Fibroepithelial Lesions of the Breast

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Fibroepithelial lesions of the breast are a group of biphasic neoplasms, lesions characterized by proliferation of both mesenchymal and epithelial elements. On the whole, these lesions constitute one of the most commonly encountered neoplasms in routine practice and span the spectrum of biological significance from benign to malignant. Prototypic examples of these neoplasms include the fibroadenoma (FA) and phyllodes tumor (PT), with the phyllodes tumor requiring further subtyping into benign, borderline/intermediate, and malignant in accordance with the World Health Organization (WHO) recommendations [1]. These specific lesions within this group have diverse clinical behavior, natural history, and therapeutic implications, despite showing considerable morphologic overlap at times. Since many of the initial diagnoses are rendered in core biopsies, this can potentially compound a diagnostic challenge, and clinical-pathological correlation is imperative. Here, we present a review of fibroepithelial lesions with an emphasis on morphology and distinguishing features. Hamartomas, also considered a fibroepithelial lesion, is discussed below under the differential diagnosis section of fibroadenoma.

9.1 Fibroadenoma

The clinical presentation of the fibroadenoma (FA) mirrors its natural history. Fibroadenomas usually occur in women less than 30 years of age. Additionally, immunosuppressive therapy with cyclosporine has been associated with increased development of fibroadenomas [2, 3]. Typically, fibroadenomas are well-demarcated, mobile, round, and rubbery lesions [4]. Although the average diameter is 2 cm, larger fibroadenomas may occur; fibroadenomas greater than 10 cm are sometimes referred to as "giant fibroadenomas" [4]. The larger fibroadenomas are usually encountered in adolescents. They can be single or present as multiple nodules in one or both breasts in a synchronous or metachronous fashion (Fig. 9.1). Current work suggests that the growth of fibroadenomas is hormonally-dependent and influenced by estrogen-status [5, 6]. This helps to explain why most fibroadenomas may regress with time and the quality of the stroma changes with patient age. The presence of FAs in older women outside of the range of childbearing years may

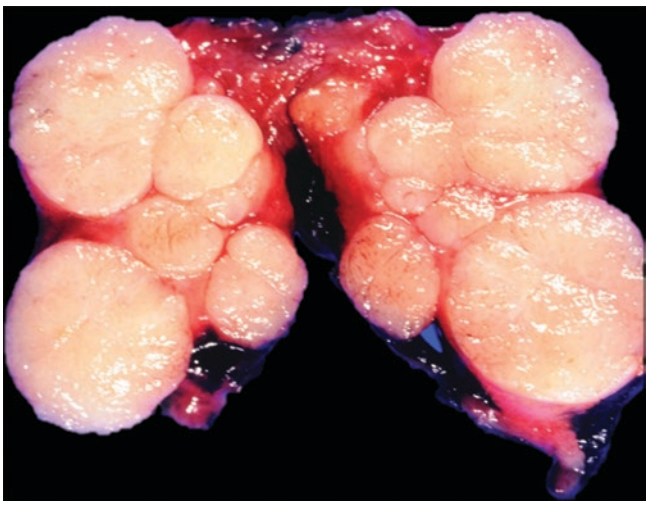

Fig. 9.1 Gross appearance of fibroadenoma shows lobulation and nodularity. It is sharply demarcated from the small amount of attached tissue

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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_9

be related to exogenous hormone therapy (estrogen replacement) or obesity.

Radiographically, fibroadenomas typically appear as well-circumscribed or lobulated masses (Fig. 9.2). Frequently calcifications are present, and the most common calcification pattern shows initial small peripheral, punctate dots which coalesce over time with coarser features [7]. Occasionally, dystrophic or pleomorphic calcifications may be associated with fibroadenomas, especially when accompanying extensive stromal hyalinization.

Similar to their radiographic appearance, fibroadenomas at the gross bench are well-circumscribed nodules with occasional lobulation (Fig. 9.1). Stromal variations, such as myxoid change and hyalinization, are reflected in its gross texture and appearance of the cut surface. Calcifications impart a gritty surface.

Although biphasic, the stromal component of the FA typically predominates over the epithelial component, but the overall ratio of the two components is variable, not only among FAs but even in a single lesion. On low power, the initial histologic impression is classically described by the pattern by which the stroma grows around the ductal structures: intracanalicular (circumferential stromal proliferation) or pericanalicular (stromal proliferation which compresses the ductal structures into cleft-like spaces) (Figs. 9.3 and 9.4). The distinction between these two growth patterns is not of prognostic significance, but these patterns are important in that they form the underlying structure of the fibroadenoma onto which many stromal and epithelial changes can be subsequently applied. Additionally, both patterns can be present within the same lesion.

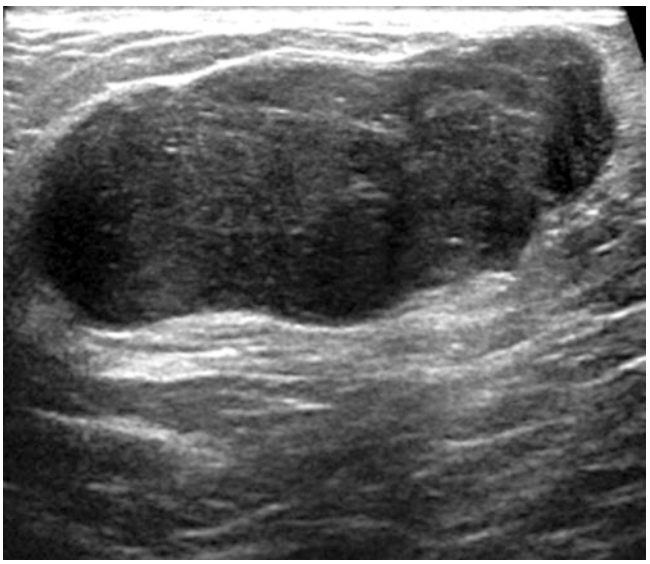


Fig. 9.2 Ultrasound image of a fibroadenoma shows an oval, lobulated, but circumscribed hypoechoic mass

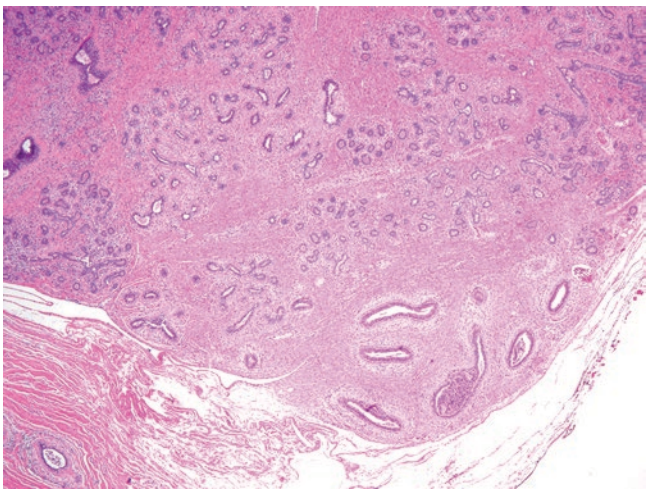


Fig. 9.3 Growth patterns of fibroadenoma. The pericanalicular pattern is comprised of stroma growing around round, open tubules

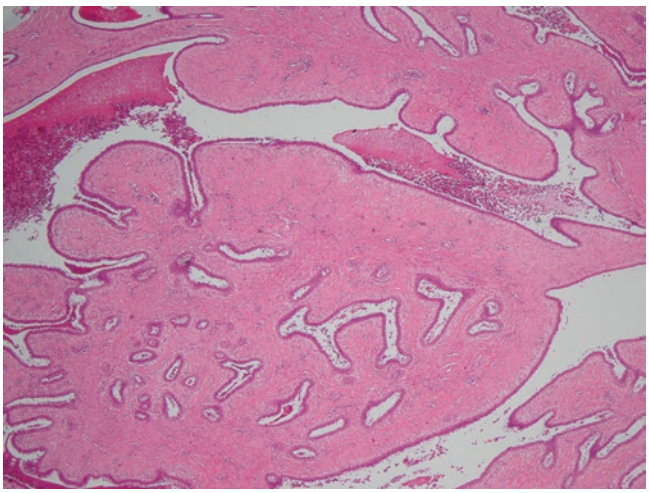


Fig. 9.4 Growth patterns of fibroadenoma. The intracanalicular pattern features stroma growing with compression of tubules

The mesenchymal aspect of the FA has two major components with variable features: the cellular component and the background stromal component. The cellular component consists of bland spindle cells with infrequent mitoses. Cellularity ranges from sparse (hypocellular) to focally/extensively hypercellular ("cellular fibroadenoma," discussed below). Stromal giant cells can also be seen; however, close inspection will reveal the degenerative quality of the nuclei. Importantly, these changes also do not qualify as stromal atypia. The stromal background can be myxoid, fibrous, or hyalinized. Calcifications are common in hyalinized FAs. Heterologous and homologous breast differentiation includes lipomatous, smooth muscle, and osteochondroid elements, and is an uncommon finding [8]. Hormonal changes seen in young or pregnant patients can yield mitoses or infarction. However, neither of these changes denote malignancy in a

typical fibroadenoma as mitoses are generally less than 3 per 10 high-power fields, even in cellular fibroadenomas [9], and infarction is secondary to ischemia, in contrast to true tumor necrosis. Figures 9.5, 9.6, 9.7, 9.8, 9.9, 9.10, 9.11, and 9.12 highlight the stromal features of fibroadenomas.

The epithelial component of the FA consists of glandular structures embedded within a stromal proliferation. The low-power appearance is quite informative as the epithelial structures are relatively uniformly distributed throughout the lesion (i.e., not haphazard). It is important to keep in mind that the epithelial component of the FA is subject to all of the epithelial changes that can be seen in background breast tissue. This includes, but is not limited to, varying degrees of epithelial proliferation with or without atypia, adenosis, and metaplasias. The low-power appearance is again helpful to appreciate the overall architecture, as well as to identify areas with epithelial changes. Figures 9.13, 9.14, 9.15, 9.16, and 9.17 show various epithelial changes seen in fibroadenomas.

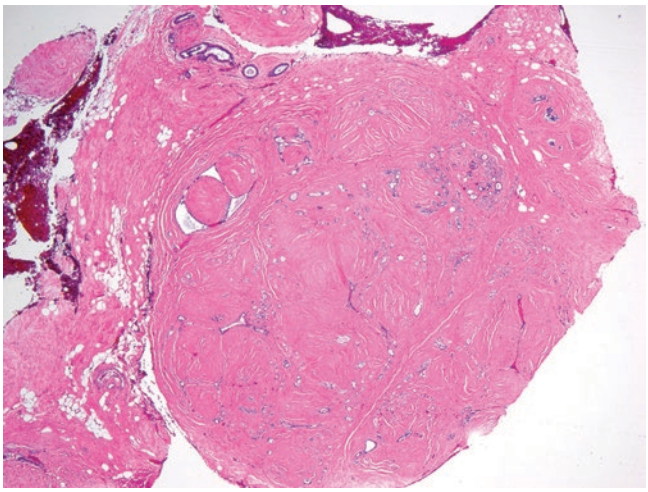


Fig. 9.5 The low-power appearance of a fibroadenoma shows a well-circumscribed and lobulated nodule. The epithelial elements are regularly distributed within the lesion

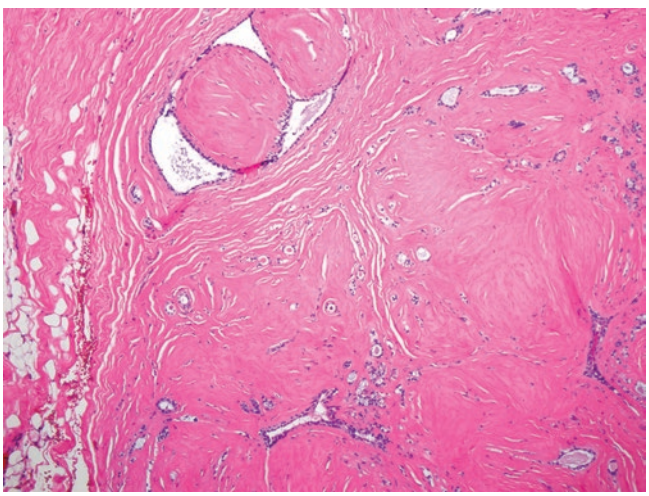


Fig. 9.6 The presence of both pericanalicular and intracanalicular patterns can be appreciated

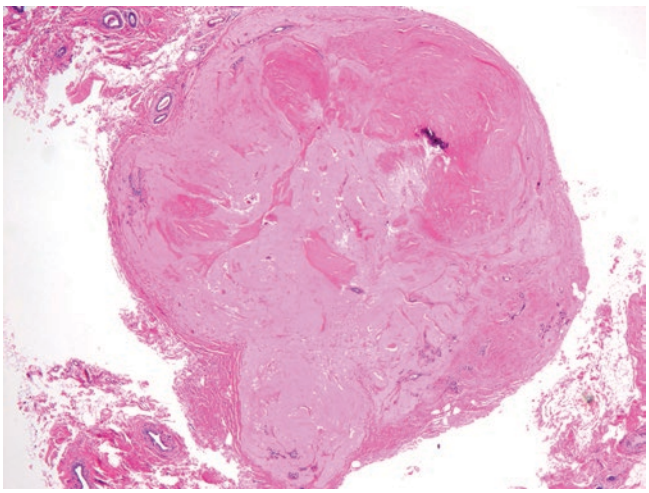


Fig. 9.7 Despite extensive stromal hyalinization and the paucity of glandular elements, the lesion maintains the low-power silhouette of a fibroadenoma

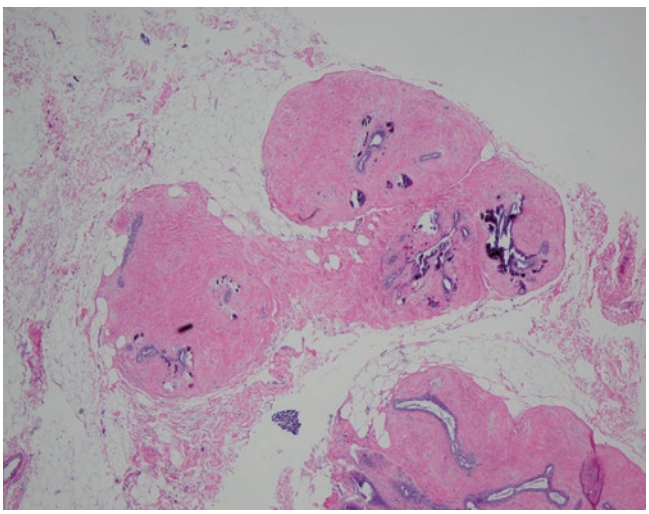


Fig. 9.8 At this magnification, the hyalinized nodules, scattered epithelial elements, and calcifications are appreciated

Fibroadenoma variants are the followings:

- **Cellular FA** (Fig. 9.18). "Cellular" refers to the stromal component. Despite the hypercellularity of the stroma here, there is no atypia of the stromal cells, no significant increase in mitotic figures present, and maintenance of the well-circumscribed border. The presence of stromal atypia or increased mitoses in what appears to be a "cellular FA" may suggest a phyllodes tumor. (See below for further discussion.)
- **Juvenile FA** (Fig. 9.19). The term "juvenile FA" refers to fibroadenomas occurring in young patients, which often

grow as large masses with occasional breast distortion. This FA variant is characterized by increased stromal cellularity with prominent stromal fascicles, pericanalicular growth pattern, and usual ductal hyperplasia. Micropapillary ductal architecture, also seen in juvenile FAs, bears a striking resemblance to the hyperplastic features seen in gynecomastia. Significant stromal nuclear atypia is lacking [10].

- **Complex fibroadenoma** (Fig. 9.20). Epithelial proliferations may occur including sclerosing adenosis, apocrine changes, and cysts greater than 0.3 cm. These changes can be prominent enough to obscure the presence of a fibroadenoma or even simulate invasive ductal carcinoma (Fig. 9.14). These are defining features of "complex fibroadenoma" which have a slight increase in the relative risk for carcinoma [11].

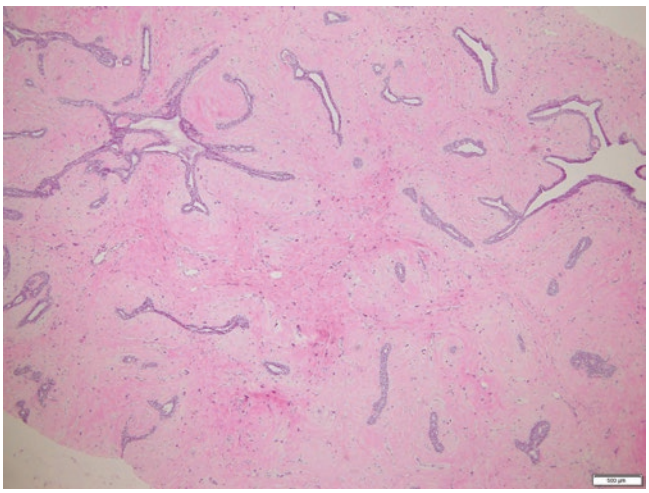


Fig. 9.11 Low-power view of a fibroadenoma showing stromal giant cells

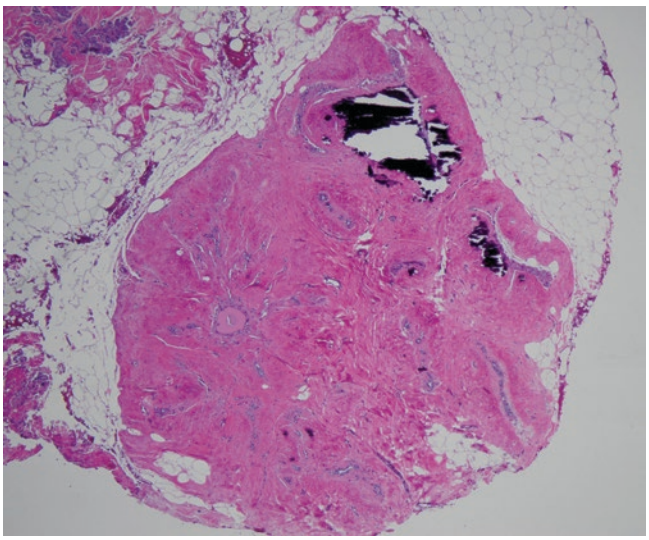


Fig. 9.9 Notice the well-demarcated and sharp margins of the fibroadenoma

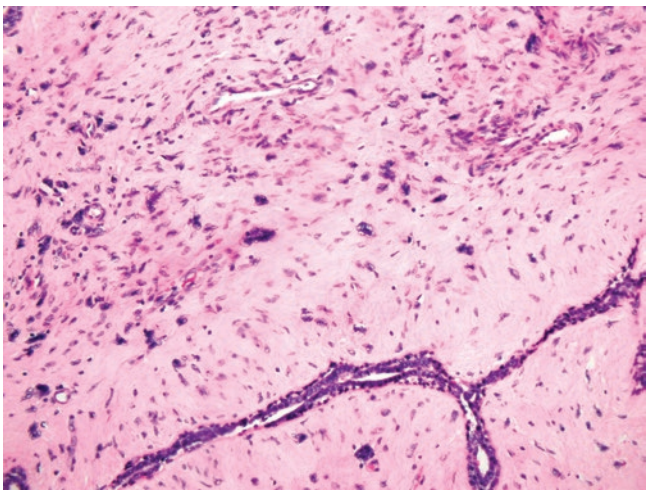


Fig. 9.12 On higher power, these cells can be further characterized as degenerative-type changes, showing a smudgy quality of the nuclei. Notice the lack of any other evidence of malignancy

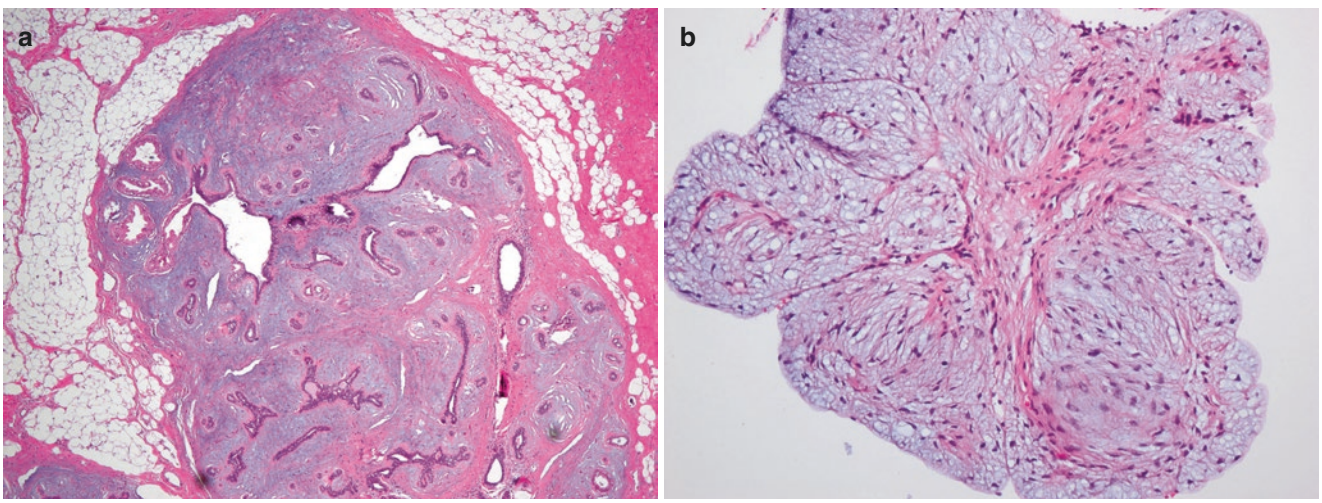


Fig. 9.10 (**a**, **b**) Myxoid stromal changes within fibroadenomas are common and can be the predominant finding in a core biopsy

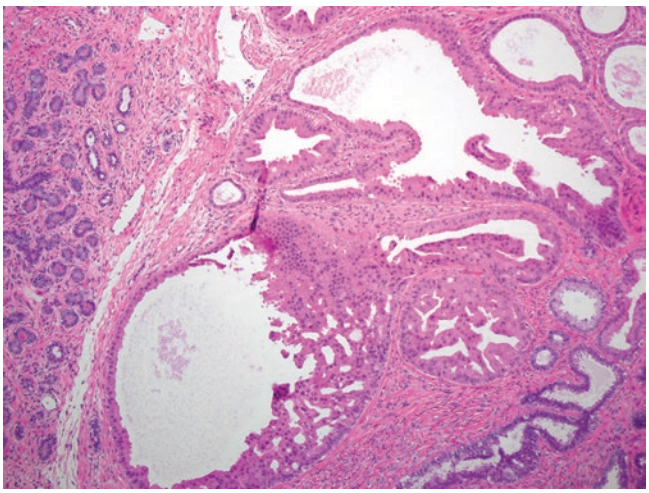


Fig. 9.13 Fibroadenoma with apocrine metaplasia, usual ductal hyperplasia (bottom), and prominent pericanalicular pattern (left)

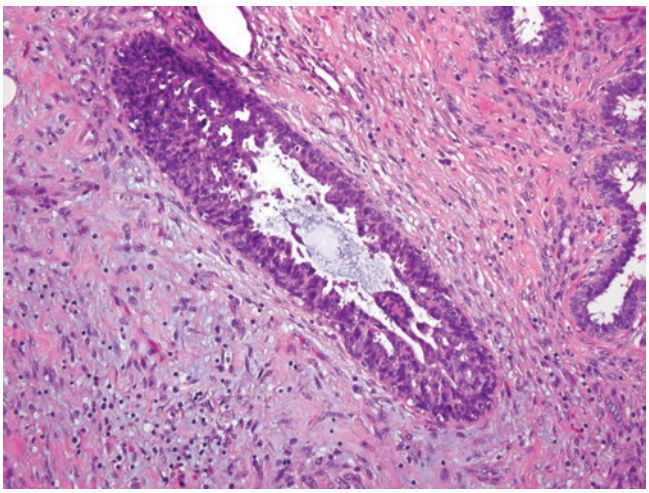


Fig. 9.14 Fibroadenoma with usual ductal hyperplasia

- **FA with atypia and malignancy** (Figs. 9.21 and 9.22). As previously mentioned, FAs are subject to epithelial proliferations encountered routinely in breast tissue, including atypia. Although considered a benign neoplasm, FAs can harbor atypical and frankly malignant ductal and lobular proliferations with the incidence of malignancy reported as 0.1–0.3%. Lobular carcinoma seems to occur more frequently than ductal carcinoma in this setting [4]. The extent of FA involvement is variable. The atypical lesion may be entirely confined to the fibroadenoma, or, on the other hand, the fibroadenoma may have been colonized by the malignancy present outside the nodule from the surrounding breast tissue. Radiographic and clinical correlation is of utmost importance in these circumstances, as its impact on clinical management is quite significant. Examples of fibroadenomas involved by these lesions are illustrated in Figs. 9.15 and 9.16.

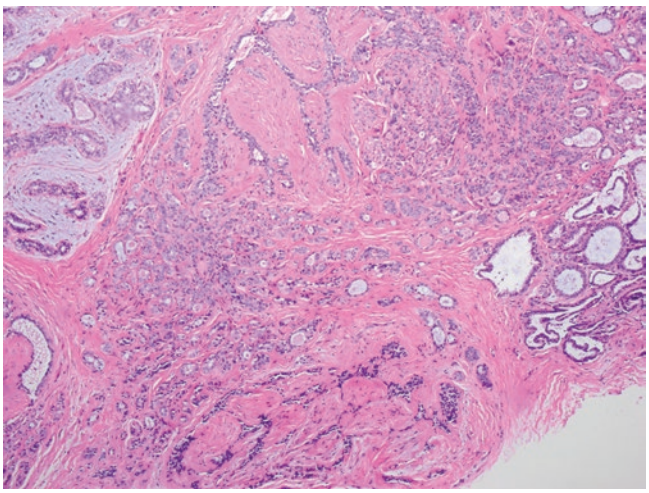


Fig. 9.15 Fibroadenoma with sclerosing adenosis. On low power, the lesion maintains the characteristic lobulation and, peripherally, typical areas of a fibroadenoma. The entire central portion of the image shows an epithelial proliferation occupying the center of the image. It is important to recognize the lobulo-centric architecture of the proliferation, a key feature of adenosis

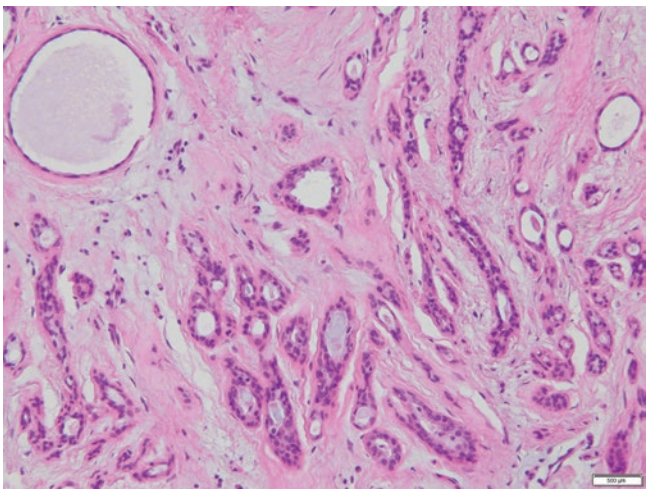


Fig. 9.16 On higher-power view of the lesion shown in Fig. 9.15, tubules lined by an attenuated myoepithelial layer can be appreciated. Immunohistochemistry for myoepithelial cell markers (p63/Calponin, S-100, CK 5/6) will demonstrate the presence of these cells in the areas of adenosis

- **Tubular adenoma** (Fig. 9.23). Tubular adenoma histologically shows a compact arrangement of uniform tubules lined by a dual cell bilayer of inner epithelial and outer myoepithelial cells. Similar to the conventional FA, these lesions are always well-circumscribed radiologically and lack a capsule. Some lesions may show areas of otherwise conventional fibroadenomas admixed with tubular adenoma areas. This supports the notion that many of these entities in fact lie on a spectrum of fibroepithelial lesions of the breast.

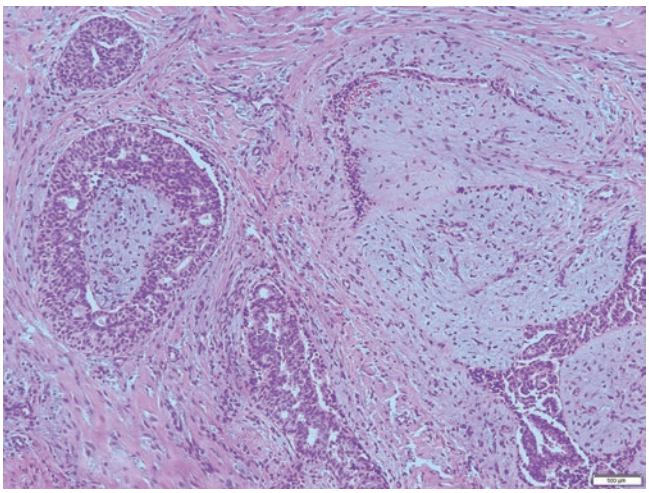
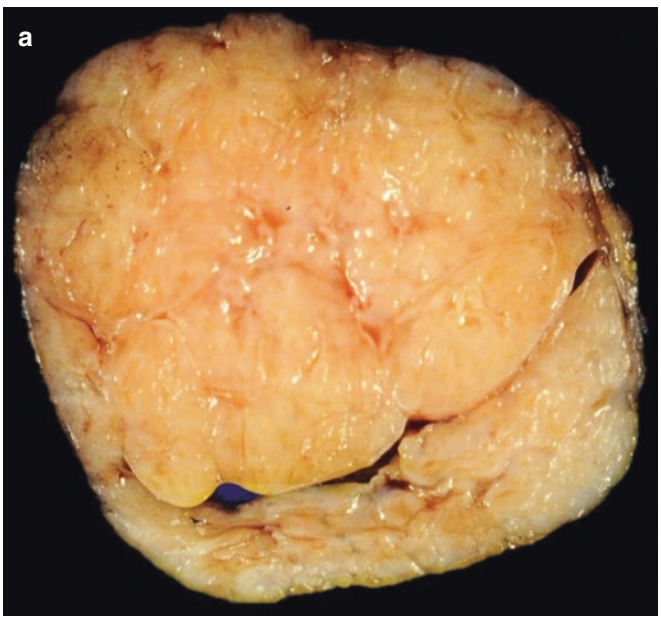
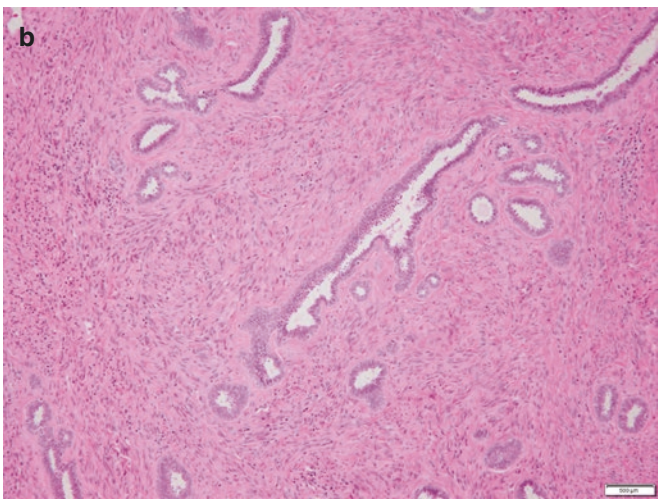


Fig. 9.17 Fibroadenoma with atypical ductal hyperplasia (left). Atypical architectural features are beginning to emerge within the epithelial elements of this fibroadenoma





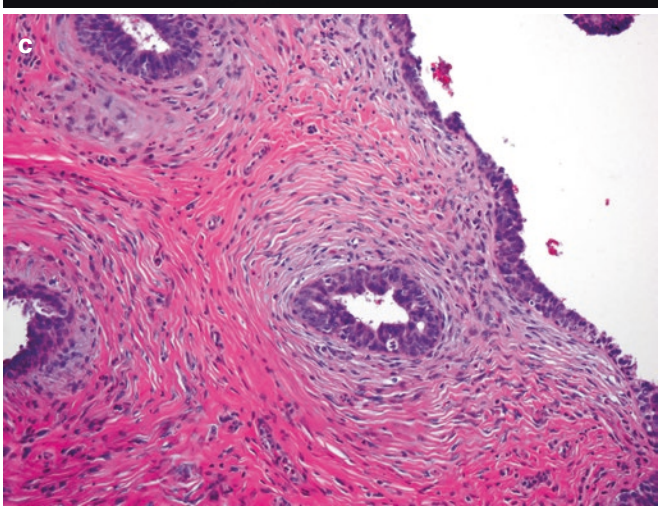


Fig. 9.18 (**a**) Cellular fibroadenoma showing a tan-yellow appearance owing to its increased cellularity. (**b**) The cleft-like space in the lower portion of the image corresponds to an intracanalicular growth pattern in that area. Histologically, there is stromal hypercellularity. (**c**) Focal areas of stromal condensation around the epithelium; however, this is typically focal. Note that there is no stromal nuclear atypia or obvious mitoses

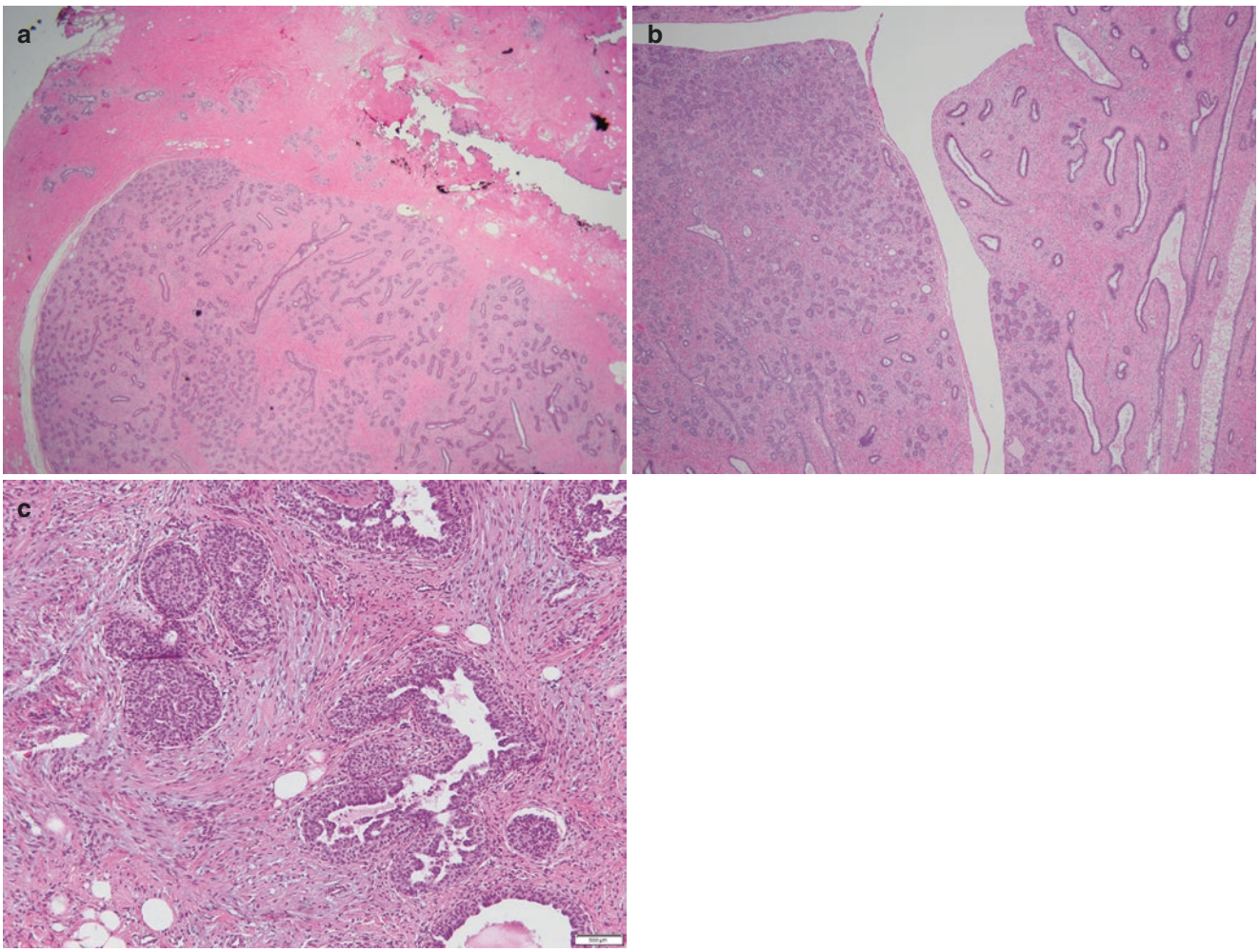


Fig. 9.19 (**a**, **b**) Juvenile fibroadenomas are well-circumscribed and, like conventional fibroadenomas, can show a mix of both pericanalicular and intracanalicular growth patterns. (**c**) These lesions often harbor areas of epithelial proliferation such as usual ductal hyperplasia seen here and micropapillary hyperplasia (bottom) with tapering papillae reminiscent of that seen in gynecomastia

- **Lactating adenoma (nodular gestational hyperplasia)** (Fig. 9.24). Depending on the author's preference, nodular gestational hyperplasia (lactating adenoma) is sometimes considered a variant of fibroadenoma showing physiologic, secretory epithelial changes. This lesion may occur during pregnancy or the postpartum period. Histologically, it shows compact arrangement and hyperplasia of true acini arranged in the alveolar pattern of the lactating breast. The luminal cells are enlarged with vacuolated cytoplasm. These lesions can become quite large, and due to their rapid growth during pregnancy can have a concerning, clinical presentation; however, they are benign. Because of this, lactating adenomas are encountered in routine biopsies. Due to their rapid proliferation, necrosis may be noted in the lesions and should not be regarded as an atypical finding [12].
- **Fibroadenomatoid changes**. "Fibroadenomatoid changes" is the term used to describe parenchymal changes which resemble a fibroadenoma, but collectively do not form a discrete, well-circumscribed mass lesion. This entity is considered to represent non-neoplastic, stromal hyperplastic changes, unlike fibroadenomas which are benign neoplasms.

Fibroadenomas are benign lesions, and after the core biopsy diagnosis, they are typically managed surgically by complete excision or non-surgically with monitoring by imaging. Fibroadenomas with a history of rapid growth in size are typically excised completely for a full histologic evaluation [13, 14]. Regarding the inherent risk of cancer harbored by FAs, when confined to the FA, the presence of atypical ductal or lobular proliferations does not denote an increase in subsequent cancer risk. Complex fibroadenomas, however, have been reported to be associated with a higher relative risk for cancer development [15].

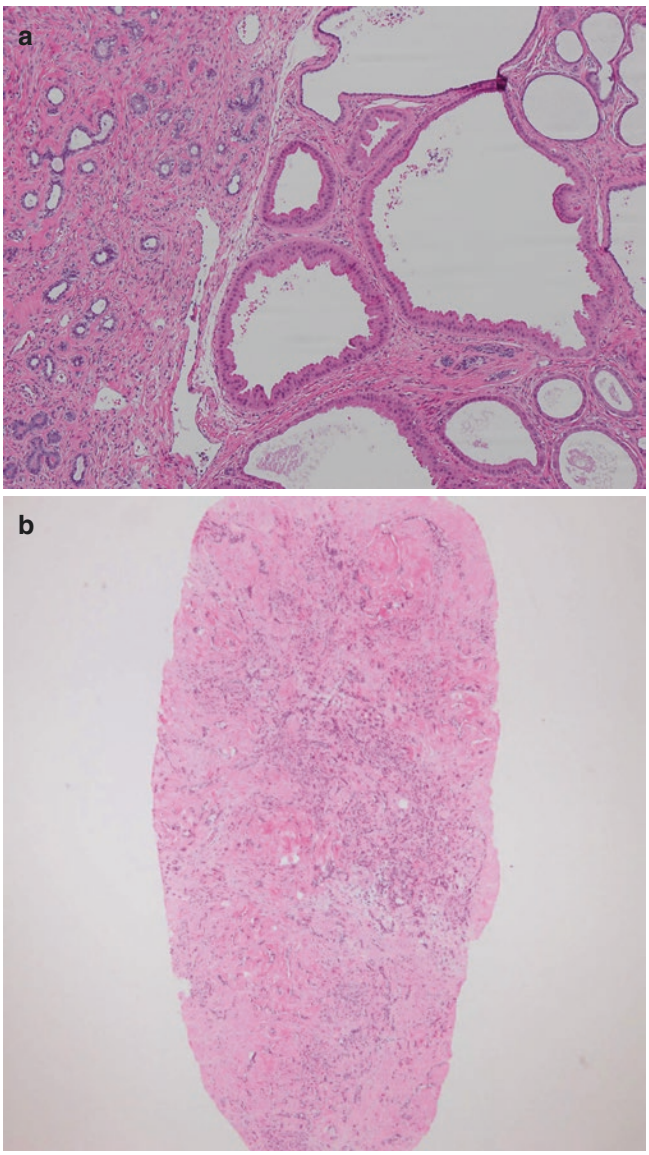


Fig. 9.20 (**a**) Complex fibroadenoma with cystic spaces, apocrine metaplasia, and (**b**) sclerosing adenosis

The phyllodes tumor is an important entity in the differential diagnosis because of its impact on clinical management and outcomes. Although the different features will be discussed below, it has been recently postulated that fibroadenomas and phyllodes tumors may not be entirely mutually exclusive. For example, a study of the long-term outcome of malignant phyllodes tumors showed that a considerable proportion of patients with phyllodes tumors had a clinical history of previous fibroadenoma, suggesting that fibroadenomas can potentially undergo malignant transformation to a phyllodes tumor [16]. Also, areas of fibroadenomatoid changes are not uncommon in phyllodes tumors, which not only complicates the diagnostic challenge but also suggests a possible relationship between these fibroepithelial lesions (Fig. 9.25).

Differential diagnosis in fibroadenoma is done with the following lesions:

- **Hamartomas** of the breast show a similar clinical presentation to that of FA: a mobile, well-circumscribed mass. Compared to the fibroadenoma, the histology shows a *dis-*

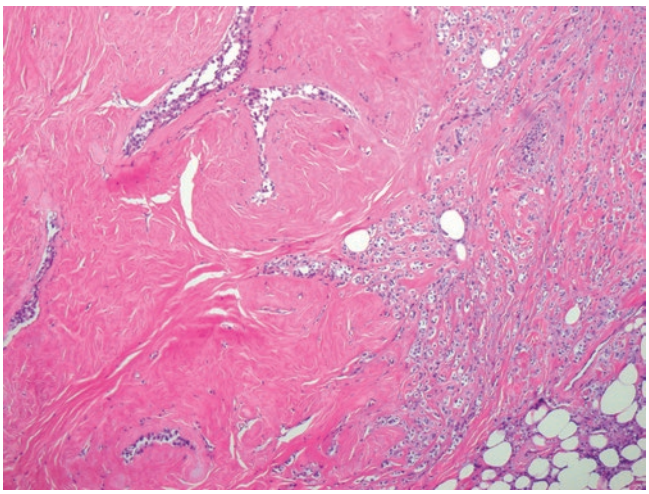


Fig. 9.22 Fibroadenoma with invasive lobular carcinoma

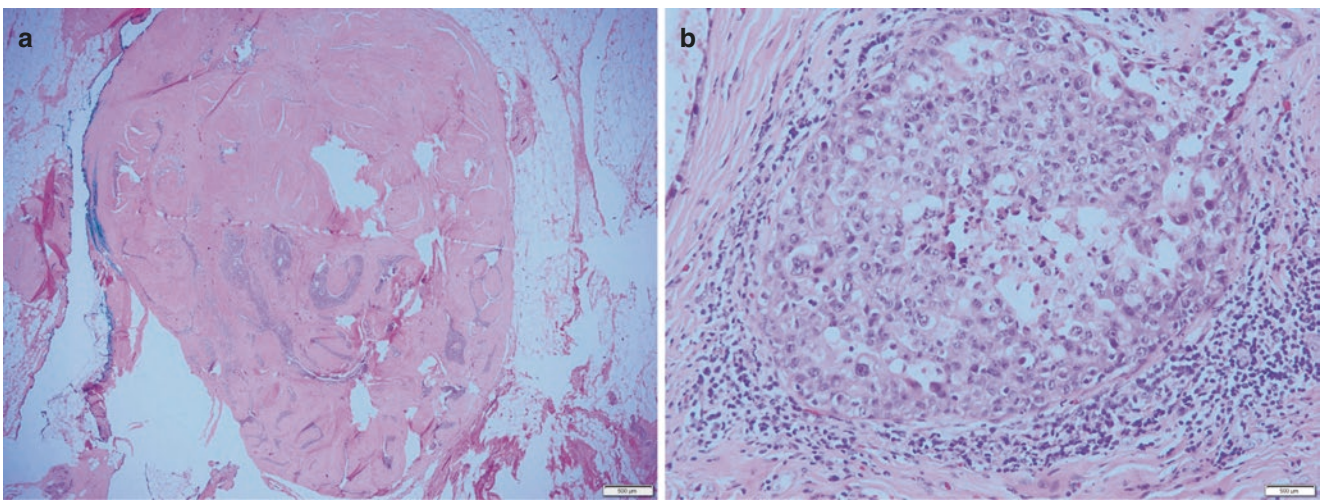


Fig. 9.21 (**a**, **b**) Fibroadenoma with DCIS. Aside from the focus of epithelial proliferation in the center of the image, this fibroadenoma is extensively hyalinized with few other epithelial elements. Higher power shows high grade DCIS with central necrosis

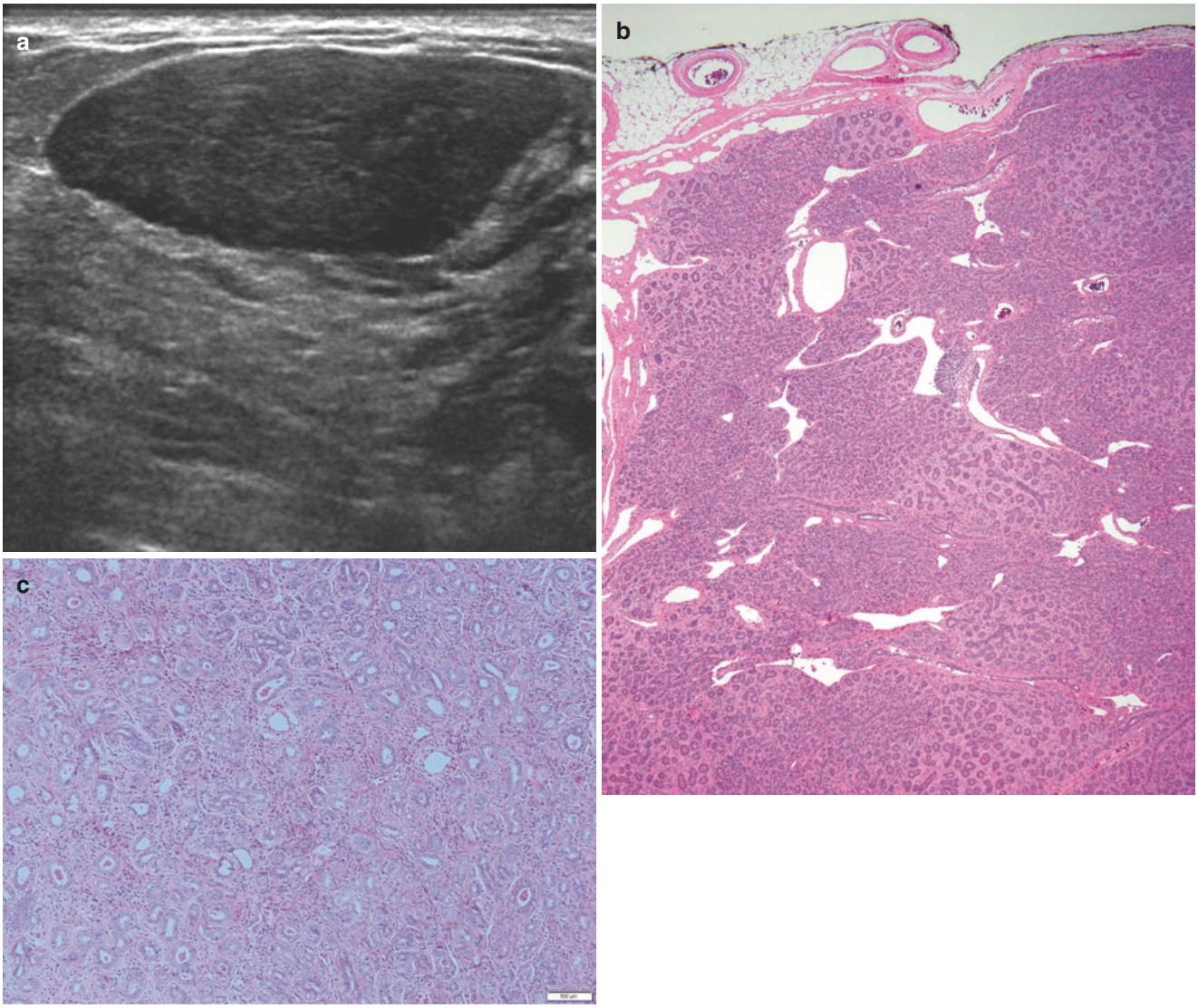


Fig. 9.23 (**a**) Tubular adenoma. Ultrasound image of a tubular adenoma shows a circumscribed, oval, hypoechoic mass. (**b**, **c**) Back-to-back tubules characterize this variant of fibroadenoma

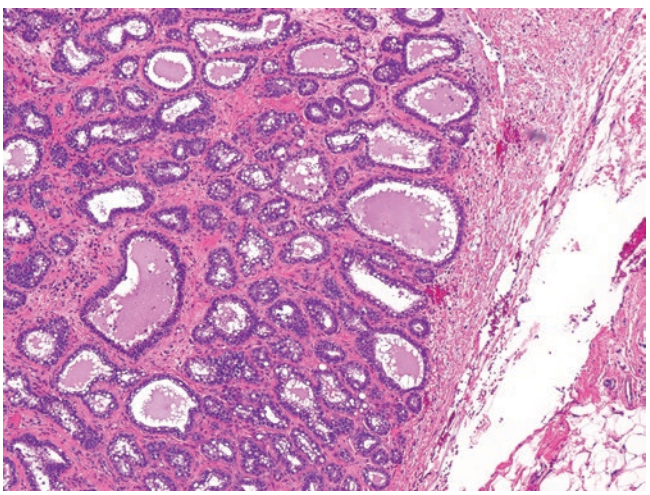


Fig. 9.24 Lactating adenoma showing numerous tubules with luminal eosinophilic secretions, lined by cells with vacuolated cytoplasms and minimal nuclear atypia

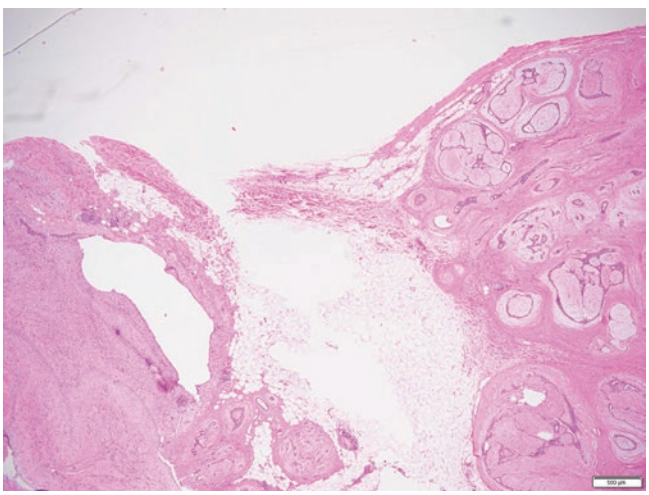


Fig. 9.25 Fibroadenoma (right) with area of phyllodes tumor (left). The bottom left (adjacent to the phyllodes tumor) shows areas of fibroadenomatoid change

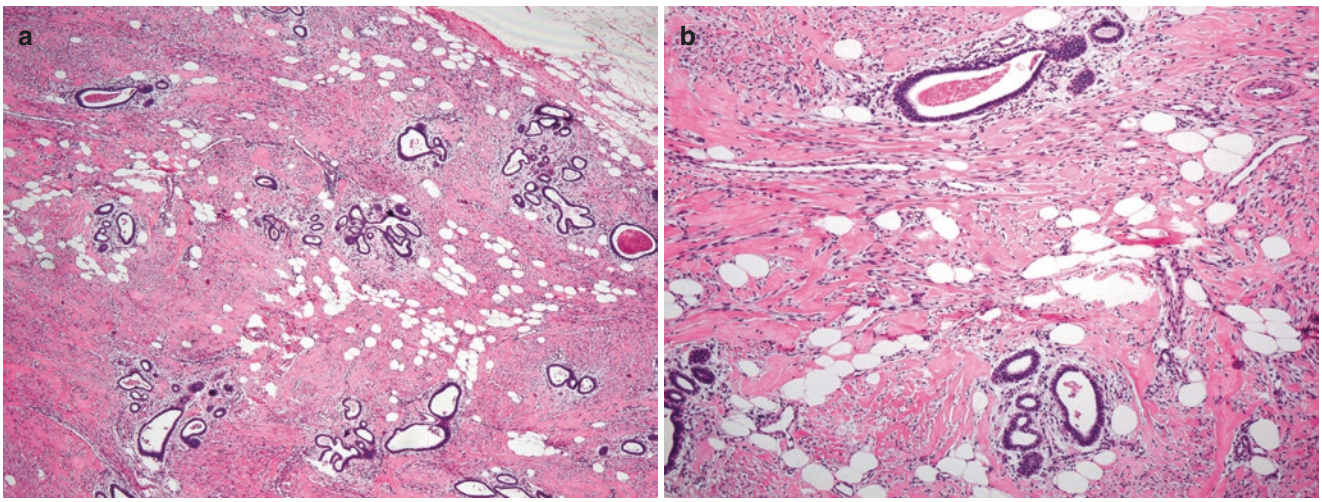


Fig. 9.26 (**a**, **b**) Breast hamartoma. This lesion is a well-circumscribed nodule of haphazardly arranged breast elements. Hamartomas frequently contain adipose tissue and pseudoangiomatoid stromal hyperplasia, both helpful features when diagnosing this entity

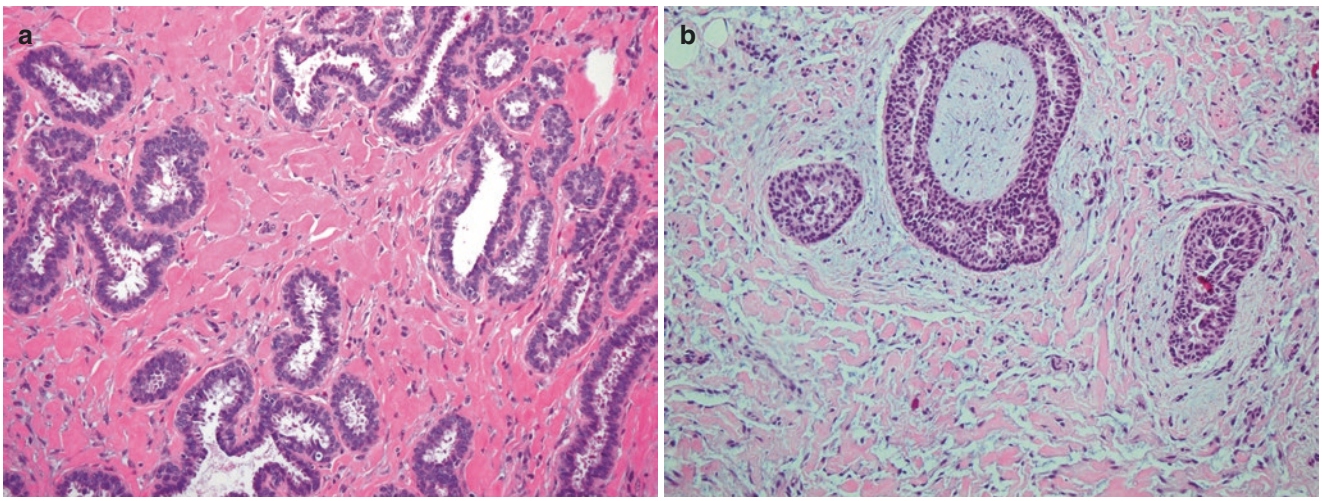


Fig. 9.27 (**a**) Pseudoangiomatous stromal hyperplasia can be a mass-forming lesion or can be seen within fibroepithelial lesions, such as in these high-power images of a hamartoma and (**b**) fibroadenoma. The fibroadenoma also shows usual ductal hyperplasia

ordered combination of histologically normal ductal and lobular structures (Fig. 9.26). This contrasts the regularly distributed epithelial components seen in a FA. On core biopsy, the well-demarcated border initially helps to identify the hamartoma as lesional breast tissue, as opposed to sampling of normal parenchyma that would lack the sharp margins seen in an hamartoma. Although hamartomas can show stromal changes similar to those seen in a FA, such as hyalinization and occasional myoid differentiation, hamartomas are not typically stroma-predominant lesions. The frequent presence of adipose tissue within the hamartoma helps to distinguish this from a FA.

- **Pseudoangiomatous stromal hyperplasia (PASH)** is a proliferation of interlobular myofibroblasts, imparting small, cleft-like spaces in the stroma reminiscent of vascular spaces (Fig. 9.27). PASH can form a well-circumscribed lesion alone; however, it is also a common finding in the stroma of fibroepithelial lesions, such as fibroadenomas and hamartomas.
- **Nodular sclerosing adenosis** is characterized by a marked proliferation of compressed, slit-like glandular structures, embedded in a background of hyalinized stroma (Fig. 9.28). Low-power magnification is critical to this diagnosis. This lesion is unencapsulated; however, the crowded glands of nodular sclerosing adenosis conform to the architecture of an expanded, but well-defined lobule. On core biopsy, this can be challenging, as the differential includes both tubular adenoma and

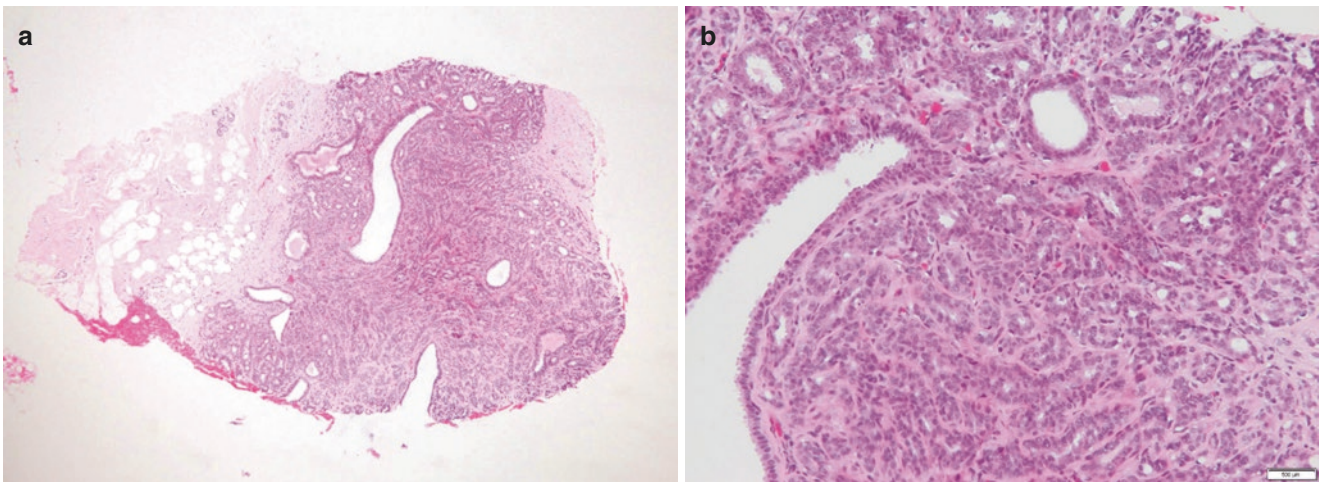


Fig. 9.28 (**a**) Nodular sclerosing adenosis as seen in a core biopsy. The lesion is relatively well-circumscribed with open and closed tubules that frequently extend beyond the main nodule. (**b**) Notice the proliferation of round and slit-like glandular spaces

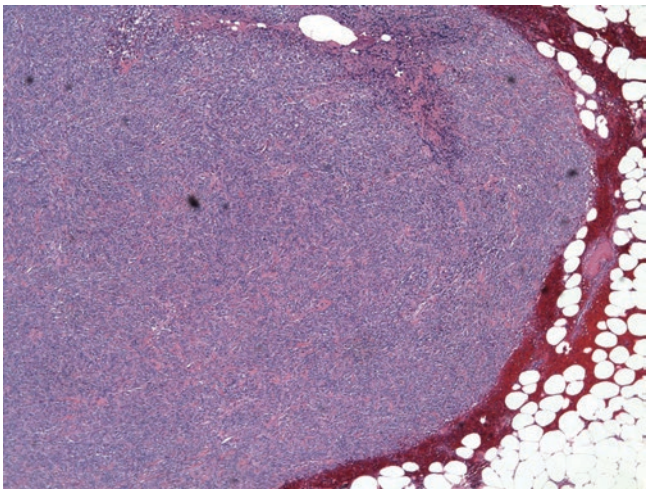


Fig. 9.29 Solitary fibrous tumors showing a well-circumscribed border. The spindle cells proliferation and dense bands of hyaline sclerosis can be appreciated

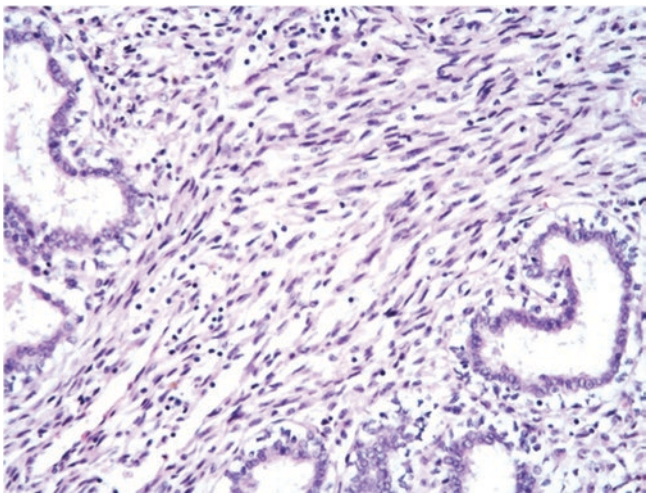


Fig. 9.30 Breast adenomyoepitheliomas are biphasic tumors with epithelial and spindle cells. They can have a variegated appearance owing in part to the morphologic spectrum of myoepithelial cells

carcinoma. The patent, round lumens of a tubular adenoma help distinguish it from nodular sclerosing adenosis. Carcinoma can be excluded with the use of myoepithelial markers as they will demonstrate the intact myoepithelial cells of nodular sclerosing adenosis.

- Although the stroma of a **solitary fibrous tumor** (SFT) can resemble a fibroadenoma, SFT fundamentally lacks an epithelial component (Fig. 9.29). SFT shows varying cellularity within the lesion, scattered bands of sclerosis, and occasionally its characteristic staghorn vasculature.
- **Adenomyoepithelioma** is a biphasic tumor with both a glandular and mesenchymal proliferation; however, its cellular stroma is comprised of myoepithelial cells, which demonstrate diffuse expression of myoepithelial cell markers with IHC. The adenomyoepithelioma has various histologic patterns, as myoepithelial cells display a wide spectrum of cellular morphology (i.e., spindled, plasmacytoid, and abundant clear cytoplasm) (Fig. 9.30). Recognizing the prominent proliferation of myoepithelial cells is key to the diagnosis.
- Although **intraductal papillomas** alone intrinsically lack the classic features of a fibroadenoma, rarely, papillomas can be a part of a fibroadenoma's epithelial component, especially in the juvenile fibroadenoma. It is imperative to correlate biopsy findings with imaging. For example, if there is a discrepancy between the size of the intraductal papilloma and the size of the mass on imaging, carefully

study the background parenchyma for stromal features suggestive of a fibroadenoma. This is to be distinguished from juvenile papillomatosis, a rather uncommon mass-like lesion composed of cysts and epithelial proliferation. This entity lacks the predominant stromal proliferation and nodular growth pattern of fibroadenomas.

- FA with prominent myxoid stroma tend be hypocellular lesions with decreased stromal cells and epithelial components. On core biopsy, the presence of only myxoid stroma could raise the possibility of a myxoma, but myxomas are uncommon lesions of the breast. However, the more important consideration when faced with acellular myxoid stroma is a **mucinous lesion**, such as a mucocele or mucinous carcinoma. Both mucocele and mucinous carcinoma can have a well-circumscribed appearance. Evaluation of the entire lesion may be necessary to resolve this distinction. In general, histologic evaluation of a mucinous lesion in its entirety is strongly encouraged to exclude mucinous carcinoma.

9.2 Phyllodes Tumor

In contrast to the patient demographics typical of fibroadenomas, phyllodes tumor (PT) characteristically presents one to two decades later and is heralded by a rapidly growing mass or sudden increased size of a pre-existing mass [17]. By imaging, phyllodes tumors present as large, multilobulated lesions that may show cleft like cystic spaces (Figs. 9.31 and 9.32).

Grossly, the cut surface is lobulated with cleft-like spaces, a reflection of its classic "leaf-like" architecture (Fig. 9.33). Necrosis may be present, secondary to either ischemic or tumor necrosis (Fig. 9.34). Overlying skin changes are not uncommon and range from discoloration to skin ulceration (Fig. 9.35). Nipple retraction can occur but is a less common physical finding [18].

As in fibroadenomas, the stromal component of a PT predominates over the epithelial component. Phyllodes tumors are diagnosed based on the presence of the following stromal features: stromal cellularity, stromal cytologic atypia, stromal mitotic activity, and prominence of stromal overgrowth [1]. Additionally, the degree to which the above diagnostic

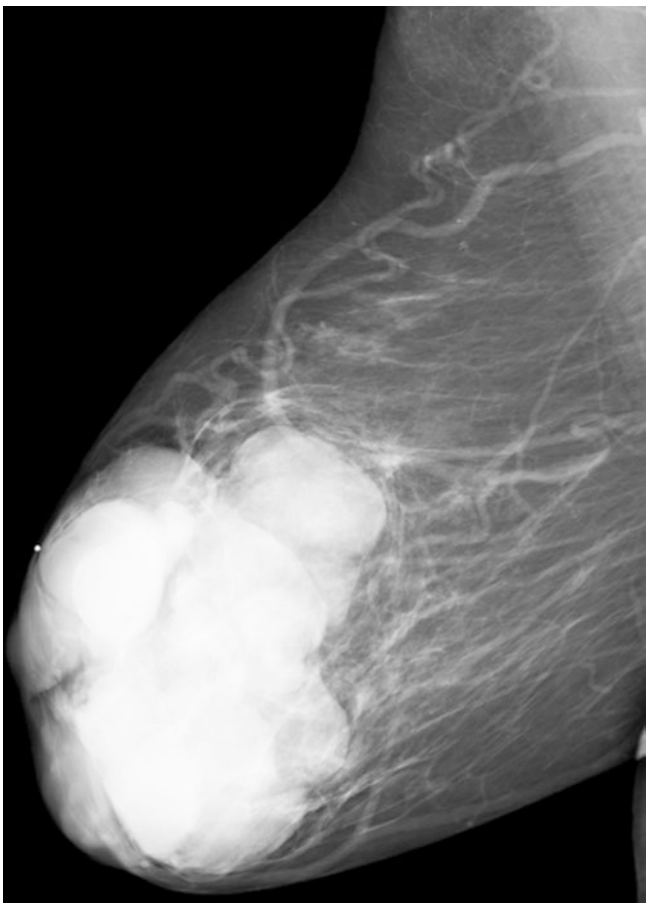


Fig. 9.31 Mammogram of a Phyllodes tumor shows a large circumscribed, multilobulated dense mass

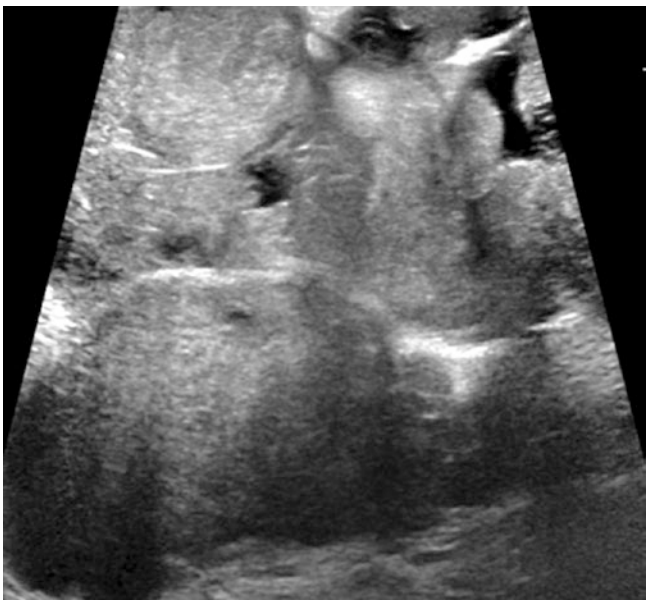


Fig. 9.32 Ultrasound, corresponding to Fig. 9.31, shows the cleft-like cystic spaces

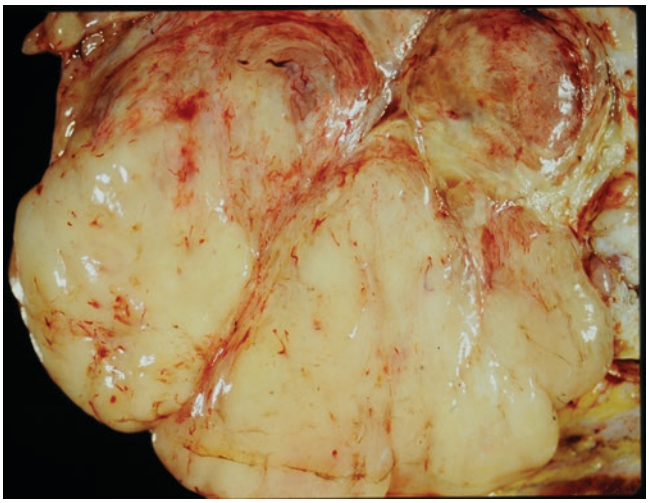


Fig. 9.33 Gross image of a benign Phyllodes tumor showing sharply accentuated nodules and deep grooves. A gelatinous cut surface suggests myxoid changes within the lesion

features are present further stratify PTs into the following major histologic subtypes: benign, borderline, and malignant. This histologic classification is based on recommendations from the World Health Organization [1]. These histologic subtypes carry important prognostic value and clinical implications (Table 9.1).

In addition to the three features used in the tumor subtyping, it is important to understand the fundamental characteristics of PT. The classic leaf-like silhouette of the PT is created by the stromal proliferation compressing the ductal elements into thin, slit-like spaces. This is an exaggerated intracanalicular pattern of growth. The other growth pattern

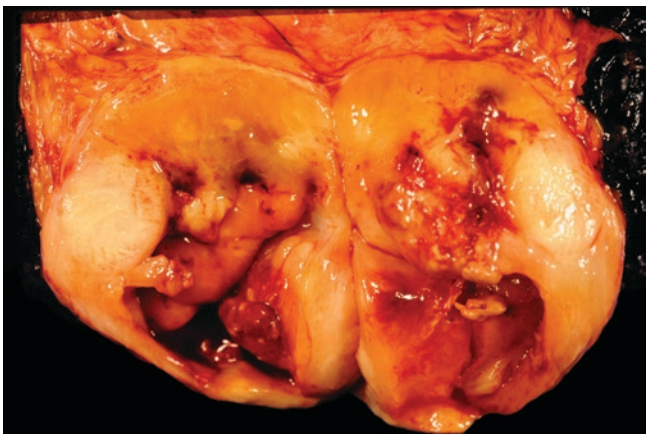


Fig. 9.34 Malignant Phyllodes tumor with a centrally hemorrhagic, friable area, consistent with necrosis

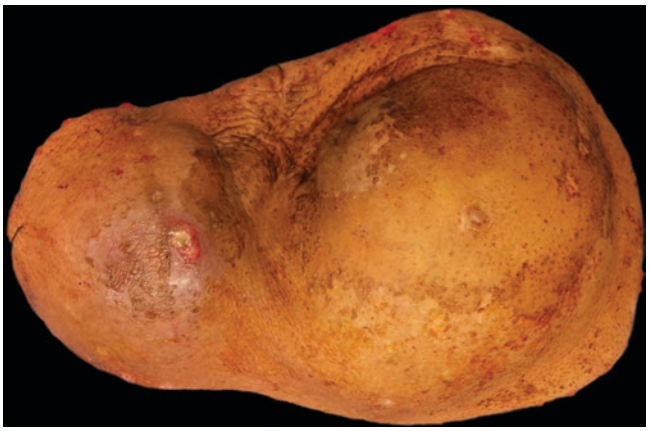


Fig. 9.35 Phyllodes tumor that has ulcerated the overlying skin

is pericanalicular, in which the stroma grows circumferentially around the epithelial structures without compression. (These patterns are analogous to those described in fibroadenomas, contributing to the extensive morphologic overlap of these lesions.) In PT, both intracanalicular and pericanalicular growth patterns are usually present.

- **Stromal overgrowth** is a feature limited to the borderline and malignant phyllodes subtypes. To assess for the presence of stromal overgrowth, one should see stromal proliferation without epithelial elements in at least one low-power field (×4) [9]. This feature is rarely observed in fibroadenoma.
- **Subepithelial stromal condensation** describes the distinct enhancement of stromal hypercellularity immediately beneath the epithelial component (Fig. 9.36). This creates a "cambium layer" similar conceptually to that seen in the embryonal rhabdomyosarcoma. The "cambium layer" can be seen in all subgroups of PT and serves as a good predictor of PT in biopsies when present [10].

Table 9.1 Phyllodes tumor subtyping into benign, borderline, and malignant

Subtype	Stromal hypercellularity	Stromal cytologic atypia	Mitotic activity (stromal) per 10 high-power fields (hpf)	Tumor border	Comments
Benign	Mild	Minimal	<5	Pushing border (well-defined)	Stromal overgrowth not present
Borderline	Moderate/high	Moderate	Frequent (5–9)	Pushing ± focal infiltrative	Features intermediate between benign and malignant
Malignant	High	Marked; + pleomorphism	>10	Infiltrative	High-grade sarcoma features with marked stromal overgrowth; ± focal fibrosarcoma-like appearance; ± heterologous elements

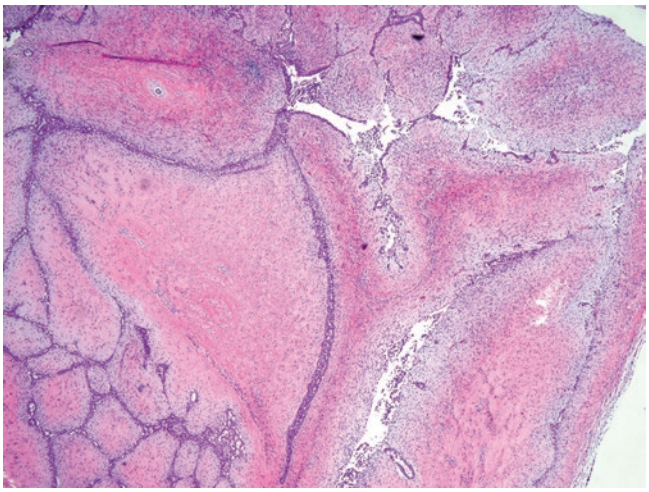


Fig. 9.36 Low-power magnification of a Phyllodes tumor showing stromal overgrowth and subepithelial stromal condensation (cambium layer)

- **Stromal atypia** refers to the nuclear membrane irregularity, degree and variation in nuclear size, and presence of nucleoli (Fig. 9.37). Frank nuclear pleomorphism is generally restricted to the malignant phyllodes. Scattered multinucleated, degenerative atypia (like stromal giant cells seen in FA, see above) is not considered pleomorphism.

In an attempt to standardize some of the above grading/subtyping criteria, previous studies have proposed different measuring sticks to grade **stromal hypercellularity**. A study by Jacobs et al. [19] used normal perilobular stroma cellularity as a reference for grading stromal hypercellularity. For instance, twice the cellularity of normal perilobular stroma along with no overlapping of stromal cells is considered mild hypercellularity. High cellularity shows stromal cells with extensive overlapping, and moderate hypercellularity is in between mild and high (Fig. 9.38).

Another informative feature included in the table is the **tumor border**: the interface between the tumor and adjacent parenchyma. As the lesion advances in histologic grade, there is a greater propensity for an invasive border, a factor which can complicate surgical excision and predispose to recurrence. Focal areas of an invasive tumor border in what appears to be a benign PT or cellular fibroadenoma warrants a careful consideration of borderline PT (Fig. 9.39).

Figures 9.40, 9.41, 9.42, and 9.43 show examples of PTs of various subtypes.

Histologic subtype (grade) of the PT is currently the major factor in predicting clinical outcome. The malignant PT carries the highest risk for recurrence and metastasis; however, all grades of PT harbor the potential (albeit of variable degrees) for local recurrence and metastasis. Overall, the rates of metastatic disease are related to histologic subtype and have been reported with much variability, ranging from 0% to 28.6% of patients. Local recurrence ranges from 10% to 30% [10, 20]. Benign PTs behave in a similar clinical fashion to FA; however, as indicated in the previous statement, a small subset of benign PT can recur and/or metastasize. Consequently, the mainstay for management of a PT of any histologic grade includes excision with clear margins. The role for chemotherapy and radiation is not entirely elucidated for malignant PT, most likely due to its uncommon occurrence. Sentinel lymph node biopsy and/or excision is not routinely performed in this setting, since metastasis of PT is generally via the hematogenous route with the common sites of metastasis being the lung and bone. Axillary lymphadenopathy is common but is frequently secondary to reactive lymph node changes; however, axillary lymph node metastasis is a rare event [18, 21].

As mentioned above, the standard of care for PT is surgical excision with clear margins. Efforts are being made in recent literature to define the adequacy of a negative margin (i.e., 1.0 cm versus narrower). Given the wide range of tumor recurrence frequency, margin status and adequacy are being

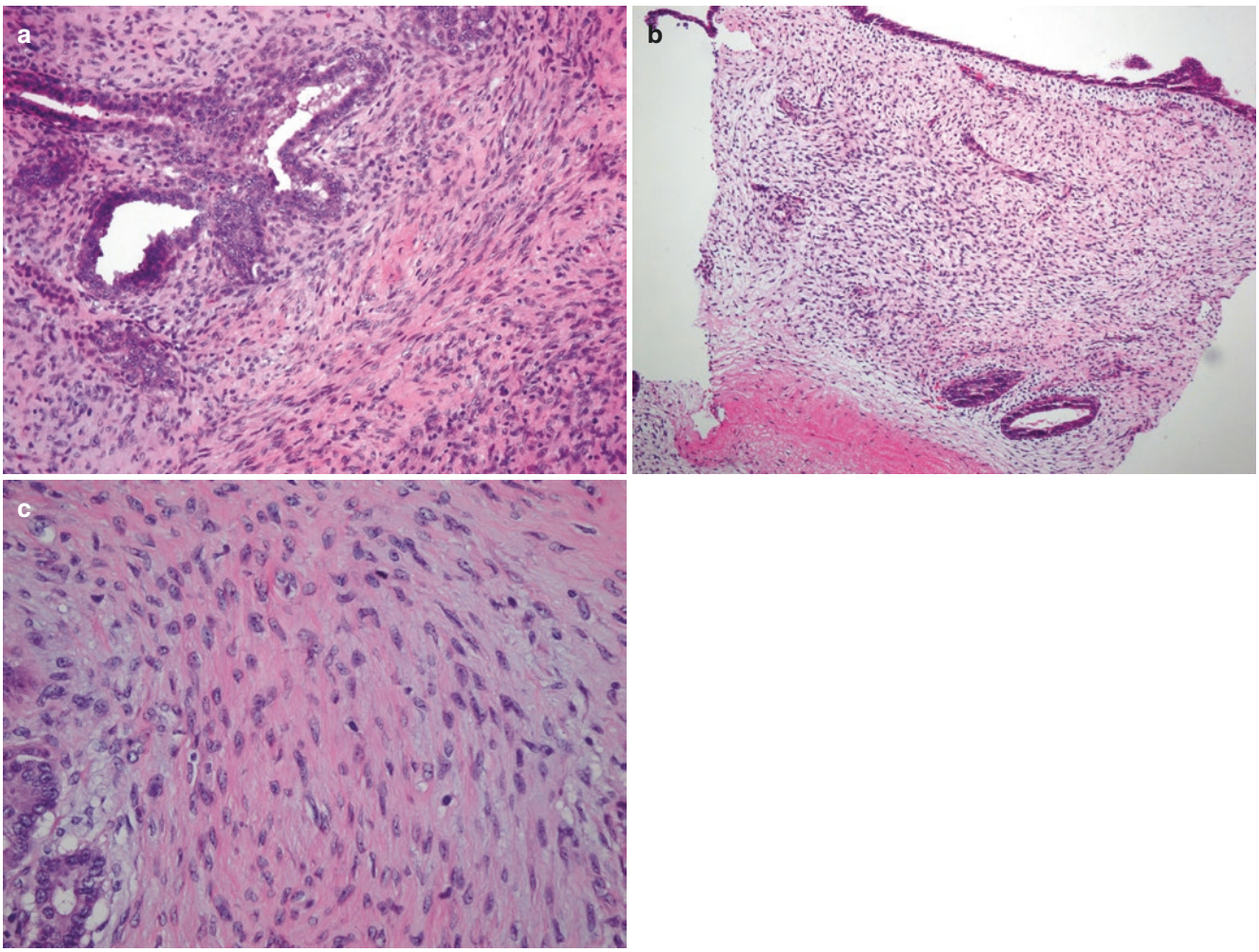


Fig. 9.37 (**a**–**c**) Phyllodes tumor demonstrating stromal hypercellularity with stromal cells showing nuclear atypia with irregular nuclear contours, variability in nuclear size, and nucleoli

studied in terms of the true correlation with recurrence rate. Conflicting data has emerged on this topic with new studies finding that a positive surgical margin does not predict recurrence [22]. Additional studies have looked at adequacy of negative margins, with a 1-cm margin showing no advantage over narrower negative margins [23]. A major discrepancy between the lack of correlation with margin status and recurrence may be related to multifocality of the tumor, as well as background fibroadenomatoid change, a potential precursor of new fibroepithelial tumor foci [23].

Within the class of fibroepithelial lesions, perhaps the most challenging distinction is between fibroadenoma and the benign and borderline PT. As previously mentioned, these biphasic tumors exhibit the same stromal growth patterns—intracanalicular and pericanalicular. The intracanalicular pattern, which contributes to the PT's classic leaf-like architecture, can also be seen in FA; however, it is usually focal and not as well developed and exaggerated as in PT. In a biopsy, this feature is sometimes present as "stromal fragmentation," in which a fragment of stroma is peripherally lined by epithelium, representing the exaggerated cleft-like spaces [9]. The cellular fibroadenoma presents a unique difficulty on core biopsy, as its increased stromal hypercellularity mimics that of PT. Recent studies have aimed to evaluate various features that may help distinguish these two entities on biopsy [9, 24]. For instance, mitotic activity in cellular FA is usually less than 3 per 10 high-power field. In other words, cellular fibroadenomas exhibit an inappropriately low mitotic rate compared to what would be expected for a PT of comparable stromal hypercellularity. Stromal overgrowth, when

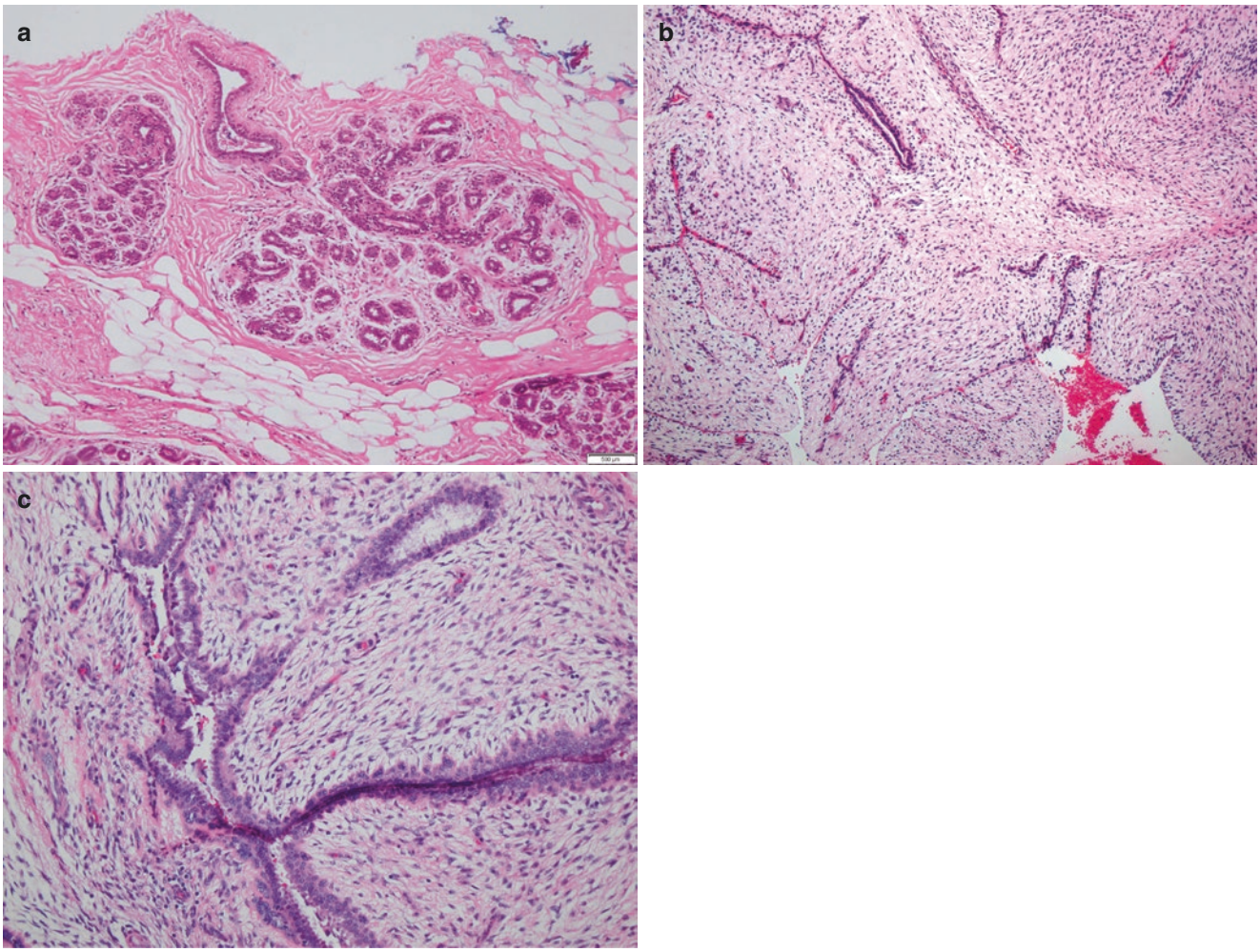


Fig. 9.38 (**a**) Normal perilobular stroma for comparison used in gauging stromal hypercellularity. (**b**, **c**) Examples of stromal hypercellularity in Phyllodes tumors

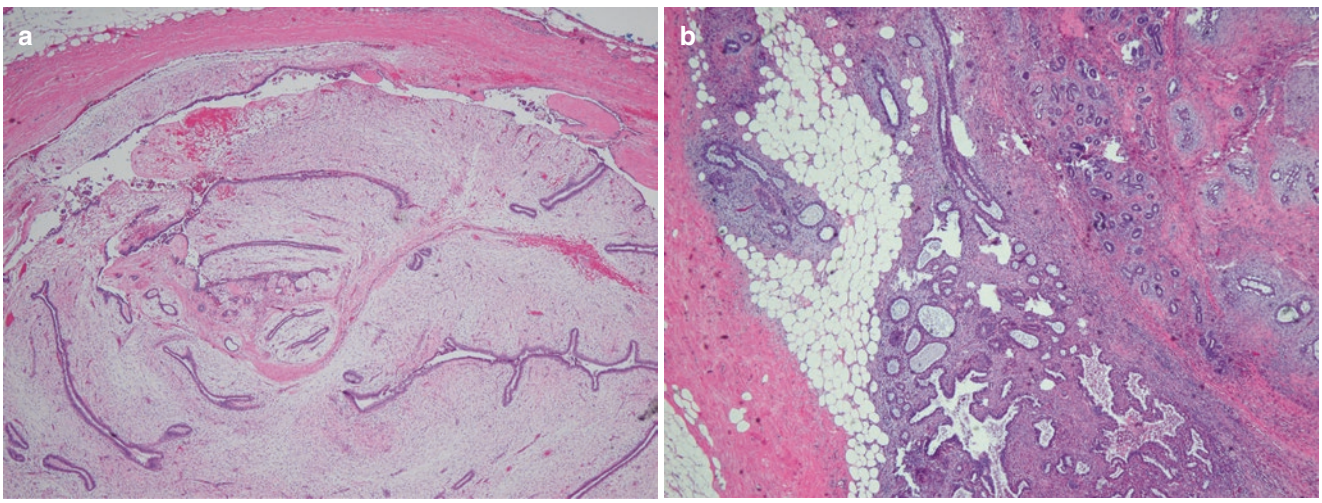


Fig. 9.39 (**a**) Benign Phyllodes tumor showing a pushing border/interface with the adjacent parenchyma. (**b**) Borderline tumors can show foci of invasion at their border

present, is strongly suggestive of a PT, as this is rarely observed in the fibroadenoma regardless of stromal cellularity. The tumor border can be very informative when examining fibroepithelial lesions. Fibroadenomas, regardless of cellularity, will show a well-defined border, unlike borderline PT, which can show focal areas of invasion. In the context of hypercellularity and stromal overgrowth, adipose tissue within the stroma has also been shown to be more frequent in PT [9, 24]. It is most important to evaluate all the aforementioned features when assessing a fibroepithelial lesion. At least three mitoses per 10 high-power fields generally favor a PT. In the absence of increased mitotic, a combination of the above helps favor PT over cellular FA [9, 24].

Despite the aforementioned features to discriminate between these two neoplasms, on core biopsies the distinction may still not be possible. The pathologist may make a diagnosis of "fibroepithelial lesion" with a qualifying statement that the differential includes both fibroadenomas and PT. The natural history of these indeterminate core biopsies has been studied with roughly one-third of patients being diagnosed with PT following surgical excision [25].

With only stromal components present in biopsy material, fibromatosis and metaplastic carcinoma, including the fibromatosis-like/spindle cell type, are in the differential diagnosis (Fig. 9.44). Cytokeratin (CK) positivity with immunohistochemistry supports metaplastic carcinoma, as borderline PT are typically negative for CK. Histologically, fibromatosis exhibits bland spindle cells that are arranged in long, sweeping fascicles with scattered bands of hyalinized collagen. Fibromatosis consistently displays an infiltrative border. Although phyllodes tumors can show occasional fascicular stromal pattern, fibromatosis is not a biphasic lesion,

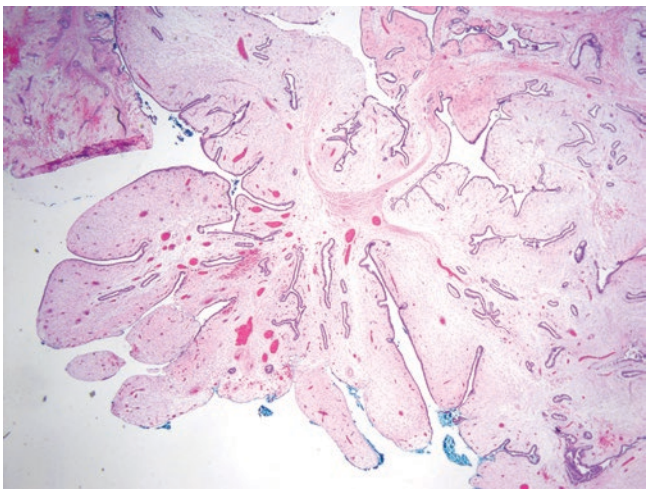


Fig. 9.40 Benign phyllodes tumor with classic leaf-like architecture, an exaggerated intracanalicular pattern of stromal growth

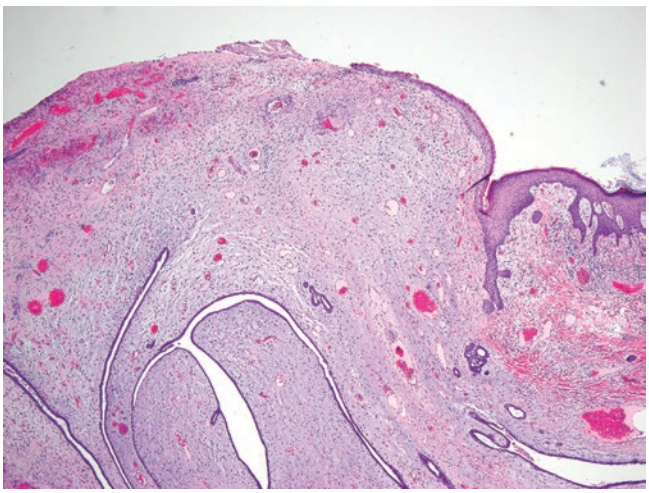


Fig. 9.42 Phyllodes tumors can cause skin changes ranging from discoloration to ulceration of overlying skin, as seen here

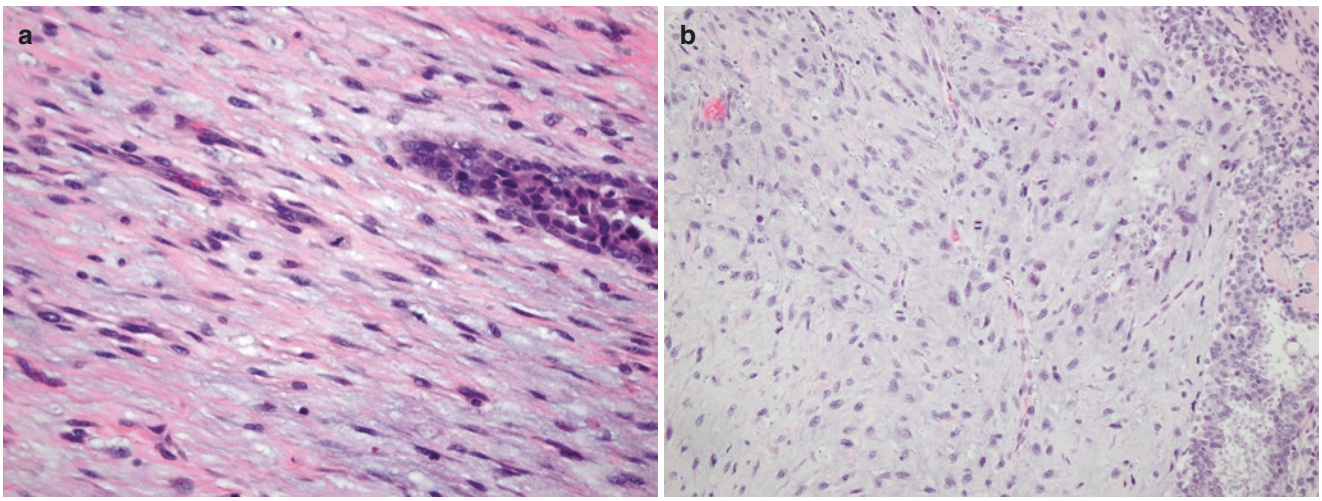


Fig. 9.41 (**a**, **b**) Mitotic figures are readily seen in the stroma of phyllodes tumors

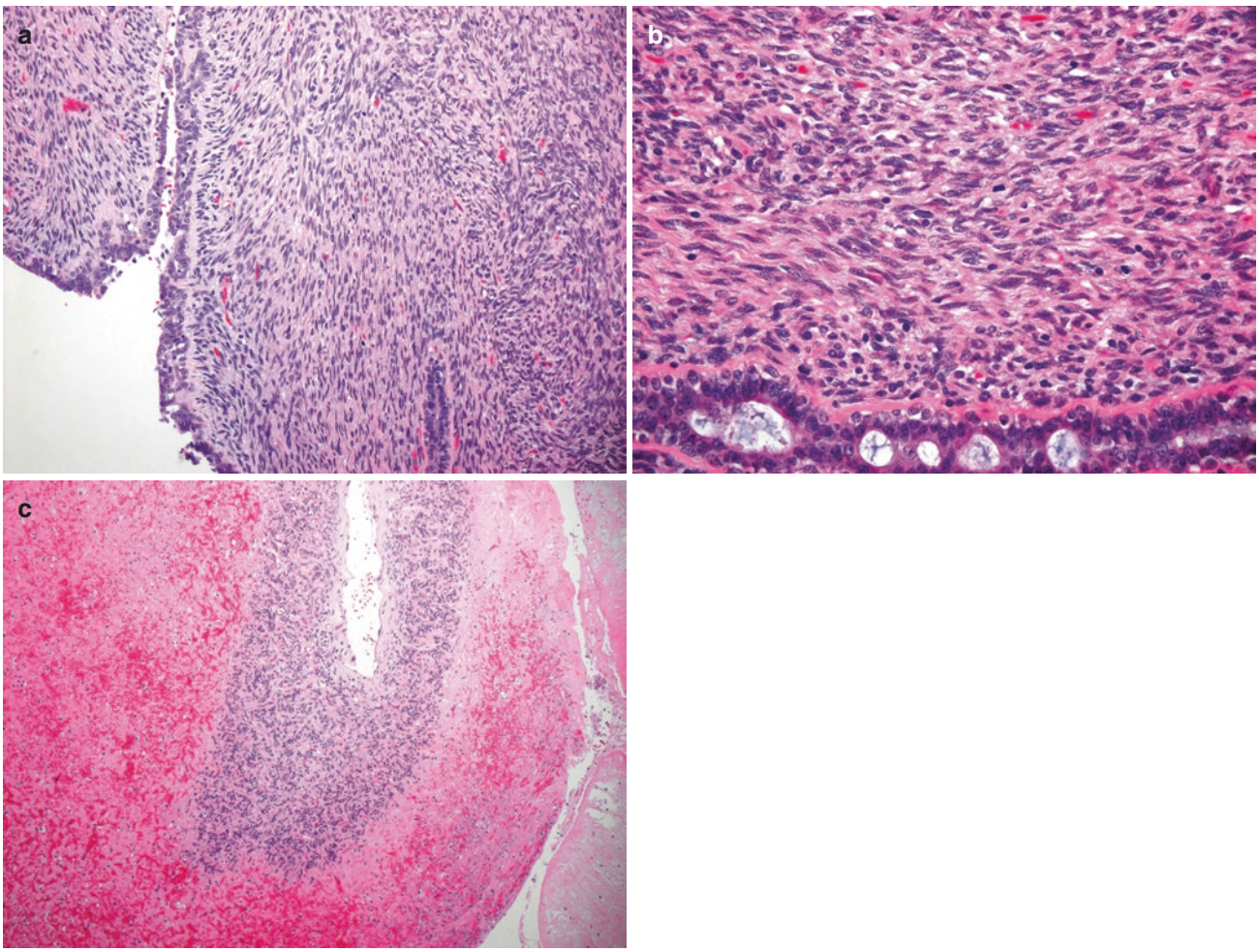


Fig. 9.43 (**a**, **b**) Malignant Phyllodes tumor. Stromal hypercellularity, mitotic figures and nuclear atypia are readily seen even at low power. (**c**) The tumor shows a peritheliomatous pattern of necrosis—prominent tumor necrosis with sparing of the tumor, which immediately surrounds a large blood vessel

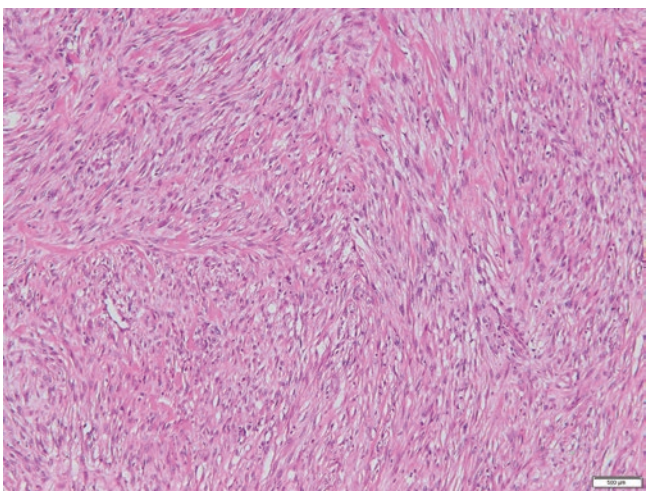


Fig. 9.44 Breast metaplastic carcinoma with spindle cells. Small fragments of tumor in a core biopsy raise the possibility of the stroma of a Phyllodes tumor. Immunohistochemical stains can be helpful in this differential

and, therefore, will not have a closely associated epithelial component other than the entrapment of the surrounding breast tissue. Beta-catenin nuclear positivity can be seen in both fibromatosis and PT [26]; therefore, morphology will be most helpful in distinguishing these two entities, and clinical and radiologic correlation are imperative.

The entity "periductal stromal tumor" refers to a low-grade, malignant fibroepithelial tumor that shows considerable morphologic overlap with phyllodes tumor. It is a rare entity and is characterized by its lack of the exaggerated intracanalicular ("leaf-like") architecture seen in PT, and instead shows a predominantly pericanalicular pattern of stromal growth [1]. Transformation to phyllodes tumor has been reported in cases of this lesion [27]. According to the WHO classification of breast tumors, this entity may represent part of the PT disease spectrum.

Malignant PT. On a core biopsy, a malignant PT will typically present as a high-grade malignancy with

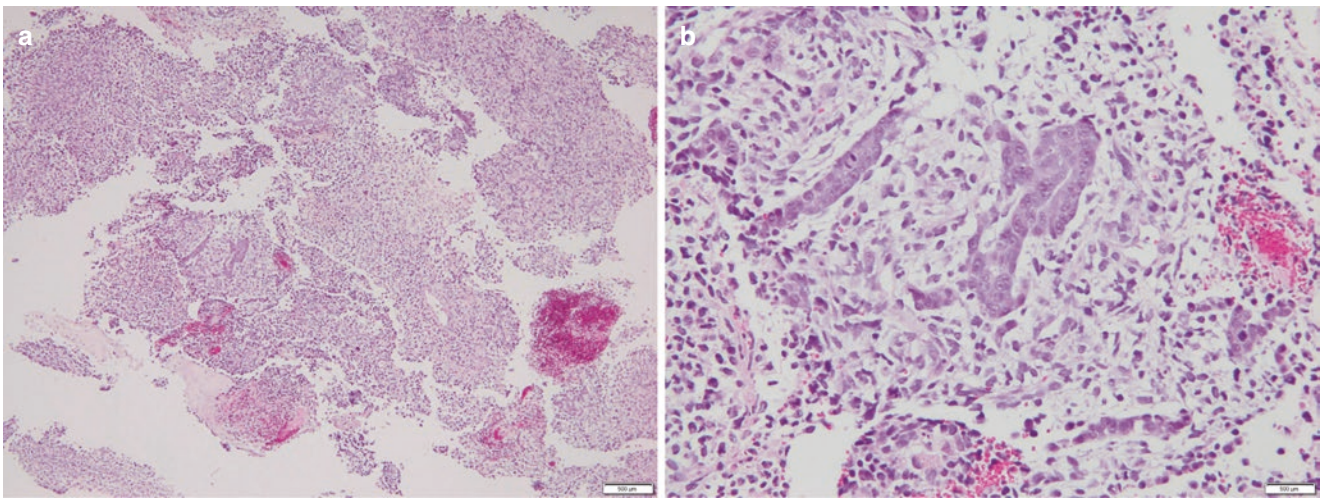


Fig. 9.45 (**a**) Breast metaplastic carcinoma. Low-power magnification shows fragments of a high grade sarcomatoid neoplasm. (**b**) Higher power shows frankly malignant ductal elements, which is highly suggestive of a carcinoma rather than a Phyllodes tumor

sarcomatous features. If a core biopsy shows a high-grade malignancy with sarcomatous features without an epithelial component, the pathologist should exclude the possibility of a malignant PT with scant evidence of the epithelial component (e.g., stromal overgrowth). Malignant PT is more common than primary or metastatic sarcomas of the breast; however, malignant PT is less common than carcinoma. With these histologic features, the most likely primary carcinoma would be a metaplastic carcinoma, sarcomatoid type. A very helpful morphologic feature favoring malignant PT is identifying the characteristic leaf-like architecture created by the intracanalicular growth of stroma. Abundant stromal overgrowth, a prominent feature of malignant PT, may make finding these areas difficult; therefore, extensive sampling of the tumor is required [10]. The findings of in situ carcinoma (DCIS) or associated malignant epithelial elements favor a metaplastic carcinoma (Fig. 9.45).

Immunohistochemistry can be a useful in this differential diagnosis. Although cytokeratins are used in routine practice to resolve the issue of carcinoma with ease, malignant PT can show some stromal CK positivity [28]. This staining is typically focal, compared to the more diffuse cytokeratin positivity in carcinoma, but keep in mind that the extent of staining may be difficult to assess with limited biopsy material. A panel of CKs is recommended if the differential diagnosis favors a metaplastic carcinoma. An example CK panel includes: pan-CK (AE1/AE3), high molecular weight CK (CK903 / cytokeratin 34βE12), CAM 5.2, CK7 [29]. CD34, a marker that is commonly positive in the stromal cells of PT, is usually negative in metaplastic carcinomas. However, CD34 positivity is only seen in approximately 50% of malignant PT [28]. In light of the above discussion, it may not be possible to render a definitive diagnosis on core biopsy. The distinction should then be made on excision as the treatment for these entities is quite different.

9.3 Immunohistochemistry in the Diagnosing of Fibroepithelial Lesions

There is no single marker that can help in the distinction between fibroadenomas and PT; therefore, this distinction relies on the clinical, radiologic, and pathologic features of the lesion. The most significant role for immunohistochemistry in fibroepithelial lesions is in the exclusion process of various entities in the differential diagnosis. When faced with a core biopsy showing a sarcomatoid process with no epithelial elements present, whether high- or intermediate-grade lesions, the use of multiple cytokeratin stains (including high molecular weight CK) and p63 to exclude a carcinoma should be considered, especially metaplastic carcinoma (sarcomatoid types). See the above differential diagnoses sections for more details on the staining patterns of respective entities. Regarding hormone receptors in fibroepithelial lesions, the stromal component of fibroadenomas shows estrogen-dependent growth. Estrogen receptor positivity is inversely related to histologic grade of PT (malignant PTs shows low positivity). While interesting in a pathophysiologic perspective, hormone receptor status does not currently play a role in routine clinical practice [30].

Conclusion

Fibroadenomas, in fact, will constitute the majority of fibroepithelial lesions seen in routine practice. However, the purpose of the core biopsy in this setting is to exclude the more biologically significant process: the phyllodes tumor. Despite considerable morphologic overlap, the clinical management and implications are quite different. A diagnosis of PT will result in surgical excision, whereas other fibroepithelial lesions may be managed conservatively. Occasionally, a lesion may show features indeterminate between fibroadenoma and PT. In these cases, it may be appropriate to diagnose a fibroepithelial lesion, noting PT cannot be excluded. Clinical and radiologic correlation is critical in all cases.

References

1. Tan P, Tse G, Lee A, Simpson J, Hanby A. Fibroepithelial tumors. In: Lakhani S, Ellis I, Schnitt S, Tan P, van de Vijver M, editors. WHO classifications of tumors of the breast. 4th ed. Lyon: IARC Press; 2012. p. 142–7.
2. Darwish A, Nasr AO, El Hassan LA, Fahal AH. Cyclosporine-A therapy-induced multiple bilateral breast and accessory axillary breast fibroadenomas: a case report. J Med Case Rep. 2010;4:267.
3. Weinstein SP, Orel SG, Collazzo L, Conant EF, Lawton TJ, Czerniecki B. Cyclosporin A-induced fibroadenomas of the breast: report of five cases. Radiology. 2001;220(2):465–8.
4. Yang X, Kandil D, Cosar EF, Khan A. Fibroepithelial tumors of the breast: pathologic and immunohistochemical features and molecular mechanisms. Arch Pathol Lab Med. 2014;138(1):25–36.
5. Cericatto R, Pozzobon A, Morsch DM, Menke CH, Brum IS, Spritzer PM. Estrogen receptor-alpha, bcl-2 and c-myc gene expression in fibroadenomas and adjacent normal breast: association with nodule size, hormonal and reproductive features. Steroids. 2005;70(3):153–60.
6. Sapino A, Bosco M, Cassoni P, Castellano I, Arisio R, Cserni G, et al. Estrogen receptor-beta is expressed in stromal cells of fibroadenoma and phyllodes tumors of the breast. Mod Pathol. 2006;19(4):599–606.
7. Goel NB, Knight TE, Pandey S, Riddick-Young M, de Paredes ES, Trivedi A. Fibrous lesions of the breast: imaging-pathologic correlation. Radiographics. 2005;25(6):1547–59.
8. Kuijper A, Mommers EC, van der Wall E, van Diest PJ. Histopathology of fibroadenoma of the breast. Am J Clin Pathol. 2001;115(5):736–42.
9. Yasir S, Gamez R, Jenkins S, Visscher DW, Nassar A. Significant histologic features differentiating cellular fibroadenoma from phyllodes tumor on core needle biopsy specimens. Am J Clin Pathol. 2014;142(3):362–9.
10. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016;68(1):5–21.
11. Diaz NM, Palmer JO, McDivitt RW. Carcinoma arising within fibroadenomas of the breast. A clinicopathologic study of 105 patients. Am J Clin Pathol. 1991;95(5):614–22.
12. Sanders M, Brooks J, Palazzo J. Mesenchymal lesions of the breast. In: Palazzo JP, editor. Difficult diagnoses in breast pathology. New York, NY: Demos Medical; 2011. p. 172–95.
13. Guray M, Sahin AA. Benign breast diseases: classification, diagnosis, and management. Oncologist. 2006;11(5):435–49.
14. Greenberg R, Skornick Y, Kaplan O. Management of breast fibroadenomas. J Gen Intern Med. 1998;13(9):640–5.
15. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, et al. Long-term risk of breast cancer in women with fibroadenoma. N Engl J Med. 1994;331(1):10–5.
16. Abe M, Miyata S, Nishimura S, Iijima K, Makita M, Akiyama F, et al. Malignant transformation of breast fibroadenoma to malignant phyllodes tumor: long-term outcome of 36 malignant phyllodes tumors. Breast Cancer. 2011;18(4):268–72.
17. Krishnamurthy S, Ashfaq R, Shin HJ, Sneige N. Distinction of phyllodes tumor from fibroadenoma: a reappraisal of an old problem. Cancer. 2000;90(6):342–9.
18. Mishra SP, Tiwary SK, Mishra M, Khanna AK. Phyllodes tumor of breast: a review article. ISRN Surg. 2013;2013:361469.
19. Jacobs TW, Chen YY, Guinee DG Jr, Holden JA, Cha I, Bauermeister DE, et al. Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision? Am J Clin Pathol. 2005;124(3):342–54.

20. Mituś JW, Blecharz P, Walasek T, Reinfuss M, Jakubowicz J, Kulpa J. Treatment of patients with distant metastases from phyllodes tumor of the breast. World J Surg. 2016;40(2):323–8.
21. Telli ML, Horst KC, Guardino AE, Dirbas FM, Carlson RW. Phyllodes tumors of the breast: natural history, diagnosis, and treatment. J Natl Compr Cancer Netw. 2007;5(3):324–30.
22. Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. Mod Pathol. 2016;29(3):259–65.
23. Jang JH, Choi MY, Lee SK, Kim S, Kim J, Lee J, et al. Clinicopathologic risk factors for the local recurrence of phyllodes tumors of the breast. Ann Surg Oncol. 2012;19(8):2612–7.
24. Lee AH, Hodi Z, Ellis IO, Elston CW. Histological features useful in the distinction of phyllodes tumour and fibroadenoma on needle core biopsy of the breast. Histopathology. 2007;51(3):336–44.
25. Van Osdol AD, Landercasper J, Andersen JJ, Ellis RL, Gensch EM, Johnson JM, et al. Determining whether excision of all fibroepithelial lesions of the breast is needed to exclude phyllodes tumor: upgrade rate of fibroepithelial lesions of the breast to phyllodes tumor. JAMA Surg. 2014;149(10):1081–5.
26. Lacroix-Triki M, Geyer FC, Lambros MB, Savage K, Ellis IO, Lee AH, et al. β-catenin/Wnt signalling pathway in fibromatosis, metaplastic carcinomas and phyllodes tumours of the breast. Mod Pathol. 2010;23(11):1438–48.
27. Burga AM, Tavassoli FA. Periductal stromal tumor: a rare lesion with low-grade sarcomatous behavior. Am J Surg Pathol. 2003;27(3):343–8.
28. Zhang Y, Kleer CG. Phyllodes tumor of the breast: histopathologic features, differential diagnosis, and molecular/genetic updates. Arch Pathol Lab Med. 2016;140(7):665–71.
29. Liu H. Application of immunohistochemistry in breast pathology: a review and update. Arch Pathol Lab Med. 2014;138(12):1629–42.
30. Tse GM, Lee CS, Kung FY, Scolyer RA, Law BK, Lau TS, et al. Hormonal receptors expression in epithelial cells of mammary phyllodes tumors correlates with pathologic grade of the tumor: a multicenter study of 143 cases. Am J Clin Pathol. 2002;118(4):522–6.