Inflammatory and Reactive Lesions of the Breast

5

Simona Stolnicu

A variety of inflammatory and reactive processes can occur in the breast. Some inflammatory processes have an infectious cause; other lesions are manifestations of systemic diseases or of an autoimmune reaction. In some cases, the etiology cannot be accurately determined. Most of these lesions require a breast biopsy to confirm the diagnosis and to exclude a malignancy. Most inflammatory and reactive lesions are rare; the exceptions are subareolar abscess and fat necrosis, which can be encountered more frequently.

5.1 Breast Inflammations

Inflammations of the breast are generally called *mastitis*. These rare lesions occur more frequently in patients under the age of 50 years. There is a spectrum of inflammatory lesions in the breast, from acute mastitis (usually associated with lactation) to chronic mastitis. Most are associated with an infectious cause, but for some, the etiology is not well understood or may reflect an idiopathic process [1].

5.1.1 Acute Mastitis

Acute mastitis, also called *puerperal mastitis*, is a lesion associated with lactation and favored by stagnation of mammary secretion. The passage of the infectious agent is represented by nipple damage, particularly nipple fissures. Onset of the lesion usually occurs 2–3 weeks after the start of lactation. Clinically, it is associated with pain and cutaneous signs of inflammation, as the overlying skin becomes swollen, red, and hot (Fig. 5.1). If the inflammatory process is caused by *Staphylococcus aureus*, an abscess develops over time, which macroscopically appears as a well-defined cavity, full of a creamy yellow substance. Microscopically, the breast tissue is destroyed and replaced by a collection of neutrophils, bordered by a pyogenic membrane (Figs. 5.2 and 5.3). Of note, acute inflammation can be associated with severe, reactive epithelial atypia in the remaining ducts and acini in the vicinity of the abscess. When these changes are present, interpretation should be conservative [2]. At a chronic stage, fistula can develop (Fig. 5.4). The differential diagnosis particularly includes inflammatory breast carcinoma, both clinically and pathologically. In cases of inflammatory breast carcinoma, the skin lesions include more than two thirds of the breast and is usually associated with a palpable mass, which is demonstrated on ultrasound and/or mammogram; pathologically, the presence of tumor emboli can be seen in the lymphatic vessels of the dermis (Fig. 5.5).

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S. Stolnicu, I. Alvarado-Cabrero (eds.), *Practical Atlas of Breast Pathology*, https://doi.org/10.1007/978-3-319-93257-6_5

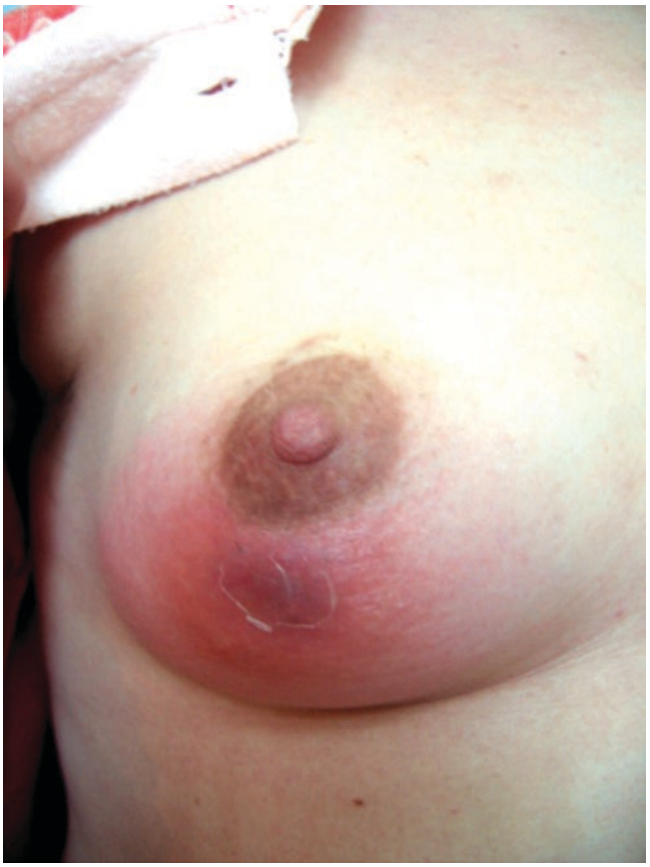

Fig. 5.1 Breast abscess: The overlying skin becomes swollen, red, and hot. (*Courtesy of* Dr. M. F. Coros)

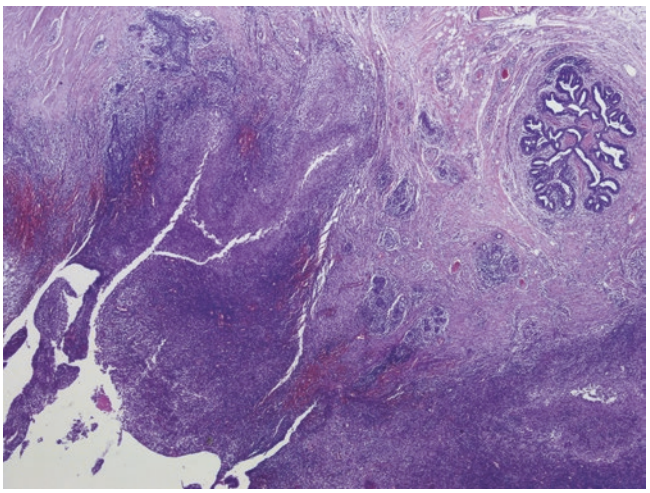

Fig. 5.2 The breast tissue is destroyed and replaced by a collection of neutrophils

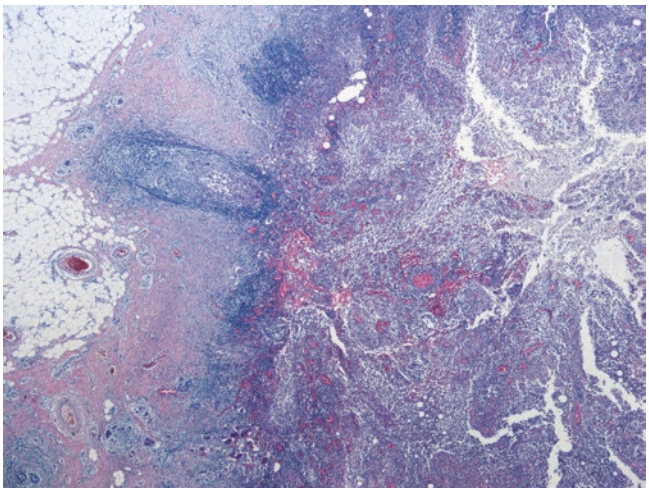

Fig. 5.3 The abscess is bordered at the periphery by a pyogenic membrane and numerous multinucleated cells

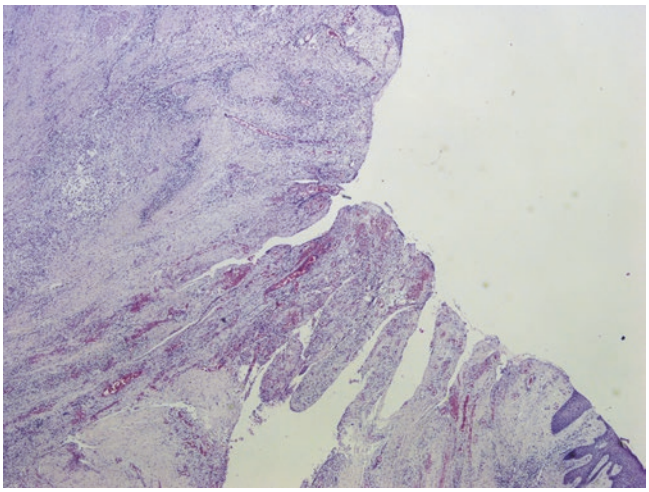

Fig. 5.4 At a chronic stage, the abscess develops fistula to the skin

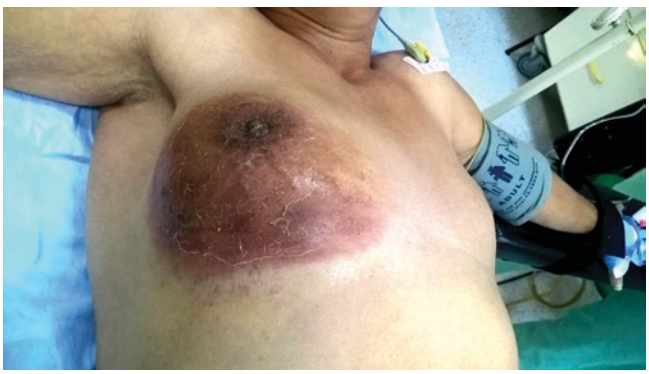

Fig. 5.5 Abscess can be confused with Inflammatory carcinoma on clinical examination; in contrast to the abscess, the inflammatory carcinoma is represented by cutaneous signs of inflammation comprising most of the breast skin, and it is associated with a malignant tumor in the breast tissue (*not shown*)

5.1.2 Subareolar Abscess

Subareolar abscess can occur during the reproductive period, but also in postmenopausal women; rare cases are reported in males. *Staphylococcus*, *Streptococcus*, and *Proteus* are the etiologic agents involved. Congenital or acquired nipple inversion and retraction may be associated in some cases. Inflammatory skin signs are sometimes present and make diagnosis easier. An imprecisely demarcated area with increased density can be noticed on mammography. The lesion develops from galactophorous ducts, whose glandular epithelium is gradually replaced by squamous metaplasia (Figs. 5.6, 5.7, and 5.8). The result is obstruction and extension of the duct by keratinous and cellular debris. The extended duct breaks, and the surrounding stroma may develop an abscess, with numerous multinucleated, foreign-body giant cells (Figs. 5.9 and 5.10). The lesion may be associated with the formation of a cutaneous fistula. Over time, this area is replaced by granulation tissue and fibrosis (Fig. 5.11). In some cases, a sinus tract may develop from the abscess to the overlying skin. The differential diagnosis includes an epithelial inclusion cyst, which is usually unassociated with inflammation.

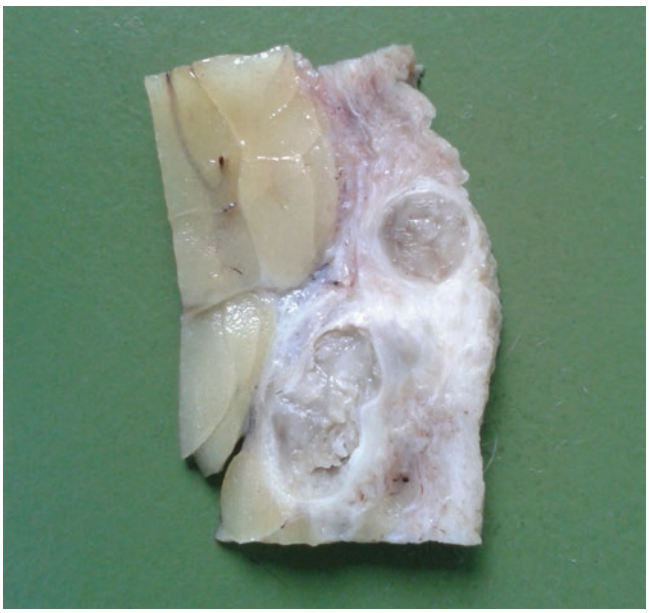

Fig. 5.6 Subareolar abscesses: Breast surgical specimen with multiple round and well-delineated cavities filled with pus on the cut surface

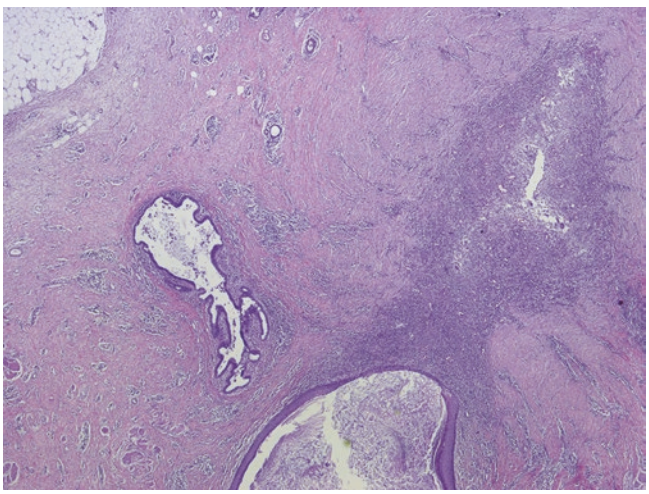

Fig. 5.7 Breast subareolar abscesses develop from galactophorous ducts whose glandular epithelium is gradually replaced by squamous metaplasia

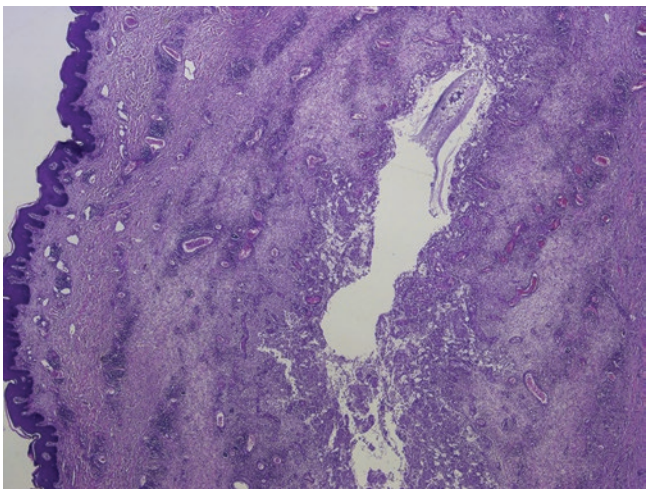

Fig. 5.8 Subareolar abscess. An abscess with numerous neutrophils developed around a galactophorous duct with squamous metaplasia

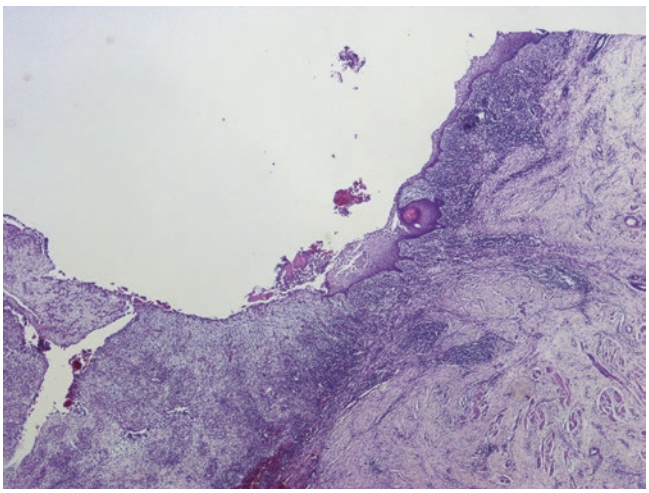

Fig. 5.9 Subareolar abscess. The cavity of the abscess is lined by squamous epithelium

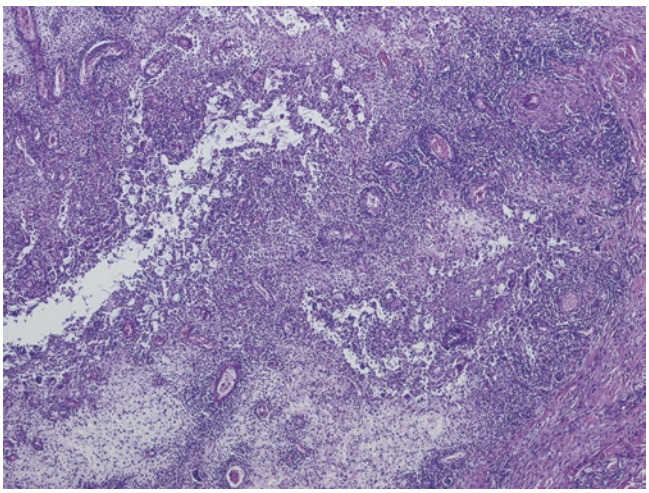

Fig. 5.10 Subareolar abscess, showing numerous neutrophils and multinucleated, foreign-body giant cells

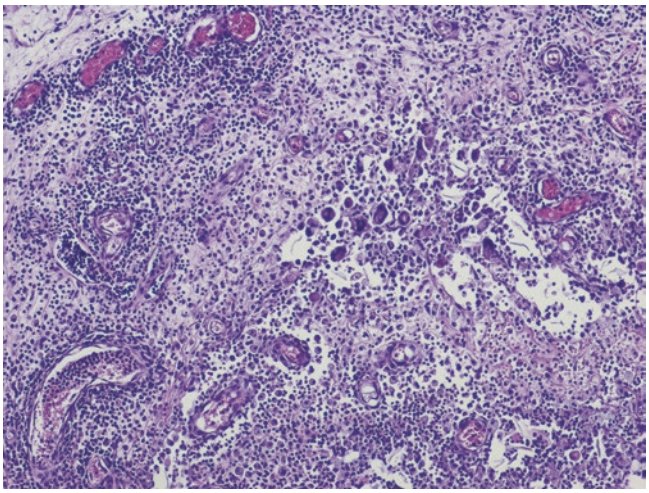

Fig. 5.11 Subareolar abscess. Over time, the abscess area is replaced by granulation tissue and fibrosis

5.1.3 Plasma Cell Mastitis

Plasma cell mastitis represents a diffuse reactive process characterized by an abundant inflammatory infiltrate rich in plasma cells, which affects the ducts and acini, as well as the adjacent stroma. It develops in postmenopausal women as a result of the presence of a lipid-rich material in the acini and the lumen ducts, which sometimes enters the periductal stroma. Clinically, it causes leakage and nipple retraction associated with the presence of an indurated and ill-defined mass, usually located at the periphery of the breast or in the subareolar area and often associated with enlarged axillary lymph nodes. This mass can mimic a carcinoma. Microscopically, the ducts are moderately dilated, containing histiocytes within the lumen, but also lipid material and desquamated epithelium. The surrounding area contains an inflammatory infiltrate with numerous plasma cells and few lymphocytes and neutrophils. Because of the presence of lipid material in the stroma, multinucleated, foreign-body giant cells may appear, in addition to plasma cells and lymphocytes. The differential diagnosis includes ductal ectasia (which affects the galactophorous ducts and not the terminal duct/lobular unit) and granulomatous mastitis (which microscopically shows the presence of granulomas).

5.1.4 Lymphocytic Mastopathy

Lymphocytic mastopathy (also called *diabetic mastopathy*) is characterized by a painless, imprecisely bordered formation. It can occur at any age and in both sexes, but it usually affects young to middle-aged women. It is considered an autoimmune reaction, which occurs in patients with Hashimoto's thyroiditis, Sjogren's syndrome, systemic lupus erythematosus, arthropathy, and diabetes (type I, insulin-dependent). Clinically, patients present with a palpable or mammographically detected breast mass, which may be bilateral in some cases. A biopsy is required to confirm benignity (Fig. 5.12). Microscopically, an inflammatory infiltrate rich in polyclonal B lymphocytes is localized around the acini in the center of the lobules, but also around ducts and vessels; it is usually accompanied by epithelioid myofibroblasts. The inflammatory infiltrate is very well-circumscribed. Germinal centers are rarely formed (Fig. 5.13). Sclerotic changes (due to stromal fibrosis with keloidal features and increased concentration of stromal spindle cells) and obliteration of acini may occur over time. The lymphocytes sometimes migrate into the epithelial layer of the acini and ducts, appearing as a lymphoepithelial lesion. In some cases, lymphocytic mastopathy has been observed in combination with *in situ* or invasive breast carcinoma or malignant lymphoma. Some authors have even suggested that lymphocytic mastopathy is the precursor of malignant lymphoma.

A number of conditions are included in the differential diagnosis:

- Plasmocytic mastitis (characterized by the presence of large numbers of plasma cells and few lymphocytes)
- Duct ectasia (the ducts are cystically dilated; it is accompanied by inflammation and fibrosis)
- Fibrocystic disease (inflammation; cystically dilated, hyperplastic ducts and acini; apocrine metaplasia of their epithelium)
- Pseudolymphoma (mixed population of inflammatory cells, forming reactive follicles with germinal centers)
- Malignant lymphoma (proliferation of atypical lymphoid cells, which destroy the acini and ducts)
- Infiltrating lobular breast carcinoma (atypical proliferation of invasive tumor cells, usually arranged in an "Indian file" pattern, sometimes with intracytoplasmic mucin or intracytoplasmic lumina with eosinophilic material and positive for cytokeratin)
- Granular cell tumor (epitheloid myofibroblasts are present, but the tumor is positive for S-100 protein)

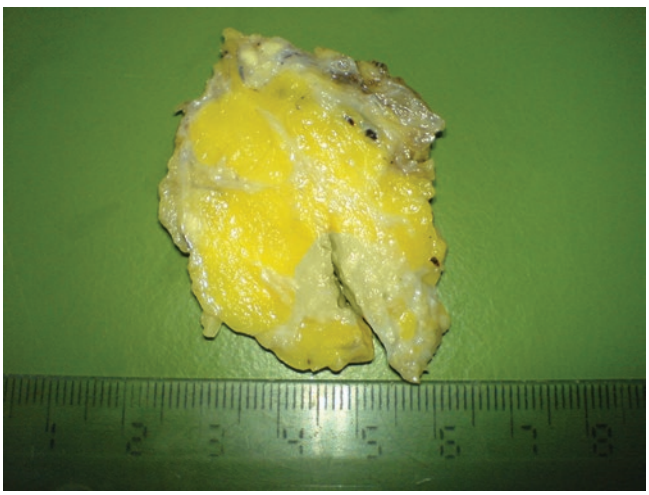

Fig. 5.12 Lymphocytic mastopathy: Surgical specimen of an ill-defined palpable mass, suspected on mammographic examination

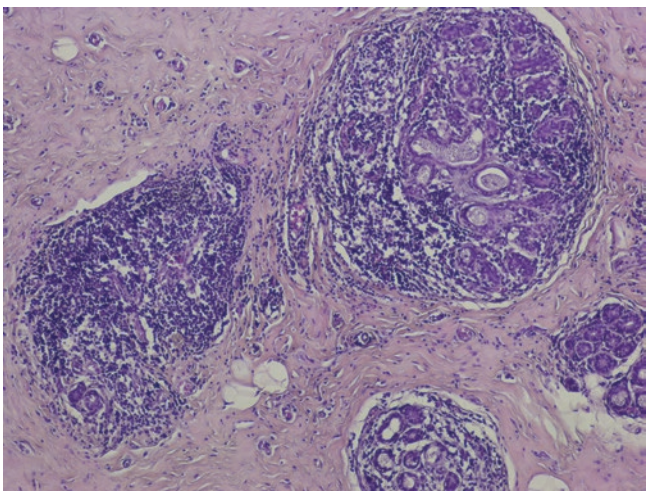

Fig. 5.13 Lymphocytic mastopathy. Well-circumscribed inflammatory infiltrate rich in lymphocytes is localized around the acini in the center of the lobules; germinal centers are lacking

5.1.5 Specific Infections

Rarely, the breast parenchyma may develop specific infections. These can include fungal infections (especially in severely immunocompromised patients), such as histoplasmosis, blastomycosis, cryptococcosis, aspergillosis, chromomycosis, or coccidioidomycosis; parasitic infections, such as filariasis, cysticercosis, sparganosis, or echinococcosis (Fig. 5.14); mycobacterial infections, especially infection by *Mycobacterium tuberculosis* (see below); other bacterial infections, such as actinomycosis and cat scratch disease (see below); and viral infections such as *Herpes simplex* infection. These lesions may present as a mass, abscess, or cyst, or they may be asymptomatic lesions detected mammographically. The clinical presentation and morphological changes induced by these organisms are highly variable. Many are associated with a granulomatous reaction, whereas others mimic a carcinoma.

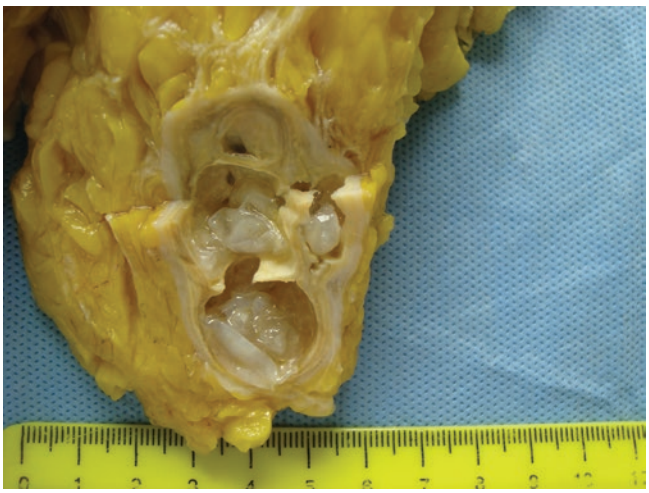

Fig. 5.14 Breast echinococcosis: large cyst filled with small vesicles containing a serous fluid

5.2 Breast Granulomatous Reactions

5.2.1 Idiopathic Granulomatous Lobular Mastitis

Idiopathic granulomatous lobular mastitis is a rare inflammatory condition of the breast of unknown etiology. This granulomatous inflammatory process may affect the breast in the absence of infection, trauma, or foreign material. The pathogenesis has not yet been fully elucidated. Most authors point to a localized autoimmune response to the presence of mammary secretion (rich in lipids and proteins) extravasated in the stroma. However, more recent papers suggest an association with *Corynebacterium*, a gram-positive bacillus in some of the cases. Granulomatous lobular mastitis occurs in patients at a mean age of 30 years, sometimes after pregnancy or lactation. A connection with drug-induced hyperprolactinemia or a prolactinoma has sometimes been highlighted. Studies have failed to prove any link between lesion development and the prolonged use of oral contraceptives. Clinically, it is characterized by a nodular, palpable mass about 3 cm in diameter, which may be confused with a malignancy (Fig. 5.15). The nodular formation is not usually located in the subareolar area. Microscopically, the lesion is characterized by multiple granulomas located within the intralobular mammary stroma, producing distortion of acini and ducts (Fig. 5.16). These granulomas are composed of multinucleated giant cells, neutrophils, lymphocytes, plasma cells, and eosinophils (Fig. 5.17). Microabscesses and squamous metaplasia can sometimes be noticed. Also, in some cases, the granulomas present cysts in the central area, lined by neutrophils and gram-positive bacilli representing *Corynebacterium* can be seen within the cystic spaces. The progression of the lesion leads to a larger, granulomatous, confluent process that eventually progresses to the interlobular stroma and will transform into fibrosis. The differential diagnosis includes other granulomatous inflammatory processes such as tuberculosis (recognized by special stains and specific tests) and sarcoidosis (Kveim test, chest X-ray), as well as a granulomatous reaction that may occur within a carcinoma.

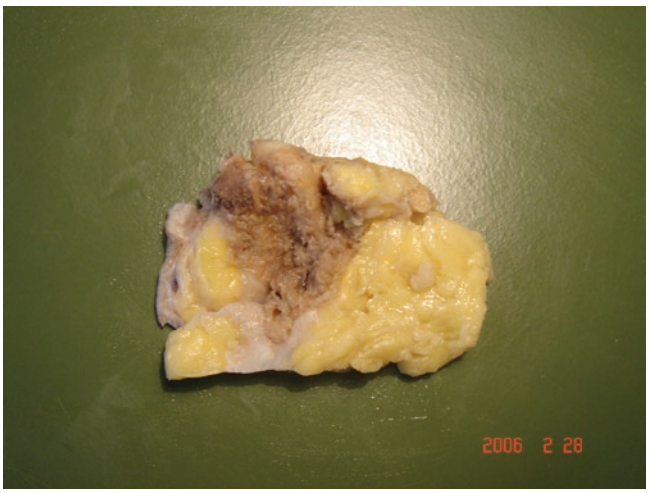

Fig. 5.15 Granulomatous lobular mastitis. A nodular, palpable mass about 3 cm in diameter may be confused with a malignancy because of the presence of central necrosis

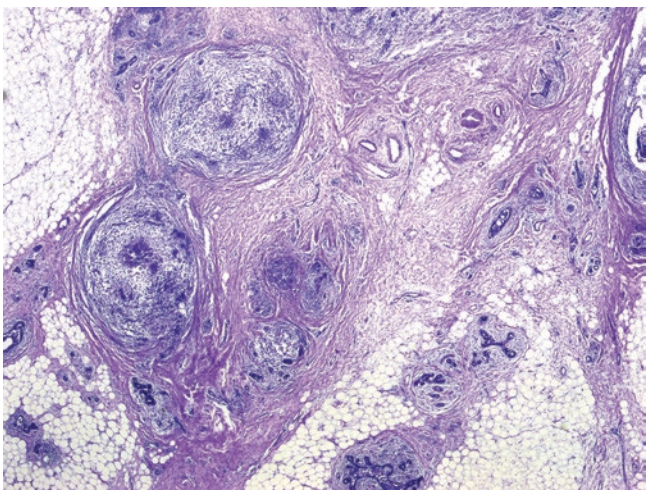

Fig. 5.16 Granulomatous lobular mastitis. Microscopically, the lesion is characterized by multiple granulomas located within the intralobular mammary stroma

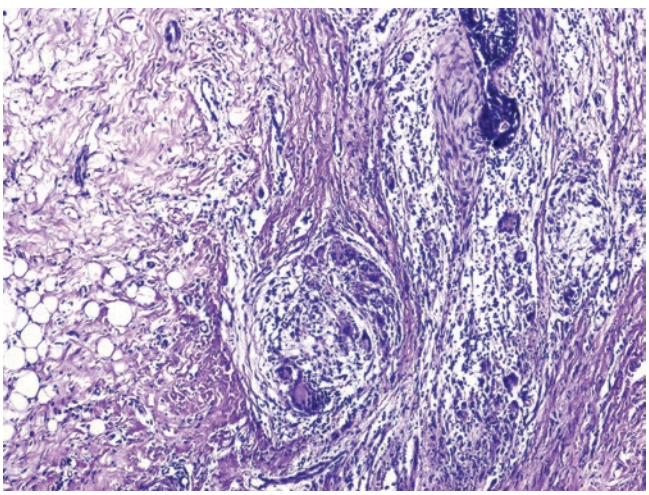

Fig. 5.17 Granulomatous lobular mastitis. The granuloma is composed of multinucleated giant cells, neutrophils, lymphocytes, plasma cells, and eosinophils

5.2.2 Tuberculous Mastitis

Tuberculous mastitis is rarely encountered in developed countries. It occurs mostly in Africa, in young patients in combination with breast carcinoma, Hodgkin's disease, or HIV infection. Tuberculous mastitis has a predilection for lactating breast, the infection inoculating dilated milk ducts, but it can also occur in males. Breast infection may rarely be the first manifestation of tuberculosis, but typically it occurs as a secondary lesion; the axillary lymph nodes are usually considered the source of the breast disease through a retrograde lymphatic spread. Clinically, it is characterized by a firm mass that can be confused with carcinoma, especially when it is associated with axillary lymphadenopathy. The nodular mass can sometimes cause ulceration of the overlying skin, and it may occasionally be associated with nipple discharge. Microscopically, numerous granulomas may be observed, which damage the lobular architecture. They are accompanied by central necrosis and surrounded by epithelioid and multinucleated giant cells and a bordering lymphocytic crown (Fig. 5.18). Special stains (Ziehl-Nielsen) may reveal *Mycobacterium tuberculosis* within the lesion, but most of the published cases were not associated with the presence of the acid-fast bacilli, even though some authors required very rigid diagnostic criteria [3]. The differential diagnosis includes granulomatous reactions caused by tularemia, syphilis, cryptococcosis, cysticercosis, hydatid cyst, injection of foreign material, trauma, and cat scratch disease as well as idiopathic granulomatous mastitis (see above). Clinical symptoms associated with clinical investigations and special stains allow differentiation between these lesions and tuberculosis. A malignant tumor may be ruled out by the microscopic examination of the lesion.

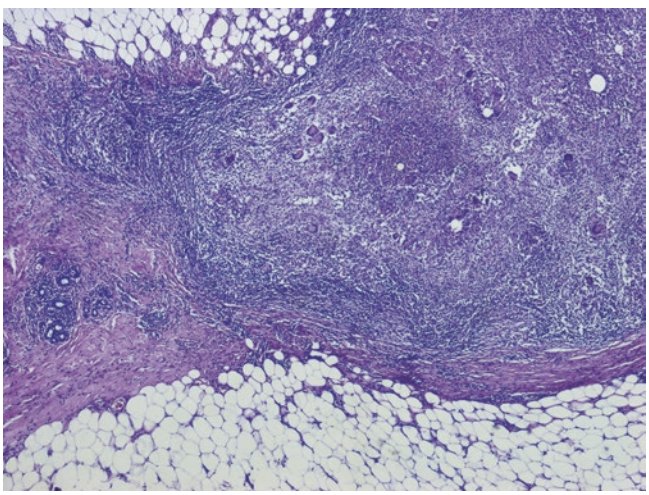

Fig. 5.18 Tuberculous mastitis. Numerous granulomas damage the lobular architecture and are accompanied by central necrosis and surrounded by epithelioid and multinucleated giant cells and a bordering lymphocytic crown

5.2.3 Sarcoidosis

Sarcoidosis is rarely located in the mammary gland; it usually refers to the impairment of the breast in a systemic disease. It occurs in young women as solitary or multiple nodules, sometimes with severe bilateral involvement simulating a carcinoma. Microscopically, characteristic granulomas are usually located in the interlobular stroma, but they also may be intralobular. They have a tendency to confluence, with no central necrosis, and are composed of variable number of epithelioid cells and multinucleated giant cells (which may have asteroid corpuscles), with a peripheral lymphocyte area. The differential diagnosis involves tuberculous mastitis (granulomas with central caseous necrosis, with a tendency for confluence and without a tendency for progression to fibrosis); idiopathic granulomatous mastitis; other infectious mammary granulomas; foreign-body granuloma; and noncaseous granulomas of ductal ectasia, in which granulomas are found in the vicinity of the dilated ducts. Of note, sarcoid-type granulomatous reaction of the mammary gland can sometimes occur in association with breast carcinoma (in both breast tissue and axillary lymph nodes), but in this case, the clinical and radiological picture generally does not indicate sarcoidosis.

5.2.4 Cat Scratch Disease

This zoonotic disease originates from *Bartonella henselae*. It usually occurs as a regional, localized granulomatous lymphadenopathy near the site of inoculation after a cat scratch. This disease rarely involves the axillary lymph nodes and the breast parenchyma, but when it occurs, it may mimic a malignant tumor. Histologically, the breast lesion is composed of granulomas with histiocytes and occasional multinucleated giant cells, extensive inflammatory infiltration at the periphery, and necrotizing inflammation in the center, usually with a star shape. A similar picture is observed in the axillary lymph nodes, in which the presence of granulomatous lesions does not disturb the normal architecture (Figs. 5.19 and 5.20). An accurate anamnestic investigation may reveal that the patient had contact with domestic animals and had observed the appearance of an erythematous papule on the breast skin prior to the breast lesion. In most cases, the specific serological test is positive for *Bartonella henselae* [4].

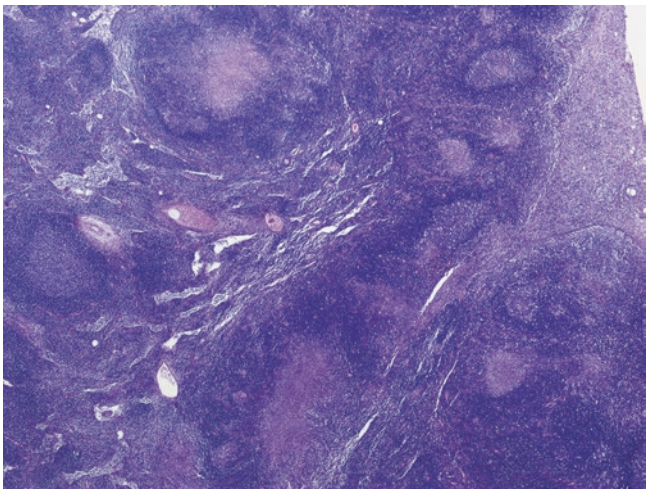

Fig. 5.19 Cat scratch disease involving an axillary lymph node, showing preserved normal architecture of the lymph node but with the presence of multiple granulomas

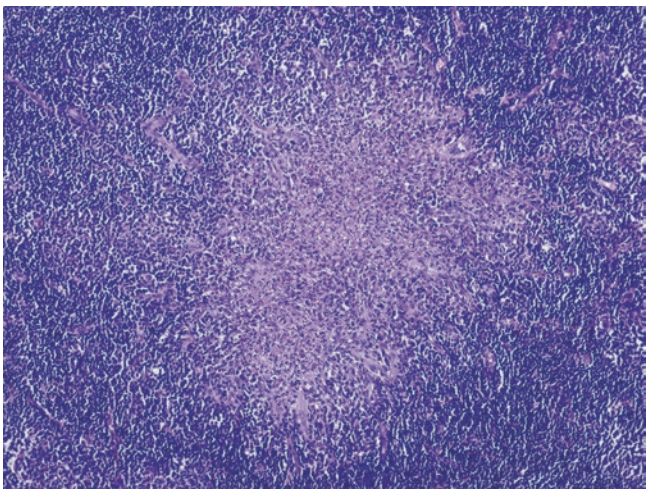

Fig. 5.20 Cat scratch disease involving an axillary lymph node. The granuloma has numerous epithelioid cells, with occasional multinucleated giant cells and extensive inflammatory infiltration at the periphery. The center is represented by a necrotizing inflammation, with a characteristic star shape

5.2.5 Suture Granuloma

Suture granuloma is a foreign-body giant cell inflammatory reaction that develops around unabsorbed surgical sutures after a biopsy or quadranectomy. Grossly, the lesion appears as a small, firm lump. Microscopically, it is characterized by a noncaseous granuloma composed of birefringent foreign material, around which numerous multinucleated, foreign-body giant cells appear, admixed with lymphocytes and histiocytes (Figs. 5.21 and 5.22).

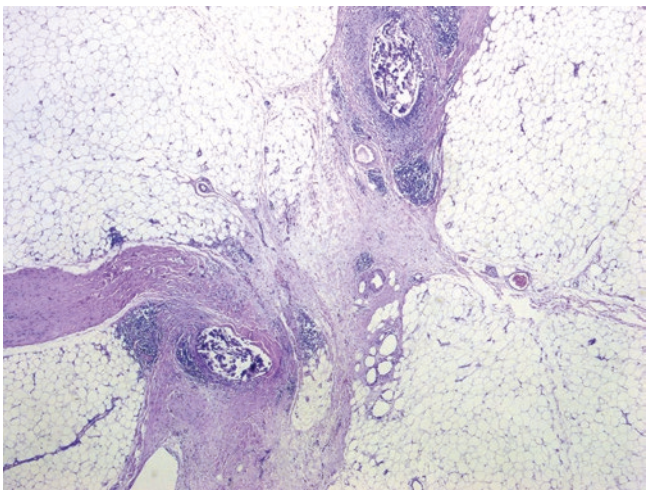

Fig. 5.21 Suture granuloma, microscopically characterized by two noncaseous granulomas involving the breast tissue

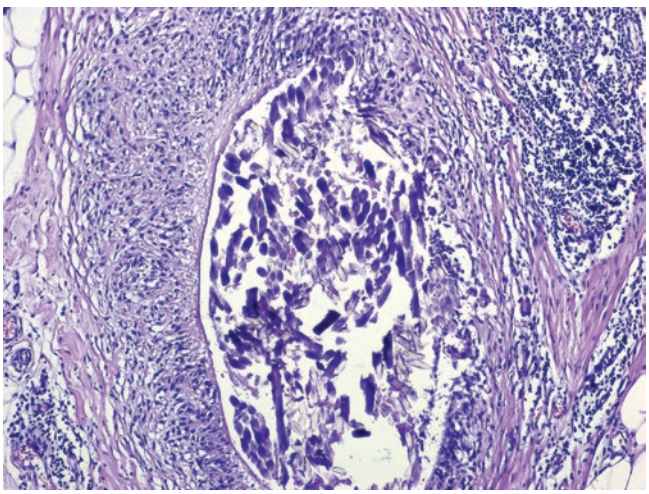

Fig. 5.22 Suture granuloma. The granuloma is composed of foreign material, around which numerous epithelioid cells and multinucleated foreign-body giant cells appear, admixed with lymphocytes and histiocytes

5.2.6 Silicone Granuloma

As a result of the increasingly frequent use of silicone breast implants, breast pathologists can often encounter breast lesions related to silicone. The changes in breast tissue due to silicone implantation are usually limited to the vicinity of the implant and may be represented by the presence of an adherent, fibrous capsule, macroscopically showing as a firm, gray to tan structure adherent to the implant. Microscopically, it is lined by a single layer of flattened macrophages and consists of myofibroblasts, fibroblasts, histiocytes, T-type lymphocytes, plasma cells, and multinucleated foreign-body giant cells containing birefringent material. The presence of the capsule may cause distortion and firmness of the breast parenchyma and can complicate with contraction, infection, or rupture.

Also, in patients with silicon gel implants, silicone may protrude within the capsule or outside, within the breast parenchyma, producing numerous round microcyst spaces. These spaces vary in size and appear empty (when the silicone is lost during the technical process). They are lined by a thick, eosinophilic film material or contain a pale (birefringent) material, surrounded by histiocytes and multinucleated giant cells, which mimic an adipose necrosis. In some cases, the silicone may enter the lumens of acini and ducts. The presence of the silicone may also produce fat necrosis. A granulomatous lesion similar to the one in breast tissue can also occur in regional axillary lymph nodes or other sites of the body, to which the silicone can diffuse through lymphatic or hematic vessels (Figs. 5.23 and 5.24).

In other patients with implants, fibrous scar, microcalcifications, and synovium-like metaplasia can occur. The metaplasia is represented by a lining epithelium resembling normal synovium but composed of multiple layers of histiocytes with an epithelioid appearance in a reticulin network, sometimes also presenting a papillary hyperplasia (which can occasionally be difficult to differentiate from papillary carcinoma) [5]. The cell linings are positive for Vimentin, CD68, alpha1-antichymotrypsin, and lysozyme, but negative for cytokeratin and factor VIII [2]. Cases in which squamous metaplasia is present have been reported. The nipple can be affected by nipple inversion or nipple discharge of silicone. Of note, the changes associated with the presence of the silicone can microscopically mimic a liposarcoma, and in these cases, knowing the clinical history of the patient is essential. In general, all these alterations associated with silicone implants make the detection of breast carcinomas (especially those of small size) difficult, so careful follow-up of these patients is advised.

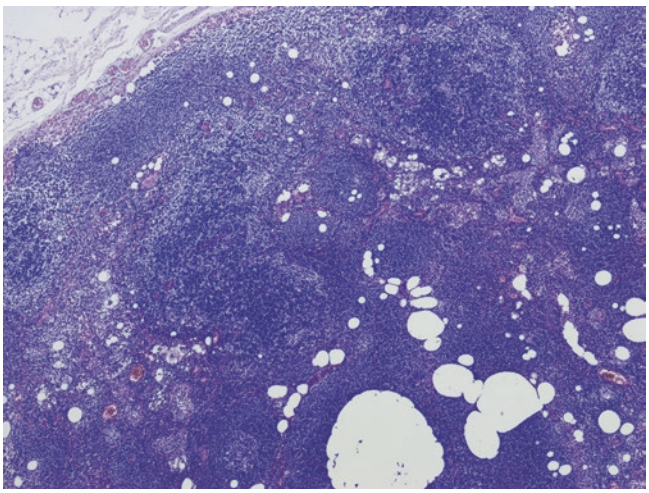

Fig. 5.23 Silicone granuloma in axillary lymph node, showing areas of inflammatory cells and multinucleated, foreign-body giant cells surrounding numerous round microcyst spaces that are variable in size and appear empty because the silicone is lost during the technical process

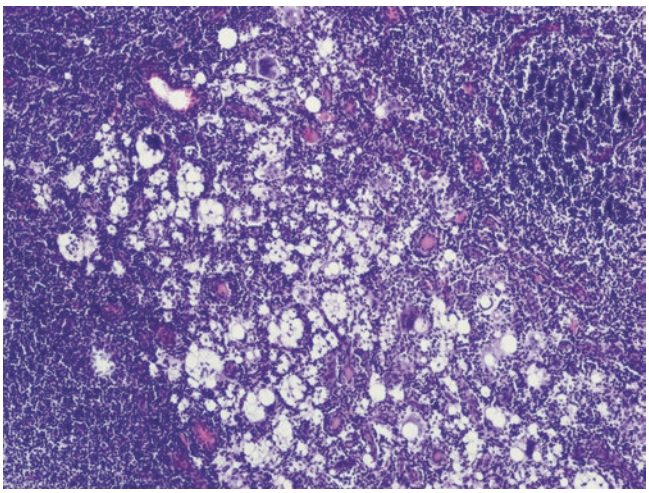

Fig. 5.24 Silicone granuloma in axillary lymph node: numerous microcysts and multinucleated foreign-body giant cells

5.3 Fat Necrosis

Fat necrosis develops as a result either of trauma (accidental or surgical, including biopsies) or of a ductal ectasia or fibrocystic disease (in which the breaking of dilated cysts leads to stromal extravasation of the luminal content). Fat necrosis after radiation therapy for breast carcinoma has also been described. In some cases, however, no history of injury or other previous lesion can be elicited. Clinically and macroscopically, the lesion appears as a painless, hard, yellow-brown or sometimes yellow-gray, solid or cystic mass, sometimes with focal hemorrhage. The cysts are a consequence of liquefactive necrosis and contain oily fluid or necrotic fat.

The lesions are imprecisely demarcated and sometimes cause skin retraction or thickening (Figs. 5.25, 5.26, and 5.27). As a consequence, the lesion can be confused with a malignancy. The differential diagnosis of fat necrosis is even more difficult clinically in patients previously diagnosed with a breast carcinoma who were treated with conservative surgery and radiotherapy, in whom a recurrent malignant lesion is usually suspected. The lesion can be confused with a carcinoma on mammography, because most fat necrosis lesions are spiculated, poorly defined, and may contain calcifications. The location of the lesion is usually superficial in the subareolar or periareolar region, but any region of the breast can be involved. On microscopy, it is characterized by adipose necrosis due to disruption of fat cells (which gives a multicystic appearance of the area) and inflammatory reaction composed of lymphocytes, plasma cells, macrophages with foamy cytoplasm or full of hemosiderin, multinucleated foreign-body giant cells, hemorrhagic infiltrate, and deposits of cholesterol crystals (Figs. 5.28, 5.29, 5.30, and 5.31). Over time, the lesion is replaced by a fibrosis process, which can be associated with areas of calcification and collagen deposits (Figs. 5.32 and 5.33) [6]. As a reactive process, a squamous metaplasia can occur, involving the epithelium of the ducts and lobules in the affected area.

The differential diagnosis for a malignancy is made clinically and on mammography. Fat necrosis is differentiated microscopically from an inflammatory process, in which usually no adipose necrosis can be observed, and from silicon granuloma, in which a history of breast implant is known. On microscopic examination, an inexperienced pathologist may confuse the process with a lipoma, but the lipoma is composed of adipose cells presenting eccentric nuclei, whereas the fat necrosis is represented by necrotic adipose cells without nuclei (Figs. 5.34 and 5.35).

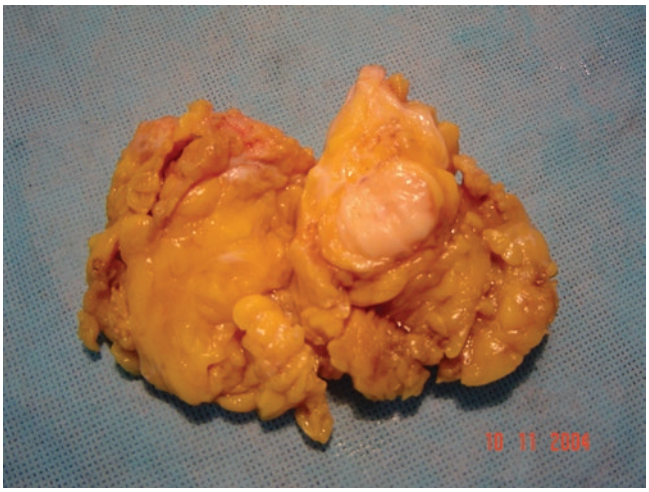

Fig. 5.25 Fat necrosis: a painless, hard, yellow-gray solid nodule, which was suspicious on mammography. Microscopic examination demonstrated fat necrosis (*not shown*)

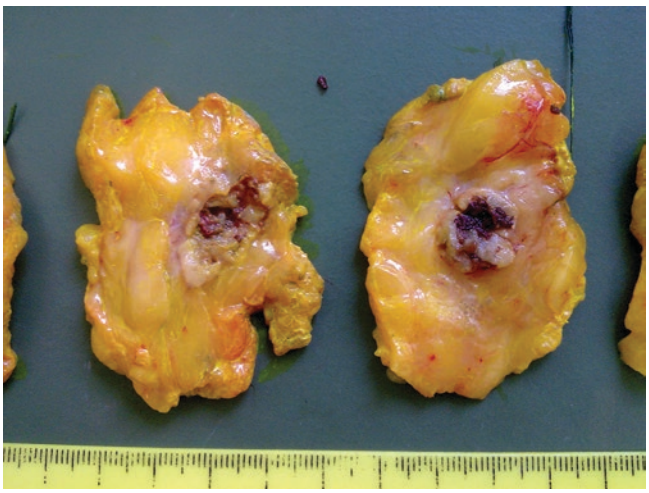

Fig. 5.26 Fat necrosis: a solid yellow nodule with focal hemorrhage and cystic areas, very suspicious for malignancy

Fig. 5.27 Fat necrosis: surgical specimen of mastectomy after a quadranectomy for invasive carcinoma with a gray, solid yellow nodule suspicious for recurrence (*arrow*). Microscopic examination proved it to be fat necrosis (*not shown*)

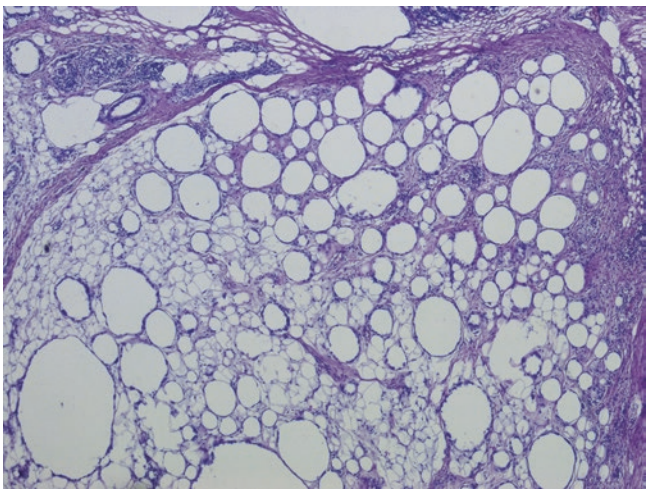

Fig. 5.30 Fat necrosis. Multiple cysts are surrounded by an inflammatory reaction composed predominantly of macrophages with foamy cytoplasm. At the periphery, lymphocytes and plasma cells can also be detected

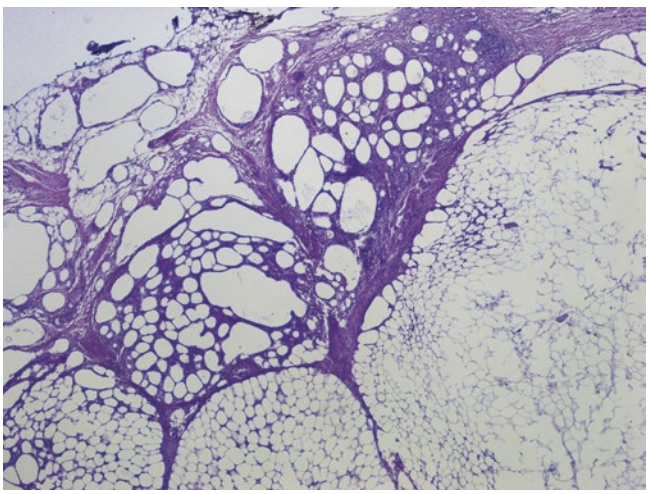

Fig. 5.28 Fat necrosis: adipose necrosis due to disruption of fat cells, which gives a multicystic appearance

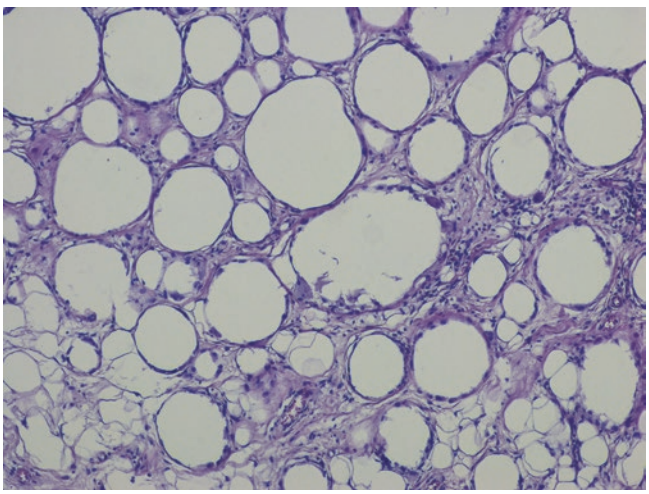

Fig. 5.31 Fat necrosis: multiple cysts surrounded by macrophages and multinucleated, foreign-body giant cells

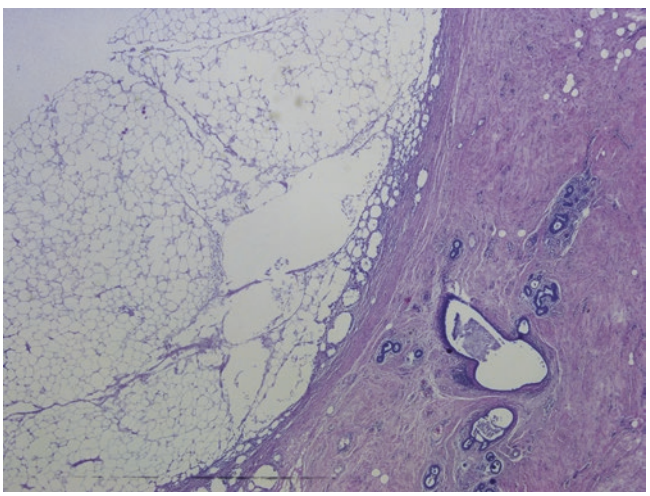

Fig. 5.29 Fat necrosis: multiple cysts, some large

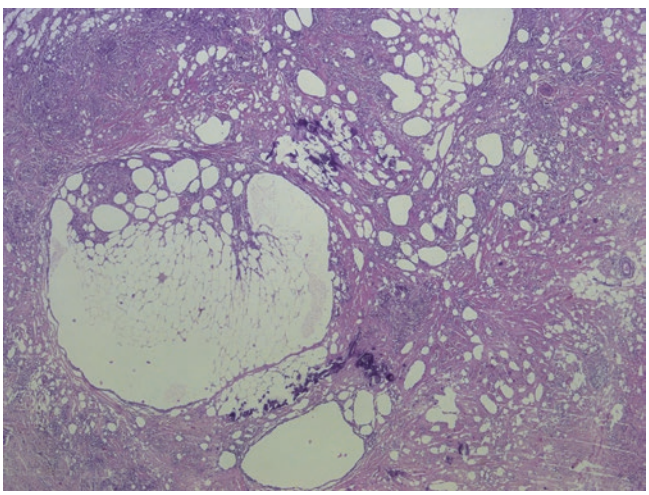

Fig. 5.32 Fat necrosis: cysts associated with areas of calcification

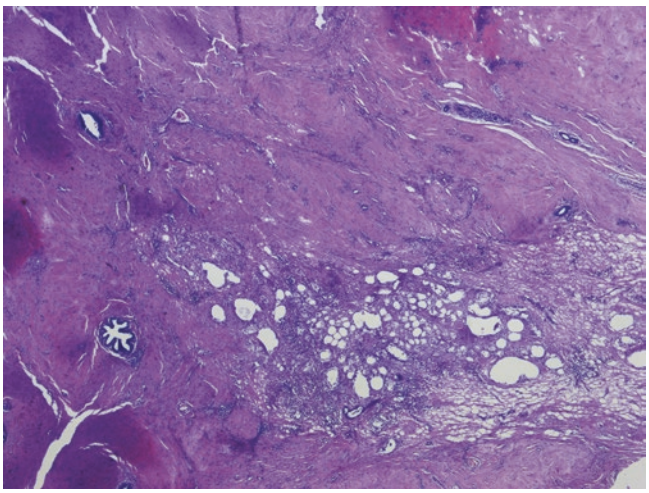

Fig. 5.33 Fat necrosis. Over time, the lesion is replaced by a fibrosis process, which can be associated with areas of collagen deposits

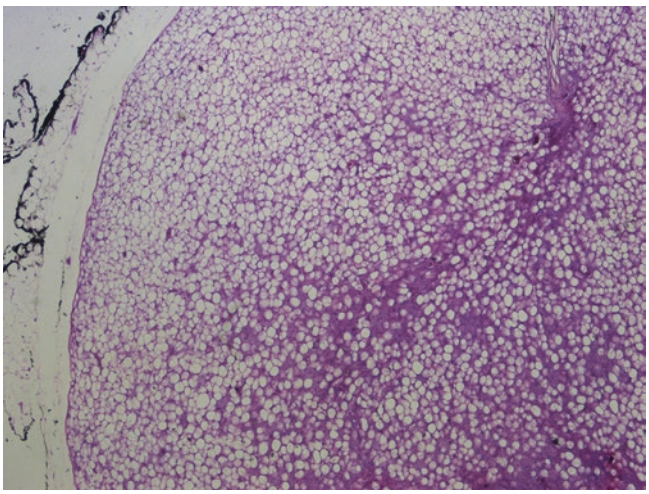

Fig. 5.34 Lipoma. On microscopic examination, fat necrosis can also be confused with a lipoma

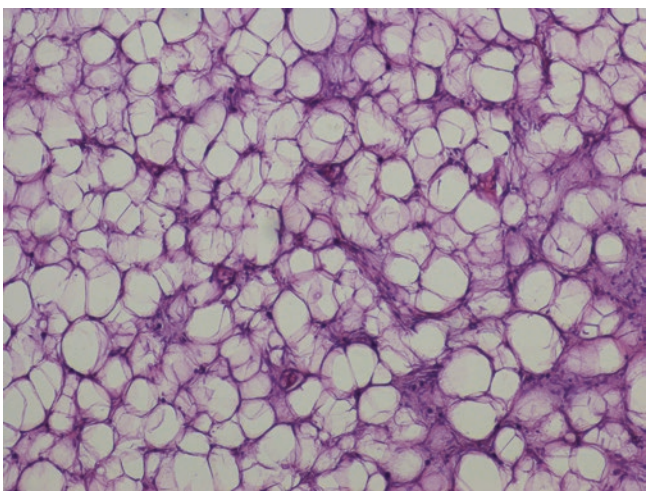

Fig. 5.35 Lipoma. This tumor is composed of adipose cells presenting an eccentric nucleus; fat necrosis is represented by necrotic adipose cells without nuclei

5.4 Mammary Duct Ectasia

Also called *periductal mastitis*, mammary duct ectasia is a distinct lesion characterized by dilated galactophorous ducts in the subareolar area, associated with inflammation and progressive periductal fibrosis. The exact etiology or pathogenesis of the lesion is unknown. Some authors believe that the lesion starts with duct dilatation and consecutive stasis, while others consider that the initial stage consists of the inflammatory process. Most authors believe that the lesion is due to atrophy and involution of the ducts associated with stagnation of the secretion in the lumen of older patients, but duct ectasia occurs at any age, including in children and males. The mean age at which it typically occurs is 50 years. Clinically, it can mimic a breast carcinoma; it can be associated with nipple retraction or discharge, pain, fistula, subareolar abscess, or pseudotumoral appearance due to a mass. On palpation, the clinician can detect the dilated ducts as a wormlike mass beneath the areola. Radiologically, it may also mimic a carcinoma of ductal *in situ* type, as the calcifications can be seen in a ductal pattern on mammography. Many pathologists microscopically confuse it with fibrocystic disease originating in the terminal duct/lobular unit. Grossly, during the sampling of the surgical specimen, dilated, thick-walled ducts can be observed; these contain a creamy secretion within the lumen, similar to the one found in ductal carcinoma *in situ* (Figs. 5.36 and 5.37). Microscopically, the galactophorous ducts are dilated and contain a secretory eosinophilic material in the lumen. The ducts are surrounded by an inflammatory infiltrate represented by lymphocytes and plasma cell, which can be abundant in several cases (Fig. 5.38 and 5.39). As the lesion progresses, macrophages with a foamy cytoplasm migrate into the lumen of the duct, or migrate within the epithelium (causing an abnormal distribution of the remaining epithelial cells into small nests that can be confused with epithelial hyperplasia by less experienced pathologists) or within the duct wall (Figs. 5.40 and 5.41) [7]. However, epithelial hyperplasia never occurs in ductal ectasia. Over time, epithelial cells can exfoliate or may flatten. There is an inflammatory infiltrate around the duct, composed of lymphocytes, plasma cells, histiocytes, multinucleated foreign-body giant cells, and ochrocytes (histiocytes containing yellow-brown ceroid pigment). Less frequently, the inflammatory infiltrate can be of the granulomatous type, or it can be of an acute form, with the presence of abscesses or fistulae. In advanced stages, a process of fibrosis replaces the periductal inflammation (Fig. 5.42). Sometimes the granulation tissue and later the fibrosis can lead to the obliteration of the ducts. Other times, the lumen can be obliterated by remnants of persisting epithelium, which may proliferate to form secondary glands, creating a pattern that resembles a recanalized thrombus of a blood vessel.

The differential diagnosis includes plasmacytic mastitis and fibrocystic disease, both of which are located at the level of the terminal duct/lobular unit. Sometimes, duct ectasia can extend deep into the breast tissue, in which case differential diagnosis is made with the presence of elastic lamina in the wall of the dilated ducts, which does not occur in the acini. (Elastic tissue stain is helpful.)

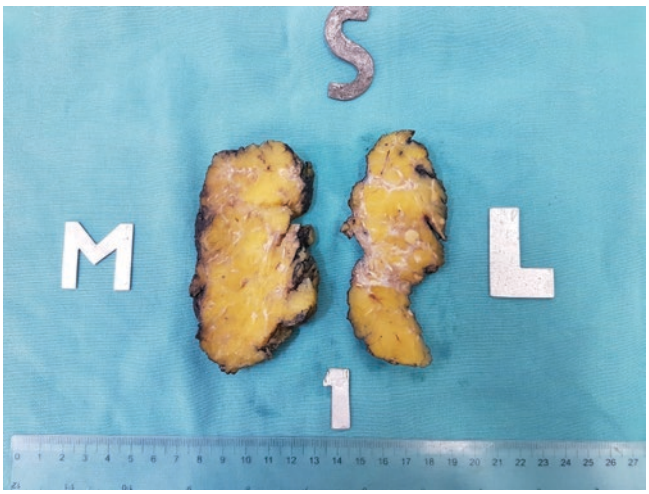

Fig. 5.36 Mammary duct ectasia: grossly, surgical specimen with dilated thick-walled ducts, which contain a creamy secretion within the lumen

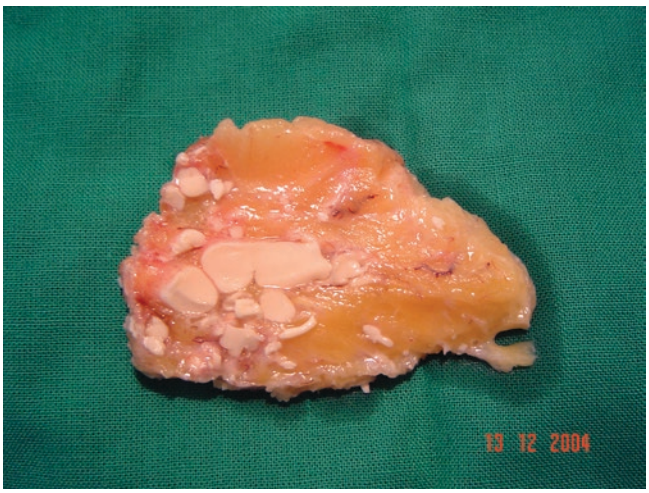

Fig. 5.37 Mammary duct ectasia: This surgical specimen with dilated, thick-walled ducts with a creamy secretion within the lumen is similar to the specimen found in ductal carcinoma in situ

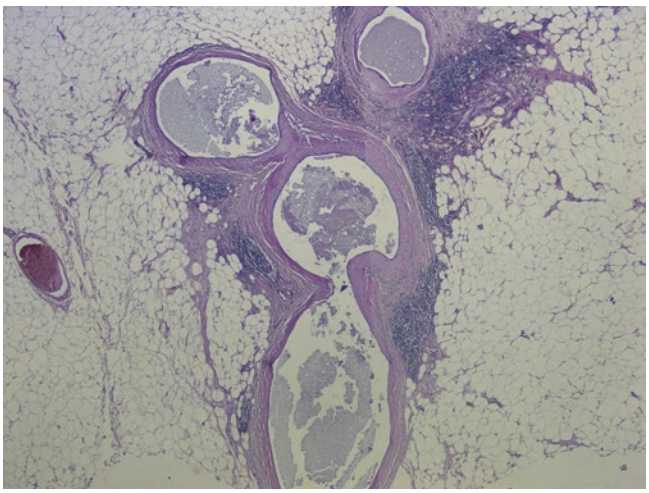

Fig. 5.38 Mammary duct ectasia: dilated galactophorous ducts containing a secretory eosinophilic material in the lumen

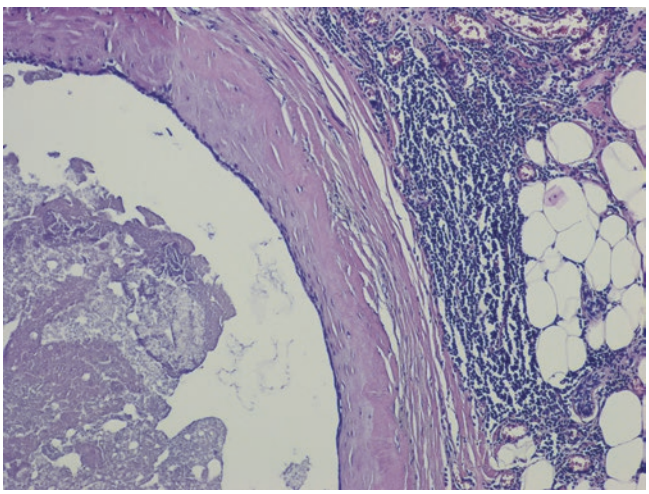

Fig. 5.39 Mammary duct ectasia: a dilated duct, surrounded by an inflammatory infiltrate represented by lymphocytes and plasma cells

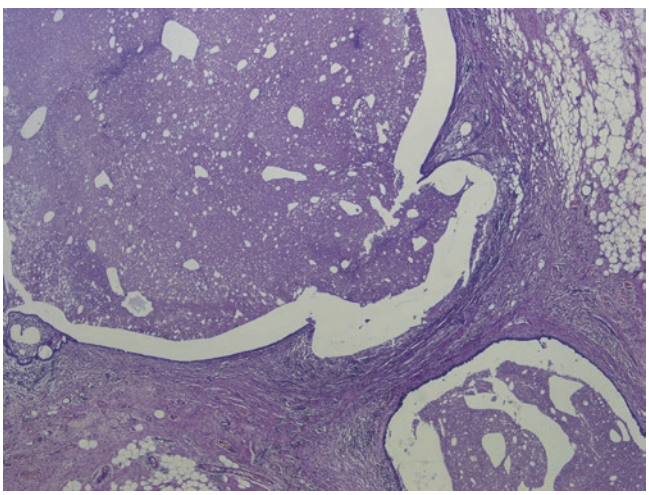

Fig. 5.40 Mammary duct ectasia: dilated galactophorous ducts containing an eosinophilic secretion and surrounded by macrophages with a foamy cytoplasm

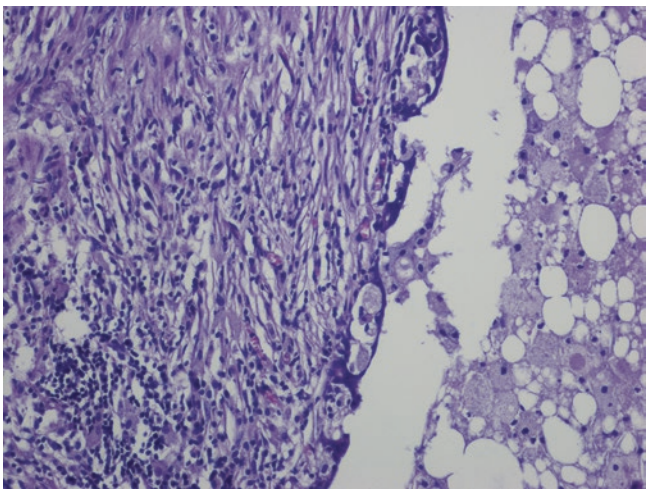

Fig. 5.41 Mammary duct ectasia. Macrophages with a foamy cytoplasm migrate into the lumen of the duct and migrate within the epithelium, causing an abnormal distribution of the remaining epithelial cells into small nests, which can be confused with epithelial hyperplasia

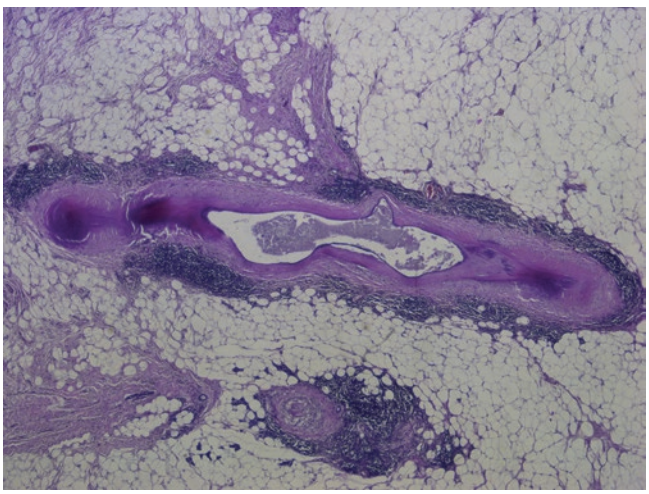

Fig. 5.42 Mammary duct ectasia. In advanced stages, a process of fibrosis replaces the periductal inflammation; later, the fibrosis can obliterate the ducts

5.5 Gouty Tophus

Gouty tophus develops in female patients with gout, but it may sometimes occur in a massive process of necrosis. The lesion may be multinodular or bilateral. Macroscopically, the white mass is well-defined. Microscopically, the breast tissue presents a nodular mass composed of feathery-shaped spaces occupied by urate crystals, surrounded by a foreign-body giant cell inflammatory reaction (Fig. 5.43) [1]. In addition to microscopic examination, the examination of the lesion should be performed using polarized light, because urate crystals are birefringent. Gouty tophus is different microscopically from a cholesterol granuloma, in which cholesterol crystals dissolve during technical processing, so that only the optical needle-shaped, empty space occupied by them can be observed during the microscopic examination (Fig. 5.44).

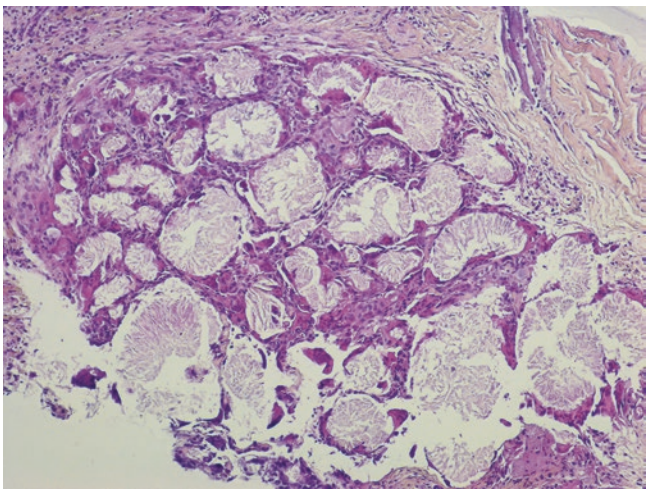

Fig. 5.43 Gouty tophus: nodular mass composed of feathery-shaped spaces occupied by urate crystals, surrounded by a foreign-body giant cell inflammatory reaction

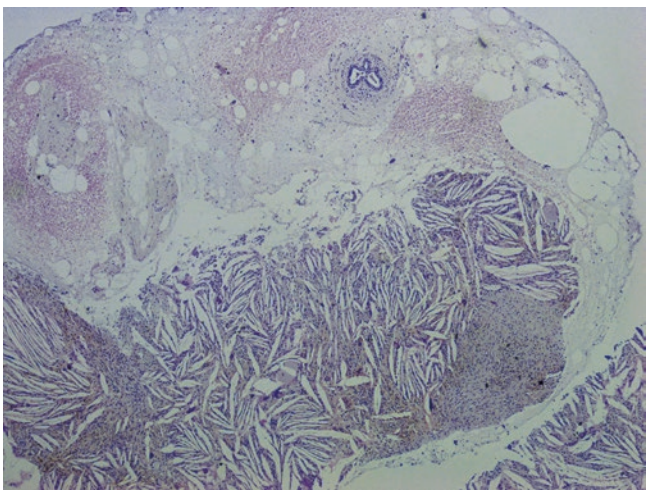

Fig. 5.44 Cholesterol granuloma. Cholesterol crystals dissolve during technical processing, so only the optical needle-shaped, empty space occupied by them can be observed during the microscopic examination

5.6 Amyloidosis

Amyloid deposits rarely occur in the breast. They are associated with benign or malignant breast lesions in patients with both systemic and localized amyloidosis, raising questions of clinical, mammographic, and microscopic diagnosis because their appearance can be confused with a process of fibrosis or elastosis. Microscopically, amyloid is deposited as a homogeneous, eosinophilic, amorphous material that is found periductally (which can lead to obstruction and atrophy of the ducts), interstitially, or vascularly. The deposits are associated with lymphoplasmacytic infiltrate, along with giant cells, but special stains (Congo red) can confirm the presence of the amyloid material, which is also birefringent in polarizing lenses.

5.7 Breast Infarct

Breast infarct is a rare lesion that clinically may be confused with carcinoma of the breast. Lesion pathogenesis is still unclear, suggesting increased metabolic activity of the breast parenchyma. Most patients who develop such lesions are middle-aged, obese, and have undergone anticoagulant therapy. It can also occur as a complication of intraductal papilloma, fibroadenoma, phylloides tumor, pregnancy or lactation (in patients who are younger), and in diabetic patients. Clinically, the lesion is associated with pain and tenderness, cutaneous ecchymosis, skin rash, and sometimes cutaneous edema (mimicking an inflammatory carcinoma). Sometimes the lesion in the breast is associated with enlargement of axillary lymph nodes, due to a reactive process. Macroscopically, the area of necrosis is purple-red. Microscopically, there is an extensive area of coagulative necrosis (where only the outlines of cells can be recognized, but the architecture is preserved), associated with hemorrhagic infiltrate, and inflammatory-type cells at the periphery. In some cases, intravascular thrombus may occur at the border of the necrosis area. Over time, a process of fibrosis replaces the affected area. The differential diagnosis includes necrotic processes with other causes, such as caseous necrosis, tumor necrosis, or fat necrosis.

5.8 Inflammatory Pseudotumor

Inflammatory pseudotumor is a very rare benign condition of unknown etiology, presenting with variable and nonspecific imaging features that may mimic a benign or malignant neoplasm. It most commonly arises in the lung, although it may also develop in various organs such as the pancreas; head and neck; thoracic, hepatic, and biliary organs; and the retroperitoneum. It has an autoimmune etiology, associated with the development of a fibrotic tumor-like lesion composed of a proliferation of spindle cells with a fascicular and vaguely storiform architecture. The spindle cells show no nuclear atypia, and mitotic figures are spare (Fig. 5.45). A prominent vascular proliferation is usually identified throughout the lesion, with some vasocentric inflammatory cells obliterating the vessels. The prominent inflammatory infiltrate consists of both diffusely distributed lymphocytes and plasma cells, as well as aggregates of inflammatory cells with rare lymphoid follicles. The architecture of the follicles may mimic a stroma-rich and vascular-rich Castleman disease, a peculiar form of immune reaction of unknown cause, characterized by lymphoid and vascular hyperplasia of the lymph nodes, but also found in the mediastinum or retroperitoneum [8]. The lesion must fulfil published criteria for IgG4-related disease [9]:

- Elevated IgG4 levels in serum (>135 mg/dL)
- Presence of an organ enlargement as a mass or nodular lesion
- Pathological examinations with the presence of numerous IgG4-positive plasma cells in the lesion tissue

The microscopic diagnosis is difficult even for an experienced breast pathologist, not only because the lesion is very rare in the breast but also because it may mimic other conditions. Immunohistochemical stain, however, shows negativity of cells for actin and desmin (excluding a peculiar leiomyoma or an inflammatory myofibroblastic tumor), for CD34 and CD31 (discarding a benign vascular tumor), for kappa and lambda (excluding a plasmacytoma), and for CD21 and CD35 (excluding a follicular dendritic cell sarcoma).

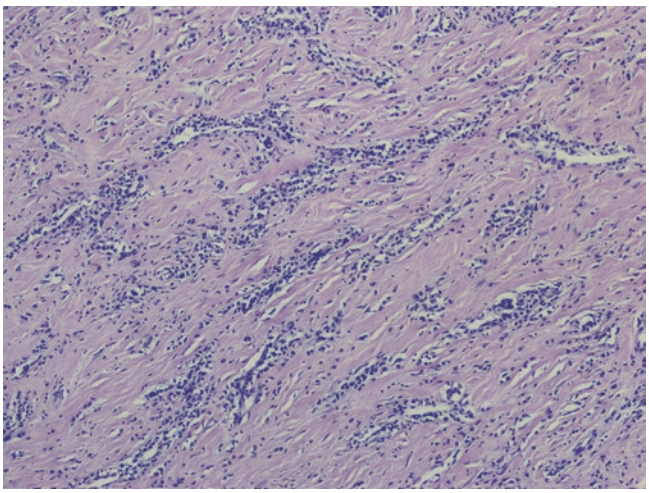

Fig. 5.45 Inflammatory pseudotumor of the breast: proliferation of spindle cells with a fascicular and vaguely storiform architecture, showing no nuclear atypia; mitotic figures are spare. A prominent vascular proliferation can be identified throughout the lesion, with some vasocentric inflammatory cells obliterating the vessels

5.9 Vasculitis

Various forms of vasculitis in a variety of systemic disorders (such as giant cell arteritis, Wegener's granulomatosis, polyarteritis, scleroderma, or dermatomyositis) may also involve the breast [5]. The breast is affected as an isolated manifestation or as part of multiorgan involvement. Of note, the breast lesions may mimic a breast carcinoma, especially from a clinical and/or radiological point of view; the biopsy is of great help in these situations.

Necrotizing granulomatous vasculitis is a nonneoplastic, inflammatory-type lesion of different tissues; breast involvement can occur in Wegener's granulomatosis, although it is very unusual. The breast lesion may present as single or multiple nodules. Some case reports have demonstrated an association of a breast mass and lung nodules at the time of diagnosis. Some authors have described the radiological appearance as an ill-defined, irregular mass or focal, asymmetric density on a mammogram that is suspicious for carcinoma, and as an irregular, hypoechoic nodular mass or a mass with parenchymal mixed echogenicity, consistent with mastitis or abscess on ultrasound examination. In very rare cases, microcalcifications are present within a suspicious breast mass on mammography [10]. Microscopically, multiple areas of necrotizing granulomatous vasculitis associated with macrophages and inflammatory cells can be detected (Figs. 5.46 and 5.47). Wegener's granulomatosis of the breast must be considered in the differential diagnosis of a single breast mass associated with microcalcifications and multiple associated lung nodules.

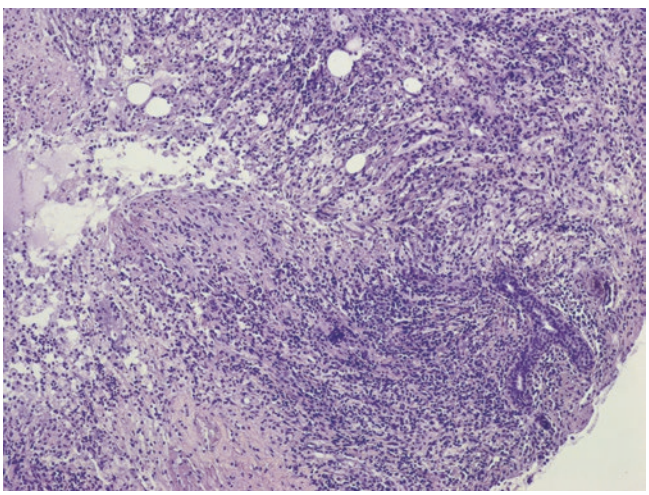

Fig. 5.46 Wegener's granulomatosis. Areas of necrotizing granuloma associated with macrophages and inflammatory cells can be detected in the vicinity of normal acini

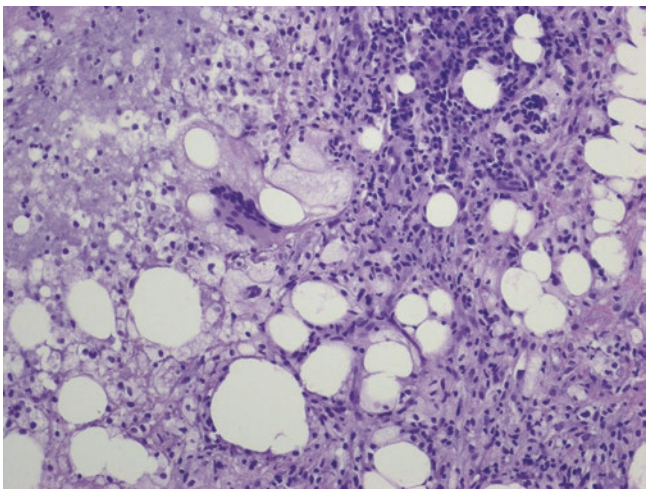

Fig. 5.47 Wegener's granulomatosis: central necrosis surrounded by inflammatory cells and foreign-body giant cells

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