications including retinopathy, nephropathy, and neuropathy [60–62]. Identical histologic changes can be seen in breast tissue from patients with non-insulin-dependent (type 2) diabetes mellitus, autoimmune and/or endocrine diseases (particularly thyroid disease), and in nondiabetic patients with no evidence of autoimmune disease [62, 63].

Diabetic mastopathy typically occurs in women in their 20s–40s, with rare cases occurring in men [60, 62–64]. Patients most often present with a non-painful palpable mass, multiple masses, or diffuse nodularity. The mass or masses may be localized to the subareolar region [63]. In other instances, an abnormality is detected on screening mammography. The disease can be unilateral or bilateral. Logan and Hoffman reported 36 patients with diabetic mastopathy who all presented with palpable abnormalities, 24 (67%) of which presented with multiple nodules [64]. In a series of 19 patients with diabetic mastopathy (17 women, 2 men) reported by Ely et al., 15 patients presented with a unifocal lesion and 4 patients presented with bilateral disease [63].

Gross and Radiologic Features

Grossly, diabetic mastopathy most often shows fibrous breast parenchyma or an ill-defined firm area but does not usually show a discrete mass. Diabetic mastopathy has a variable radiographic appearance which in some cases may be suggestive of malignancy. Mammography shows an ill-defined mass, architectural distortion, or indeterminate fibrous tissue without a discrete mass [65]. On sonography, diabetic mastopathy has been reported to appear as an irregular hypoechoic solid mass with posterior shadowing [65–67]. In some cases, ultrasound may not show a mass to correlate with an area of palpable concern [61]. Findings on MRI are nonspecific and can show patchy or diffuse homogeneous low enhancement or may not reveal any abnormality [67–69].

Microscopic and Immunohistochemical Features

Diabetic mastopathy is characterized by a constellation of findings including stromal fibrosis, epithelioid fibroblasts, and lymphocytic infiltrates in a periductal, perilobular, and perivascular distribution (Fig. 4.23). The fibrous stroma is dense with keloidal features and a glassy appearance (Fig. 4.24). Plump epithelioid stromal fibroblasts are characteristic and show round to ovoid vesicular nuclei and abundant eosinophilic cytoplasm. Their distribution is scattered within the stromal and they may be sparse or absent. Ely et al. reported epithelioid fibroblasts in 14 of 19 (74%) of cases, including three cases in nondiabetic patients [63]. These cells were not seen in the two cases occurring in men in their study. Lymphoid infiltrates are well defined and are prominent around ducts and lobules, while variably present around small vessels. Infiltrates are composed of small mature lymphocytes that are mostly B cells by immunohistochemistry and a smaller population of admixed T cells [70]. Plasma cells may be associated with the lymphocytic infiltrates. Germinal centers are not usually present.

Fine-needle aspiration cytology is difficult to perform in cases of diabetic mastopathy due to dense stroma and will be non-diagnostic in most cases due to the small quantity of tissue withdrawn [64]. Smears are hypocellular and scant and may consist of benign ductal cells, scattered fibroblasts, and fragments of collagen [71].

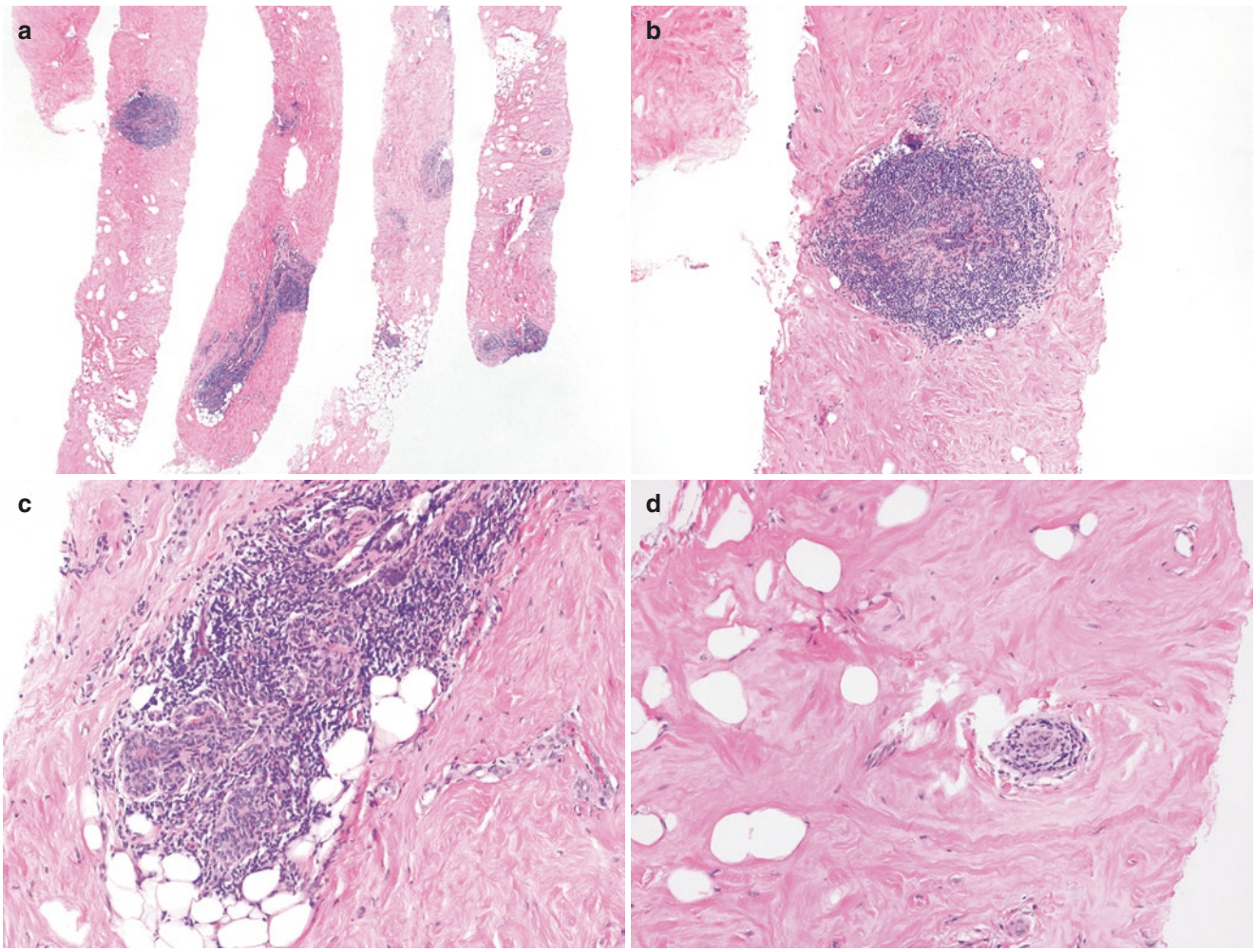

Fig. 4.23 Inflammation in diabetic mastopathy. Core biopsy in this case was performed due to the presence of an asymmetric density on ultrasound. (**a**) Low-power examination reveals lymphoid infiltrates within a fibrous stroma. (**b**, **c**) Lymphocytes are seen surrounding ducts and lobules. (**d**) Perivascular (capillary) lymphocytic inflammation is also present. The stroma shows dense fibrosis

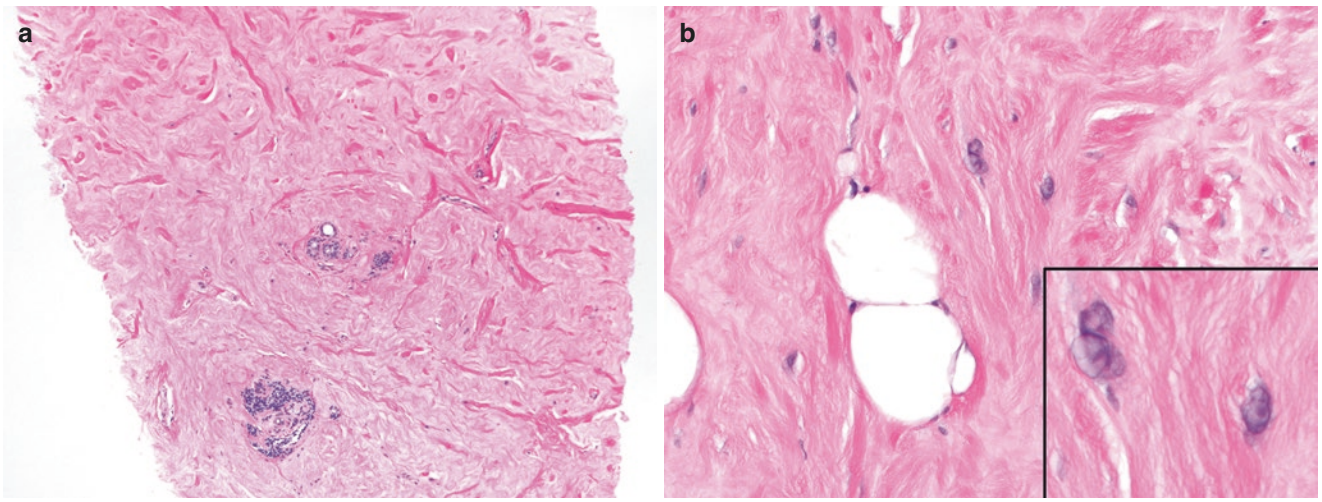

Fig. 4.24 Stromal changes in diabetic mastopathy. (**a**) Dense hypocellular fibrous tissue with broad bands of keloidal-like collagen without characteristic epithelioid fibroblasts. (**b**, **c**) Epithelioid fibroblasts are present within the hyalinized "glassy" stroma. (**d**, **e**) Case of diabetic mastopathy with cellular proliferation of fibroblasts with abundant pink cytoplasm

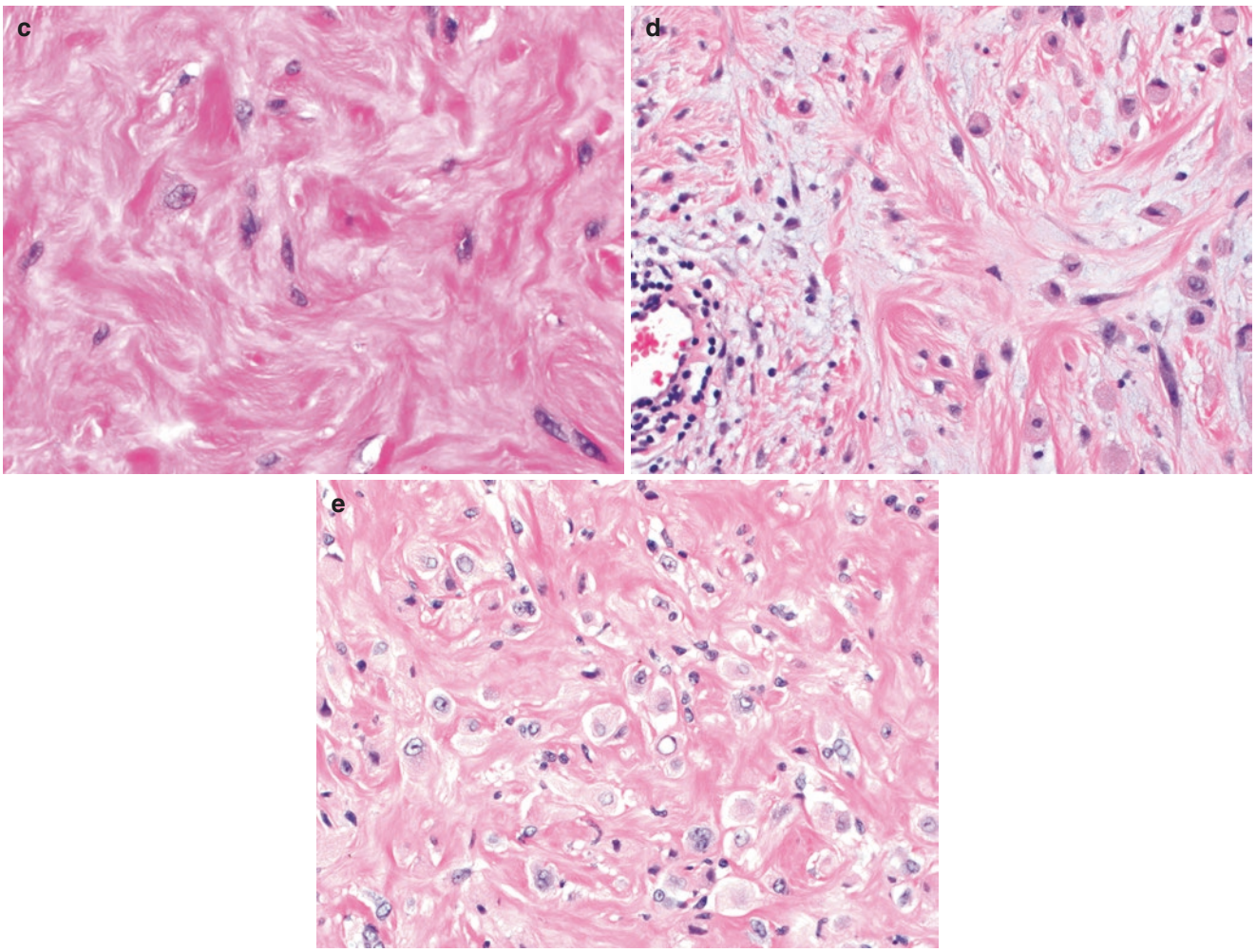

Fig. 4.24 (continued)

Differential Diagnosis

The entire constellation of findings of diabetic mastopathy may not be present, particularly in a small core biopsy sample (Fig. 4.25). When diabetic mastopathy is suspected in a core biopsy, knowing whether the patient is diabetic or has an autoimmune disease is helpful in establishing a diagnosis. Epithelioid fibroblasts with abundant cytoplasm can mimic invasive carcinoma and in suspicious cases, a cytokeratin immunostain can be performed to rule out carcinoma. Granular cell tumor can have a similar appearance to these cells in some cases and can be distinguished from diabetic mastopathy due to its granular cytoplasm and immunoreactivity with S100 protein and CD68. Multinucleated stromal giant cells can also be present within a fibrotic stroma and can mimic epithelioid fibroblasts in diabetic mastopathy. Stromal fibrosis as a component of fibrocystic changes can have a similar clinical and radiographic appearance as diabetic mastopathy and can show similar stromal changes on histology; however, epithelioid fibroblasts are not a feature of stromal fibrosis. Periductal, perilobular, and perivascular lymphoid infiltrates are not usually present in the aforementioned lesions in the differential diagnosis.

Lymphoid infiltrates/aggregates can be seen in a variety of reactive and neoplastic breast lesions, but do not show the same distribution as diabetic mastopathy and are not associated with stromal findings discussed above. Lymphoma involving the breast, for example, does not form well-defined infiltrates of cells, but rather shows diffuse infiltration of glands and stroma by neoplastic lymphoid cells. Immunostains and/or molecular studies show a clonal population of cells in lymphoma, which is not seen in diabetic mastopathy.

Pathogenesis

Multiple factors may be involved in the pathogenesis of diabetic mastopathy. One theory is that the fibrous stroma seen in diabetic mastopathy is due to glycosylation of col-

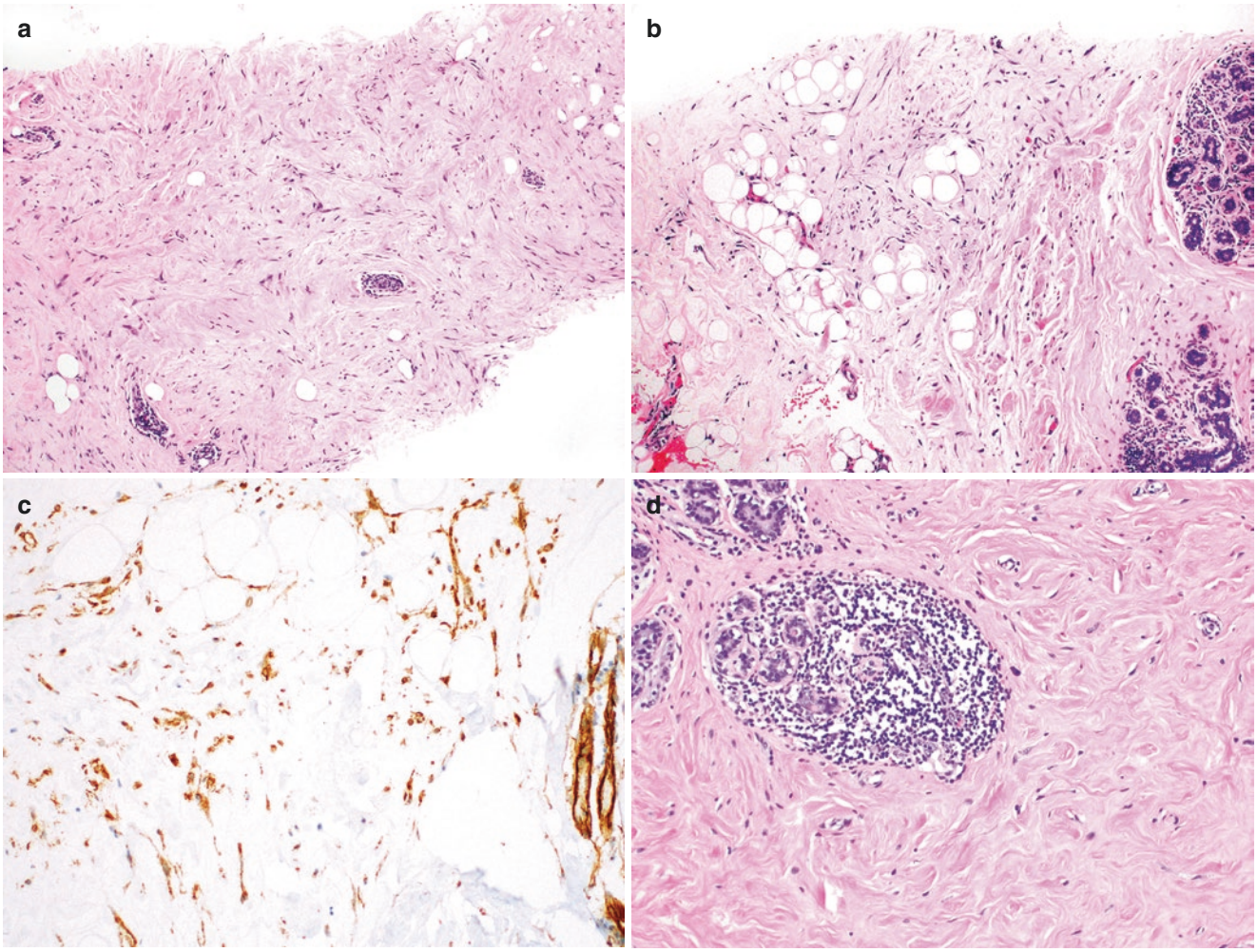

Fig. 4.25 Diabetic mastopathy appearing as a spindle cell lesion in a core biopsy. (**a**) Dense fibrous tissue containing stellate spindle cells with lymphocytes surrounding capillaries. (**b**) Spindle cells appear to infiltrate fat. Benign lobules (right) show scant inflammatory cells. (**c**) A beta-catenin immunostain was performed because fibromatosis was considered. Beta-catenin shows nonspecific cytoplasmic staining. (**d**) Excision of the lesion revealed more classic features of diabetic mastopathy with dense perilobular lymphoid aggregates and epithelioid fibroblasts

lagen, making it more resistant to degradation [62]. Seidman et al. suggested that diabetic mastopathy develops as a result of an immunologic response to exogenous insulin, its vehicle, or a contaminant in the vehicle [72]. Tomaszewski et al. hypothesized a sequence of events to explain the development of diabetic mastopathy, which included stromal matrix expansion due to hyperglycemia, accumulation of advanced glycosylation end products that possibly act as neoantigens, which lead to a B cell autoimmune lymphocytic response. This results in cytokine release and further matrix expansion [60].

Autoimmunity has been suggested to play a role because of the association between diabetic mastopathy and autoimmune diseases, in both diabetics and nondiabetics [62, 73]. As seen in autoimmune diseases, the lymphocytic infiltrates in diabetic mastopathy are predominantly composed of B lymphocytes, while other types of mastitis are composed mainly of T lymphocytes [60, 70, 73]. The lymphocytes in diabetic mastopathy have not shown evidence of clonality by immunoglobulin heavy chain gene rearrangement studies [70].

Prognosis

Diabetic mastopathy is a benign condition, and affected patients do not appear to have an increased risk for the development of carcinoma or lymphoma [64, 70, 74]. Unilateral and/or bilateral recurrences of diabetic mastopathy may occur following surgical excision. Ely et al. reported recurrences in 6 of 19 (32%) patients, including 3 patients that had multiple recurrences [63]. Five of 34 (15%) cases of diabetic mastopathy recurred (2 ipsilateral, 3 bilateral) in another report [67]. When identified in a core biopsy, surgical excision is not recommended unless findings are clinically or radiographically suspicious for malignancy or if histologic findings do not correlate with imaging.

Amyloidosis

Overview

Amyloidosis is a heterogeneous group of diseases that cause tissue damage by extracellular deposition of abnormal fibrous proteins called amyloid. Breast amyloidosis is rare and can be part of systemic disease, where amyloid is present in multiple organs, or localized without extramammary involvement. Most reported cases have been identified in postmenopausal women with a mean age at diagnosis of 63 years, ranging from 43 to 86 [75, 76]. The clinical and radiologic findings are nonspecific, commonly presenting as painless, solitary mass or multiple breast masses with or without associated calcifications [77]. Typically breast biopsies are done to exclude malignancy. Recognition of amyloid deposits is essential to exclude an association with a significant underlying disease as approximately 50% of patients have a hematologic disorder, predominantly malignant B cell neoplasms, including extranodal marginal zone lymphoma, diffuse B cell lymphoma, or plasma cell proliferations [78]. Diagnosis can only be made through histologic examination where the presence of pink, amorphous amyloid deposits can be confirmed with Congo red staining which shows a characteristic green birefringence under polarized light. The prognosis depends on whether the disease is localized or systemic.

Pathogenesis

To date 36 different types of amyloid protein structures have been described in humans. The most common types are primary immunoglobulin light-chain amyloidosis (AL) and secondary (AA) amyloidosis. AL amyloidosis is associated with plasma cell dyscrasias or multiple myeloma whereas AA amyloidosis is associated with chronic inflammatory conditions, including autoimmune disease such as rheumatoid arthritis [77]. Most commonly amyloid diffusely involves the breast in the systemic form of AL type amyloidosis [75]. The pathogenesis of localized AL amyloidosis in the breast without a concomitant hematolymphoid disorder is unknown though may be related to immunoglobulins secreted by plasma cells along with other undetermined factors [78]. Sjogren syndrome, an autoimmune disease of unknown etiology, has been associated with breast amyloidosis in 7 reported cases [79].

Gross and Radiologic Findings

There are no specific gross features of amyloidosis. The most common mammographic presentation is single or multiple masses with or without grouped calcifications [75–77]. Infrequently, breast amyloidosis can present as a spiculated density or pleomorphic calcifications without an associated mass. Rarely, in systemic amyloidosis, there may be diffuse involvement with skin thickening mimicking an inflammatory carcinoma [80]. Ultrasound features are nonspecific and include an ill-defined hypoechoic mass or heterogeneous masses with posterior acoustic shadowing [81]. Amyloidosis demonstrates low signal intensity on T1 and high signal on T2-weighted MRI [82].

Microscopic Features

Amyloid has a uniform, pink, waxy appearance and forms nodular deposits around ducts and lobules and the epithelial basement membranes can be markedly thickened (Fig. 4.26). Deposition can also be seen in fibrous and adipose tissue

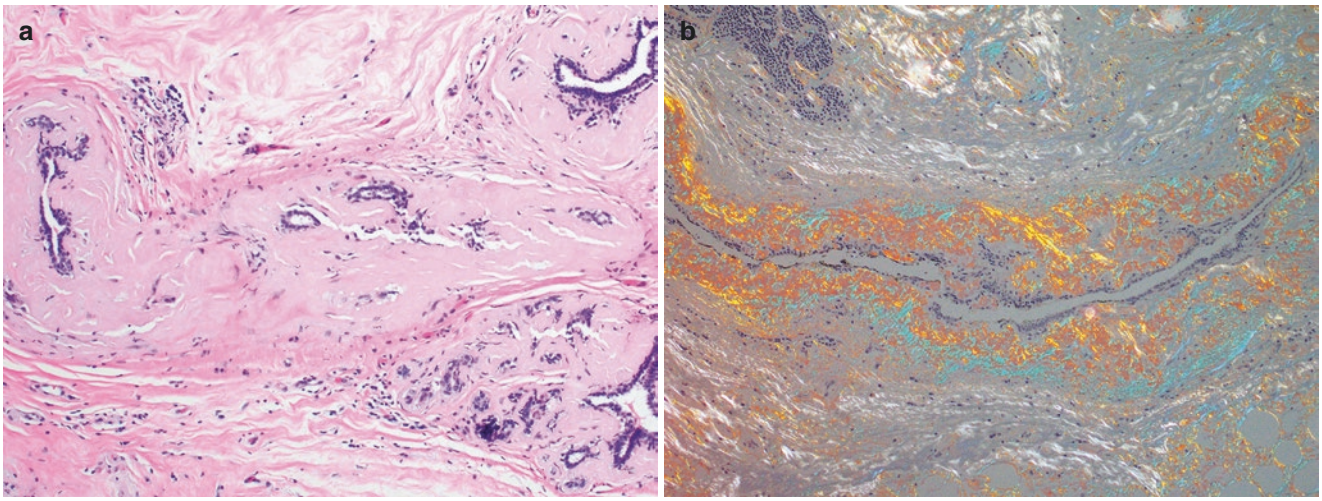

Fig. 4.26 Amyloidosis in the breast (**a**) Amyloidosis in a periductal distribution. (**b**) Congo red shows apple green birefringence of amyloid

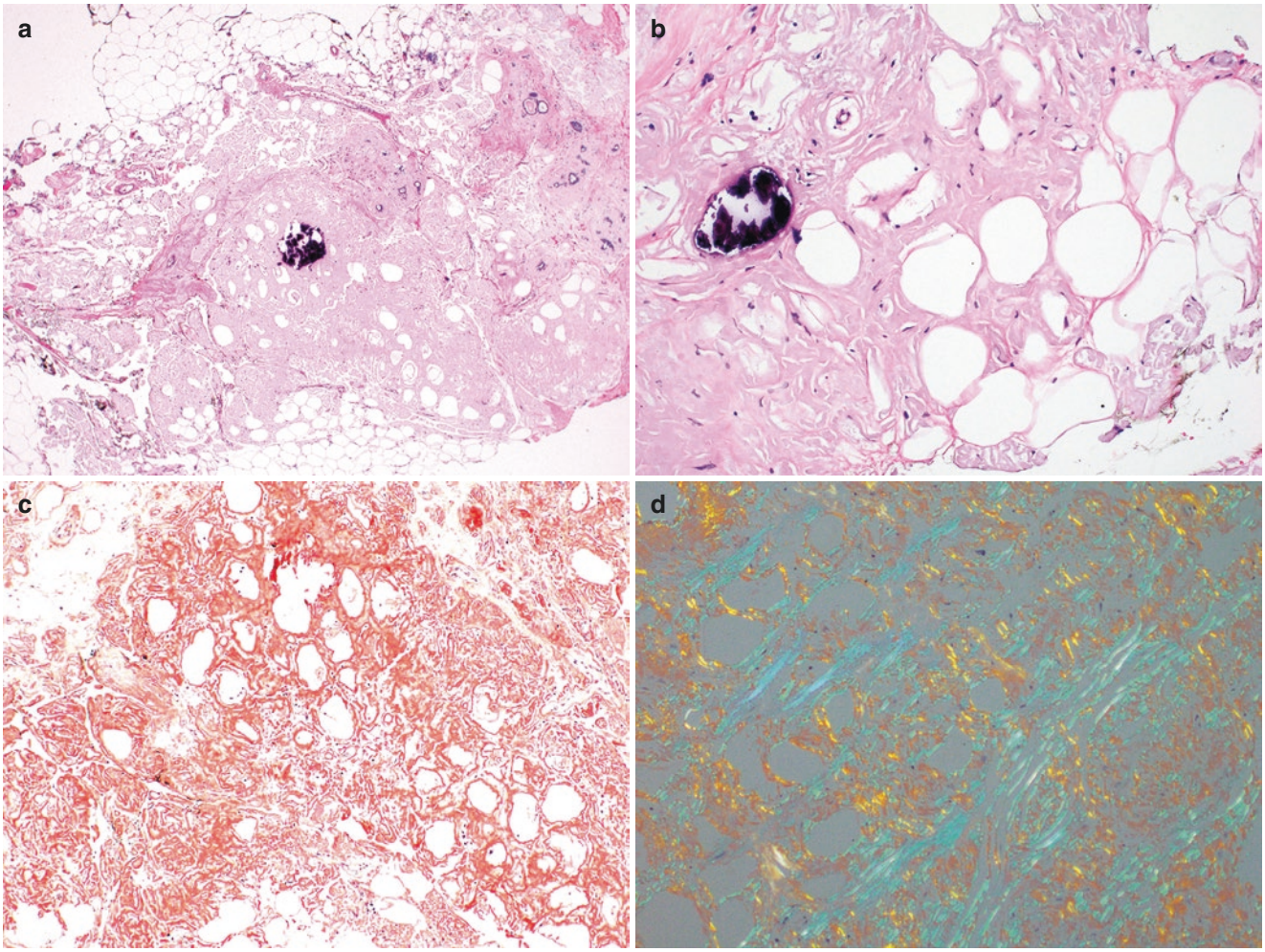

Fig. 4.27 Amyloidosis in a stereotactic biopsy performed for mammographic calcifications. (**a**) Eosinophilic material is present in association with fat and is calcified. (**b**) Higher power reveals waxy amorphous amyloid and calcification. (**c**) A Congo red special histochemical stain shows deep orange-red staining. (**d**) The Congo red stain shows apple green birefringence under polarized light

(Fig. 4.27) and along vascular channels, in the form of small nodules. Scattered multinucleated giant cells and calcifications are frequently present with amyloid. Amyloid in axillary lymph nodes has been described as sheet-like patchy deposits intermixed with lymphocytic proliferations with plasmacytic differentiation [77]. Amyloid stained with Congo red will show an orange-red color on light microscopy and will reveal characteristic apple green birefringence under polarized light (Figs. 4.26b and 4.27d). Because at least 50% of patients have a concurrent B cell lymphoma, most commonly extranodal marginal zone lymphoma, this diagnosis should be excluded through appropriate pathologic and clinical evaluation in any patient with mammary amyloidosis. Further, Congo red stains are recommended in patients with extranodal marginal zone lymphoma on breast core needle biopsy to exclude coexistent amyloidosis [78].

Differential Diagnosis

Due to the significant association of amyloidosis with hematologic disorders, lymphoma should be suspected and must be ruled out in cases where amyloid is identified, especially in the presence of a lymphocytic infiltrate. Amorphous amyloid deposits in fibroadipose tissue can resemble fat necrosis; a complete clinical history could be helpful in making this distinction. Densely collagenized tissue or elastosis can have the appearance of amyloid and large nodular deposits may mimic fibroadenomatoid changes; however, the small nodular deposits along basement membranes and vascular channels typical of amyloid would not be seen. Likewise, diabetic mastopathy shows a keloidal-like hyalinized stroma but amyloid lacks the dense lymphocytic infiltrates characteristically seen around lobules and blood vessels.

Prognosis

Localized primary breast amyloidosis is benign and has a good prognosis. The main treatment is surgical excision [76]. In contrast, patients with systemic amyloidosis have systemic disease with abnormal amyloid proteins causing organ dysfunction or failure. These patients have a generally poor prognosis and are managed medically [80].

IgG4-Related Sclerosing Mastitis

Overview

Immunoglobulin G4-related disease (IgG4-RD) is a chronic fibroinflammatory condition whose exact cause is unknown but is likely due to an autoimmune response to an inciting antigen which has yet to be elucidated. First identified in the pancreas as autoimmune pancreatitis, IgG4-RD has now been described in almost every organ of the body. Multiple organ sites can be affected, each showing a similar triad of histologic findings characteristic of the disease: a dense lymphoplasmacytic infiltrate rich in IgG4-positive plasma cells, fibrosis, and obliterative phlebitis. Serum concentrations of IgG4 are often elevated; however, 5% of the normal population can have elevated IgG4 levels and further up to 40% of patients with histomorphologic and immunhistochemical findings of IgG4-RD can have normal immunoglobulin concentrations [83, 84].

Breast involvement, presenting as IgG4-related sclerosing mastitis (IgG4-SM), is rare, with less than 50 cases described to date [85]. Affected patients range in age from 40 to 69 years old and all but two reported cases have been in women, in contrast to extramammary sites where males outnumber females 3 to 1 [84, 86]. Patients typically present with a discrete painless breast mass along with suspicious imaging findings, which can be concerning for malignancy. The recognition of this rare entity is important as the clinical features mimic carcinoma while the clinical course appears to be benign and in many cases the condition responds to steroid therapy [87].

Gross and Radiologic Features

Grossly the lesions of IgG4-SM are firm, tan, yellow masses. Necrosis and hemorrhage are not seen. Radiographic images demonstrate an ill-defined, asymmetric density [86].

Microscopic Features

An international symposium held in Boston in 2011 released consensus guidelines for the diagnosis of IgG4-RD, stating that two of three major histologic features are required along with either increased IgG4-positive plasma cells or an elevated IgG4/IgG plasma cell ratio. However, these guidelines allowed for site-specific criteria to be introduced as certain features may be inconspicuous or absent in some organs [83]. The first, and most consistent, major histologic feature is a dense lymphoplasmacytic infiltrate composed of small lymphocytes, predominantly T cells with admixed B cells, forming diffuse sheets or nodular aggregates with interspersed germinal centers along with a prominent plasma cell component (Fig. 4.28). An increase in the number of eosinophils is a minor supporting feature. The second feature is stromal fibrosis, arranged at least focally in a storiform pattern in which fibroblasts resemble a cartwheel or pinwheel in that spindle cells radiate around a common point. The final major criterion is obliterative phlebitis where veins are obliterated by a dense lymphoplasmacytic infiltrate; elastin stains may be helpful to identify venous walls. Phlebitis without obliteration of the lumen is a minor supporting feature. While it may be difficult to identify these features due to the inherent limitations of small core needle biopsy samples, it should be noted that in the breast, storiform fibrosis and obliterative phlebitis are reported to be infrequently identified and are often absent compared to other sites involved by IgG4-RD [86, 88, 89]. In IgG4-SM, breast lobules are lost in areas with heavy infiltrate and lymphoepithelial lesions are not seen [90]. Large aggregates of macrophages, especially foamy histiocytes and multinucleate giant cells, are inconsistent with IgG4-RD. Likewise, granulomas, prominent neutrophilic infiltrate and necrosis argue strongly against the diagnosis [84]. While histopathologic evaluation is the best method for detecting IgG4-SM, the diagnosis cannot be established without an immunohistochemical stain for IgG4.

An increased IgG4-positive plasma cell count or an IgG4/IgG plasma cell ratio is needed to meet the second consensus requirement (Fig. 4.29). An absolute IgG4-positive plasma cell count of >50 per high-power field is highly specific; however, in biopsy samples the presence of >10 IgG4-positive plasma cells could be sufficient, depending on the organ [83]. Therefore the IgG4/IgG plasma cell ratio is a better way to establish elevated IgG4 levels than absolute counts. A ratio of >40% is considered to be high in any organ.

Differential Diagnosis

Despite the worrisome clinical impression of IgG4-SM for mammary carcinoma these two diagnoses can be easily distinguished by the lack of neoplastic epithelial cells. However, it is important to not mistake benign ductal cells which may become entrapped in the lesion as malignant epithelium. The diffuse proliferation of lymphoid cells may give an initial low magnification impression of a lymphoma, but closer

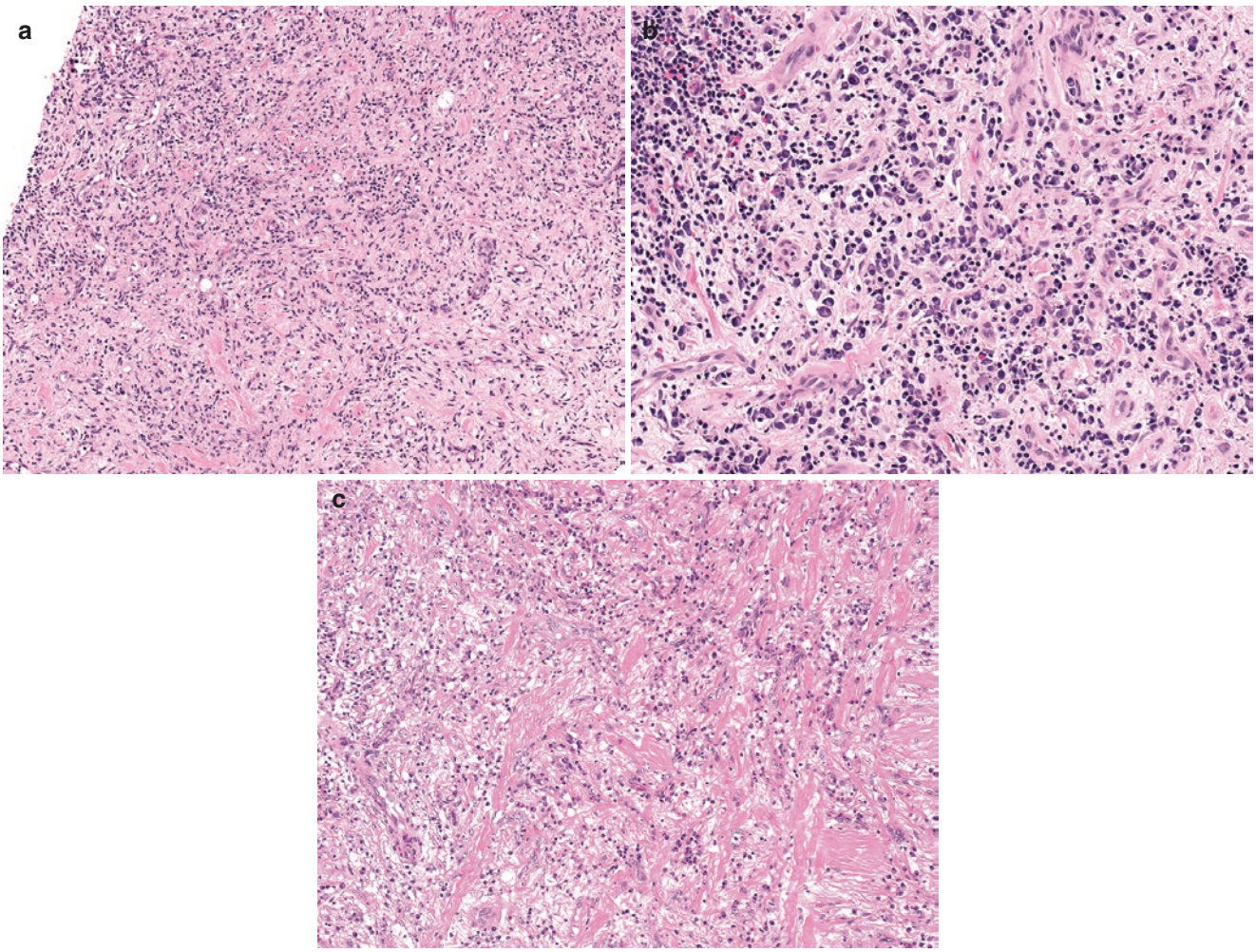

Fig. 4.28 IgG4-related sclerosing mastitis in a core biopsy of a breast mass. (**a**) A mixed inflammatory infiltrate associated with fibrosis is evident. (**b**) Higher power shows an abundance of plasma cells, scattered lymphocytes, and rare eosinophils. (**c**) Fibrosis is seen as broad bands of collagen. (*Images courtesy of Gulisa Turashvili, MD, PhD*, Mount Sinai Hospital, University of Toronto, with permission)

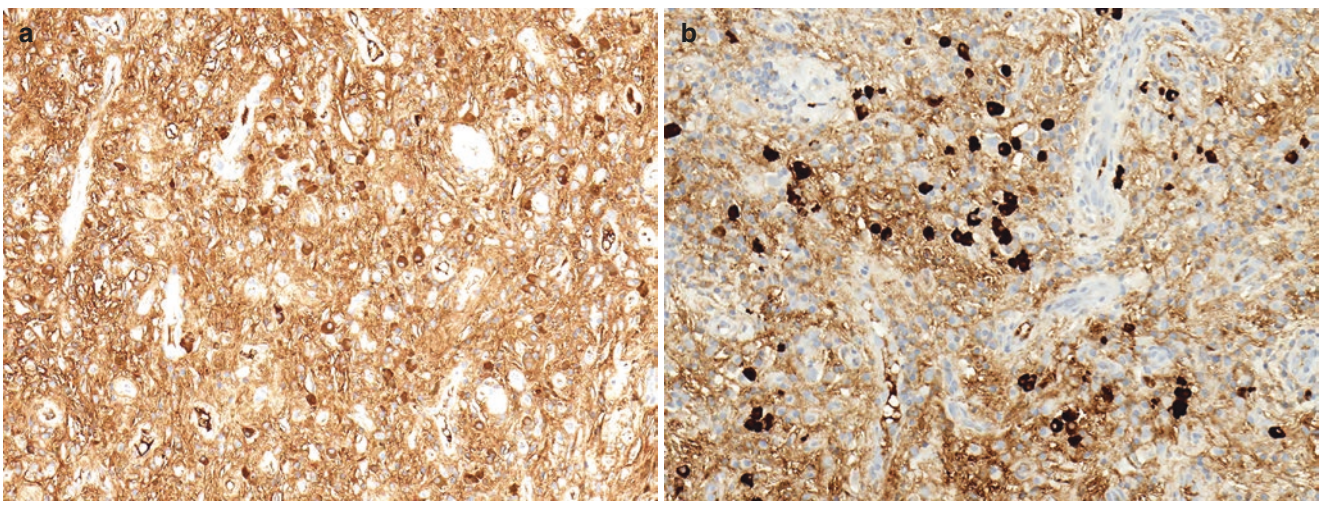

Fig. 4.29 IgG and IgG4 immunohistochemistry in IgG4-related sclerosing mastitis. (**a**) An IgG immunostain highlights IgG-positive plasma cells. (**b**) An IgG4 immunostain shows that a high proportion of IgG-positive plasma cells express IgG4. (*Images courtesy of Gulisa Turashvili, MD, PhD*, Mount Sinai Hospital, University of Toronto, with permission)

examination will reveal a polymorphous population of inflammatory cells, including plasma cells, T and B lymphocytes, and eosinophils. Plasma cell mastitis presents acutely as a painful or tender breast mass and the histologic appearance is one of extravasated secretions inciting an inflammatory reaction composed of histiocytes, giant cells and a periductal plasma cell infiltrate. Thus, the clinical and histologic features are discordant with IgG4-SM. Granulomatous lobular mastitis is characterized by lobulocentric, non-necrotizing granulomas composed of giant cells, epithelioid histiocytes, neutrophils, and plasma cells. IgG4-SM lacks a lobulocentric pattern, granulomas, and neutrophils. Diabetic mastopathy, like IgG4-SM, is characterized by stromal fibrosis and a lymphocytic infiltrate; however, the fibrosis in diabetic mastopathy is keloidal-like and tends to predominate over the lymphocytic infiltrates, comprised predominantly of B cells with scant plasma cells, which are well defined and tightly circumscribed around the lobules and blood vessels. More commonly seen in lymph nodes, Rosai–Dorfman disease shows atypical S100 protein-positive histiocytes with prominent nucleoli, abundant cytoplasm and engulfed neutrophils and erythrocytes, known as emperipolesis. Elevated levels of IgG4-positive plasma cells have been identified in cases of Rosai–Dorfman disease; however, none met the criteria defined for IgG4-SM [91]. Inflammatory myofibroblastic tumor is a bland spindle cell proliferation with an associated lymphoplasmacytic infiltrate. These lesions lack lymphoid aggregates and obliterative phlebitis and approximately half are positive for anaplastic lymphoma kinase (ALK) by immunohistochemistry. A caveat is that a small subset has been observed to have increased numbers of IgG4-positive plasma cells and an elevated IgG4/IgG ratio with half also being negative for ALK and so could be classified as IgG4-SM [92].

Prognosis

The clinical course is benign, and IgG4-SM responds to and improves with steroid therapy [87]. In 15 reported cases with available outcome information, all showed complete resolution and no recurrence after a median of 12 months following either surgical excision or steroid therapy [86].

Inflammatory Myofibroblastic Tumor

Overview

Inflammatory myofibroblastic tumors (IMT) are low-grade neoplasms composed of myofibroblastic and fibroblastic spindle cells with prominent admixed inflammatory cells which can occur at any anatomic site with the most common presentation being in the lung or soft tissues of children and young adults. IMT is rare in the breast, with only 31 reported cases to date since its initial description [93, 94]. The etiology is unclear but approximately half of cases harbor a clonal chromosomal rearrangement that activates the *ALK* receptor tyrosine kinase gene, leading to the formation of a fusion protein that can be detected by immunohistochemistry or fluorescence in situ hybridization [95].

Affected patients present with nonspecific signs and symptoms such as fever, weight loss, anemia, or hyperproteinemia, seen in 15–30% of cases [96, 97]. Most patients with IMT are children or young adults; however, the tumor can occur at any age. Of the reported breast IMT cases, the average patient age is 44, ranging between 13 and 86 years, with approximately 1/3 of cases occurring in women less than 30 years old [93]. Patients generally present with a palpable, slightly tender breast mass that may be adherent to the skin. IMTs can be concerning for malignancy based on clinical and imaging findings. IMTs in the breast typically follow a benign course following complete surgical resection [98].

Gross and Radiologic Features

Gross examination reveals firm, circumscribed nodules ranging in size from 1 to more than 20 cm, with a mean size of 6 cm [96]. The cut surface is gray-white to yellow, fleshy, or gelatinous. The radiologic findings are nonspecific with ultrasound showing ill-defined or well-defined hypoechoic masses, with an average lesion diameter of 29 mm [93].

Microscopic Features

The morphology is characterized by a proliferation of bland myofibroblasts admixed with an inflammatory infiltrate (Fig. 4.30). The spindle cells of IMT are uniform in appearance with ovoid to tapered nuclei, small nucleoli, pale to eosinophilic cytoplasm, and are arranged in one of three patterns. These include a myxoid/granulation-tissue type (fasciitis-like) pattern, a compact spindle cell pattern, and a fibromatosis or scar-like pattern. Combinations of these patterns often occur in the same tumor. The myxoid/granulation tissue pattern has a nodular fasciitis-like appearance consisting of plump spindle cells loosely arranged in a myxoid or edematous stroma with a prominent inflammatory infiltrate, composed of plasma cells, neutrophils, and eosinophils. A conspicuous vasculature can also be appreciated. The second pattern shows a compact, solid, and confluent spindle cell proliferation with fascicular growth and numerous plasma cells and lymphocytes. The fibromatosis-like pattern is paucicellular with elongated spindle cells in a background of abundant hyalinized collagen, resembling scar tissue, and

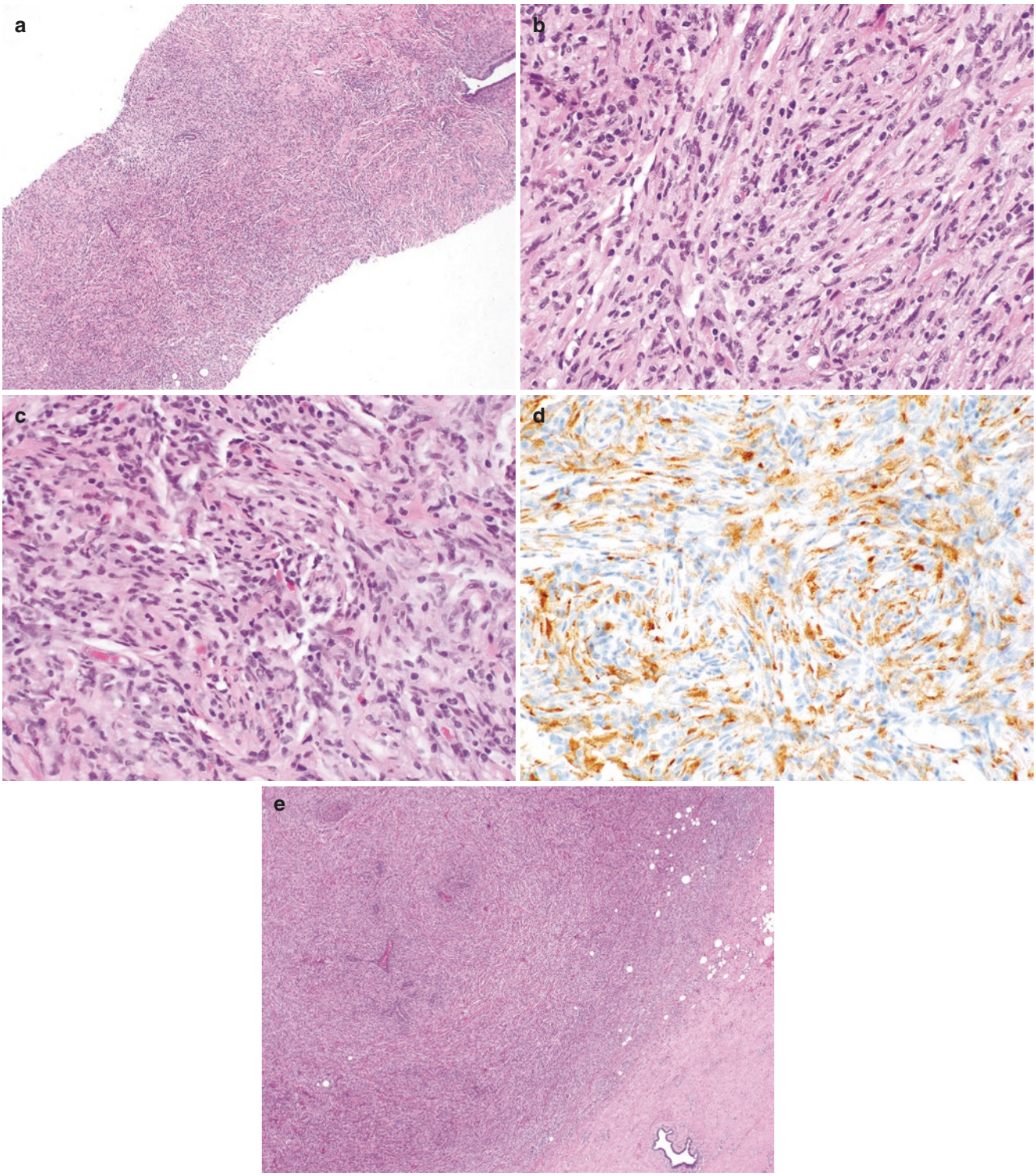

Fig. 4.30 Inflammatory myofibroblastic tumor of the breast. (**a**) Core biopsy shows a cellular proliferation with rare benign ducts. (**b**) Higher power shows fascicles of spindle cells with scattered lymphocytes. (**c**) Spindled myofibroblasts growing in a vaguely storiform patterns with scattered lymphocytes and eosinophils. (**d**) ALK immunohistochemistry shows diffuse staining in spindle cells. (**e**) Low-power view of excision specimen for IMT seen in **a-d**

contains scattered inflammatory cells. High-grade cytologic features, mitotic activity, and necrosis are uncommon features of IMT.

Immunohistochemistry

The spindle cells of IMT are myofibroblasts that show strong positivity for smooth muscle actin, desmin, and calponin in the majority of cases, although expression can be focal. Approximately 1/3 co-express cytokeratin, which can show focal reactivity [94]. The plasma cell infiltrate is polyclonal. Roughly half of IMTs are positive for ALK by immunohistochemistry (Fig. 4.30d); this expression has been reported to be more common in younger patients [96]. It should be noted that in one study, up to 24% of fusion-positive IMTs did not express ALK and thus it is recommended to perform fluorescence in situ hybridization testing on those ALK-negative tumors with morphologic features highly suggestive of IMT [95].

Differential Diagnosis

An important differentiating feature of IMT is ALK positivity, which when present aids in the diagnosis. Yet around half of IMTs are negative for ALK staining making the distinction from other spindle cell neoplasms more challenging. The most consequential differential diagnosis is metaplastic spindle cell carcinoma which can be confused for the compact spindle cell pattern, especially in those tumors which show keratin positivity. However, large aggregates of plasma cells are uncommon in metaplastic carcinomas and the carcinomas will often show at least focal nuclear hyperchromasia, brisk mitotic activity, or necrosis which are not typically identified in IMT. Similarly, fibromyxoid sarcomas are exceedingly rare in the breast and as with carcinoma would show spindled cells with marked nuclear pleomorphism and higher mitotic rates, features unusual in IMT. The hypocellular fibromatosis-like patterned IMTs raise the differential of fibromatosis which shows long, sweeping fascicles of bland spindle cells without atypia or mitoses in a background of variable stromal collagenization with irregular infiltrating margins. The associated lymphocytic infiltrate is often located peripherally and typically does not show abundant plasma cells. Like IMT, the spindle cells of fibromatosis are positive for smooth muscle actin and/or desmin while in contrast to IMT are negative for cytokeratin and characteristically show nuclear beta-catenin expression. Nodular fasciitis is rare in the breast, presenting typically as a small nodule, generally less than 2 cm, with rapid onset, pain and tenderness, contrary to the usually large painless mass associated with IMT. Histologically, it can mimic the myxoid/granulation-tissue type pattern showing a spindle cell proliferation with so-called tissue-culture like growth in a loose myxoid stroma. Mitotic activity is high and extravasated red blood cells can be seen scattered throughout while lacking the prominent inflammatory infiltrate of IMT. Biopsy site or surgical scarring with extensive granulation tissue can be excluded with the appropriate clinical history and/or the presence of fat necrosis in the adjacent soft tissues. Given the plasma cell rich infiltrate of IMT, it may be confused with IgG4-SM; however, IgG4-SM does not show plump, ovoid spindled cells or ALK positivity. Additionally, IgG4-RD is normally seen in adults, and it is important to remember IMT is uncommon in middle-aged or elderly patients. Evaluation with IgG4 immunohistochemistry is advised as this could identify IgG4-SM and prevent unnecessary surgery.

Prognosis

IMTs have different outcomes based on the tissue of origin, but most frequently follow a benign course. Surgical resection is considered the treatment of choice. Recurrence rates vary by location and completeness of resection, occurring in less than 2% for tumors in the lung and up to 25% in extrapulmonary sites. Distant metastases are observed in less than 5% of cases [96]. There have been at least two cases of distant metastases of breast IMT to date [99]. Rare malignant transformation has been reported [96]. It has been shown that a subgroup of ALK-fusion proteins are sensitive to ALK-inhibition, which suggests targeted kinase inhibition is a therapeutic option in these more aggressive forms of IMT [100].

Abscess and Infectious Conditions of the Breast

Overview

Infections in the breast (infectious mastitis) is uncommon. Infectious mastitis is most often bacterial and is seen in the setting of lactational mastitis and abscess. Much less frequently, other infectious processes including mycobacterial, fungal, and parasitic infections occur in the breast and can sometimes be the source of the mammographic abnormality leading to core biopsy.

Recognition of certain infections in the breast is important in the core biopsy setting so that appropriate medical therapy can be initiated, and unnecessary surgery can be avoided. This chapter will mainly focus on abscess, which is the most common infectious process encountered in a core biopsy. Other less common infectious processes will also be discussed.

Abscess

Overview

Abscess in the breast occurs most commonly during breastfeeding (lactational/puerperal abscess) or in the non-lactating breast as a subareolar (non-puerperal) abscess. In both settings, abscesses develop as a result of duct stasis. Core biopsy may be performed in cases of abscess to rule out malignancy because of suspicious clinical and radiographic features.

Lactational (puerperal) mastitis occurs in approximately 1–10% of lactating women and may be complicated by the development of abscess if not adequately treated [101–103]. Mastitis and abscess most often occur during the first 6 weeks of breastfeeding, but may also occur during the time of weaning, when milk stagnates within engorged ducts [104]. Patients with mastitis present with redness, warmth, swelling, tenderness, and sometimes fever. An abscess will show a tender fluctuant mass in addition to these findings [103]. Cracking of the nipple skin of the affected breast may serve as a point of entry for bacteria [103]. Other risk factors for the development of mastitis and abscess include primiparity, mastitis with a previous infant, poor hygiene, and improper nursing technique [101–103].

Non-puerperal abscesses are typically subareolar in location, and most often develop as consequence of squamous metaplasia of lactiferous ducts (described below under pathogenesis). The resulting clinical picture of recurring subareolar abscesses and fistula formation has been referred to as Zuska's disease and periductal mastitis [105]. Patients with subareolar abscesses are typically premenopausal women, but older women and males may also be affected [106, 107]. Patients present with a painful subareolar or periareolar mass that may be accompanied by a draining sinus. Nipple retraction can be seen [108]. Nipple discharge, if present, may have a pasty consistency. Bilateral disease is not uncommon. In a series of 152 patients reported by Habif et al., 40 (26%) presented with bilateral abscesses [106]. Cigarette smoking is strongly associated with the development of subareolar abscesses, and a history of smoking has been elicited in approximately 70–90% of patients [109–111]. In some reports, subareolar abscesses have developed following nipple piercing [111, 112]. Diabetes and obesity are other risk factors for the development of subareolar abscesses [111].

Radiologic Features

Ultrasound is the most effective imaging abnormality for evaluation of suspected abscess. Abscess appears as a hypoechoic mass or a hypoechoic collection that is often multiloculated and with a thick echogenic periphery [102, 108]. Mammography is not specific and can show an asymmetric density, mass, distortion, or skin thickening [101, 102]. Calcifications are not a feature of abscess [101].

Microscopic Features

A mixed inflammatory infiltrate mainly composed of neutrophils is seen involving breast tissue (Fig. 4.31). Glands may show lactational changes in lactational abscess (Fig. 4.32). Granulation tissue and chronic inflammation are seen as the abscess resolves. In a core biopsy of a subareolar abscess, dilated ducts may be identified, but squamous metaplasia is not always evident. Keratin material may be seen within the abscess with an associated foreign body giant cell reaction (Fig. 4.33). Bacteria may be identified and, in most cases, will be Gram-positive cocci in clusters (*Staphylococcus aureus*).

Differential Diagnosis

Clinically, the most important differential diagnosis for abscess is invasive carcinoma, particularly inflammatory carcinoma. In the pregnant or lactating patient, galactocele, nodular lactational hyperplasia (lactating adenoma), and fibroadenoma should be included in the differential diagnosis of a new mass. Infarcts may also occur during pregnancy and can present as a palpable tender mass [104]. Subareolar abscesses can clinically mimic malignancy, duct ectasia, and granulomatous mastitis. The histologic diagnosis of abscess is fairly straightforward based on the characteristic inflammatory and reactive findings. Granulomatous lobular mastitis and duct ectasia can be associated with the development of abscesses.

Pathogenesis

Abscess is the result of duct stasis in both lactational and non-lactational abscesses. With lactation, milk stasis within engorged ducts provides a lactose-rich environment for bacteria that enter through duct openings or cracks and fissures in the nipple. Subareolar abscesses develop when keratin debris accumulates in lactiferous ducts undergoing squamous metaplasia. This leads to duct rupture with spillage of contents into the stroma. A mixed inflammatory response is elicited with bacterial invasion, resulting in abscess formation [106, 108]. The abscess may eventually rupture spontaneously with the formation of a draining sinus. The

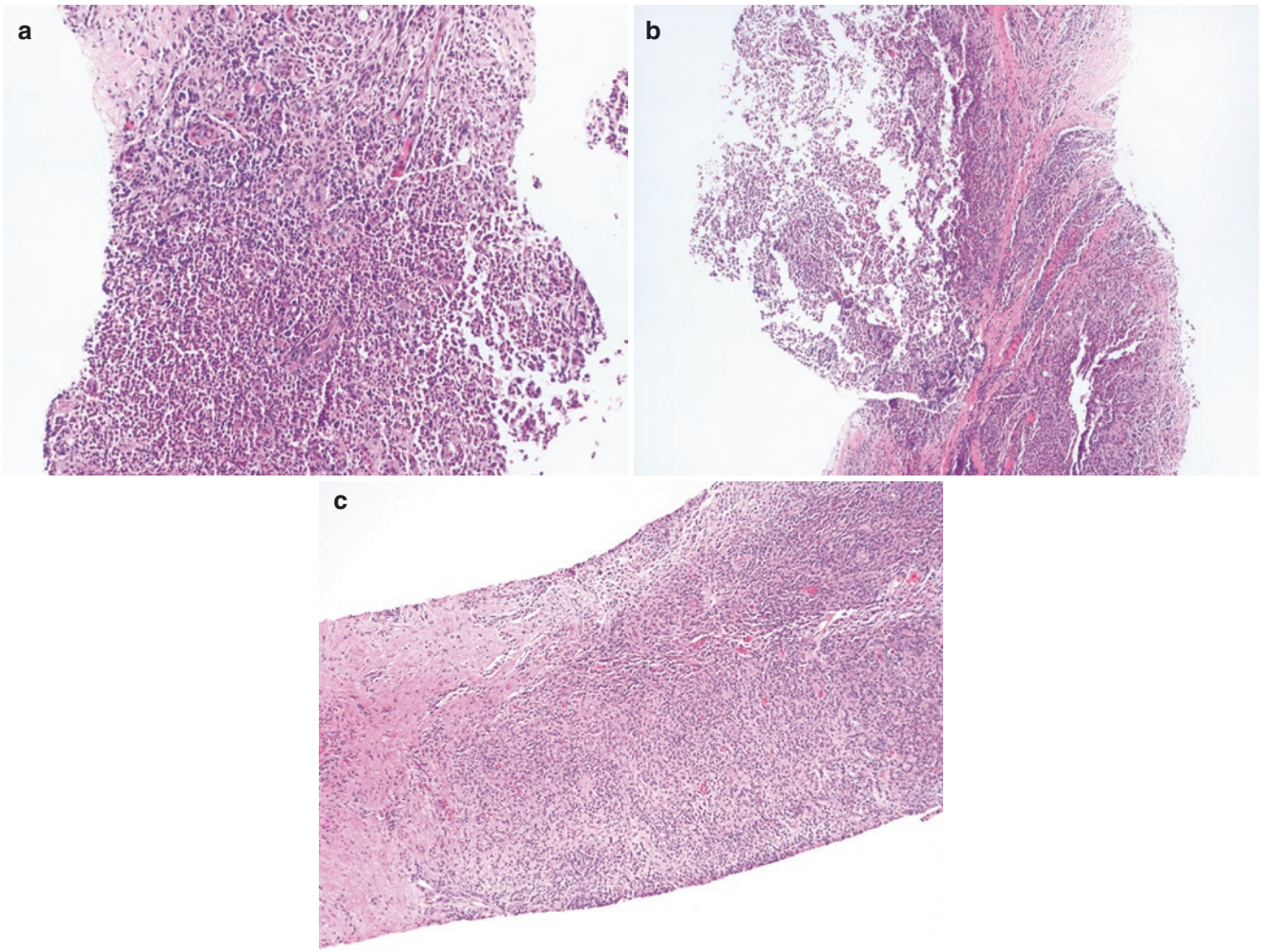

Fig. 4.31 Abscess in non-lactating breast. (**a**, **b**) Abscess centered on lobules with abundant neutrophils and plasma cells. (**c**) Core biopsy of resolving abscess with granulation tissue and plasma cells

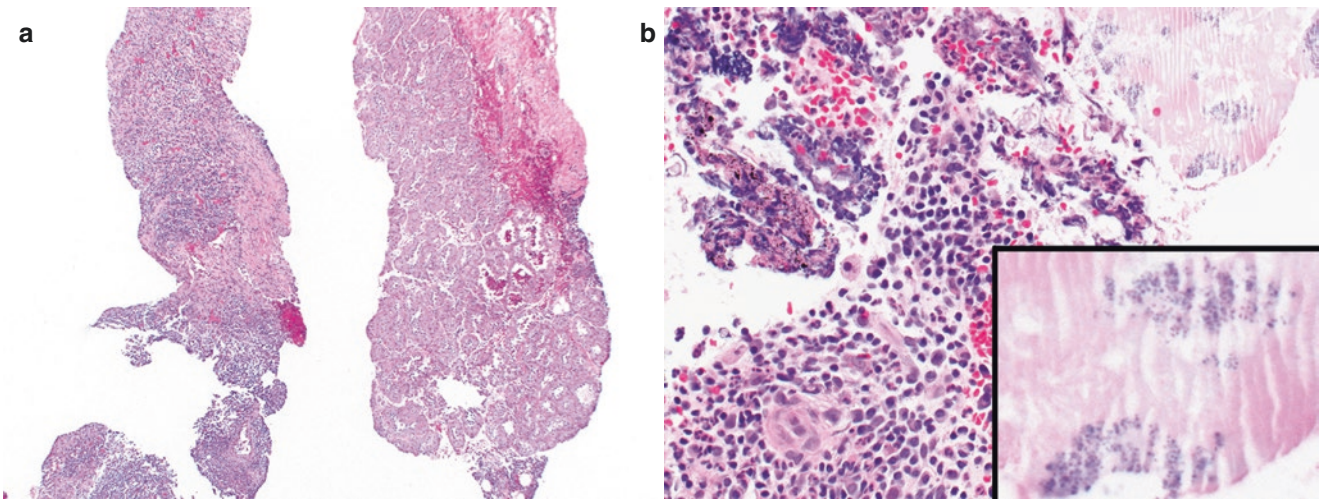

Fig. 4.32 Lactational abscess. (**a**) Core biopsy reveals and abscess with associated fibrosis (*left*) involving lactational breast tissue (*right*). (**b**) A mixed inflammatory infiltrate with plasma cells and neutrophils constitutes the abscess. Clusters of cocci bacteria (*top right* and high-power inset) are visible on H&E examination and are present within secretion (not necrosis)

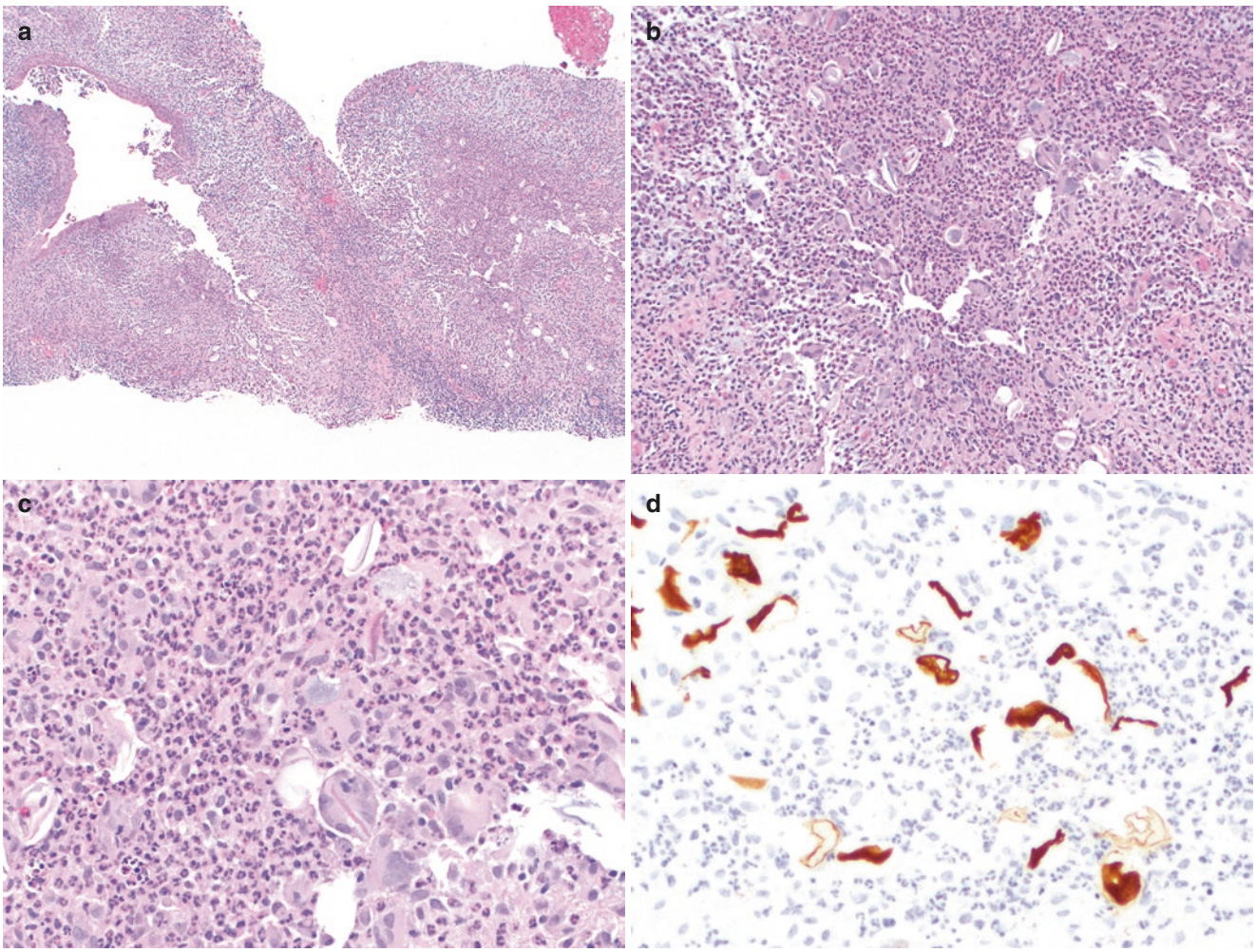

Fig. 4.33 Subareolar abscess in a core biopsy. (**a**) Core biopsy shows a mixed inflammatory infiltrate composed mainly of neutrophils. A duct with squamous metaplasia is seen on the left part of the image. (**b**, **c**) Keratin material is present within the abscess and is associated with a foreign body giant cell reaction. (**d**) A cytokeratin (AE1/AE3) immunostain highlights keratin material in the abscess

association of smoking with subareolar abscesses may be due to vitamin A deficiency, low blood levels of β-carotene, direct toxic effects, or hormonal stimulation [110, 111].

The most common organism isolated from breast abscesses is *S. aureus*, identified in approximately 50% of cases [103, 106, 109, 113]. In a series of 189 patients with breast abscess, *S. aureus* was isolated in 51.3% of positive cultures overall and in 67.7% of lactational abscesses (vs. 30.5% of non-lactational abscesses) [113]. Seven (8.6%) isolates were methicillin-resistant *S. aureus*. Subareolar abscesses tend to show mixed flora [111]. In a series of non-puerperal breast abscesses reported by Walker et al., most cultures showed a mixed flora of predominantly anaerobes, with coagulase-negative staphylococci being the most common aerobic organism isolated [114]. Other organisms that may be isolated from breast abscesses include mixed anaerobes, anaerobic cocci, Group D streptococci, and *Bacteroides* [113]. Cultures are negative in some cases, which may be a result of previous antibiotic therapy.

Prognosis

Lactational mastitis usually responds to antibiotics. Abscesses require surgical drainage along with antibiotics for the process to resolve and do not typically recur [115]. Nursing should be continued during treatment for most cases of mastitis and abscess and may help in resolving the process.

Subareolar abscess is a chronic and recurring condition with longer times to resolution and higher rates of recurrence compared with lactational abscesses [102, 109, 115]. Treatment involves a combination of antibiotics and surgery which includes excision of the abscess, sinus tract (if present), and

involved lactiferous duct. Significantly lower rates of recurrence are seen when the involved duct is excised compared with surgery that does not include duct excision [109, 110].

Other Infectious Conditions

Bacterial Infections

S. aureus, described above, is the most common bacteria isolated from mastitis and breast abscesses (described above). Granulomatous lobular mastitis with a "cystic neutrophilic granulomatous mastitis" pattern has been associated with *Corynebacterium* species [44].

Tuberculous Mastitis

Tuberculous mastitis is rare and occurs most often in patients with established infection with *Mycobacterium tuberculosis*. Patients present with palpable mass or masses in the breast that may be painful [116]. Most cases are unilateral [116, 117]. Aggressive cases can show skin ulceration and draining sinuses [118]. Nipple discharge may be present and AFB may be identified in smears from nipple discharge using a Ziehl–Neelsen stain [119]. Ipsilateral axillary lymph node involvement is seen in most cases and enlarged lymph nodes can be seen on mammography and ultrasound [117]. Imaging findings in the breast may be suggestive of abscess or can mimic malignancy if tuberculosis is unexpected [118]. In older lesions, calcified healed granulomas can be evident on mammogram [117].

Tuberculous granulomas are seen within lobules, surrounding ducts, and are present in the interlobular stroma. Granulomas are typically composed of epithelioid histiocytes and Langhans giant cells surrounding "caseous"-type necrosis. Acid-fast bacilli may not be detected in histologic sections. The gold standard for diagnosis is detection of *M. tuberculosis* by culture [120].

Fungal Infections

Histoplasmosis is caused by infection of *Histoplasma capsulatum*, a thermally dimorphic fungus common in river valleys in the United States [121]. Infection occurs via inhalation of spores, and most people infected are asymptomatic [121, 122]. Involvement of the breast is rare and histologically shows necrotizing granulomatous inflammation involving lobules. Narrow-based budding and non-budding yeast forms 2 to 4 μm in size can be demonstrated within histiocytes with a Grocott-Gomori's (or Gömöri) methenamine silver stain [122].

Mastitis or abscesses caused by Cryptococcus (*C. neoformans*) have been reported in immunocompetent and immunosuppressed patients and in the setting of disseminated cryptococcal infection [123, 124]. Budding yeast forms can be seen within sheets of foamy histiocytes on H&E (Fig. 4.34) and Periodic acid–Schiff or Grocott-Gomori's (or Gömöri) methenamine silver stains. Mucicarmine stains the polysaccharide capsule of the yeast.

Blastomycosis (*Blastomyces dermatitidis* or *B. gilchristii*) can occur in immunocompetent patients and may present as a breast mass in the setting of disseminated disease [125]. Infection occurs by inhalation of lung spores. Wooded areas and river valleys in the central United States are common areas of infection [126]. Infection can spread from the lungs to the skin and other organs. Necrotizing granulomas and abscesses are evident that may contain broad-based budding yeast that can be seen with a GMS stain [127].

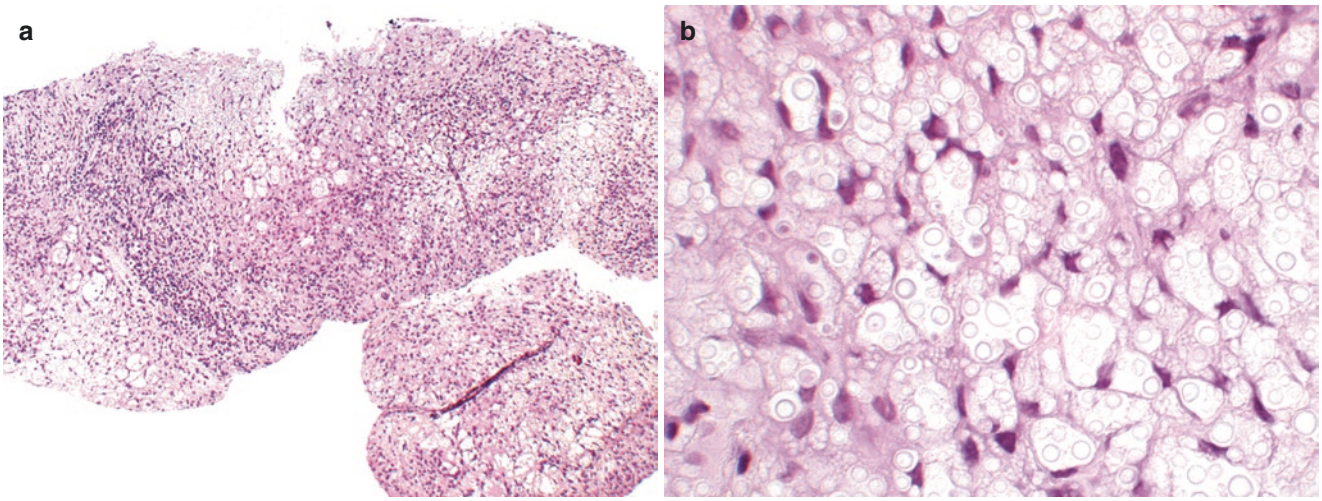

Fig. 4.34 Cryptococcus in a core biopsy. (**a**) Sheets of foamy histiocytes and lymphocytes are present in the biopsy. (**b**) Round yeast forms are present within the histiocytes. (*Courtesy of Susan Lester, MD*, Brigham and Women's Hospital, with permission)

Parasitic Infections

Schistosomiasis is a parasitic fluke that is uncommon in the United States but may be seen in patients from South East Asia, South America, and the Caribbean. Involvement of the breast by schistosomiasis comes to attention due to the presence of mammographic calcifications. Calcifications can show a segmental or clustered distribution that can mimic DCIS on mammography [128–130]. On histology, calcified ova are present around lobules and in the stroma, but not within ducts (Fig. 4.35). It is not possible to discern the species of schistosomiasis in most cases. *Schistosoma japonicum* is endemic to southeast Asia, while patients from the Caribbean and South America will likely be infected with *S. mansoni*, which is also endemic in parts of Africa. *S. haematobium* is found in Africa and the Middle East [131, 132].

Sparganosis, which usually occurs in Southeast Asia, is caused by infection with larvae of the tapeworm of the genus *Spirometra* [133]. Infection may be the result of drinking water contaminated with copepods containing *Spirometra* larvae. Consumption of raw snakes and frogs, the parasite's second intermediate host, is another way humans acquire the larvae [134]. Larvae migrate to subcutaneous tissue and the reported cases involving the breast typically occur in subcutaneous tissue, rather than breast glandular tissue. Patients present with a palpable mass that may be associated with pain or itching [133]. Biopsies of sparganosis show granulomatous inflammation with eosinophils associated with the body of the worm. The worm is lined by an eosinophilic tegument and has a myxoid appearing matrix that contains smooth muscle fibers and calcospherules (Fig. 4.36).

Cysticercosis can be distinguished from sparganosis by its scolex, hooks, and fluid-filled "bladder" surrounding the worm (Fig. 4.37) [135]. Cysticercosis is caused by infection of the larval form of *Taenia solium*. Larvae penetrate the intestinal mucosa and migrate to sites such as skeletal muscle, skin, and brain, and form cysts. Breast involvement has been reported in rare cases in which cystic lesions are formed [136, 137].

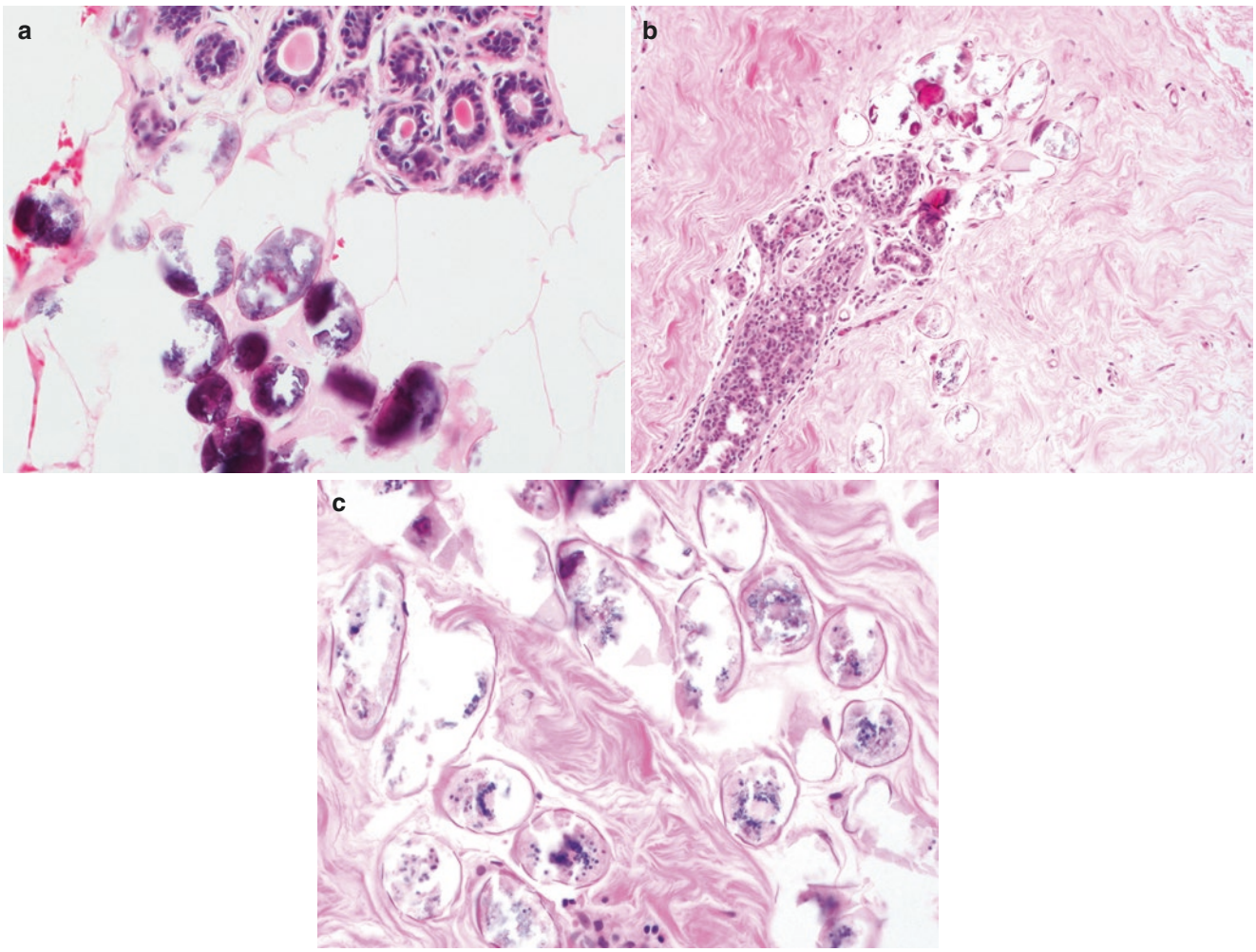

Fig. 4.35 Schistosomiasis in stereotactic biopsies performed for mammographic microcalcifications. (**a**–**c**) Calcified ova are present in perilobular stroma. ((**b**, **c**) *Courtesy of Adam Gersten, MD*, Albert Einstein College of Medicine, with permission)

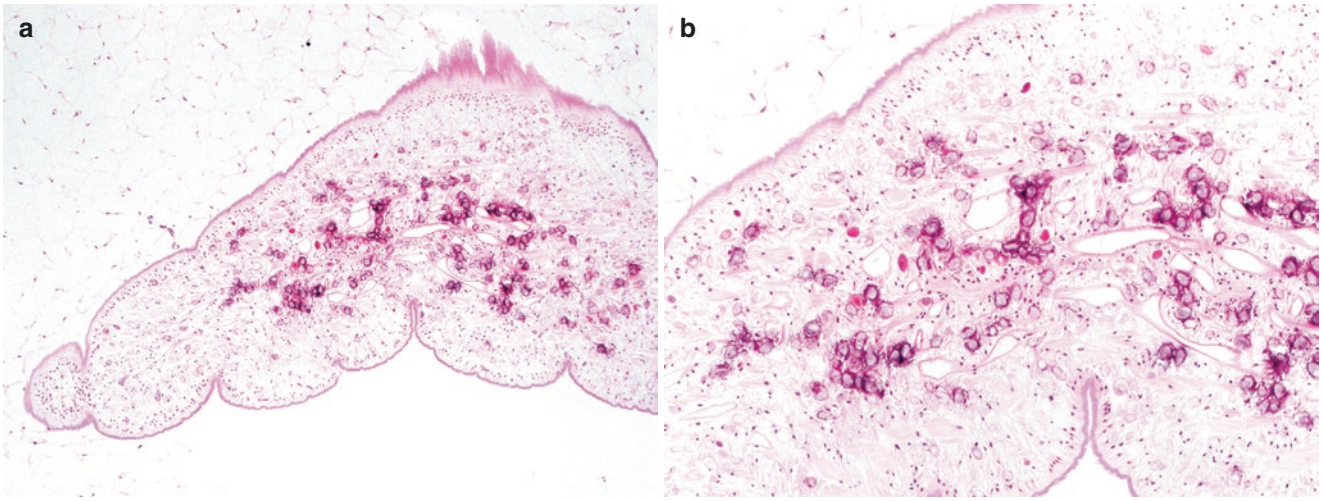

Fig. 4.36 Sparganosis. (**a**) The larva shows a myxoid matrix and contains calcified spherules. (**b**) Smooth muscle fibers can be seen on higher power

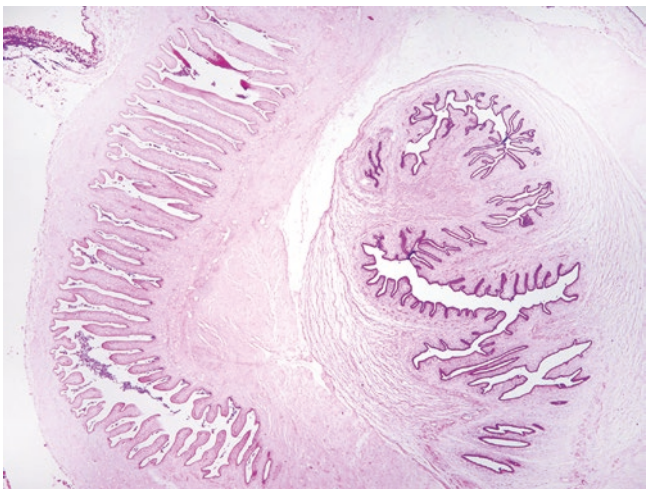

Fig. 4.37 Cysticercosis. The body of the larva is seen inside a fluid-filled "bladder"

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