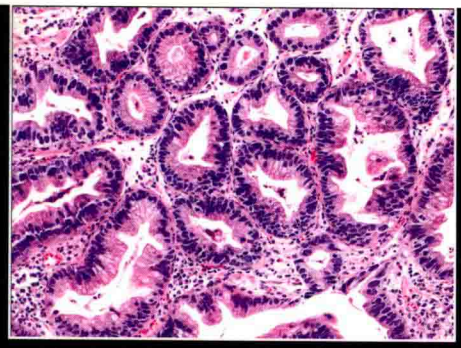

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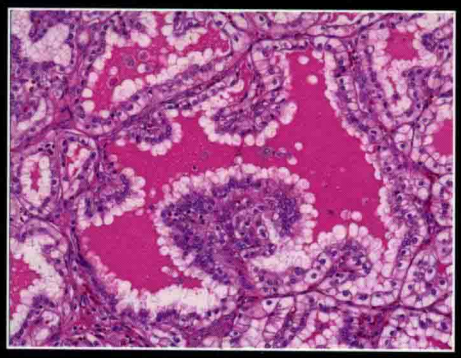

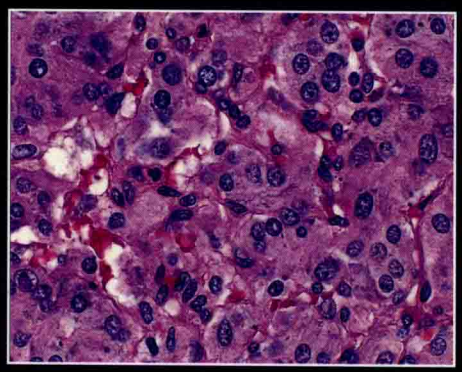

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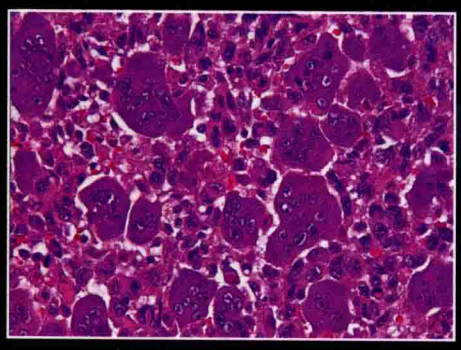

Volume 2

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Preface

In the five-year interval since publication of *Diagnostic Histopathology of Tumors, Third Edition*, conventional morphologic and immunohistochemical assessment has continued to hold sway as the pre-eminent, most reliable, and most cost-effective means to provide a diagnosis, prognostic assessment, and in most cases, determination of the adequacy of excision for human tumors. Such interpretation also helps to guide therapy in many settings. The continued utility of such "traditional" technologies and interpretive skills is somewhat reassuring in the setting of the ever-widening disparities in the availability of more expensive modern technologies, such as molecular genetic diagnosis, gene expression profiling, and genomics, not only (to a depressing degree) between the developed and still developing (or underdeveloped) areas of the world, but even among different developed countries or regions.

The role of molecular diagnosis is now very well established and firmly integrated in the practice of modern surgical pathology, and is especially valuable in confirming the presence of diagnostically important gene fusions or mutations, in helping with therapeutic target identification and, not least, in enhancing diagnostic reproducibility and tumor classification schemes. Whereas some targets can be identified immunohistochemically, mutational analysis may better enable treatment selection in some contexts, especially in the setting of treatment resistance. A more complex issue, however, in some of the developed countries (with dangerously expanding health care expenditure) is the interface between pathology and genomic medicine. Expression profiling as well as whole genome sequencing are increasingly being promulgated as providing additional information of critical clinical importance—yet, at this point in time, the value of such testing has only rarely been demonstrated and validated, for example in prognostication for invasive carcinoma of the breast (Onco*type* Dx and Mammaprint assays)—while most other such testing remains unvalidated, analytically or clinically, and of unproven clinical value. In particular, there are no good data confirming that identification of a potentially targetable mutation in a tumor type in which the role of that specific gene has never been demonstrated represents anything more than a sophisticated (and expensive) shot in the dark. Similarly, gene expression profiling as a means of identifying the primary site in metastatic carcinomas is rarely more effective than high-quality immunohistochemistry combined with morphologic expertise, is more expensive and, in any event, does not very often lead to clinically significant change in treatment or outcome (as many of the more treatable metastases are easily recognized by conventional means). It is troubling that many such commercial tests are being marketed directly to clinicians and patients, who are often completely unable to distinguish snake oil from clinically worthwhile testing. Although it is likely that genomic data will ultimately prove their (progressively more affordable) value, until then pathologists have a responsibility to ensure (a) that often limited patient tissue is used judiciously, and (b) that, in the routine (non-trial) setting, testing of any kind has proven clinical value that might merit action by the treating physician.

Remarkably, and seemingly with no evident slowing of the pace, morphologic tumor classifications and methods of prognostication continue to evolve and be ever more refined, constantly enhancing the value of high-quality anatomic pathology. Many of these advances have been codified in the new WHO classifications, which are currently being updated in a fourth edition of the "blue books." Furthermore, "new" (newly recognized) tumor types or subtypes of clinical or therapeutic relevance continue to be characterized, both morphologically and genetically, in a seemingly limitless fashion. The fourth edition of this text has been substantially revised and updated to incorporate this broad range of new information. Some chapters have been entirely rewritten, notably those dealing with tumors of the small and large intestines, the heart, and the ear.

As always, any and all errors or omissions are entirely the responsibility of the editor, and I remain deeply indebted to the contributors for the unfailingly high quality of the material that they provide, as well as the enthusiasm with which they do so. Finally, I should like to warmly acknowledge, with considerable gratitude, the hard work and unfailing support of my outstanding secretary, Kathleen Radzikowski, and also of the "key players" at Elsevier—Bill Schmitt, Katie DeFrancesco, and Louise King.

Christopher D.M. Fletcher
Boston, 2012

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CHAPTER 16

Tumors of the Breast

Ian O. Ellis • Andrew H.S. Lee • Sarah E. Pinder • Emad A. Rakha

CHAPTER OUTLINE

CLASSIFICATION OF BREAST DISEASE

For the most part, consistency now exists in the terminology, definitions, and systems used for pathologic and clinical classification of breast disease. The World Health Organization (WHO),[1] American College of Pathologists,[2] Royal College of Pathologists,[3,4] and European Commission[5] have produced guidelines on reporting breast disease. These propose virtually identical systems of classification of benign conditions that pathologists are encouraged to adopt.[2,3,5,6] The Royal College and European Commission have also produced guidelines on classification of breast carcinoma and assessment of prognostic factors.[3-5]

In this chapter we use and endorse these classifications. Benign breast tumors are presented according to the major accepted groupings of fibrocystic change, fibroadenoma and variants, sclerosing lesions, papilloma and proliferative breast disease, and malignant epithelial tumors according to type, with relevant descriptions of prognostic and predictive factor assessment.

FIBROCYSTIC CHANGE AND ASSOCIATED CONDITIONS

Fibrocystic Change

Fibrocystic change is the preferred term used by pathologists to note combinations of breast changes including cyst formation, apocrine metaplasia, blunt duct adenosis, and various other forms of adenosis. Minor changes including fibrosis, microcyst formation, lobular involution, and minor degrees of sclerosing adenosis or columnar cell change should be regarded as variants of normality and classified as minimal alteration or "aberrations of normal development and involution."[7] The use of an umbrella category such as fibrocystic change, which covers a variety of alterations in the breast that may have differences in etiology or clinical relevance, is acceptable only when a dominant distinct histologic process is not present.

After publication of retrospective studies of breast cancer risk related to benign breast disease, the importance of the presence of epithelial proliferation in association with fibrocystic change and other benign conditions such as papilloma has become increasingly recognized. The presence or absence of epithelial hyperplasia and its character is now regarded as a mandatory form of subclassification of fibrocystic change[2,4] (see later discussion of proliferative breast disease).

Clinical Features

In symptomatic breast practice, fibrocystic change usually presents as a mass of variable size that may be ill defined or well defined. Ultrasound and imaging investigations may reveal cyst formation and microcalcification. The entity is rare before the age of 25 years, and most patients are seen clinically between the ages of 35 and 50 years. Cyst formation occurs rarely after menopause.[8]

Macroscopic Appearances

No characteristic gross appearances of fibrocystic change are seen. In general, areas of breast involved by this

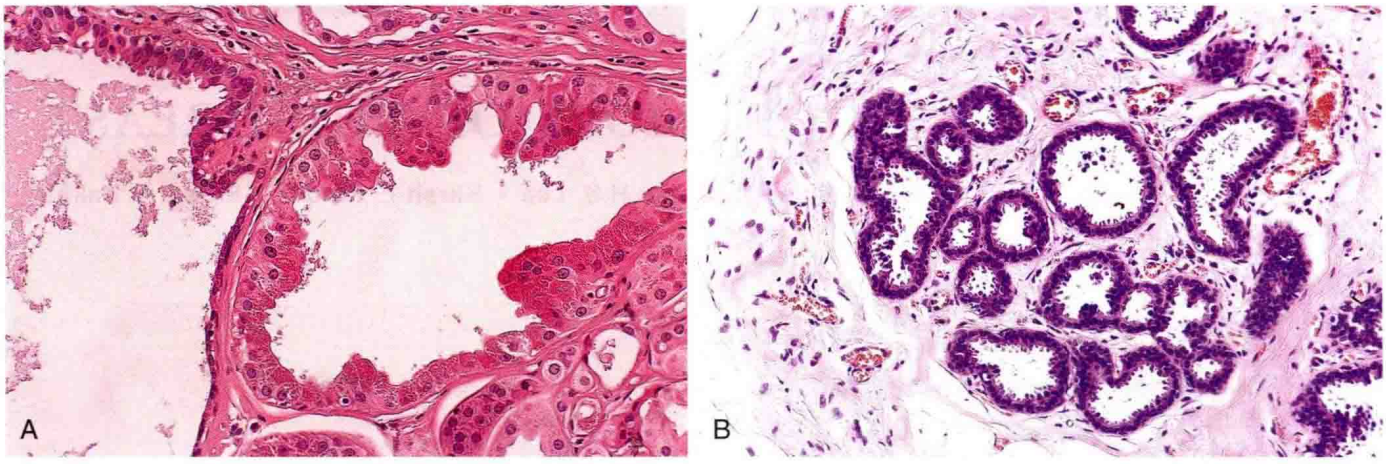

FIGURE 16-1 ■ Patterns of fibrocystic change. **A,** Two small adjacent cysts. The one on the *left* is lined by cuboidal epithelium; the one on the *right* is lined by apocrine epithelium. **B,** Columnar cell change. Columnar cells replace the normal acinar lining cells, and the normal configuration of the terminal duct lobular unit is changed to a group of visibly dilated duct-like structure. It is found commonly as part of the spectrum of changes seen in fibrocystic change.

process are ill-defined and contain areas of firm fibrofatty tissue and multiple cysts of varying size.

Histologic Appearances

As defined previously, fibrocystic change characteristically is a mixture of several benign entities that are dealt with individually as follows or elsewhere in this chapter.

Cysts

Clinical Features

Cysts are believed to arise from a process of lobular "involution,"[9,10] with microcyst formation in lobular acini progressing through expansion or coalescence into macroscopic cysts. They are very common, occurring in 19% of the general population[11] and being palpable in 7%.[8] Management is usually by aspiration. The cyst fluid can be examined cytologically, although this is not regarded as worthwhile unless the fluid is bloodstained or a residual mass is present, as the incidence of intracystic carcinoma is very low in comparison with the frequency of symptomatic cysts. No association is known between single cysts and breast cancer.[12]

Macroscopic Appearances

Cysts may be single or multiple. They are rarely removed, exceptions being recurrent large cysts and multiple cysts causing disfigurement or discomfort or the presence of an intracystic lesion. Cysts may be found incidentally in approximately 77% of cancer-bearing breasts.[13] They vary in size, are rounded, and contain a range of fluid types from thin, clear, straw-colored fluid to thick, opaque, green or brown material.

Histologic Appearances

Two main forms of cyst are recognized, those lined by a single layer of cuboidal (Fig. 16-1) or flattened attenuated epithelium and, more commonly, those lined by apocrine epithelium (see Fig. 16-1). This type of epithelium resembles normal apocrine sweat gland epithelium, the cells being large and columnar with abundant granular eosinophilic cytoplasm and basally positioned nuclei. The cytoplasm may protrude into the lumen in the form of apical snouts. The granules show Sudan black and periodic acid–Schiff (PAS) diastase-resistant positivity.[10] The apocrine epithelial layer is usually single, but hyperplasia resulting in a papillary structure can occur. The significance of papillary apocrine change and apocrine metaplasia is dealt with later in the sections on epithelial hyperplasia.

The distinction of two principal cyst types is supported by biochemical studies of cyst fluid. Cysts with a high pH and a low sodium to potassium ratio (similar to that of intracellular fluid) are more frequently recurrent and usually of apocrine type, in contrast with those with a lower pH and higher sodium to potassium ratio (corresponding to plasma), which are less likely to recur and are lined by a cuboidal or attenuated epithelial layer.[14,15]

Apocrine Metaplasia

Apocrine metaplasia is a frequent finding in the breast and is associated with cyst formation (see previous discussion). In its usual form, regular columnar cells are arranged in a single layer above a normal myoepithelial layer. Apocrine proliferation may be more florid and take on a papillary configuration; usually these are well structured with fine fibrovascular cores. More rarely, complex patterns of apocrine hyperplasia may be found in the form of sheets or complex architectural patterns with multiple irregular luminal spaces.

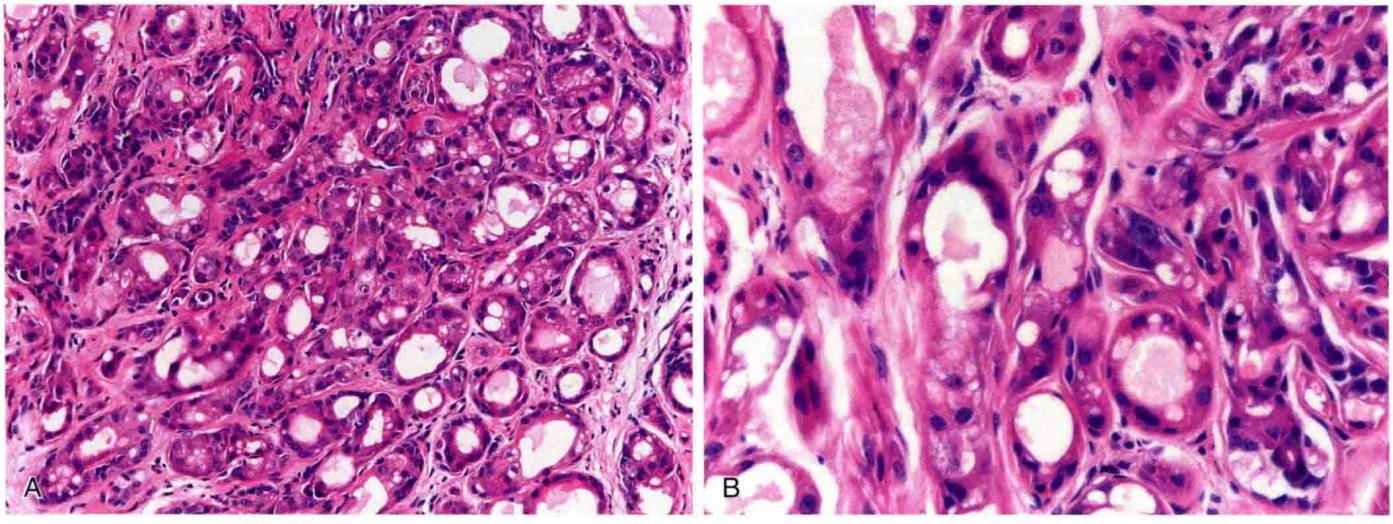

FIGURE 16-2 ■ **A** and **B,** A case of atypical apocrine adenosis showing highly pleomorphic atypical apocrine cells involving an area of sclerosing adenosis.

In addition to its usual association with cysts, apocrine metaplasia can extend to involve other benign processes including sclerosing adenosis (which is described as apocrine adenosis; Fig. 16-2), papillomas, and fibroadenomas. No particular significance is attributed to this phenomenon.

Although usually regular in nuclear and cytologic morphology, DNA tetraploidy has been identified in apocrine metaplasia.[16] This is believed to be the explanation for forms of "apocrine atypia," in which nuclear enlargement and variation in size with prominence of nucleoli can be observed (see Fig. 16-2). At present, the relevance of apocrine atypia is poorly understood. Some authorities[17] believe this to be a purely benign phenomenon, whereas others have suggested it may be a precursor lesion of some forms of carcinoma such as apocrine carcinoma or medullary carcinoma.[8] Although pure apocrine change is currently regarded as carrying a low but significant increased risk of subsequent development of breast cancer,[2] most of the increased risk is related to the presence of coexisting atypical hyperplasia.[12]

Differential Diagnosis

Apocrine metaplasia is generally easily recognized and distinguishable from other epithelial proliferative lesions. Apocrine metaplasia may be associated with cytologic and/or architectural atypia. Cytologic atypia is defined by the presence of a threefold variation in nuclear size and prominent nucleoli (see Fig. 16-2), features that are not often seen in standard papillary apocrine change.[12] Apocrine atypia may occur with apocrine metaplasia in areas of sclerosing adenosis. This has been classified as atypical apocrine adenosis.[18] The combination of large cells with atypical features in a pseudoinfiltrative process such as sclerosing adenosis may be mistaken for invasive adenocarcinoma. The presence of a myoepithelial component and the apocrine nature of the cells should be used to differentiate these conditions.

INFLAMMATORY DISORDERS

Most inflammatory disorders of the breast are straightforward to diagnose pathologically, but sclerosing lymphocytic lobulitis can be mistaken for malignancy both clinically and histologically.

Sclerosing Lymphocytic Lobulitis

Sclerosing lymphocytic lobulitis, also known as lymphocytic mastopathy, is a recently recognized inflammatory disorder of the breast.[19,20] Evidence supports an autoimmune etiology. A strong association exists with autoimmune diseases, particularly with long-standing insulin-dependent diabetes mellitus and thyroiditis. The pattern of inflammation and expression of HLA class II antigens by breast epithelium is similar to that seen in autoimmune disorders such as Hashimoto thyroiditis.

Clinical Features

Sclerosing lymphocytic lobulitis usually presents as a mass and can mimic carcinoma. The masses can be multiple or bilateral. Thus, by recognizing this condition, unnecessary surgery may be avoided. It can be seen in women from about 20 to 65 years old but is most common in women in their 30s. It has also been described in men.

Macroscopic Features

Typically a poorly defined firm gray-white mass is seen, but sometimes the appearance is like normal fibrous breast tissue.

Histologic Appearances

The characteristic feature is circumscribed clusters of lymphocytes in and around lobules and ducts and around

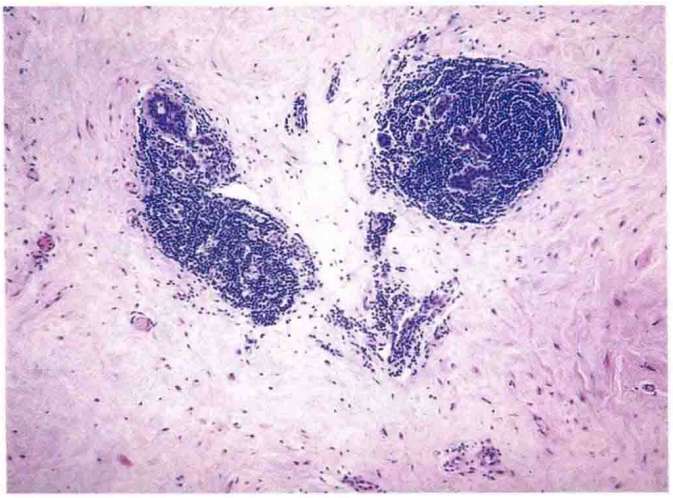

FIGURE 16-3 ■ Sclerosing lymphocytic lobulitis showing circumscribed clusters of small mature lymphocytes around lobules and vessels.

blood vessels (Fig. 16-3). Typically the lymphocytes are predominantly B cells. Germinal centers may be present. Lobular atrophy is frequently evident. Fibrosis is usually present between lobules and sometimes within lobules. Epithelioid fibroblasts may be present[21] but are not specific for this disorder. Patients with sclerosing lymphocytic lobulitis who have had a series of biopsies often show progression from dense inflammation to increasing lobular atrophy and fibrosis with decreasing inflammation.[20] The changes seen later in the disease (lobular atrophy and fibrosis with little inflammation) are not specific to this disorder. The pathologic features in patients with and without diabetes mellitus are similar. Thus a general pathologic term such as sclerosing lymphocytic lobulitis or lymphocytic mastopathy is preferable to diabetic mastopathy.

Differential Diagnosis

The diagnosis of sclerosing lymphocytic lobulitis is usually straightforward. It may be confused with lymphoma, but lymphoma typically has a different architecture, composed of sheets of cells, often with centroblastic morphology. An association between lymphoma and sclerosing lymphocytic lobulitis has been described in Japan[22] but was not seen in European[23] or American series.[24] A pattern of inflammation like that of sclerosing lymphocytic lobulitis may be associated with carcinomas, particularly invasive lobular carcinoma,[25] and, if marked, the inflammation may obscure the carcinoma.

FIBROADENOMA, VARIANTS, AND RELATED CONDITIONS

Fibroadenoma

Although fibroadenomas are still designated as benign tumors in many standard textbooks,[8,26-28] it is now believed that they are not true neoplasms but may arise as a result of hyperplasia of normal lobules. The epithelial and stromal cells in most fibroadenomas are polyclonal,[29] although occasionally areas of stromal expansion within a fibroadenoma may be monoclonal.[30] The etiology is unknown, although studies support the concept that they are due to the proliferation of hormone-responsive tissue in the presence of a relative excess of circulating estradiol over progesterone.[31] They are included here because they produce palpable breast lumps that may be indistinguishable clinically from carcinomas.

Clinical Features

Fibroadenoma is one of the most common causes of a benign lump in the breast. They may occur at any age after puberty but are most frequent in the third decade. They may be single or multiple and unilateral or bilateral. Clinically they present as firm or rubbery, mobile, well-defined masses that are painless. Most measure between 1 and 2 cm in diameter, but fibroadenomas measuring up to 4 cm are not uncommon.

After the advent of screening programs for breast cancer, impalpable fibroadenomas have been detected increasingly by mammography.

The great majority of fibroadenomas behave in a benign way clinically and do not recur after adequate resection. Because they may be multiple it is not unusual for new lesions to become apparent, even close to the site of a previous biopsy.

The trend is increasing for surgeons to adopt a more conservative approach to the management of women with suspected fibroadenoma using the triple approach of clinical examination, imaging, and fine-needle aspiration cytology or needle core biopsy.[32-34] Provided that all the criteria for benignity are satisfied, surgery may safely be avoided in most patients. We recommend excision of fibroadenomas over 3 cm or if the lesion is growing.

Malignant change is exceedingly uncommon, and to date fewer than 200 cases of in situ or invasive carcinoma associated with fibroadenoma have been reported.[35] The majority, about 50%, are lobular carcinoma in situ (LCIS). In fewer than 40% the tumor is invasive, and the rest are ductal carcinomas in situ (DCIS). In a substantial proportion of cases tumor is present in the adjacent tissues, and it may be difficult to establish whether involvement of the fibroadenoma is merely coincidental. Epidemiologic studies have shown a very slight increase in relative risk for subsequent invasive carcinoma of approximately twofold in patients with fibroadenoma.[36,37] This risk is increased to threefold for fibroadenomas with a "complex" morphologic pattern (see later discussion) and to fourfold for patients with a family history of breast cancer.[36] However, the absolute risk for uncomplicated fibroadenomas remains very low at 4%.

Macroscopic Appearances

The gross appearances of a fibroadenoma are distinctive (Fig. 16-4). They are sharply circumscribed, spherical or ovoid nodules, gray-white in color and clearly separate from the adjacent breast tissue. The cut surface is usually slightly lobulated and often has a glistening myxoid appearance. Most lesions are firm to the touch, but in older women they may be hard and sclerotic, even calcified.

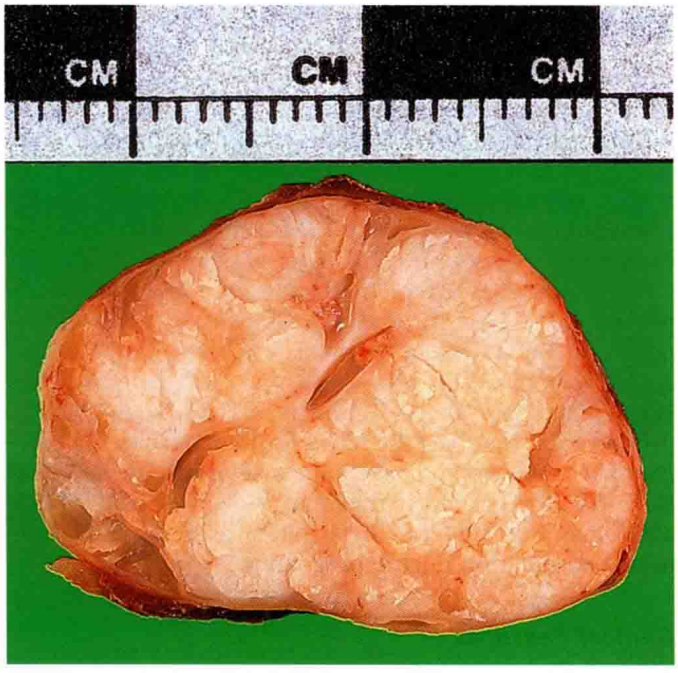

FIGURE 16-4 ■ A benign fibroadenoma; note the circumscribed outline and a lobulated cut surface.

Histologic Appearances

The dominant element is a proliferation of loose cellular stromal connective tissue, which surrounds a variable number of ductular structures (Figs. 16-5 and 16-6). The stromal nuclei are spindle shaped and normally exhibit little pleomorphism with infrequent mitoses. The quality of the stromal matrix can vary markedly, some fibroadenomas having a definite myxoid background whereas others are hyalinized. The ductules also vary in configuration, and two classic patterns are described, intracanalicular when they are compressed by the stroma into clefts (see Fig. 16-5, *B*) and pericanalicular when the stroma appears to surround ductules in a circumferential fashion (see Fig. 16-6). In fact both patterns may be seen in the same lesion, and the differences in appearance are probably related to the plane in which the section is taken. The terms have no practical or prognostic significance and are purely descriptive. In about 20% of cases cysts (greater than 3 mm in diameter), sclerosing adenosis, epithelial calcifications, and papillary apocrine change are seen, either alone or in combination; such lesions have been termed *complex fibroadenoma* by Dupont and colleagues.[36] Epithelial hyperplasia is common, and, although tangential sectioning may produce worrying patterns, true atypical hyperplasia is rarely seen.[27]

In older patients, especially after the menopause, the stroma of fibroadenomas becomes less cellular and hyalinized. Calcification may also develop.

Differential Diagnosis

The most important lesion to consider in the differential diagnosis is phyllodes tumor (see later discussion). Although the latter is more often seen in an older age group, difficulties may be experienced with large fibroadenomas having a cellular stroma and numerous epithelial clefts. The distinction between fibroadenoma and benign phyllodes tumor may indeed be impossible to establish, but relative uniformity of stromal nuclei and

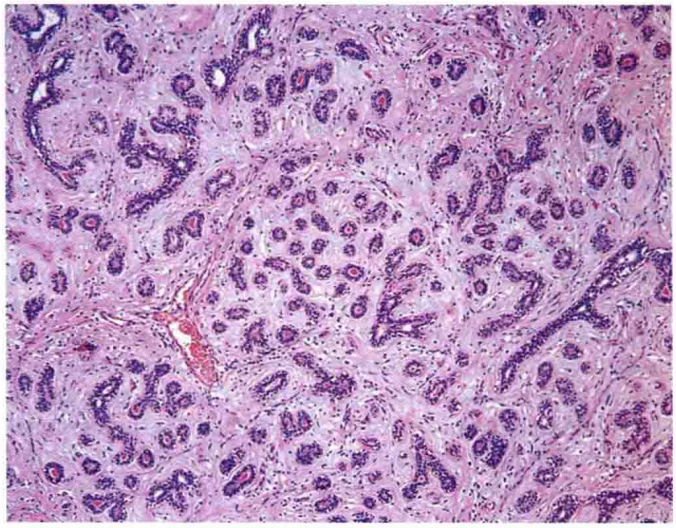

FIGURE 16-6 ■ Fibroadenoma with a pericanalicular pattern.

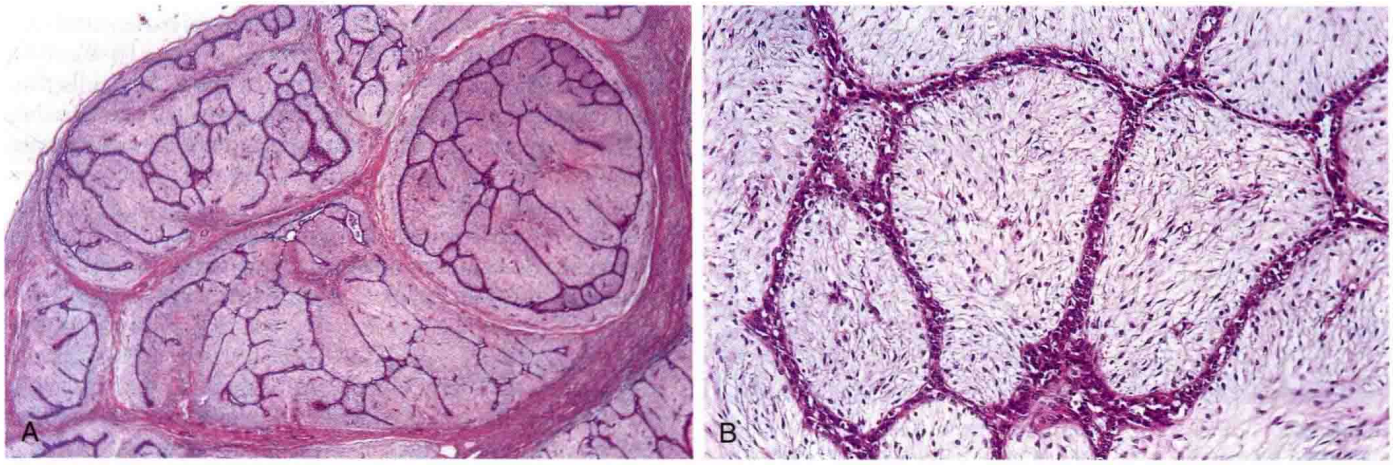

FIGURE 16-5 ■ Fibroadenoma. In this example the lesion demonstrates a typical intracanalicular pattern. The nodular structure is evident in **A**, whereas the characteristic combination of epithelial clefts and cellular intralobular stroma is seen in **B**.

lack of mitoses would favor the former. Although we disagree with use of the term *fibroadenoma phyllodes*,[38] it may be necessary to issue an equivocal report in exceptionally rare circumstances. Complete excision of such cases is advisable to avoid the risk of local recurrence.

The distinction of fibroadenoma from mammary hamartoma is discussed later.

Fibromatosis[39] is a rare cause of a breast lump, and the fibroblastic proliferation around ductular structures may resemble a fibroadenoma. The infiltrative edge, cellularity of stroma, and relatively scanty epithelial component are all points in favor of a fibromatosis (see later discussion). The stroma of a fibroadenoma is typically strongly positive for CD34, whereas fibromatosis is CD34 negative[40] and may be nuclear β-catenin positive.

Juvenile Fibroadenoma

Much confusion has been produced by inconsistent use of the terms *juvenile* and *giant* fibroadenoma. Indeed the latter has been used to describe both large fibroadenomas and, incorrectly, benign phyllodes tumor. In practice all juvenile fibroadenomas are large, and the term is best reserved for those fibroadenomas that occur in adolescents and have a very rapid growth rate. They are well-circumscribed lobulated masses that may reach 15 to 20 cm in diameter, stretching the skin and distorting the nipple.[41,42] Morphologically they have an identical structure to that of the more typical fibroadenoma. The basic pericanalicular and intracanalicular growth patterns are seen, but the stroma is likely to be cellular rather than hyalinized (Fig. 16-7). Nevertheless the stroma remains in proportion to the epithelium without stromal overgrowth. Epithelial proliferation is usually present and often florid; some authors have emphasized the variety of patterns that may be encountered[28,41,42]; care must be taken not to misinterpret the appearances as atypical ductal hyperplasia (ADH). Juvenile fibroadenomas are entirely benign and do not recur after complete local excision.

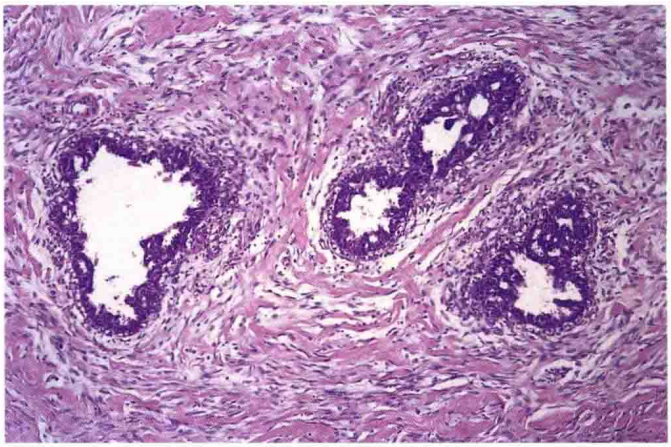

FIGURE 16-7 ■ Juvenile fibroadenoma. Note the cellular stroma, and mild epithelial proliferation with a gynecomastia-like appearance is present.

Tubular Adenoma

Although most authorities have now accepted the entity of a pure mammary adenoma,[27,38,43] Rosen[28] considers tubular adenoma to be an unusual type of fibroadenoma. It is true that some fibroadenomas contain focal areas with a tubular structure, but we exclude such cases by following the strict morphologic criteria laid down by Hertel and colleagues.[44] They emphasized the well-circumscribed nature of the lesion composed of closely packed tubules with very little associated stroma. The nature of the so-called pregnancy or lactating adenoma is also dubious. The great majority of lesions given this label are in fact simply nodules of physiologic lobular proliferation that become more prominent than the adjacent breast tissue and may appear clinically to be a distinct mass.[45] Very rarely they may indeed be true tubular adenomas that undergo hyperplasia as a result of hormonal stimulation during pregnancy.[46]

Clinical Features

The clinical features of tubular adenoma are similar to those of fibroadenoma.

A variety of benign noninflammatory mass lesions may present during pregnancy. In a consecutive series of 28 patients with an age range of 16 to 48 years (mean 23 years), three types of lesions were identified.[46] Adenomas in the form of fibroadenoma (16 cases) and tubular adenoma (two cases) were the most common lesions and usually showed lactational changes with "lactational adenoma" (10 cases) being less frequent. The lesions presented either during pregnancy or in the postpartum period (up to a few months) usually as nontender masses.

Macroscopic Appearances

Tubular adenomas are well-circumscribed nodules measuring between 1 and 4 cm in diameter, the majority being no greater than 2 cm. The cut surface is finely nodular.[47]

Histologic Appearances

The lesions are sharply demarcated from adjacent breast tissue but lack a true capsule. They consist of closely packed tubular structures of approximately the same size as the acini within a normal lobule (Fig. 16-8). The tubules are lined by a single layer of secretory cells, but scanty flattened myoepithelial cells are also present. No nuclear atypia is seen, and mitoses are usually infrequent. A small amount of fine connective tissue stroma is seen between the tubules.

In the "lactational adenomas," dilated acini are present and show the typical alveolar pattern of lactating breast tissue. Luminal secretion is usually present.

Differential Diagnosis

The only lesions to be considered are fibroadenoma and tubular carcinoma. In the former the stroma is much more prominent, and the tubular structures present are