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Breast Cancer

Benign Breast Diseases: Classification, Diagnosis, and Management

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Key Words. Benign breast disease • Developmental abnormalities • Inflammatory lesions
Fibrocystic changes • Benign • Neoplasms

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Discuss the clinical and histopathologic features of benign conditions of the breast.
2. Identify the risks of benign lesions in relation to developing subsequent breast cancer.
3. Describe the clinicopathologic features of benign neoplasms.

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ABSTRACT

Benign breast diseases constitute a heterogeneous group of lesions including developmental abnormalities, inflammatory lesions, epithelial and stromal proliferations, and neoplasms. In this review, common benign lesions are summarized and their relationship to the development of subsequent breast cancer is emphasized.
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INTRODUCTION

The vast majority of the lesions that occur in the breast are benign. Much concern is given to malignant lesions of the breast because breast cancer is the most common malignancy in women in Western countries; however, benign lesions of the breast are far more frequent than malignant ones [1–9]. With the use of mammography, ultrasound, and magnetic resonance imaging of the breast and the extensive use of needle biopsies, the diagnosis of a benign breast disease can be accomplished without surgery in the majority of patients. Because the majority of benign lesions are not associated with an increased risk for subsequent breast cancer, unnecessary surgical procedures should be avoided. It is important for pathologists, radiologists, and oncologists to recognize benign lesions, both to distinguish them from in situ and invasive breast cancer and to assess a patient's risk of developing breast cancer, so that the most appropriate treatment modality for each case can be established.

The term "benign breast diseases" encompasses a heterogeneous group of lesions that may present a wide range of symptoms or may be detected as incidental microscopic findings. The incidence of benign breast lesions begins to rise during the second decade of life and peaks in the fourth and fifth decades, as opposed to malignant diseases, for which the incidence continues to increase after menopause, although at a less rapid pace [2–14].

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In this review, the most frequently seen benign lesions of the breast are summarized as developmental abnormalities, inflammatory lesions, fibrocystic changes, stromal lesions, and neoplasms.

Developmental Abnormalities

Ectopic breast (mammary heterotopia), which has been described as both supernumerary and aberrant breast tissue, is the most common congenital abnormality of the breast. Supernumerary breast tissue is seen mostly along the milk line; the most frequent sites are the chest wall, vulva, and axilla. It may vary in its components of nipple (polythelia), areola, and glandular tissue (polymastia). However, an anatomic location outside the milk line should not preclude a diagnosis of ectopic breast tissue, because there are many well-documented, unusual sites of such tissue, including the knee, lateral thigh, buttock, face, ear, and neck [15]. Aberrant breast tissue is usually located near the breast, most commonly in the axilla. They usually have a nipple and areola and a separate duct system from that of the normal breast. When the nipple is absent, the presence of the accessory breast tissue is difficult to identify. The accessory breast tissue responds in the same way as normal breast tissue to physiological influences. The absence of a duct system may cause symptoms of obstruction during lactation and may be mistaken clinically for a carcinoma. Accessory breast tissue and polymastia are more common among Asians, especially Japanese, than whites [16]. Recognition of ectopic breast tissue is important because it can serve as a milieu for the development of a variety of benign and malignant lesions encountered in the normal breast. It has been reported that ectopic breast tissue is more prone to malignant change and that ectopic breast cancer occurs at an earlier age; however, malignancies in ectopic breasts are very rare [16–18]. Excessive breast growth (macromastia) can be seen in pregnancy as well as during adolescence.

Underdevelopment of the breast (hypoplasia), when congenital, is usually associated with genetic disorders, such as ulnar-mammary syndrome [19], Poland's syndrome, Turner's syndrome, and congenital adrenal hyperplasia. Among these disorders, Poland's syndrome is the congenital anomaly that has been reported to be associated with breast cancer most often [20]. There are some recent studies suggesting the association of ulnar-mammary syndrome and breast cancer; however, breast cancer has not been recorded in patients with Turner's syndrome [21, 22]. Acquired hypoplasia, on the other hand, is usually iatrogenic, most commonly subsequent to trauma or radiotherapy. The complete absence of both breast and nipple (amastia) or presence of only nipple without breast tissue (amazia) is rare [23].

Inflammatory and Related Lesions

Mastitis

A variety of inflammatory and reactive changes can be seen in the breast. While some of these changes are a result of infectious agents, others do not have a well-understood etiology and may represent local reaction to a systemic disease, or a localized antigen-antibody reaction, and are classified as idiopathic.

Inflammatory breast cancer, as the name suggests, mimics an infectious or inflammatory etiology. It often develops without a palpable mass lesion and is often initially misdiagnosed. In fact, most patients with inflammatory breast cancer are diagnosed after an initial treatment with antibiotics or anti-inflammatory therapies failed to show clinical improvement. Mammographic and sonographic evaluation are helpful in establishing the diagnosis. Image-guided biopsy of the abnormal breast parenchyma or skin biopsy confirms the diagnosis. A negative skin biopsy should not be used to exclude the diagnosis.

Acute Mastitis

Acute mastitis usually occurs during the first 3 months postpartum as a result of breast feeding. Also known as puerperal or lactation mastitis, this disorder is a cellulitis of the interlobular connective tissue within the mammary gland, which can result in abscess formation and septicemia. It is diagnosed based on clinical symptoms and signs indicating inflammation. Risk factors fall into two general categories: improper nursing technique, leading to milk stasis and cracks or fissures of the nipple, which may facilitate entrance of microorganisms through the skin; and stress and sleep deprivation, which both lower the mother's immune status and inhibit milk flow, thus causing engorgement [24, 25].

Because the duration of symptoms before starting treatment is found to be the only independent risk factor for abscess development, early diagnosis and early management of mastitis is of value [26]. However, there is little consensus on the type or duration of antibiotic therapy and when to begin antibiotics. Because lactation mastitis is a process of subcutaneous cellulitis, detection of pathogens in breast milk may not always be possible, so breast emptying with frequent nursing or manual pumping and beginning empiric antibiotherapy seems to be the most appropriate approach [26, 27]. When puerperal mastitis-associated abscess occurs, incision and drainage are usually recommended; however, suitable patients assessed by ultrasonography can also be treated without surgery by needle aspiration and antibiotics with excellent cosmesis [26].

Granulomatous Mastitis

Granulomatous reactions resulting from an infectious etiology, foreign material, or systemic autoimmune diseases such as sarcoidosis and Wegener's granulomatosis can involve the breast. Identification of the etiology requires microbiologic and immunologic testing in addition to histopathologic evaluation. Many different types of organisms can cause granulomatous mastitis [28, 29].

Tuberculosis of the breast is a very rare disease. However, both clinical and radiological features of tuberculous mastitis are not diagnostic and easily can be confused with either breast cancer or pyogenic breast abscess by clinicians. Remembering the fact that traveling from one place to another in the global world has been increasing and that the prognosis for complete cure with appropriate antituberculous drug therapy is excellent, this entity should also be taken into consideration. Definitive diagnosis of the disease is based on identification of typical histological features under microscopy or detection of the tubercle bacilli with mycobacterial culture [30].

The term "idiopathic granulomatous mastitis" is used for granulomatous lesions without an identifiable cause. This diagnosis can be made only by excluding other possible causes of granulomatous lesions. An autoimmune localized response to retained and extravasated fat- and protein-rich secretions in the duct has been postulated, but the etiology of the disease remains largely unknown [31]. Histologically, chronic noncaseating granulomatous inflammation is typically limited to lobuli. The recommended therapy of idiopathic granulomatous mastitis is complete surgical excision whenever possible plus steroid therapy. Even when idiopathic granulomatous mastitis is treated appropriately, in about 50% of the cases, persistence, recurrence, and complications such as abscess formation, fistulae, and chronic suppuration are encountered, so long-term follow-up is necessary in these patients [29, 31].

Foreign Body Reactions

Foreign materials, such as silicone and paraffin, which are used for both breast augmentation and reconstruction after cancer surgery, may cause a foreign body-type granulomatous reaction in the breast. Silicone granulomas ("siliconomas") usually occur after direct injection of silicone into the breast tissue or after extracapsular rupture of an implant [32]. Foreign body granulomatous response associated with multinucleated giant cells surround silicone. Fibrosis and contractions may lead to clinically apparent firm nodules that may be tender.

Recurring Subareolar Abscess

Recurring subareolar abscess (Zuska's disease) is a rare bacterial infection of the breast that is characterized by a triad of draining cutaneous fistula from the subareolar tissue; a chronic thick, pasty discharge from the nipple; and a history of multiple, recurrent mammary abscesses [33]. The disease is caused by squamous metaplasia of one or more lactiferous ducts in their passage through the nipple, probably induced by smoking [10]. Keratin plugs obstruct and dilate the proximal duct, which then becomes infected and ruptures. The inflammation eventuates in abscess formation beneath the nipple, which typically drains at the margin of the areola [10, 33]. Abscess drainage to allow for resolution of the acute inflammation and then complete excision of the affected duct and sinus tract is successful in most cases, but abscesses may recur when the process develops in another duct [33, 34].

Mammary Duct Ectasia

Mammary duct ectasia, also called periductal mastitis is a distinctive clinical entity that can mimic invasive carcinoma clinically. It is a disease of primarily middle-aged to elderly parous women, who usually present with nipple discharge, a palpable subareolar mass, noncyclical mastalgia, or nipple inversion or retraction. The pathogenesis and the etiology of the disease are still being debated. Smoking has been implicated as an etiologic factor in mammary duct ectasia [35, 36]. This association appears to be more important in young women who smoke [37]. Mammary duct ectasia is usually an asymptomatic lesion and is detected mammographically because of microcalcifications.

The most important histologic feature of this disorder is the dilatation of major ducts in the subareolar region. These ducts contain eosinophilic, granular secretions and foamy histiocytes both within the duct epithelium and the lumen. The inspissated luminal secretions may undergo calcifications that may be the presenting sign in many patients [38].

Mammary duct ectasia generally does not require surgery and should be managed conservatively [39]. There is no evidence in the literature indicating that mammary duct ectasia is associated with an increased risk for breast cancer. In some patients, clinical presentation and mammographic findings may suggest malignancy, and biopsy may be required to exclude malignancy.

Fat Necrosis

Fat necrosis of the breast is a benign nonsuppurative inflammatory process of adipose tissue. It can occur secondary to accidental or surgical trauma, or it may be associated with carcinoma or any lesion that provokes suppurative or necrotic degeneration, such as mammary duct ectasia and, to a lesser extent, fibrocystic disease with large cyst formation [40, 41].

Clinically, fat necrosis may mimic breast cancer if it appears as an ill-defined or spiculated dense mass, associated with skin retraction, ecchymosis, erythema, and skin thickness [41]. Mammographic, sonographic, and magnetic resonance imaging findings may not always distinguish fat necrosis from a malignant lesion. Even the macroscopic appearance of the benign lesion can suggest a malignant tumor. Histologically, however, the diagnosis of fat necrosis presents no problem, as it is characterized by anuclear fat cells often surrounded by histiocytic giant cells and foamy phagocytic histiocytes [42, 43]. Excisional biopsy is required if carcinoma cannot be excluded preoperatively [44].

Fibrocystic Changes

Fibrocystic changes (FCCs) constitute the most frequent benign disorder of the breast. Such changes generally affect premenopausal women between 20 and 50 years of age [2–9]. Although many other names have been used to describe this entity over the years, (including fibrocystic disease, cystic mastopathy, chronic cystic disease, mazoplasia, Reclus's disease), the term "fibrocystic changes" is now preferred, because this process is observed clinically in up to 50% and histologically in 90% of women [40, 45, 46].

FCCs may be multifocal and bilateral. The most common presenting symptoms are breast pain and tender nodularities in breasts. Although the exact pathogenesis of the entity is not clear, hormonal imbalance, particularly estrogen predominance over progesterone, seems to play an important role in its development [47]. FCCs comprise both cysts (macro and micro) and solid lesions, including adenosis, epithelial hyperplasia with or without atypia, apocrine metaplasia, radial scar, and papilloma. Over the years, it has been one of the major issues to determine whether these lesions are a risk factor for the subsequent development of breast cancer. As the use of mammography and the identification of benign breast diseases become more common, it is crucial to identify women who are at an increased risk for breast cancer. Therefore, it is practical to evaluate FCCs under a classification system first proposed by Dupont and Page [48], as nonproliferative lesions, proliferative lesions without atypia, and proliferative lesions with atypia (atypical hyperplasia). In various studies, it has been shown that the great majority of breast biopsies (up to 70%) show nonproliferative lesions.

Nonproliferative lesions include cysts, papillary apocrine change, epithelial-related calcifications, mild epithelial hyperplasia, as well as ductal ectasia, nonsclerosing adenosis, and periductal fibrosis. Proliferative lesions without atypia include moderate or florid ductal hyperplasia of the usual type, sclerosing adenosis, radial scar, and intraductal papilloma or papillomatosis. Proliferative lesions with atypia include atypical ductal and lobular hyperplasia. In each of these lesions, the subsequent risk for breast cancer is associated with the histologic appearance of the lesion [48–51]: compared with the general population, women with nonproliferative lesions on breast biopsy have no elevation in breast cancer risk, whereas women with proliferative disease without atypia and women with atypical ductal or lobular hyperplasia have a greater breast cancer risk, with relative risks ranging from 1.3–1.9 and 3.9–13.0, respectively, according to various studies [48–50, 52]. Apart from the histologic features, the age at biopsy and the degree of family history of breast cancer are reported to be the major determinants of breast cancer risk after the diagnosis of benign breast disease [51]. According to Hartmann et al. [51], the risk for breast cancer in young women with a diagnosis of atypical epithelial proliferation is twice the risk observed among women over 55 years with a diagnosis of atypical epithelial proliferation. It was also reported, in the same study, that family history of breast cancer is an independent risk factor and that strong family history may increase breast cancer risk even in patients with nonproliferative lesions [51]. Absolute risk, however, for both atypical and nonatypical epithelial proliferations is quite low. More than 80% of patients with a diagnosis of atypical hyperplasia do not develop invasive cancer during their lifetimes.

Cysts

Cysts are fluid-filled, round or ovoid structures that are found in as many as one third of women between 35 and 50 years old. Although most are subclinical "microcysts," in about 20%–25% of cases, palpable (gross) cystic change, which generally presents as a simple cyst, is encountered [10, 53]. Cysts cannot reliably be distinguished from solid masses by clinical breast examination or mammography; in these cases, ultrasonography and fine needle aspiration (FNA) cytology, which are highly accurate, are used.

Cysts are derived from the terminal duct lobular unit. In most cysts, the epithelial lining is either flattened or totally absent. In only a small number of cysts, an apocrine epithelial lining is observed. Because gross cysts are not associated with an increased risk of carcinoma development, the current consensus on the management of gross cysts is routine follow-up of the patient, without further therapy [53].

Complex (or complicated or atypical) cyst is a sonographic diagnosis that is characterized by internal echoes or thin septations, thickened and/or irregular wall, and absent posterior enhancement [54]. They are reported in approximately 5%–5.5% of all breast ultrasound examinations. The malignancy rate of complex cysts, which is 0.3% as described by Venta et al., is lower than that for lesions classified as "probably benign." These patients can be man-

aged with follow-up imaging studies [54, 55]. However, if the lesion also includes an intracystic mass (intracystic nodule), it should be regarded as "suspicious for neoplasm" and managed as solid lesions. Either a core needle biopsy or surgical biopsy is indicated for these lesions [54, 56].

Adenosis

Adenosis of the breast is a proliferative lesion that is characterized by an increased number or size of glandular components, mostly involving the lobular units. Various types of adenosis have been described, of which sclerosing adenosis and microglandular adenosis merit detailed description [57].

Sclerosing adenosis of the breast is defined as a benign lobulocentric lesion of disordered acinar, myoepithelial, and connective tissue elements, which can mimic infiltrating carcinoma both grossly and microscopically [58]. Sclerosing adenosis can manifest as a palpable mass or as a suspicious finding at mammography. It is strongly associated with various proliferative lesions, including epithelial hyperplasias, intraductal or sclerosing papilloma, complex sclerosing lesion, calcification, and apocrine changes (Fig. 1). It can coexist with both invasive and in situ cancers [59]. Studies found sclerosing adenosis to be a risk factor for invasive breast cancer apart from its association with other proliferative lesions of the breast [58, 60].

Microglandular adenosis of the breast is characterized by a proliferation of round, small glands distributed irregularly within dense fibrous and/or adipose tissue. Most of the glandular structures have open lumina in which eosinophilic material is usually seen. The most important histological feature of microglandular adenosis is that it may lack the outer myoepithelial layer seen in other types of adenosis. The lack of myoepithelial layer makes it harder to differentiate microglandular adenosis from tubular carcinoma [61, 62]. However, the presence of basal lamina encircling glandular structures, which can also be shown by laminin or type IV collagen immunohistochemical stains, and the absence of epithelial membrane antigen staining in the luminal epithelial cells distinguish microglandular adenosis from tubular carcinoma [62].

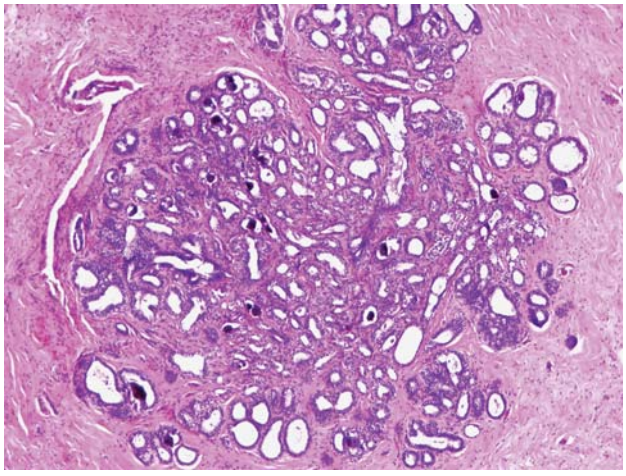

Figure 1. Sclerosing adenosis. Proliferation of small glands associated with microcalcifications. Low-power examination demonstrates the lobulocentricity of the lesion.

Although microglandular adenosis is considered benign, there is some evidence of the potential of this lesion to become invasive carcinoma. Microglandular adenosis also has a tendency to recur if not completely excised [63].

Apocrine (adenomyoepithelial) adenosis, which seems to be a variant of microglandular adenosis, was first described in association with adenomyoepithelioma. It is an apocrine change in deformed lobular units, sclerosing adenosis, radial scars, and complex sclerosing lesions. The term apocrine adenosis is used to describe a wide spectrum of apocrine lesions, and to prevent its inappropriate use, this term has been proposed to describe apocrine changes in the specific underlying lesions [53].

Tubular adenosis of the breast is another and rare variant of microglandular adenosis that should be distinguished from tubular carcinoma. The presence of an intact myoepithelial layer around the tubules is the most helpful feature [57].

Metaplasia

Apocrine metaplasia is characterized by the presence of columnar cells with abundant granular, eosinophilic cytoplasm and luminal cytoplasmic projections or apical snouts. These cells line dilated ducts or can be seen in papillary proliferations. They are more frequently found in younger women. All normal and metaplastic apocrine cells can be stained with gross cystic disease fluid protein 15.

Atypical apocrine metaplasia should be diagnosed only when the nuclei of the apocrine cells display significant cytologic atypia [64].

Clear cell metaplasia of the breast is a rare lesion. Its significance comes from its morphologic similarity to clear cell carcinoma. However, the similarity of its immunohistochemical staining profile with that of eccrine sweat glands suggests that clear cell metaplasia may in fact represent "eccrine metaplasia" [65].

Epithelial Hyperplasia

Epithelial hyperplasia (ductal or lobular type) is one of the most challenging FCCs to diagnose properly. Epithelial hyperplasia is the most common form of proliferative breast disease. It can be difficult to distinguish between ductal and lobular hyperplasias. In addition, it can also be difficult to distinguish between usual ductal or lobular

hyperplasias and their atypical counterparts—atypical ductal hyperplasia and atypical lobular hyperplasia. Table 1 lists the various types of epithelial hyperplasia and associated risk of carcinoma.

Ductal Lesions

Normally, breast ducts are lined by two layers of low cuboidal cells with specialized luminal borders and basal contractile myoepithelial cells. Any increase in cell number within the ductal space is regarded as epithelial hyperplasia. Further classification is based on the degree and architectural and cytologic features of the proliferating cells. Usual ductal hyperplasia or simple hyperplasia denotes an increased number of cells without architectural distortion or distention of the ductal contour. Usual ductal hyperplasia does not increase the risk for breast cancer. In mild hyperplasia of the usual type, proliferating epithelial cells are a three- to four-cell layer, whereas moderate hyperplasia describes epithelial proliferation more than four cells thick, often with accompanying bridging of the luminal space (Fig. 2A). In florid hyperplasia, the lumen is distended and may be obliterated (Fig. 2B). The most important cytologic features of mild, moderate, or florid epithelial hyperplasia are an admixture of cell types (epithelial cells, myoepithelial cells, and metaplastic apocrine cells) and variation in the appearances of epithelial cells and their nuclei [66, 67].

The term atypical ductal hyperplasia is defined as a type of a ductal hyperplasia that morphologically mimics low-grade ductal carcinoma in situ (DCIS). Characteristically, it has a uniform population of cells. Most lesions of atypical ductal hyperplasia are small and focal. They involve only a portion of a duct or only a few small ducts measuring <2 mm (Fig. 2C) [66]. With the increasing use of mammography, and detection of calcifications, atypical ductal hyperplasias are being diagnosed more frequently. Atypical ductal hyperplasia is a rare condition among patients having biopsies for a palpable mass, seen in 4% of symptomatic benign biopsies. In contrast, 31% of biopsies performed because of microcalcifications show atypical ductal hyperplasia [68]. The significance of this lesion comes from the fact that the patient has an increased risk for invasive breast cancer, which is about four to five times that of the general population, and reaching nearly a tenfold risk if the patient has a first-degree relative with breast cancer [68, 69]. The risk for breast cancer is higher in the ipsilateral breast, but the contralateral breast is also at risk [51, 70–72]. Women with atypical ductal hyperplasia develop cancer usually within 10–15 years of the diagnosis. The risk for cancer declines after 15 years [70, 73]. The risk for breast cancer in women with atypical ductal hyperplasia is also related to the patient's menopausal status. Premenopausal women with atypical ductal hyperplasia have a substantially higher risk than postmenopausal women with that diagnosis. Routine follow-up for both breasts is recommended. Therapy options, such as chemoprevention, should be determined on the basis of other risk factors for breast cancer.

Table 1. Histologic category of benign breast lesions associated with the relative risk for breast cancer for patients with no family history

Histologic category	Relative risk[a]
Nonproliferative lesions Cysts Mild hyperplasia of the usual type Columnar cell change	1
Proliferative lesions without atypia Sclerosing adenosis Moderate or florid ductal hyperplasia of the usual type Radial scar Intraductal papilloma Fibroadenoma	1.3–1.9
Atypical hyperplasia Atypical ductal hyperplasia Atypical lobular hyperplasia	3.9–13.0

[a]Relative risk represents the range of relative risks reported in one retrospective cohort study [43] and three case-control studies [44, 45, 47].

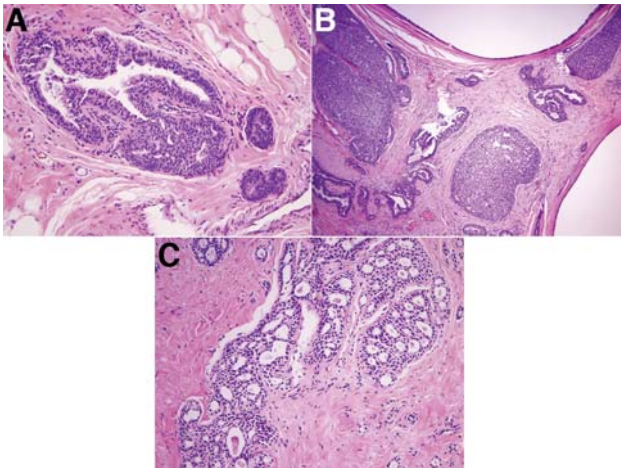

Figure 2. Ductal epithelial hyperplasias. **(A):** Usual ductal hyperplasia. The epithelial proliferation is composed of polymorphic cell types that partially occlude the lumen. **(B):** Florid epithelial hyperplasia. Proliferating solid clusters of hyperplastic cells with the typical appearance of overlapped and uneven distribution of nuclei. The epithelial proliferation obliterates and distends the ductal lumens. **(C):** Atypical ductal hyperplasia is characterized by monotonous proliferation of regularly arranged cells; in this photograph, forming a cribriform pattern. Although displaying features of low-grade intraductal carcinoma, quantitatively, being a single and small focus, this lesion is interpreted as atypical ductal hyperplasia.

Lobular Lesions

Lobular-type epithelial proliferations, both atypical lobular hyperplasia and lobular carcinoma in situ, are collectively termed lobular neoplasia because, unlike ductal lesions, which exhibit heterogeneous morphologic features, the histologic features of lobular type epithelial proliferations are very similar, and the only difference between atypical lobular hyperplasia and lobular carcinoma in situ is the extent and degree of epithelial proliferation. Because both lesions are regarded and managed as a risk factor rather than well-established precursor lesions, lobular neoplasia terminology has gained general acceptance. Lobular neoplasia is a relatively rare breast lesion. It rarely manifests itself clinically. Lobular neoplasia is identified as an incidental finding in biopsies excised for other abnormalities. The frequency of detection depends on the volume of tissue removed during surgery and extent of histological examination. Lobular neoplasia is most prevalent in perimenopausal women. It is a multifocal lesion, and many patients have lesions involving multiple quadrants of the breast. Both atypical lobular hyperplasia and lobular carcinoma in situ increase the risk for the subsequent development of invasive carcinoma, by about fourfold for atypical lobular hyperplasia and tenfold for lobular carcinoma in situ. Although subsequent carcinomas can occur in either breast without a direct relationship to the previous site of biopsy, in a recent retrospective study, Page et al. [74] reported that the development of invasive carcinoma after atypical lobular hyperplasia was three times more likely to arise in the ipsilateral breast than in the opposite breast. Invasive carcinomas may arise 15–20 years after diagnosis. Systemic follow-up and appropriate risk assessment is recommended for patients with lobular neoplasia.

Lobular carcinoma in situ is considered to be a risk marker rather than an obligatory precursor lesion of invasive breast cancer; therefore, in general, it does not warrant surgical therapy. Most women with a diagnosis of lobular carcinoma in situ do not develop invasive breast cancer within their natural lifetimes. The risk for developing invasive cancer appears to be similar in both the ipsilateral and contralateral breasts. Therefore, if one has to choose surgery for lobular carcinoma in situ, the only logical approach would be a bilateral total mastectomy. Because this is an excessively morbid procedure for patients who have a moderate risk associated with the diagnosis of lobular carcinoma in situ, chemoprevention is the preferred approach for these patients. However, if the patient has other risk factors, such as a high-risk family history, prophylactic bilateral mastectomy with or without reconstruction would be a consideration.

Columnar Cell Lesions

Columnar cell lesions of the breast represent a spectrum of lesions that have been encountered with increasing frequency in needle core breast biopsies because these lesions are commonly associated with microcalcifications and detected by mammographic screening. A working classification of these lesions has been proposed by Schnitt and Vincent-Salomon [75] as columnar cell change and columnar cell hyperplasia, each of which may have atypia or not. Ongoing studies on the clinical significance of atypical columnar cell lesions, which are also known as flat epithelial atypia, have shown that the likelihood of local recurrence or progression to invasive breast cancer is exceedingly low. However, based on the foregoing observations, it has been suggested that at least some lesions are probably neoplastic proliferations that may represent either a precursor of low-grade DCIS or even invasive carcinoma, particularly tubular carcinoma [76].

When an atypical columnar lesion is encountered in a needle core biopsy, excision is suggested to exclude more advanced lesions such as in situ or invasive cancer. On excisional biopsy specimen, a careful histologic search for areas with diagnostic features of in situ or invasive cancer should be performed. Because this lesion has been referred to by several different names in the literature, including blunt duct adenosis, columnar alteration of lobules, hypersecretory hyperplasia with atypia, pretubular hyperplasia, and columnar alteration with prominent snouts and secretions, it is difficult to assess its significance as a risk marker for development of invasive cancer. Without having firm data, close follow-up of the patient with columnar cell changes is recommended at this point [76, 77].

Radial Scar and Complex Sclerosing Lesion

Radial scars are benign pseudoinfiltrative lesions of uncertain significance. They are characterized by a fibroelastotic core with entrapped ducts, surrounded by radiating ducts and lobules displaying variable epithelial hyperplasia, adenosis, duct ectasia, and papillomatosis [64]. Previously, radial scars were an incidental finding in breast specimens excised for other diagnostic reasons, but their incidence has increased dramatically as a result of population-based screening programs [78]. Some authors have suggested using the term "radial scar" for lesions measuring <1 cm, whereas the term "complex sclerosing lesion" was reserved for lesions measuring 1 cm or larger [78, 79].

Radial scars may serve as a milieu for the development of atypical epithelial proliferations, including atypical intraductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma in situ, and DCIS [80]. Over the years, many authors have studied the biologic significance of radial scars. In a

postmortem study by Nielsen et al. [81], these lesions were commonly associated with benign breast diseases, whereas Jacobs et al. [82] found that radial scars were associated with a doubling of the risk for breast cancer, regardless of the type of primary breast disease, and that the risk was even greater in women with larger or multiple radial scars.

The radiographic features of radial scars are nonspecific and may mimic carcinoma (Fig. 3A, B). The role of FNA cytology in diagnosis is limited. Recent publications have shown the importance of core needle biopsy of these lesions for diagnosis, but because malignancy cannot be reliably excluded with limited sampling, a spiculated lesion suggestive of radial scar or complex sclerosing lesion at mammography may be excised on the basis of its size and amount of sampling performed by core biopsy [78, 79, 83].

Intraductal Papilloma and Papillomatosis

Intraductal papilloma is a discrete benign tumor of the epithelium of mammary ducts. It can arise at any point in the ductal system and shows a predilection for the extreme ends of the ductal system: the lactiferous sinuses and the terminal ductules [84]. The central papillomas tend to be solitary, whereas the peripheral ones are usually multiple. Serous or serosanguinous nipple discharge is the presenting symptom in most women. Papillomas are characterized by formation of epithelial fronds that have both the luminal epithelial and the outer myoepithelial cell layers, supported by a fibrovascular stroma. The epithelial component can be subject to a spectrum of morphologic changes ranging from metaplasia to hyperplasia, atypical intraductal hyperplasia, and in situ carcinoma. The risk represented by the occurrence of such abnormalities in an otherwise benign papilloma is currently debated [85]. Central single papillomas have not been considered premalignant or markers of risk when they are not associated with atypia. Two recent studies found significant correlation between the presence of atypical ductal hyperplasia in papillary lesions on core biopsies and the presence of invasive or preinvasive carcinoma of the breast in excisional biopsies [86, 87]. In another clinicopathologic study, MacGrogan and Tavassoli [85] suggested that the recurrence of papillomas is related to the presence of proliferative breast lesions (including usual ductal hyperplasia, atypical ductal hyperplasia, and lobular neoplasia) in the surrounding breast tissue. Epithelial atypia, even to the extent of low-grade DCIS has no known prognostic significance or impact on outcome when it is confined to the central papilloma. Therefore, if atypia is encountered in a papilloma on an excisional biopsy, the surrounding breast tissue should be carefully examined for further follow-up of the patient [85].

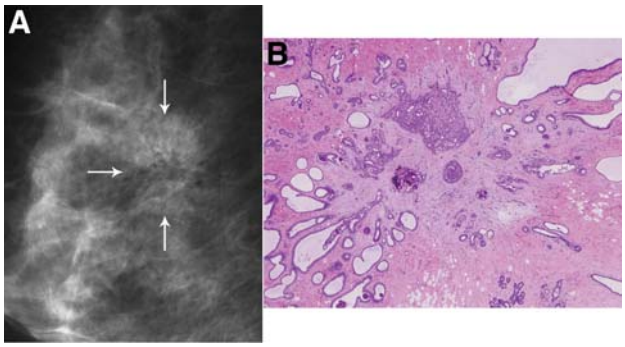

Figure 3. Radial scar. **(A):** The mammographic appearance of radial scar. Spiculated lesion with central radiolucency. Radiating spicules frequently mislead the diagnosis of carcinoma. **(B):** Low-power view of radial scar shows fibroelastotic core and radiating ducts exhibiting duct epithelial hyperplasia without atypia, cystic structures, and microcalcifications.

Papillomatosis (multiple papillomas) is defined as a minimum of five clearly separate papillomas within a localized segment of breast tissue, usually in a peripheral or subareolar location. Multiple papillomas are more likely to occur bilaterally, and their probability of having an in situ or invasive carcinoma is higher than with the central papilloma. Therefore, in patients with multiple papillomas on excisional biopsy, thorough sampling of the specimen, as well as diagnostic radiographic imaging of contralateral breast tissue is suggested to rule out malignancy [88]. All the available data suggest that the finding of a solitary, central, benign duct papilloma does not carry any increased risk for subsequent breast cancer, while multiple papillomas may indicate a slightly elevated risk for subsequent breast cancer [89–91].

Juvenile papillomatosis of the breast is defined as severe ductal papillomatosis occurring in young women of <30 years old. There are only eight male juvenile papillomatosis cases reported in the literature [92]. This disease is associated with a heightened risk for breast cancer. Because both a family history of breast cancer and an increased risk for breast cancer are associated with the diagnosis of juvenile papillomatosis, long-term follow-up is recommended both for the patient and the family [93, 94].

Proliferative Stromal Lesions

Diabetic Fibrous Mastopathy

Diabetic fibrous mastopathy is an uncommon form of lymphocytic mastitis and stromal fibrosis. It occurs both in premenopausal women and (rarely) in men with long-standing type 1 insulin-dependent diabetes mellitus, who have severe diabetic microvascular complications. Clinically, diabetic fibrous mastopathy is characterized by solitary or multiple ill-defined, painless, immobile, discrete lesions in one or

both breasts that raise the suspicion of carcinoma. The mammographic and sonographic findings of these lesions are also highly suspicious for breast cancer, so a biopsy is always essential for definitive diagnosis [95, 96]. The characteristic pathologic findings of this entity are dense keloid-like fibrosis; periductal, lobular, or perivascular lymphocytic infiltration with predominantly B cells; lobular atrophy; and epithelioid fibroblasts embedded in dense fibrous stroma. The pathogenesis of diabetic fibrous mastopathy is unknown. The disease probably represents an immune reaction to the abnormal accumulation of altered extracellular matrix in the breast, which is a manifestation of the effects of hyperglycemia on connective tissue [95, 97].

Routine annual follow-up of patients with diabetic fibrous mastopathy is recommended [95–97]. Core needle biopsy may be useful in the diagnosis of recurrent lesions on follow-up [95].

Pseudoangiomatous Stromal Hyperplasia of the Breast

Pseudoangiomatous stromal hyperplasia (PASH) is a benign myofibroblastic proliferation of nonspecialized mammary stroma. Its clinicopathologic spectrum ranges from incidental, microscopic foci to clinically and mammographically evident breast masses [98]. Originally, hormonal stimulation (particularly with progesterone) was suggested in the etiology of PASH, on the basis of observations that this disease is most frequently seen in premenopausal women or in elderly women taking hormone-replacement therapy, and because similar histologic findings are seen in normal mammary stroma during the luteal phase of the menstrual cycle. However, the lesion has since been found in men and in women not taking hormone therapy, and only a small percentage of PASH cases are positive for estrogen receptors or for progesterone receptors [98, 99].

Clinically, rare cases of PASH present as a well-circumscribed, dense, rubbery mass mimicking a fibroadenoma or a phyllodes tumor. Both the mammographic and sonographic features in PASH are nonspecific, so biopsy of these lesions is necessary to exclude a malignancy [99, 100].

On gross examination, PASH is usually a well-demarcated mass with a smooth external surface. The cut surface consists of homogeneous white and rubbery tissue. Histologically, a complex network of anastomosing slit-like spaces within a densely collagenous stroma characterizes PASH. The histologic appearance may cause confusion with mammary angiosarcoma, so immunohistochemical vascular markers are used for distinction. Immunohistochemically, the bland spindle cells that line these spaces are strongly positive for vimentin and CD34 and negative for cytokeratin and factor VIII.

The recommended treatment for PASH is wide local excision. Although PASH can recur, patient prognosis is good [98].

Neoplasms

Fibroadenoma

Fibroadenoma is the most common lesion of the breast; it occurs in 25% of asymptomatic women [101]. It is usually a disease of early reproductive life; the peak incidence is between the ages of 15 and 35 years. Conventionally regarded as a benign tumor of the breast, fibroadenoma is also thought to represent a group of hyperplastic breast lobules called "aberrations of normal development and involution" [10, 101, 102]. The lesion is a hormone-dependent neoplasm that lactates during pregnancy and involutes along with the rest of the breast in perimenopause [102]. A direct association has been noted between oral contraceptive use before age 20 and the risk of fibroadenoma [103]. The Epstein-Barr virus might play a causative role in the development of this tumor in immunosuppressed patients [104].

Fibroadenoma presents as a highly mobile, firm, nontender, and often palpable breast mass. Although most frequently unilateral, in 20% of cases, multiple lesions occur in the same breast or bilaterally. Fibroadenoma develops from the special stroma of the lobule. It has been postulated that the tumor might arise from bcl-2-positive mesenchymal cells in the breast, in a manner similar to that proposed for solitary fibrous tumors [105]. Macroscopically, the lesion is a well-circumscribed, firm mass, <3 cm in diameter, the cut surface of which appears lobulated and bulging (Fig. 4A). If the tumor assumes massive proportions (>10 cm), more commonly observed in female adolescents, it is called "giant fibroadenoma." Microscopically, fibroadenoma consists of a proliferation of epithelial and mesenchymal elements. The stroma proliferates around tubular

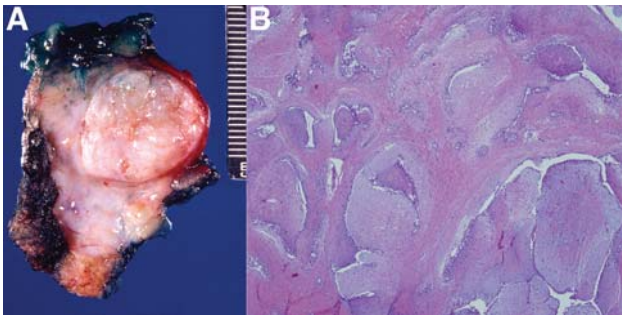

Figure 4. Fibroadenoma. **(A):** The cut surface of fibroadenoma is lobulated, solid, and gray-white, with a characteristic bulging appearance. **(B):** Histologically the lesion consists of densely fibrotic stroma and compressed cleft-like ducts.

glands (pericanalicular growth) or compressed cleft-like ducts (intracanalicular growth). Often both types of growth are seen in the same lesion (Fig. 4 B) [103].

Cytogenetic studies have reported chromosomal aberrations in both epithelial and stromal cells, suggesting that the two components may involve neoplastic changes [106, 107]. Phyllodes tumor is a fibroepithelial tumor of the breast with a spectrum of changes. Benign phyllodes tumor is usually difficult to differentiate from fibroadenoma. Hypercellular stroma with cytologic atypia, increased mitoses, and infiltrative margins of the lesion are the most reliable discriminators to separate lesions with recurrence and malignant behavior. In terms of surgical treatment of these tumors, it is important to recognize phyllodes tumor because it should be excised completely with clear margins to obviate any chance of local recurrence. In cases of recurrent disease, mastectomy is often performed [108, 109].

Approximately 50% of fibroadenomas contain other proliferative changes of breast, such as sclerosing adenosis, adenosis, and duct epithelial hyperplasia. Fibroadenomas that contain these elements are called complex fibroadenomas. Simple fibroadenomas are not associated with any increased risk for subsequent breast cancer. However, women with complex fibroadenomas may have a slightly higher risk for subsequent cancer [110]. The presence of atypia (either ductal or lobular) confined to a fibroadenoma does not lead to a greater risk for long-term breast carcinoma compared with fibroadenomas in general [110].

Fibroadenomas in older women or in women with a family history of breast cancer have a higher incidence of associated carcinoma [101, 111]. Two studies, which were considered to provide strong evidence of reliability according to El-Wakeel et al. [101], show that the relative risk of developing breast cancer in patients who had surgically excised fibroadenomas increases in the presence of complex features within the fibroadenomas, ductal hyperplasias, or a family history of breast carcinoma (in a first-degree relative). Progressive somatic genetic alterations that are associated with the development of breast cancer have been studied in fibroadenomas. No genetic instabilities, manifested as loss of heterozygosity or microsatellite instability, have been found in any fibroadenoma components regardless of their association with breast cancer or their histologic complexity [106].

The current management of patients with clinically or radiologically suspected fibroadenoma varies. Some physicians prefer excision for tissue diagnosis, but conservative management will likely replace surgical treatment in the near future, on the basis of the young age of the patient, findings of benign imaging and clinical characteristics, and benign findings on either FNA biopsy or needle core biopsy [110, 112]. Minimally invasive techniques, such as ultrasound-guided cryoablation, seem to be an excellent treatment option for fibroadenoma in women who wish to avoid surgery [1], or else the lesion may simply be treated with observation and followed up periodically.

Juvenile fibroadenoma is a variant of fibroadenoma that presents between 10 and 18 years of age, usually as a painless, solitary, unilateral mass >5 cm. It can reach up to 15 or 20 cm in dimension, so although it is an entirely benign lesion, surgical removal is recommended [113].

Lipoma

Lipoma of the breast is a benign, usually solitary tumor composed of mature fat cells. It is occasionally difficult to distinguish lipoma from other conditions clinically, thus causing diagnostic and therapeutic challenges [114].

Clinically, a lipoma presents as a well-circumscribed, smooth or lobulated mass that is soft and usually nontender. FNA biopsy of these lesions reveals fat cells with or without normal epithelial cells. Usually both mammography and ultrasound scanning give negative results, unless the tumor is large [10, 114].

If the clinical diagnosis of lipoma is confirmed by either FNA biopsy or core biopsy, and the mammogram and the ultrasonogram show nothing suspicious for malignancy at the site, the patient is normally followed through palpation after 6 months. However, if the diagnosis is not certain or the lesion grows rapidly, the tumor should be surgically removed [10, 114].

Adenoma

An adenoma is pure epithelial neoplasm of the breast. This lesion is divided into tubular, lactating, apocrine, ductal, and so-called pleomorphic (i.e., benign mixed tumor) adenoma [43]. Except for lactating and tubular adenomas, these lesions are uncommon. Both lactating and tubular adenomas occur during the reproductive ages.

Lactating adenoma is the most prevalent breast mass during pregnancy and puerperium. It presents as a solitary or multiple, discrete, palpable, freely movable breast mass that tends to be small (<3 cm). On gross examination, the lesion is well circumscribed and lobulated. It is characterized by hyperplastic lobules in which proliferated acini are lined by actively secreting cuboidal cells. Lactating adenoma may also develop in ectopic locations, such as the axilla, chest wall, or vulva [40, 115, 116]. Although the tumor may spontaneously involute, surgical removal may be necessary because of the mass effect it produces, and in cases when lactation is not of concern, medical therapy may be given to shrink the tumor. This tumor does not tend to recur locally, and there is no proven malignant potential [115].

Tubular adenoma (also termed pure adenoma) of the breast presents as a solitary, well-circumscribed, firm mass. It may resemble the appearance of noncalcified fibroadenoma radiographically. Histologically, tightly packed tubular or acinar structures that are very regular in size and shape are seen in a sparsely cellular stroma. Microcalcifications inside dilated acini have been described; numerous tiny, punctuate, and irregular microcalcifications are prominent on mammography and ultrasonography [117].

Both lactating and tubular adenomas, (the true breast adenomas) can be distinguished from fibroadenoma and nipple adenoma by the presence of scant stroma in the former [10].

Nipple Adenoma

Nipple adenoma, also known as florid papillomatosis of the nipple ducts or erosive adenomatosis, is a benign tumor of the ductal epithelium that often clinically mimics Paget's disease and pathologically may be misinterpreted as an adenocarcinoma. Typically, nipple adenoma presents as a discrete, palpable tumor of the papilla of the nipple. Erosion of the nipple and nipple discharge are usually seen. Histologically, the tumor is characterized by proliferating ductal structures that invade the surrounding stroma. A double layer of epithelium lines these ductal structures. The presence of keratin cysts and tiny apical snouts are other distinguishing features of the disease [118]. Generally, a biopsy is necessary for diagnosis. Nipple adenoma can be successfully treated by complete excision of the tumor with normal surgical margins. Recurrences of incompletely excised lesions have been documented. Nipple adenoma is considered a benign lesion, but rarely malignant change within or contiguous with nipple adenoma has been defined [10, 118].

Hamartoma

Hamartoma of the breast is an uncommon benign tumorlike nodule, also known as fibroadenolipoma, lipofibroadenoma, or adenolipoma, composed of varying amounts of glandular, adipose, and fibrous tissue. Clinically, hamartoma presents as a discrete, encapsulated, painless mass. Although the pathogenesis of the lesion is not clear, it is thought to result from a dysgenesis rather than a true tumorous process. Some cases have been reported to be related to a genetic defect called Cowden's disease. The classic mammographic appearance is a circumscribed area consisting of both soft tissue and lipomatous elements, surrounded by a thin radiolucent zone [119, 120].

On macroscopic examination, hamartomas are typically well-circumscribed lesions with smooth contours. Histologically, the most characteristic appearance is otherwise normal breast and fat tissue distributed in a nodular fashion within a fibrotic stroma that surrounds and extends to between individual lobules and obliterates the usual interlobular specialized loose stroma [119, 121].

There are some issues that should be taken into consideration when evaluating hamartomas. First, this lesion can be very easily underestimated if the clinical finding of a distinct lump or breast asymmetry and the imaging features are not interpreted thoroughly. Second, the pathologist should always be careful about a coincidental epithelial malignancy occurring in the lesion, and the lesion has a potential problem of recurrence. Third, the lesion should be placed in the differential diagnosis of biphasic breast tumors [120, 121].

The current management of hamartomas is surgical removal.

Granular Cell Tumor

Granular cell tumor is an uncommon, usually benign neoplasm that originates from Schwann cells of the peripheral nervous system. It is most frequently found in the head and neck region, particularly in the oral cavity. The tumor occurs in the breast in only 5%–6% of cases [122].

Clinically, granular cell tumor can simulate carcinoma because of its fibrous consistency, fixation to the pectoral fascia, skin retraction, and ulceration. Mammographic and ultrasonographic findings may further increase the suspicion of a malignant lesion [123].

Grossly, granular cell tumor is generally 3 cm or smaller and appears almost well circumscribed when bisected; in some tumors, however, infiltrative margins suggestive of a malignant lesion may be encountered. Histologically, nests and sheets of polygonal cells with distinct cell borders and abundant granular eosinophilic cytoplasm are characteristic (Fig. 5). The S-100 protein

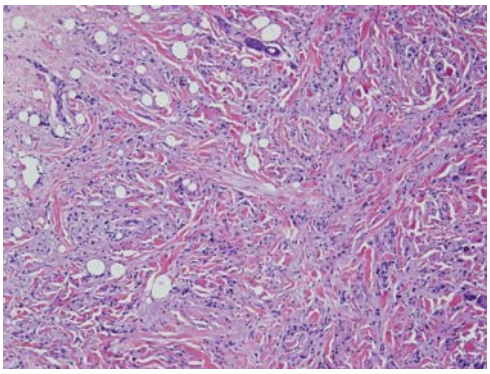

Figure 5. Granular cell tumor. Sheets or nests of large polygonal cells with abundant, coarsely granular, eosinophilic cytoplasm and prominent, round to oval nucleus.

immunoreactivity of these cells supports the hypothesis that granular cell tumor derives from Schwann cells [122, 124].

Although granular cell tumor is mostly benign, there are a few cases in the literature reported as malignant [125]. Features suggestive of malignancy are tumor size (>5 cm), cellular and nuclear pleomorphism, prominent nucleoli, increased mitotic activity, presence of necrosis, and local recurrence [126].

Wide local excision is the treatment of choice for both benign and malignant granular cell tumors. Complete removal may require inclusion of muscle and other adjacent structures, and histologically it is recommended that the margins be completely free of tumor. Incomplete excision may result in local recurrences. Adjuvant therapy is not given unless the tumor is malignant [124].

Disclosure of Potential Conflicts of Interest

The authors indicate no potential conflicts of interest.

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