Management of the High-Risk Breast Lesion

5

Jared Linebarger, Jon Zellmer, and Monica Rizzo

Introduction

The clinical management of high-risk breast lesions is intellectually challenging, continually evolving over time and occasionally controversial. The evaluation of all breast conditions begins with a thorough history and physical exam, appropriate breast imaging, and cytologic or histologic evaluation when indicated. Percutaneous core needle biopsy (CNB) has become the diagnostic modality of choice for both palpable and non-palpable breast lesions when histologic assessment is desired [1–3]. In the treatment of breast cancer, preoperative diagnosis by CNB offers many advantages over open surgical biopsy. CNB provides preoperative clinical staging and tumor marker assessment, enables discussion of neoadjuvant options, and increases the rate of breast-conserving therapy. Yet, the majority of image-detected breast lesions are benign, and most patients who undergo a breast biopsy will not have a diagnosis of malignancy. When there is concordance among clinical history, physical examination, imaging, and needle biopsy pathology, CNB may obviate the need for surgery to prevent under- and overtreatment of patients. However, some CNB findings are considered "borderline" because the CNB reveals a nonmalignant diagnosis, but cancer might be present at the biopsy site, implying a sampling error. The management of these high-risk lesions may be variable among practitioners, and a need for consensus in management of many of these lesions exists. In a position statement in 2011, the American Society of Breast Surgeons (ASBrS) defined a subset of benign and borderline breast lesions discovered on CNB that are associated with an upgrade in diagnosis to malignancy when CNB is followed by surgical excisional biopsy.

These lesions will be described in this chapter and include:

- Atypical ductal hyperplasia (ADH)
- Lobular neoplasia (lobular carcinoma in situ and atypical lobular hyperplasia)
- Columnar cell lesions (hyperplasia or flat epithelial atypia)
- Papillary lesions
- Radial scar (complex sclerosing lesions)
- Fibroepithelial lesion (with or without cellular stroma)

J. Linebarger, MD
Department of General Surgery, Gundersen Health System, La Crosse, WI, USA

Norma J Vinger Center for Breast Care (NJVCBC), La Crosse, WI, USA
e-mail: jhlineba@gundluth.org

J. Zellmer, MD
Department of Medical Education, Gundersen Lutheran Medical Foundation (GLMF), La Crosse, WI, USA
e-mail: jdzellme@gundluth.org

M. Rizzo, MD, FACS (✉)
Division of Surgical Oncology, Department of Surgery, Emory University School of Medicine, Winship Cancer Institute, 550 Peachtree Street, 9th floor, Atlanta, GA 30308, USA
e-mail: monica.rizzo@emory.edu

A.I. Riker (ed.), *Breast Disease: Comprehensive Management*,
DOI 10.1007/978-1-4939-1145-5_5,

- Mucocele-like lesion
- Spindle cell lesion

The upgrade rate to ductal carcinoma in situ (DCIS) or invasive ductal carcinoma (IDC) when a borderline breast lesion in diagnosed on CNB is summarized in Table 5.1.

Patient counseling following identification of a borderline breast lesion must take into account an assessment of concordance between the clinical suspicion and CNB result, an estimation of the risk and implications of associated lesions of greater clinical significance (such as malignancy), and knowledge of the natural history of the specific high-risk lesion identified. The Gail risk model, along with other risk assessment models, has been increasingly used to estimate future breast cancer risk based on the results of breast biopsy [21, 22]. Utilizing the Gail model in clinical trial enrollment, the NSABP P-1 study first showed a significant reduction in the incidence of breast cancer in women at higher risk, including those with ADH and lobular neoplasia, when tamoxifen therapy was administered. Subsequently, risk assessment along with individual care plans for borderline breast lesions has become standard of care [23, 24]. In the clinical management of borderline breast lesions today, risk assessment assists in informing appropriate follow-up, prevention, and screening discussions, including the use of breast MRI [25]. When these high-risk lesions are identified by CNB, management may include structured observation, repeat CNB, or surgical excision, and the chosen care pathway must represent a practice of informed discussion with the patient and shared decision-making.

Table 5.1 Summary of the upgrade rate (%) to ductal carcinoma in situ (DCIS) or invasive ductal cancer (IDC) or invasive lobular carcinoma (ILC) when a borderline breast lesion is diagnosed on core needle biopsy (CNB) and followed by surgical excision

Borderline breast lesio(ns diagnosed on core needle biopsy	Upgrade to malignancy DCIS (%)	Upgrade to malignancy IDC (%)	Increase relative risk of breast ca
ADH [4–7]	30–40	20	4–6
Lobular neoplasia			
ALH [8, 9]	20*		4–5
LCIS [8, 9]	30*		8–12
pLCIS [8, 10, 11]		40–60 (ILC)	
Columnar cell lesions			
CCH with atypia [4, 5, 12]	25–33*		
FEA [13, 14]	9–15*		
Papillary breast lesion			
Intraductal papilloma (IDP) [15]	8*		
Radial scar [10, 16, 17]	5–9*		1.8–3
Mucocele-like lesions [18–20]	18–30**		

ADH atypical ductal hyperplasia, *ALH* atypical lobular hyperplasia, *LCIS* lobular carcinoma in situ, *pLCIS* pleomorphic lobular carcinoma in situ, *CCH* columnar cell hyperplasia, *FEA* flat epithelial atypia
The numbers in superscript in the first column indicate the bibliographic reference. The asterisk sign * indicates the % of upgrade to DCIS and IDC combined. ** includes also the % of upgrade to ADH

Atypical Ductal Hyperplasia (ADH)

Atypical ductal hyperplasia (ADH) is described as a breast lesion involving the epithelial cells within the ductal system that is felt to be not only a precursor on the continuum from normal breast tissue to breast carcinoma but also a risk factor for future breast cancer. The model for a linear progression from hyperplasia to invasive breast carcinoma was initially described by Wellings and Jensen [26]. This model proposes a natural progression along a histologic continuum through an accumulation of molecular changes, ultimately resulting in an invasive phenotype. Flat epithelial atypia (FEA), ADH, and DCIS are accepted as the non-obligate precursors to invasive ductal carcinoma. This model is supported by morphologic, immunohistochemical, and transcriptional profiling data [27]. For example, ADH is described as a ductal epithelial lesion containing some, but not all, of the features of DCIS. A diagnosis of ADH on CNB is complicated by its similar

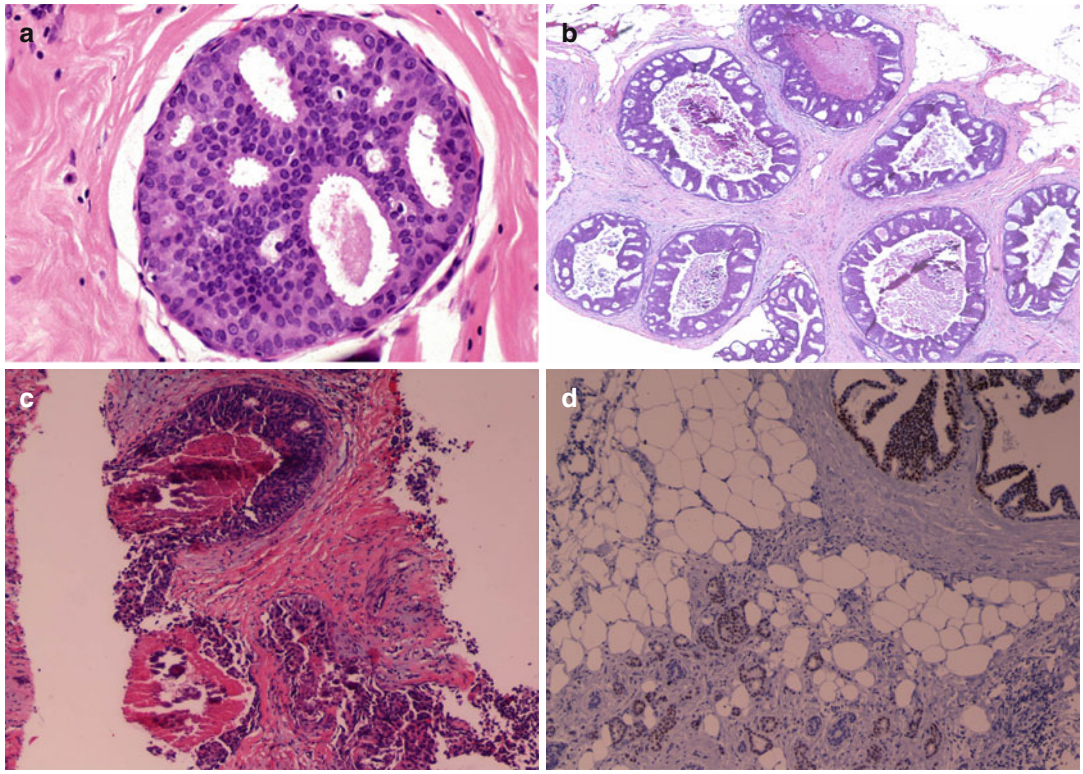

Fig. 5.1 (**a**) Single duct with monotonous, atypical, but uniform epithelial cells which partially or completely fill the ductal spaces with maximal dimension of 2 mm consistent with ADH. If more ducts like this present or expanded duct measures more than 2 mm, then it qualifies as low-grade cribriform DCIS. (**b**, **c**) DCIS with central comedo necrosis and calcification in the middle, in purple. (**d**) Cribriform DCIS (upper right) and invasive ductal carcinoma both strongly positive with nuclear estrogen receptor (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

appearance to low-grade DCIS, with only quantitative differences.

Typically, ADH is detected by screening mammography as microcalcifications in an asymptomatic patient, and ADH represents 10 % of radiographically detected lesions [4]. Morphologically, a diagnosis of ADH requires atypical but uniform epithelial cells which partially or completely fill the ductal spaces, with a maximal dimension of 2 mm for each focus, distinguishing it from low-grade DCIS [5, 10, 28] (Fig. 5.1a, b). Due to the limited tissue sampling with CNB and the varied benign and malignant lesions associated with ADH, a diagnosis of ADH by CNB has a well-recognized potential for coexistent DCIS or invasive cancer that is related to sampling size [28] (Fig. 5.1c, d). Furthermore, FEA, ADH, and DCIS have been shown to display similar genetic alterations and chromosomal aberrations, such as loss of 16q, and progression to invasive cancer has been proposed to occur along potentially multiple such pathways through the acquisition of genetic alterations under selective pressure [27]. As a result, ADH is commonly found to be coexistent in the setting of other high-risk breast lesions as well as DCIS and invasive carcinoma [5, 10, 28].

At the same time, ADH also represents a marker for elevated risk of future cancer. Even in the absence of synchronous associated malignancy, a diagnosis of ADH incurs at least a four to five times relative risk of subsequent breast cancer diagnosis, perhaps as high as sixfold in premenopausal women [6]. This increased risk is evident in both the ipsilateral and contralateral breast [4, 7]. When malignancy is found in a surgical excision

following a CNB diagnosis of ADH, an "upgrade" in diagnosis is said to have occurred. A wide range of upgrade percentages have been reported in the literature, with rates as low as 4 % and as high as 87 % [5]. One of largest recent retrospective studies looking at 422 CNB diagnoses of ADH reported an upgrade percentage of 31.3 %, with the majority upgrading to DCIS (22.7 %) [7].

Additionally, the presence of multiple radiographic foci of ADH has been shown to increase the rate of associated malignancy identified if excisional biopsy is subsequently performed (7 % for 1–2 foci vs. 39 % for >2 foci) [4]. In addition to discussion of the risk of concurrent malignancy, management of ADH must also include an estimation of the implied relative risk for future diagnosis of breast cancer. Lifestyle modifications, including avoiding risk factors such as prolonged use of hormone replacement therapy and increasing protective factors such as low fat diet and exercise, are believed to impart a modest risk reduction for development of future breast cancer. The original report of the breast cancer prevention trial, NSABP P-1, in 1998 [23] established the efficacy of tamoxifen use in reducing the risk of future breast cancer in patients with above-average risk by almost 50 %. Importantly, ADH patients in this trial received the most benefit, reducing risk of cancer by 86 %. Meanwhile, prophylactic surgery for the diagnosis of ADH alone is controversial [29, 30]. In summary, when ADH is identified by CNB, excision should be strongly considered in order to evaluate for coexistent malignancy. When malignancy is not identified following excision, informed discussion should include an estimation of future risk of malignancy as well as an acceptable plan for surveillance and risk reduction, including lifestyle modifications and chemoprevention with hormonal therapy.

Lobular Neoplasia: Atypical Lobular Hyperplasia (ALH) and Lobular Carcinoma In Situ (LCIS)

Lobular proliferative lesions include atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). LCIS was first describe by Ewing in 1919, and later the term lobular neoplasia (LN) was coined by Haagensen in 1978 to encompass both ALH and LCIS [31]; however, the term has not gained universal acceptance. Linear progression models for lobular breast changes are less well studied than their ductal counterpart, although some recent genetic and molecular studies have displayed similar genetic changes in ALH and LCIS with both IDC and invasive lobular carcinoma (ILC) [27]. LN represents a continuum from ALH to pleomorphic LCIS (pLCIS), the most aggressive subtype of LCIS [8]. LN is characterized by atypical epithelial cells with intraepithelial lobular proliferation of terminal duct-lobular units with differing degrees of filling and atypia. ALH and LCIS can be distinguished by the amount of acini involvement. LCIS is diagnosed by acini involvement of more than half with no central lumina where ALH has less than half of the acini affected [8, 10] (Fig. 5.2a, b). When unable to differentiate ductal versus lobular features, particularly important in the pleomorphic variant, the cellular adhesion molecule E-cadherin is utilized. Negativity for E-cadherin is a hallmark molecular feature of lobular histology (Fig. 5.2c, d).

Pleomorphic LCIS, which can be thought of as a separate entity due to its aggressive natural history, is distinguished by its approximately four-times larger nuclei and significant nuclear pleomorphism. Although LCIS and pLCIS are normally ER/PR positive (pLCIS can be negative), and E-cadherin negative, pLCIS may show HER2 overexpression, p53 positivity, and an elevated Ki67 index compared with LCIS. pLCIS also shows similarities to DCIS with occasional chromosomal deletions and ontogenesis. These features have significant implications when evaluating upgrade percentage and breast cancer risk with pLCIS, which is universally considered as a precursor lesion to breast cancer [8, 10]. LN is typically an incidental diagnosis without specific physical exam or radiographic findings, although it may be associated with microcalcifications in the pLCIS subtype. When LN is diagnosed, up to 85 % are multicentric and 50 % are multifocal, with up to one third with LN identified in the contralateral breast [4, 10].

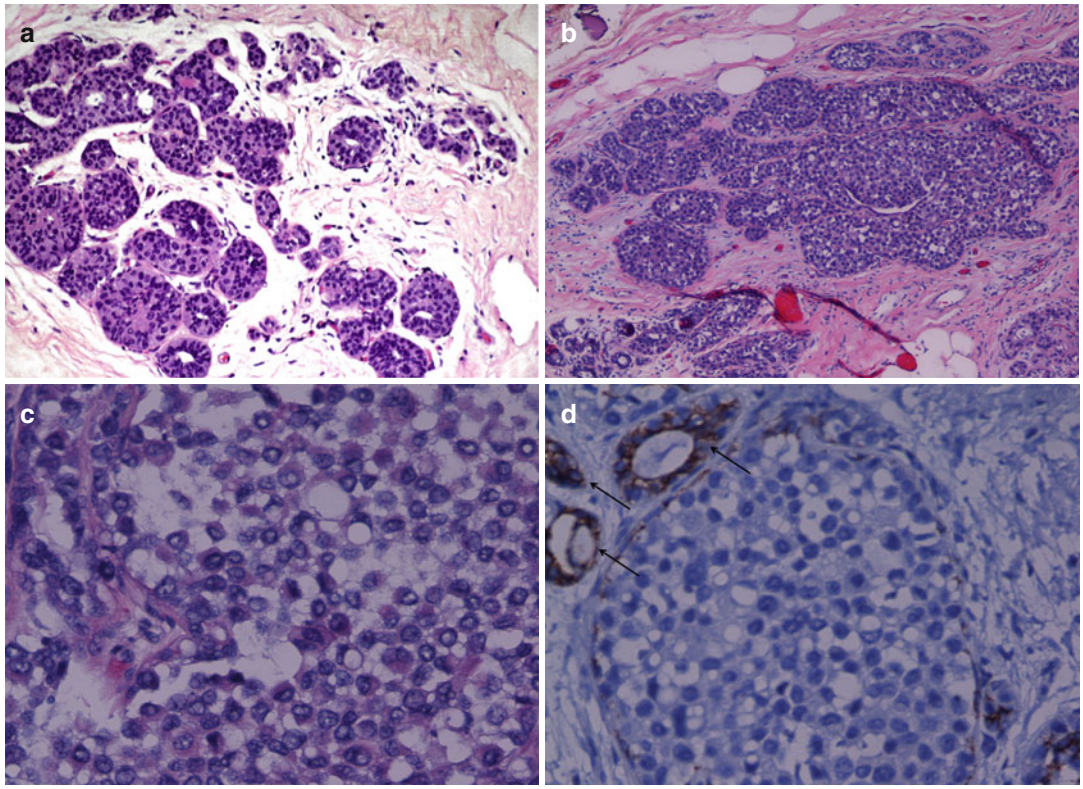

Fig. 5.2 (**a**) Atypical lobular hyperplasia ALH with mildly expanded lobules with monotonous smaller cells, not enough for LCIS. (**b**) Lobular carcinoma in situ. Extended lobules filled with small dyscohesive uniform cells. There is a feel of "bag of marbles," and if you were to turn the slide upside down, the marbles would fall out, different from DCIS where cells usually are more tightly packed. (**c**) Lobular carcinoma in situ: at higher power, the dyscohesiveness of the LCIS cells. (**d**) E-cadherin, membranous stain, not staining LCIS but staining adjacent ducts (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

LN has classically been considered a marker of future breast cancer risk, and not a precursor lesion, and management is still somewhat controversial, particularly in cases without a radiographic abnormality. The average age for the diagnosis of LN is between 44 and 47 years. It is 12 times more common in white than black patients [32]. The relative risk for the development of breast cancer in a patient diagnosed with LN is four- to fivefold for ALH and about eight- to ninefold for LCIS [9]. With LCIS, the cumulative risk of ipsilateral and contralateral breast cancer is similar (18 % and 14 %, respectively) with 40 % being ILC and 60 % IDC [11]. When excised, an upgrade in diagnosis from LN to malignancy is reported to occur at rates ranging from 0 to 50 % [8]. This wide range is likely related to the limited radiographic findings, variable indications for excision, and inherent differences between the subtypes of LN. A recent meta-analysis of over 1,200 LN patients displayed upgrade percentages of 19 % of the ALH cases, 32 % of the LCIS cases, and 41 % (40–60 % in the literature) of the pLCIS cases [8].

Management of LN diagnosed by CNB must start with an assessment of clinical and pathologic concordance, as the diagnosis of LN often is not related to the underlying clinical findings. LN typically presents with limited suggestive history or exam and imaging findings (excluding the pLCIS subtype), indicating a need to consider the possibility of misdiagnosis following CNB and the possibility for alternative diagnoses following

any proposed excision. Management of pLCIS is unique from management of LN in general. Due to its high associated underlying risk of invasive lobular carcinoma of about 40–60 %, it is considered a precursor lesion, and excision with negative margins should be recommended in all patients when seen on CNB.

For the remaining LN lesions, surveillance may be appropriate when another concordant benign pathologic lesion, such as a fibroadenoma, is identified in the CNB specimen. Repeat biopsy or surgical excision may be considered appropriate in the setting of clinical-pathologic discordance, identification of another associated high-risk lesion, or presence of unusual histologic features such as mitoses or necrosis. In such instances, underlying DCIS and invasive carcinoma are more likely to be identified [5]. Compared to the general population, ALH carries 4- to 5-fold and LCIS 8- to 12-fold greater lifetime risk of developing invasive cancer [33, 34]. When ALH or LCIS is diagnosed, an informed discussion must also include an established plan for surveillance, including possible MRI, lifestyle modifications, chemoprevention with hormonal therapy, and bilateral prophylactic mastectomy.

Columnar Cell Lesions: Flat Epithelial Atypia and Columnar Cell Hyperplasia with Atypia

Columnar cell lesions (CCLs) were first described in the literature in 1979 [35, 36] as "monomorphic clinging carcinoma in situ," and the term flat epithelial atypia (FEA) was more recently recognized by the World Health Organization to describe CCLs with atypia. The overall incidence of finding CCLs by CNB has been increasing recently with a current prevalence of 3.7–10 % [13]. CCLs are not normally diagnosed on physical exam, but radiographically they can be associated with pleomorphic calcifications [4]. Histologically, CCLs are characterized by enlarged terminal ductal-lobular units with dilated acini lined with columnar cells and with associated apical snouts. Columnar cells are epithelial cells that are columnar in shape, giving them their name (Fig. 5.3a, b). Elongated nuclei and intraluminal secretions are also noted. Cytologically, CCLs are composed of similar progenitor cells to ADH and DCIS and include a spectrum of lesions, including columnar cell change (CCC), columnar cell hyperplasia (CCH), and FEA. As previously discussed, these lesions, particularly FEA, are felt to be early in the spectrum from normal breast tissue to carcinoma. CCC is distinguished by having only two layers of cells, without atypia, lining the ductal components, while CCH exhibits greater than 2 layers of cells, and FEA displays associated atypia (Fig. 5.4a, b).

A grading system (low, medium, high) has been proposed to describe the degree of atypia noted [10, 13]. ADH is distinguished from columnar cell lesions (CCLs) by the degree of cytonuclear atypia and abnormal architecture [13]. The majority of CCLs display ER/PR positivity. While considered benign lesions, CCLs have a known association with other high-risk benign lesions and malignancy. The diagnosis of CCLs may possibly represent a risk factor for and/or early precursor to carcinoma, although this is yet to be proven [5, 13, 27]. When excised, CCLs with atypia are found to occur concurrently with other high-risk benign lesions 25–33 % of the time, with associated ALH and ADH being identified at a rate of 5 and 3.5 %, respectively [4, 5, 12].

Additionally, the reported rate of upgrade in diagnosis to in situ or invasive cancer following excisional biopsy for CCLs has been reported at rates ranging from 0 to 26 %. These rates have been shown to be significantly higher for CCH (20 %) and FEA (9 %) when compared to CCC; however, the true rate of associated malignancy is difficult to estimate, as many lesions are managed without excision [13, 14]. In practice, the management of CCH and FEA often differs from the management of CCC based on the described disparity in associated risk. Surgical excision should be presented as the preferred management whenever CNB of a breast lesion yields a diagnosis of CCH or FEA. Occasionally, continued surveillance is also discussed with patients in the setting of

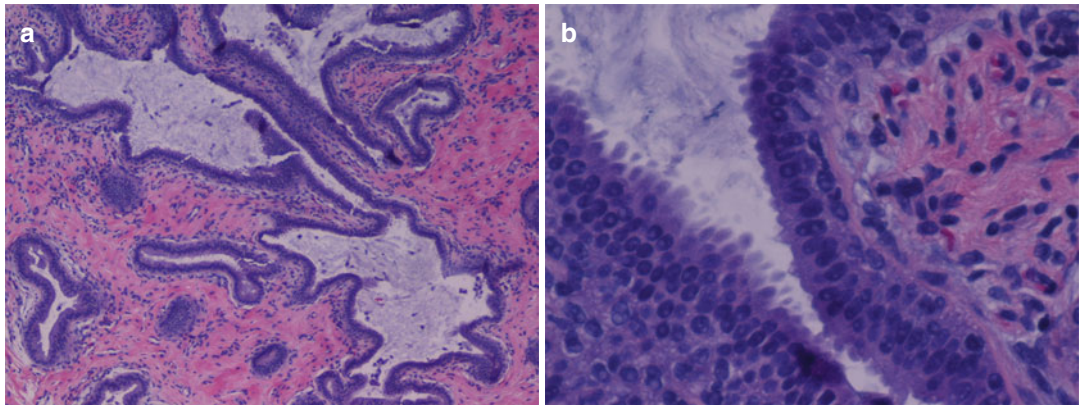

Fig. 5.3 (**a**, **b**) Columnar cell lesions are characterized by enlarged terminal ductal-lobular units with dilated acini lined with columnar cells and with associated apical snouts. Columnar cells are epithelial cells that are columnar in shape, giving them their name (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

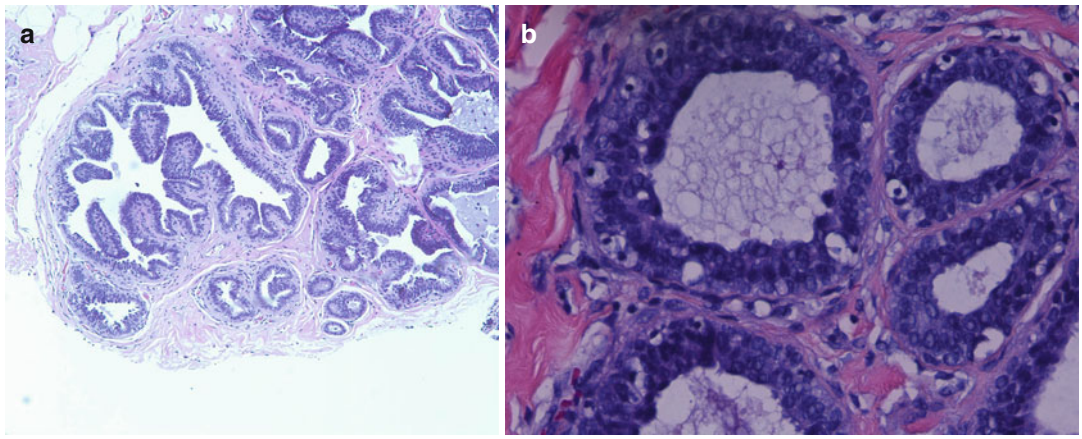

Fig. 5.4 (**a**) Columnar cell hyperplasia. Cysts lined by orderly columnar cells with minimal atypia. (**b**) Flat epithelial atypia (FEA) cysts lined by pseudostratified slightly disordered larger atypical cells (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

an informed discussion. Interval clinical and imaging follow-up is more often practiced following a CNB diagnosis of CCC.

Papillary Lesions

Papillary breast lesions (PBLs) span a wide pathologic spectrum ranging from benign to malignant and include intraductal papilloma (IDP), atypical papilloma, intracystic papillary carcinoma, and invasive papillary carcinoma. PBLs present with a diverse clinical behavior and radiographic presentation. Radiographically, PBLs can present as architectural distortion, asymmetric density, and occasionally a palpable breast mass with or without associated microcalcifications, or microcalcifications alone. However, mammography and ultrasonography cannot reliably distinguish benign from malignant PBLs [37]. The hallmark of PBLs is the formation of papillary structures composed of two layers of cells, one epithelial and one myoepithelial, on a fibrovascular core (Fig. 5.5a–c). Distinguishing among the spectrum of papillary lesions, such as an atypical papilloma versus DCIS arising within a papilloma, can be very challenging for the pathologist. Additionally, other proliferative lesions can

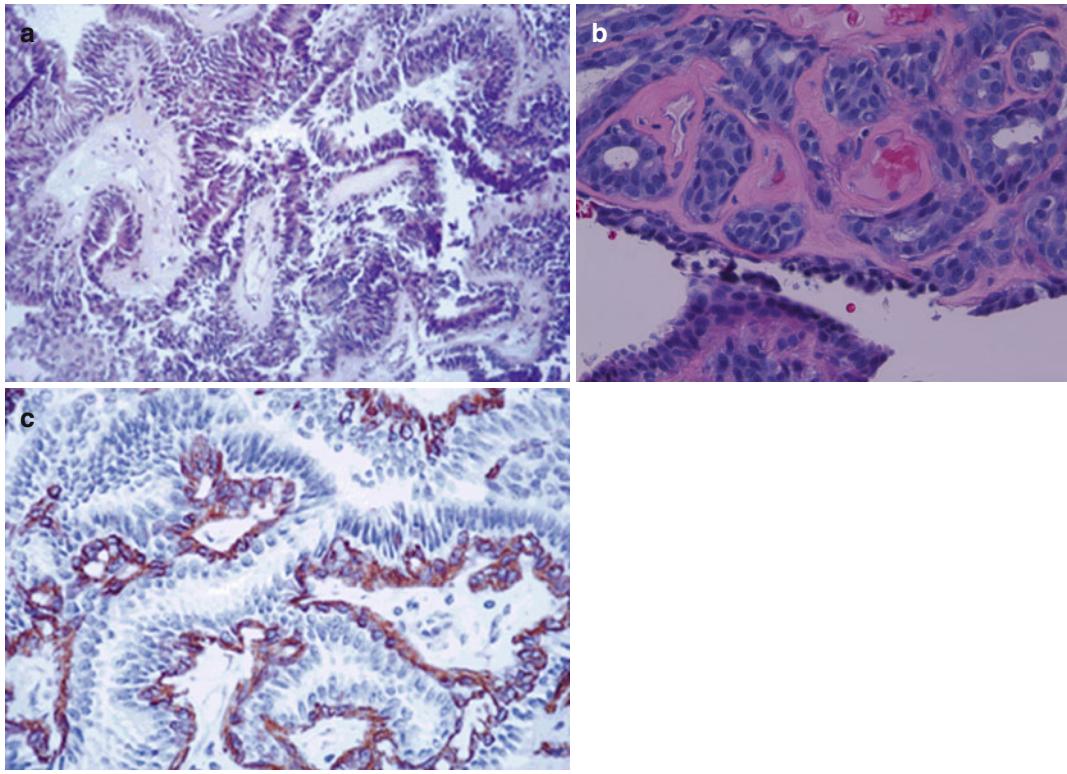

Fig. 5.5 (**a**, **b**) Benign intraductal papilloma (IDP) of the breast showing fibrovascular cores lined by two distinct layers of cells, myoepithelial cells and ductal cells. (**c**) Calponin stain (×400) specifically delineates myoepithelial cells in a benign IDP (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

be present at the periphery of the suspicious mass or area, further complicating the diagnosis.

Moreover, the accurate diagnosis on CNB can be difficult because of fragmentation, limited material, sampling error, or presence of other nonneoplastic proliferations, such as florid papillomatosis, radial sclerosing lesions (RSLs), and micropapillary hyperplasia [10]. Yet, as percutaneous stereotactic or ultrasound-guided CNB has been used increasingly in the diagnosis of clinically occult and palpable breast lesions, recent data have suggested that benign papillary lesions (mainly IDPs) can be diagnosed accurately by CNB [38, 39]. In spite of the inherent limitations of CNB, papillary lesions account for approximately 5–10 % of all CNBs, and the subsequent decision about clinical treatment is now based largely on the CNB diagnosis [40, 41].

A number of studies have been published on the management of atypical papillary lesions, inclusive of IDP with atypia or IDP with associated ADH, with most recommending surgical excision based upon the increased risk of associated DCIS and invasive carcinoma [37, 40–42]. In contrast to atypical papillary lesions, the management of benign IDP remains controversial, with no clear consensus on the optimal approach to management. The reported incidence of finding a more advanced lesion (ADH, DCIS, and invasive carcinoma) on follow-up excisional biopsy after the diagnosis of benign IDP on CNB ranges from 0 to 25 % [43]. In one retrospective review [44] of 276 consecutive cases of IDP undergoing surgical excision, there was a clear higher rate of upgrade in diagnosis to DCIS/IDC when compared to isolated IDP, 33 %/5 % vs. 8 %/1 %, respectively. For isolated IDP, an 18 % upgrade in diagnosis to ADH was also noted. Therefore, even when CNB demonstrated benign IDP, an upgrade in diagnosis to a lesion of greater clini-

cal significance was demonstrated 27 % of the time following excisional biopsy [44]. While the clinical significance of identifying IDC/DCIS is appreciated, an upgrade in diagnosis to a benign lesion such as ADH can have significant patient management implications. Surgical excision is the current recommendation considered as optimal management for all breast papillary lesions identified on CNB.

Radial Sclerosing Lesions: Radial Scar and Complex Sclerosing Lesions

Radial sclerosing lesions (RSLs) of the breast are a group of benign, stellate-appearing breast lesions, with the incidence of radial scars identified on CNB ranging from 4 to 26 %. These lesions have been referred to by several different names, including scleroelastotic lesion, indurative mastopathy, nonencapsulated sclerosing lesion, and sclerosing papillary proliferation [45]. RSLs are often categorized by size as either radial scar (<1 cm) or complex sclerosing lesion (>1 cm). These lesions can have a clinical and radiologic presentation as well as gross pathologic appearance resembling that of carcinoma [10]. Typically, patients diagnosed with RSLs have no particular exam or imaging findings, and RSL is often an incidental finding on CNB biopsy for another concordant abnormality. However, patients may also present with a palpable breast mass. Mammographic findings, when present, usually display a spiculated lesion with dense radiolucent cores and thin spicules radiating out from the core, which can be nearly impossible to distinguish from carcinoma [15, 46] (Fig. 5.6a, b). Histologically, RSL are characterized by fibroelastotic cores with ducts and lobules radiating centrifugally with typical or atypical epithelial proliferative changes or cysts [10, 15, 45].

The clinical significance of RSLs lies in both the implicit associated increase risk of developing breast cancer in the future and the associated risk of concurrent malignancy. The relative risk increase imparted by a diagnosis of RSL ranges from 1.8 to 3 [47, 48], and a diagnosis of associated malignancy following excision has been reported at a rate of 0–40 % [10]. Due to the similarities in clinical appearance to carcinoma and the potential risk of associated breast cancer, RSLs have traditionally been treated with excisional biopsy. The more recent literature showing percutaneous underestimation rates of malignancy in the 5–9 % range makes management more complex, with options for surveillance seeming more acceptable, particularly in higher operative risk or multiply-comorbid patients [15, 46]. The absence of cytologic atypia, increased number of cores taken at the time of CNB, and extensive sampling with vacuum-assisted needle biopsy have all been described as methods to identify patients that may safely be monitored. However, no clear clinical radiographic predictors have been identified to determine lesions at increased risk for associated malignancy, and surgical excision recommendations should be made independent of imaging findings [45]. For most patients of acceptable operative risk, optimal management continues to be complete surgical excision.

Fibroepithelial Lesions with Cellular Stroma

Fibroepithelial tumors of the breast represent a varied group of lesions containing both mesenchymal and epithelial components. The epithelial elements contain Ck5/14-positive progenitor cells with their glandular and myoepithelial progeny, whereas the stromal component shows vimentin/CD34 positivity with potential for multi-lineage differentiation as seen in spindle cell lesions of the breast [16, 17]. The proliferation of fibroepithelial elements along divergent pathways gives rise to fibroadenomas, phyllodes tumors, sclerosing lobular hyperplasia, and hamartomas.

Fibroadenoma is the most common benign breast tumor and clinically presents as a palpable mass or as an abnormal imaging finding. Lesions may be identified in women at any age, typically presenting during early adolescence, with a mean age of 30 at presentation. Multiple

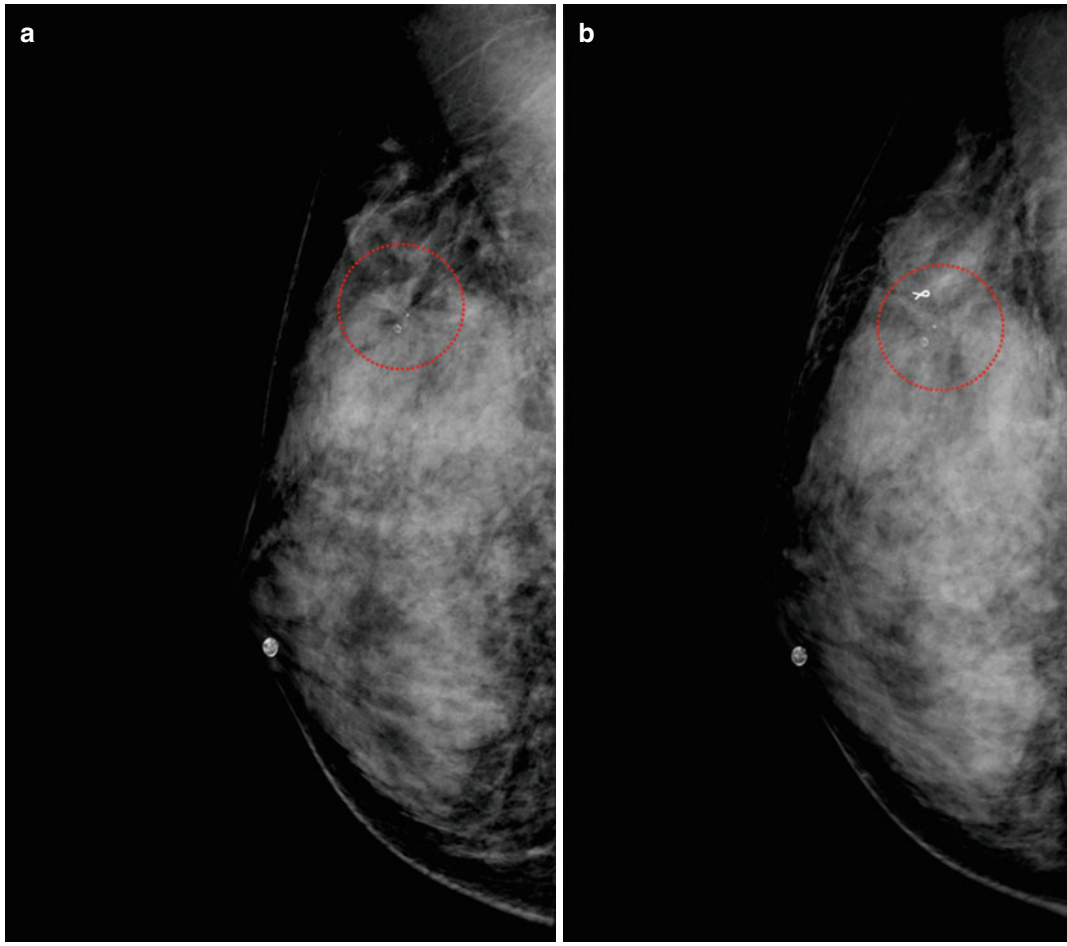

Fig. 5.6 Forty-three-year-old asymptomatic female presenting with an abnormal screening mammogram showing architectural distortion (*circle*) with radiating spicules (**a**). She underwent ultrasound-guided core needle biopsy with clip placement. Pathology from the core needle biopsy showed a radial scar (**b**) (Courtesy Dr Michael Cohen Emory University Atlanta)

fibroadenomas can be identified at presentation approximately 15 % of the time. When palpable, fibroadenomas are typically small, smooth, mobile, and firm or rubbery masses with >90 % smaller than 4 cm. Fibroadenomas may develop into very large masses particularly in adolescent girls and young women, often called juvenile giant fibroadenomas (Fig. 5.7a, b) [49]. On mammography, fibroadenomas appear as well-defined round, oval, or lobulated masses, which may be calcified. On ultrasound, fibroadenomas are well-circumscribed, uniform hypoechoic or isoechoic ovoid masses, and the lesions are typically wider than tall with a well-demarcated margin [50].

Fibroadenomas arise from the epithelium and stroma of the terminal duct-lobular unit, with pathologic findings typically revealing well-defined borders consisting of elongated ducts lined with two layers of epithelium and situated in a stroma with low cellularity. When the diagnosis is made by CNB, a decision must be made whether to monitor or excise the lesion. In rare cases, fibroadenomas can progress in both epithelial and stromal directions to malignant tumors [51]. However, most fibroadenomas tend to be self-limited or even regress, and it is not necessary to remove them all, while percutaneous excisional or ablative treatment may be appropriate in select patients as defined recently by the ASBrS. Size

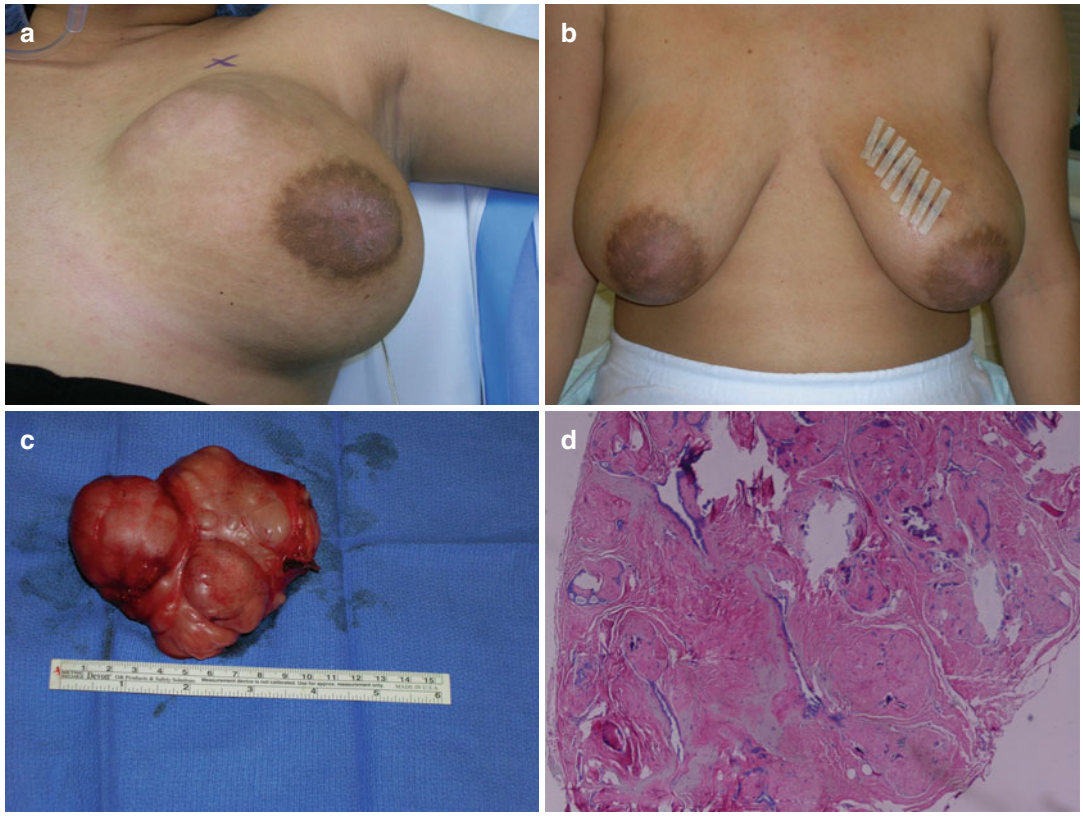

Fig. 5.7 Juvenile giant fibroadenoma of the breast. (**a**) Eighteen-year-old female at presentation. (**b**) One week after surgery. (**c**) Surgical specimen 12×11×8 cm. (**d**) Microscopically, the fibroadenoma showed mainly a hyalinized component (Courtesy of Monica Rizzo, MD and Marina Mosunjac, MD Emory University Atlanta)

(greater than 2.0–2.5 cm), growth, symptoms, positive family history, discordance, and age (greater than 35 years) are reasonable indications for surgical excision. It should be discussed that there is a potential for upgrade in the final pathologic diagnosis to a phyllodes tumor, in situ, or even invasive carcinoma in rare instances [51].

Phyllodes tumor is an exceedingly rare lesion with an estimated incidence of 2.1 per million women. Presentation typically occurs between the ages of 45 and 49, typically about 15 years later in age compared to fibroadenomas [52]. The presentation of a phyllodes tumor is clinically indistinguishable from that of a fibroadenoma [53]. Phyllodes tumor is felt to arise from the perilobular-periductal stroma. Microscopically, a circumscribed lesion with mixed epithelial and mesenchymal components is seen with a double-layered epithelial component and overgrowth of a hypercellular stromal component. FNA and CNB typically cannot discriminate between fibroadenoma and phyllodes tumor; however, the diagnosis may be suggested [54, 55]. Several systems for grading of phyllodes tumors exist, and while many authors use a three-tiered system to distinguish between benign, borderline, and malignant cases, others omit the intermediate category [56, 57].

A benign phyllodes tumor is characterized as having few mitoses in a high-power field (HPF), <2 per 10 HPF; no more than mild atypia, and no stromal overgrowth. Borderline phyllodes tumor has 2–5 mitoses per 10 HPF, more atypia with no stromal overgrowth. Malignant phyllodes tumor has marked atypia, more than 10 mitoses per HPF and stromal overgrowth (Fig. 5.8a, b). The grading system reflects the clinical behavior, with local recurrence and rare metastases noted in benign cases and distant metastases more common in

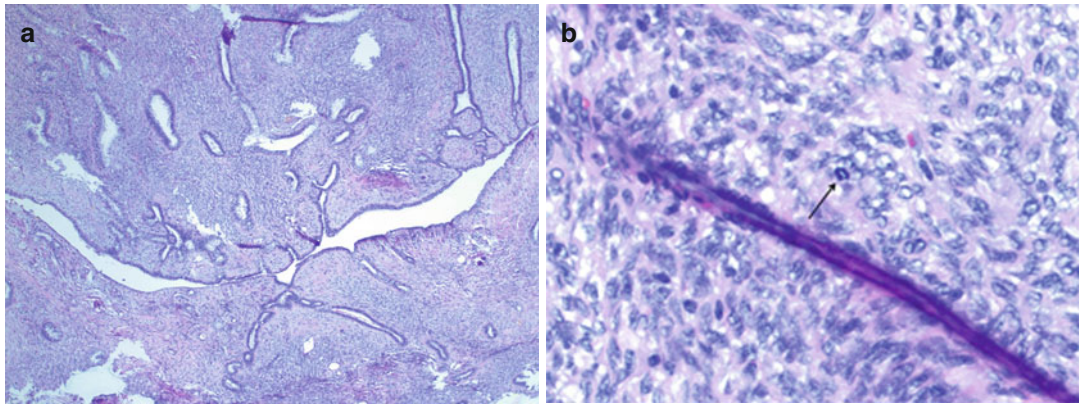

Fig. 5.8 (**a**) Phyllodes tumor. Ducts embedded into hypercellular stroma. (**b**) Stroma contains mitoses (*arrows*) (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

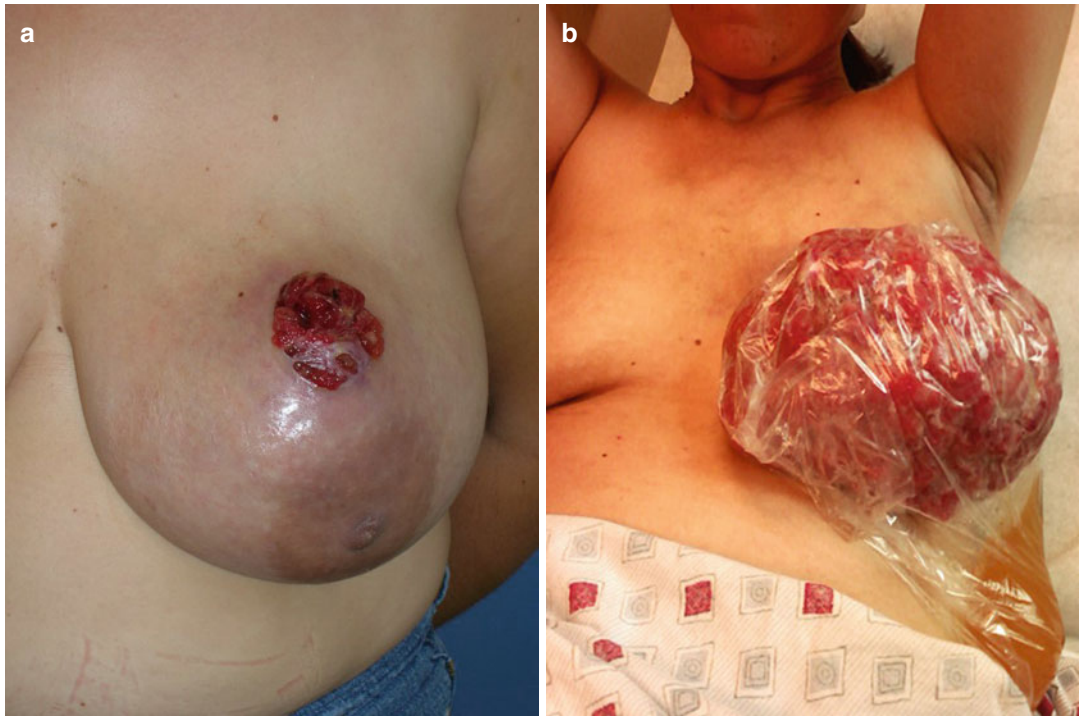

Fig. 5.9 Malignant phyllodes tumor. The patient refused surgical treatment when originally diagnosed (**a**). She developed a large ulcerated growth over 3 years (**b**) (Courtesy of Monica Rizzo, MD Emory University Atlanta)

malignant cases. When phyllodes tumor is diagnosed by CNB, the ability to differentiate benign, intermediate, and malignant lesions is unreliable [56]. Wide local excision with the intent of removing >1 cm margins is the preferred treatment of a phyllodes tumor (Fig. 5.9a, b). There is a relatively high incidence of local recurrence, reported from 8 to 46 % in cases of positive surgical margins [57]. Often, the diagnosis of phyllodes tumor is not made until excisional biopsy has been performed. When excising a fibroadenoma, removal of a rim of normal breast tissue around the lesion is acceptable, in case an upgrade in diagnosis to a phyllodes tumor does occur.

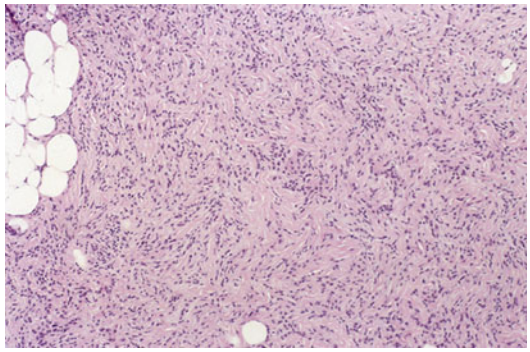

Fig. 5.10 Breast hamartoma. Microscopically, the tumor shows fibrous stroma with scattered ductal elements and adipose tissue on the left without any lobular units (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

Hamartomas and sclerosing lobular hyperplasia are rare benign fibroepithelial lesions with a nonspecific presentation that may be suspicious for fibroadenoma clinically and radiographically [58, 59]. While hamartomas are typically benign, malignant transformation has been rarely reported (Fig. 5.10). Hamartomas can occur at any age but are more common between the ages of 30 and 50 [60]. Diagnosis of hamartoma on CNB is problematic, with CNB results usually revealing benign breast tissue. Excisional biopsy to completely remove the lesion typically results in a very low local recurrence rate. However, they can be seen in high frequency in Cowden's syndrome and suggest an elevated lifetime risk of breast cancer [61]. Sclerosing lobular hyperplasia can be difficult to distinguish from fibroadenoma by needle biopsy, and excisional biopsy may be recommended for reasons identical to those considered in recommending excision of fibroadenoma. While the lesion itself is benign and does not require excision, the diagnosis often is only made upon complete surgical removal [59].

Mucocele-Like Lesions

Mucocele-like tumors of the breast were originally described by Rosen in 1986 [62] as an uncommon benign cystic lesion containing abundant mucin with extravasation into the surrounding stroma. Histologically, these lesions are difficult to distinguish from colloid carcinoma on fine-needle aspiration. At gross inspection, mucocele-like tumors are multicystic or multi-loculated, with multiple cysts in fibrous stroma seen by microscopy. Mucocele-like lesions of the breast may be identified on breast self-exam or on clinical exam as a palpable mass. Mammographically, they are identified in the setting of indeterminate microcalcifications, from dystrophic calcification of the mucin pool, or as a nodule. Sonographically, they appear to be hypoechoic lesions resembling complex cysts, and multiple oval or tubular structures with low-level internal acoustic echoes may be seen along with calcified or non-calcified mural nodules [63, 64] (Fig. 5.11a, b).

While originally reported as a benign lesion, a high incidence of associated ADH and carcinoma has subsequently been reported [65–67]. Weaver et al. postulated the existence of a pathologic continuum of mucinous breast lesions spanning the spectrum from benign mucocele-like tumor to invasive mucinous carcinoma. They examined a series of 23 consecutive invasive mucinous carcinomas of the breast for the association with intermediate mucinous lesions. The associated intermediate lesions included mucin-filled ducts (MFD) with unremarkable epithelium (65 %), MFD with typical ductal hyperplasia (39 %), MFD with atypical ductal hyperplasia (22 %), and MFD with intraductal carcinoma (57 %) [67]. The potential to reliably differentiate benign mucocele-like lesions from those with associated ADH or carcinoma based on imaging is unclear and continues to be studied [64, 68, 69]. When mucocele-like lesions are diagnosed on CNB, a high rate of upgrade in diagnosis to ADH or carcinoma continues to be reported in the literature, ranging from 18 to 30 % [69–71]. Due to concerns for sampling error, the high rate of coexistent lesions, and the unclear natural history, surgical excision following CNB diagnosis of a benign mucocele-like lesion of the breast represents optimal management.

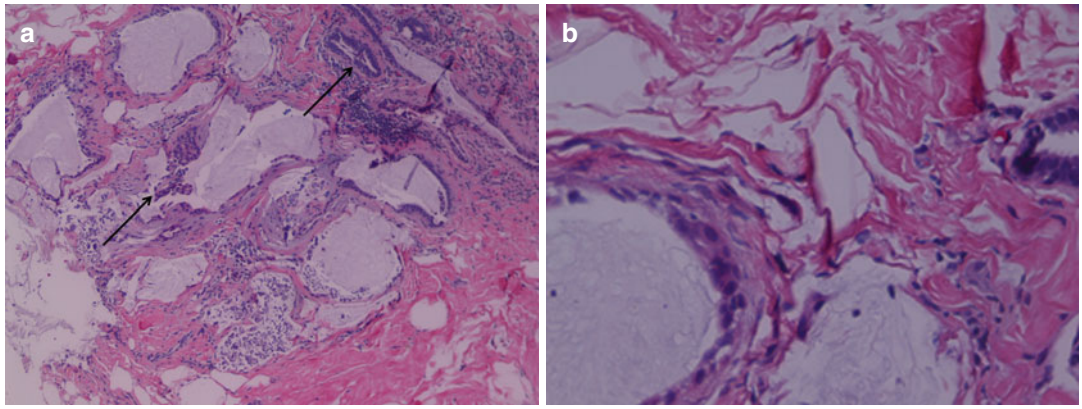

Fig. 5.11 (**a**) Mucocele-like lesion: large mucin-filled cysts focally disrupted and adjacent cysts with columnar cell change (*arrows*). (**b**) High power of mucocele-like lesion (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

Spindle Cell Lesions

While epithelial and fibroepithelial lesions comprise most of the proliferations arising within the breast, a diverse group of lesions displaying a predominantly monomorphic proliferation of spindle cells has been described as well. As with fibroepithelial lesions of the breast, such as fibroadenomas and phyllodes tumors, the putative precursor of these lesions is the uncommitted vimentin+/CD34+ fibroblast of the mammary stroma. It is capable of divergent mesenchymal differentiation, and the clinical behavior of these lesions can span a wide spectrum from benign to malignant [18, 19, 72].

Benign spindle cell tumors (BSCTs) of the mammary stroma were first described by Toker in 1981, [20] though consensus on the current nomenclature occurred much later. In the initial report of four cases, Toker et al. described the histologic relationship of these tumors to benign spindle cell lipomas, as well as the benign clinical history following complete excision [20]. A cytologically diverse population of fibroblasts, myofibroblasts, smooth muscle cells, and undifferentiated mesenchymal cells was noted, and the possibility of a common mesenchymal precursor was suggested [20]. Numerous case reports subsequently emerged in the literature, describing different unique benign spindle cell lesions of the breast with varied histologic and immunophenotypical permutations. Furthermore, these variations were noted not only among different tumors but also seen within the same tumor. Consequently, a multitude of designations, often used interchangeably, emerged in the literature to describe these benign monomorphic proliferations of bland-looking spindle cell lesions of the breast [17, 18, 73–76] including spindle cell lipoma, myofibroblastoma, solitary fibrous tumor, myogenic stromal tumor, and atypical variant of leiomyoma. A continuous morphologic and immunophenotypical spectrum resulting in lesions of subtle variable heterogeneity has been described, and the term "benign spindle cell tumor (BSCT) of the mammary stroma" has been advocated to cover the entire continuum of such lesions.

BSCTs of the mammary stroma have been divided into four main categories by light microscopy and immunocytochemistry: fibroblastic (benign spindle cell tumor NOS, benign spindle cell tumor with adipocyte component, solitary fibrous tumor), myofibroblastic (myofibroblastoma, leiomyoma), fibrohistiocytic (benign fibrous histiocytoma), and mixed tumors (components of the above) [18]. They clinically present as a one-sided, rounded, well-circumscribed, and slowly enlarging lesion during the course of several months. Mammography usually reveals a well-defined, ovoid dense mass in the absence of microcalcifications, although irregular

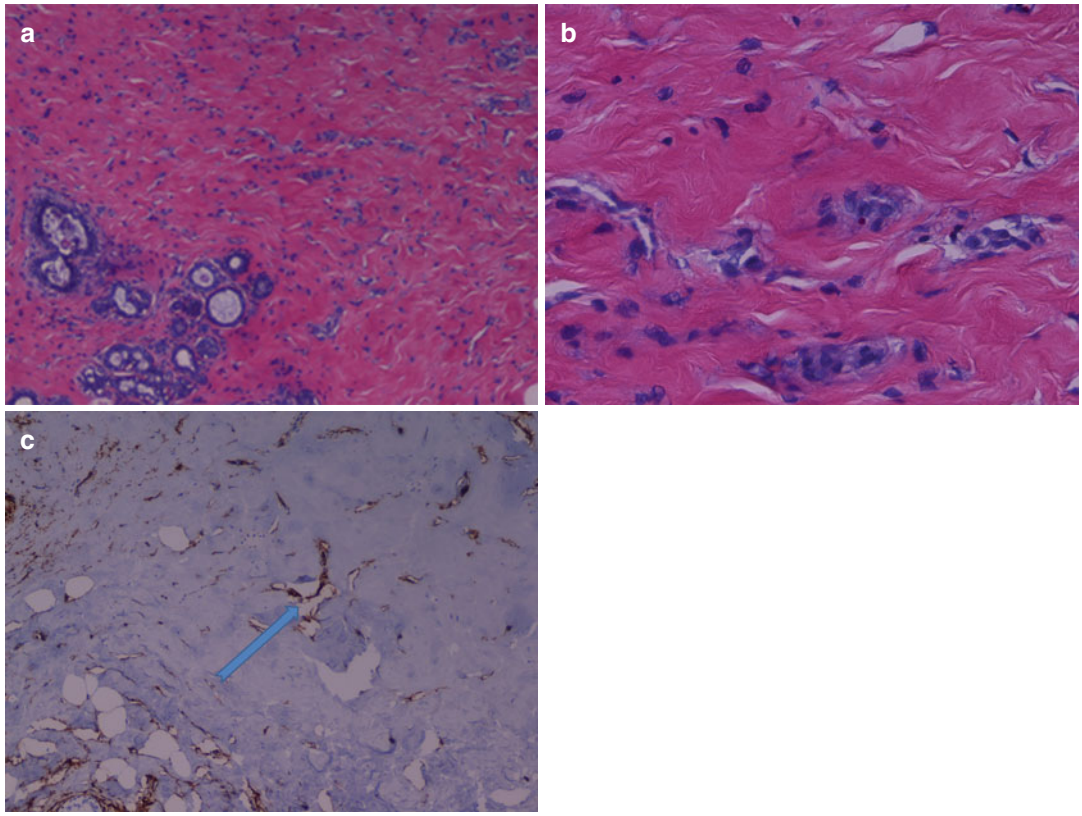

Fig. 5.12 Pseudoangiomatous stromal hyperplasia (PASH) consists of anastomosing slit-like spaces lined by myofibroblasts with intervening band-like segments of eosinophilic hyalinized stroma. Dense fibrotic (*pink*) tissue with slit-like (*white*) cracks and small vessels. (**a**, **b**) The spindle cell component is positive for CD34 (**c**, *arrow*) (Courtesy of Marina Mosunjac, MD Emory University Atlanta)

margins can infrequently be seen. Ultrasound findings may include a homogeneously solid and hypoechoic mass, with or without increased vascularity on Doppler sonogram [17].

By definition, BSCTs of the mammary stroma have a benign clinical course following surgical excision [17, 20]. However, the natural history of BSCTs observed following a diagnosis by CNB and rates of upgrade in diagnosis to a lesion of greater clinical significance are lacking in the literature. Toker et al. was the first to emphasize the importance of differentiating BSCT of the mammary stroma from other bland-looking monomorphic spindle cell lesions of the breast [20]. The differential diagnosis includes other benign but low-grade tumors and tumorlike lesions: pseudoangiomatous stromal hyperplasia (PASH), nodular fasciitis, primary mammary fibromatosis (PMF), and inflammatory myofibroblastic tumor (IMF).

PASH was first described by Vuitch et al. in 1986 [77] and was subsequently recognized as a common occurrence, found in one retrospective review in 23 % of biopsy and mastectomy specimens [78]. The age of diagnosis ranges from the late teens to the mid-50s. Microscopically, PASH consists of anastomosing slit-like spaces lined by myofibroblasts with intervening band-like segments of eosinophilic hyalinized stroma. The spindle cell component is positive for CD34 and vimentin, with morphology reminiscent of myofibroblastoma, and the absence of atypia or mitoses in the lobules and ducts helps to differentiate from borderline fibroepithelial lesions [19] (Fig. 5.12a–c). Infrequently, PASH may form a mass ("tumoral PASH") that is generally

non-tender, circumscribed, and nonencapsulated, and imaging findings may be concerning for malignancy [79].

Typically, tumoral PASH presents as a small lesion; however, tumors up to 12 cm and occupying much of the breast have been reported [80]. PASH is not recognized as being associated with synchronous malignancy, a premalignant lesion, or a pathologic finding suggestive of a higher risk of future malignancy [81]. No treatment is generally recommended for PASH unless it forms a mass, and the purpose of excision is generally to differentiate from fibroepithelial or spindle cell neoplasms. A selective approach to surgical excision is felt to be appropriate for enlarging or symptomatic lesions. Recurrence in the ipsilateral or contralateral breast is reported but rarely occurs [82].

Nodular fasciitis is a rare spindle cell lesion of the breast parenchyma or subcutaneous tissue that presents as an unencapsulated mass with expansile growth that typically displaces the adjacent ducts and lobules. This growth pattern may mimic invasion into the adjacent tissue, and the radiographic findings, which usually mimic that of a fibroadenoma, may also simulate invasive carcinoma. Microscopically, the spindle cells are arranged in short fascicles, and an inflammatory component is noted with microcystic degeneration and extravasated erythrocytes [18, 19]. The natural history of nodular fasciitis is not well understood, since most lesions are treated with excision; however, regression after FNA biopsy has been reported [83]. Nevertheless, excision is typically recommended to rule out lesions of greater clinical significance such as fibromatosis, metaplastic spindle cell carcinoma, fibromatosis-like carcinoma, and low-grade sarcoma. Rare local recurrence has been reported [18].

Primary mammary fibromatosis (PMF) is a spindle cell tumor identical to desmoid tumors occurring at other anatomic sites and is sometimes seen in association with familial adenomatous polyposis and Gardner's syndromes [84, 85]. The lesions almost always present as a firm, palpable, painless mass that often causes retraction of the skin or nipple, and the clinical presentation often mimics invasive carcinoma [19, 86]. Infrequently, the lesions may be initially detected by mammography, [87] which normally displays a stellate or spiculated tumor indistinguishable from carcinoma but devoid of calcifications [88]. Like desmoid tumors elsewhere, previous trauma has often been described at the site of mammary fibromatosis in some patients, but the incidence is infrequent for mammary lesions and the role of trauma or previous surgery in the pathogenesis is considered controversial [19, 86]. PMF may be diagnosed by CNB, and the histologic findings consist of spindle cells arranged in long and sweeping fascicles with variable amounts of fibrous stroma and an infiltrative pattern. While a benign lesion, PMF is locally aggressive and wide excision with negative margins is the optimal management [19, 86]. Local recurrence is more common in younger women and, in cases with positive margins, usually occurs within 3 years and may be disfiguring, be difficult to control, and spread to the chest wall. The role of sulindac or tamoxifen remains unclear in the management of PMF [86].

Inflammatory myofibroblastic tumor (IMT), also known as inflammatory pseudotumor of the breast, is a very rare low-grade spindle cell lesion of the breast that clinically and radiographically may mimic cancer. The lesion was first described by Pettinato et al. in 1988 as an extrapulmonary presentation of plasma cell granuloma of the breast [89]. Like other benign spindle cell lesions of the breast, IMT typically presents as a painless palpable breast mass. Mammographic findings may be suggestive of malignancy and include a high-density mass with irregular, spiculated margins and devoid of calcifications. Sonography typically shows a hypoechoic and heterogeneous solid mass with irregular margins [30, 90]. The benign diagnosis may be suggested on CNB and confirmed on excisional biopsy [89]. Histologic evaluation shows spindle to oval cells in a myxoid to fibrous keloid-like stroma with a marked component of plasma cells, lymphocytes, and eosinophils [18, 89, 90]. While benign, local recurrence and malignant transformation may occur, thus wide local excision is the optimal management [18, 30, 90].

Conclusion

The identification of a high-risk or borderline breast lesion on CNB may have implications regarding future breast cancer risk, screening and surveillance, breast cancer prevention, and surgery. The current lack of a consensus regarding the optimal management of many of the high-risk lesions continues to manifest itself in the medical literature. The position statement published by the American Society of Breast Surgeons in 2011 regarding the management of high-risk breast lesions and NCCN guidelines for "breast cancer screening and diagnosis" offer valuable advice in the management of these lesions. Repeat percutaneous CNB, surgical excision, and surveillance are all acceptable clinical management options in the appropriate clinical scenarios, and the relative merits of each alternative must be considered on a unique case-by-case basis. A multidisciplinary approach is optimal, and discussion of lesion associated risk and individual estimated risk is appropriate. Ultimately, clinical management must account for patient preferences, informed discussion, and shared decision-making between the patient and breast care providers.

References

1. Silverstein MJ, Recht A, Lagios MD, et al. Special report: consensus conference III. Image-detected breast cancer: state-of-the-art diagnosis and treatment. J Am Coll Surg. 2009;209(4):504–20.
2. Silverstein M. Where's the outrage? J Am Coll Surg. 2009;208(1):78–9.
3. Linebarger JH, Landercasper J, Ellis RL, et al. Core needle biopsy rate for new cancer diagnosis in an interdisciplinary breast center: evaluation of quality of care 2007–2008. Ann Surg. 2012;255(1):38–43.
4. Neal L, Tortorelli CL, Nassar A. Clinician's guide to imaging and pathologic findings in benign breast disease. Mayo Clin Proc. 2010;85(3):274–9.
5. Corben AD, Edelweiss M, Brogi E. Challenges in the interpretation of breast core biopsies. Breast J. 2010;16 Suppl 1:S5–9.
6. Pinder SE, Ellis IO. The diagnosis and management of pre-invasive breast disease: ductal carcinoma in situ (DCIS) and atypical ductal hyperplasia (ADH)–current definitions and classification. Breast Cancer Res. 2003;5(5):254–7.
7. Deshaies I, Provencher L, Jacob S, et al. Factors associated with upgrading to malignancy at surgery of atypical ductal hyperplasia diagnosed on core biopsy. Breast. 2011;20(1):50–5.
8. Hussain M, Cunnick GH. Management of lobular carcinoma in-situ and atypical lobular hyperplasia of the breast–a review. Eur J Surg Oncol. 2011;37(4):279–89.
9. O'Malley FP. Lobular neoplasia: morphology, biological potential and management in core biopsies. Mod Pathol. 2010;23 Suppl 2:S14–25.
10. Masood S, Rosa M. Borderline breast lesions: diagnostic challenges and clinical implications. Adv Anat Pathol. 2011;18(3):190–8.
11. Fentiman IS. 8. The dilemma of in situ carcinoma of the breast. Int J Clin Pract. 2001;55(10):680–3.
12. Verschuur-Maes AH, van Deurzen CH, Monninkhof EM, van Diest PJ. Columnar cell lesions on breast needle biopsies: is surgical excision necessary? A systematic review. Ann Surg. 2012;255(2):259–65.
13. Sudarshan M, Meguerditchian AN, Mesurolle B, Meterissian S. Flat epithelial atypia of the breast: characteristics and behaviors. Am J Surg. 2011;201(2):245–50.
14. Verschuur-Maes AH, de Bruin PC, van Diest PJ. Epigenetic progression of columnar cell lesions of the breast to invasive breast cancer. Breast Cancer Res Treat. 2012;136(3):705–15.
15. Bianchi S, Giannotti E, Vanzi E, et al. Radial scar without associated atypical epithelial proliferation on image-guided 14-gauge needle core biopsy: analysis of 49 cases from a single-centre and review of the literature. Breast. 2012;21(2):159–64.
16. Moore T, Lee AH. Expression of CD34 and bcl-2 in phyllodes tumours, fibroadenomas and spindle cell lesions of the breast. Histopathology. 2001;38(1):62–7.
17. Magro G, Bisceglia M, Michal M, Eusebi V. Spindle cell lipoma-like tumor, solitary fibrous tumor and myofibroblastoma of the breast: a clinicopathological analysis of 13 cases in favor of a unifying histogenetic concept. Virchows Arch. 2002;440(3):249–60.
18. Magro G, Michal M, Bisceglia M. Benign spindle cell tumors of the mammary stroma: diagnostic criteria, classification, and histogenesis. Pathol Res Pract. 2001;197(7):453–66.
19. Brogi E. Benign and malignant spindle cell lesions of the breast. Semin Diagn Pathol. 2004;21(1):57–64.
20. Toker C, Tang CK, Whitely JF, Berkheiser SW, Rachman R. Benign spindle cell breast tumor. Cancer. 1981;48(7):1615–22.
21. Gail MH, Brinton LA, Byar DP, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879–86.
22. Costantino JP, Gail MH, Pee D, et al. Validation studies for models projecting the risk of invasive and total breast cancer incidence. J Natl Cancer Inst. 1999;91(18):1541–8.

23. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for prevention of breast cancer: report of the National Surgical Adjuvant Breast and Bowel Project P-1 Study. J Natl Cancer Inst. 1998;90(18):1371–88.
24. Fisher B, Costantino JP, Wickerham DL, et al. Tamoxifen for the prevention of breast cancer: current status of the National Surgical Adjuvant Breast and Bowel Project P-1 study. J Natl Cancer Inst. 2005;97(22):1652–62.
25. Rockhill B, Spiegelman D, Byrne C, Hunter DJ, Colditz GA. Validation of the Gail et al. model of breast cancer risk prediction and implications for chemoprevention. J Natl Cancer Inst. 2001;93(5):358–66.
26. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. J Natl Cancer Inst. 1975;55(2):231–73.
27. Bombonati A, Sgroi DC. The molecular pathology of breast cancer progression. J Pathol. 2011;223(2):307–17.
28. Krishnamurthy S, Bevers T, Kuerer H, Yang WT. Multidisciplinary considerations in the management of high-risk breast lesions. AJR Am J Roentgenol. 2012;198(2):W132–40.
29. Wood WC. Should the use of contralateral prophylactic mastectomy be increasing as it is? Breast. 2009;18 Suppl 3:S93–5.
30. Haj M, Weiss M, Loberant N, Cohen I. Inflammatory pseudotumor of the breast: case report and literature review. Breast J. 2003;9(5):423–5.
31. Haagensen CD, Lane N, Lattes R, Bodian C. Lobular neoplasia (so-called lobular carcinoma in situ) of the breast. Cancer. 1978;42(2):737–69.
32. Rosner D, Bedwani RN, Vana J, Baker HW, Murphy GP. Noninvasive breast carcinoma: results of a national survey by the American College of Surgeons. Ann Surg. 1980;192(2):139–47.
33. Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast. A long-term follow-up study. Cancer. 1985;55(11):2698–708.
34. McLaren BK, Schuyler PA, Sanders ME, et al. Excellent survival, cancer type, and Nottingham grade after atypical lobular hyperplasia on initial breast biopsy. Cancer. 2006;107(6):1227–33.
35. Martinez V, Azzopardi JG. Invasive lobular carcinoma of the breast: incidence and variants. Histopathology. 1979;3(6):467–88.
36. Azzopardi JG, Ahmed A, Millis RR. Problems in breast pathology. Major Probl Pathol. 1979;11:i–xvi, 1–466.
37. Jacobs TW, Connolly JL, Schnitt SJ. Nonmalignant lesions in breast core needle biopsies: to excise or not to excise? Am J Surg Pathol. 2002;26(9):1095–110.
38. Agoff SN, Lawton TJ. Papillary lesions of the breast with and without atypical ductal hyperplasia: can we accurately predict benign behavior from core needle biopsy? Am J Clin Pathol. 2004;122(3):440–3.
39. Ivan D, Selinko V, Sahin AA, Sneige N, Middleton LP. Accuracy of core needle biopsy diagnosis in assessing papillary breast lesions: histologic predictors of malignancy. Mod Pathol. 2004;17(2):165–71.
40. Irfan K, Brem RF. Surgical and mammographic follow-up of papillary lesions and atypical lobular hyperplasia diagnosed with stereotactic vacuum-assisted biopsy. Breast J. 2002;8(4):230–3.
41. MacGrogan G, Tavassoli FA. Central atypical papillomas of the breast: a clinicopathological study of 119 cases. Virchows Arch. 2003;443(5):609–17.
42. Kil WH, Cho EY, Kim JH, Nam SJ, Yang JH. Is surgical excision necessary in benign papillary lesions initially diagnosed at core biopsy? Breast. 2008;17(3):258–62.
43. Rizzo M, Lund MJ, Oprea G, Schniederjan M, Wood WC, Mosunjac M. Surgical follow-up and clinical presentation of 142 breast papillary lesions diagnosed by ultrasound-guided core-needle biopsy. Ann Surg Oncol. 2008;15(4):1040–7.
44. Rizzo M, Linebarger J, Lowe MC, et al. Management of papillary breast lesions diagnosed on core-needle biopsy: clinical pathologic and radiologic analysis of 276 cases with surgical follow-up. J Am Coll Surg. 2012;214(3):280–7.
45. Linda A, Zuiani C, Furlan A, et al. Radial scars without atypia diagnosed at imaging-guided needle biopsy: how often is associated malignancy found at subsequent surgical excision, and do mammography and sonography predict which lesions are malignant? AJR Am J Roentgenol. 2010;194(4):1146–51.
46. Sohn VY, Causey MW, Steele SR, Keylock JB, Brown TA. The treatment of radial scars in the modern era–surgical excision is not required. Am Surg. 2010;76(5):522–5.
47. Sanders ME, Page DL, Simpson JF, Schuyler PA, Dale Plummer W, Dupont WD. Interdependence of radial scar and proliferative disease with respect to invasive breast carcinoma risk in patients with benign breast biopsies. Cancer. 2006;106(7):1453–61.
48. Jacobs TW, Byrne C, Colditz G, Connolly JL, Schnitt SJ. Radial scars in benign breast-biopsy specimens and the risk of breast cancer. N Engl J Med. 1999;340(6):430–6.
49. Wechselberger G, Schoeller T, Piza-Katzer H. Juvenile fibroadenoma of the breast. Surgery. 2002;132(1):106–7.
50. 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.
51. Kuijper A, Buerger H, Simon R, et al. Analysis of the progression of fibroepithelial tumours of the breast by PCR-based clonality assay. J Pathol. 2002;197(5):575–81.
52. Bernstein L, Deapen D, Ross RK. The descriptive epidemiology of malignant cystosarcoma phyllodes tumors of the breast. Cancer. 1993;71(10):3020–4.

53. Cohn-Cedermark G, Rutqvist LE, Rosendahl I, Silfversward C. Prognostic factors in cystosarcoma phyllodes. A clinicopathologic study of 77 patients. Cancer. 1991;68(9):2017–22.
54. Norris HJ, Taylor HB. Relationship of histologic features to behavior of cystosarcoma phyllodes. Analysis of ninety-four cases. Cancer. 1967;20(12):2090–9.
55. Moffat CJ, Pinder SE, Dixon AR, Elston CW, Blamey RW, Ellis IO. Phyllodes tumours of the breast: a clinicopathological review of thirty-two cases. Histopathology. 1995;27(3):205–18.
56. Choi J, Koo JS. Comparative study of histological features between core needle biopsy and surgical excision in phyllodes tumor. Pathol Int. 2012;62(2):120–6.
57. Taira N, Takabatake D, Aogi K, et al. Phyllodes tumor of the breast: stromal overgrowth and histological classification are useful prognosis-predictive factors for local recurrence in patients with a positive surgical margin. Jpn J Clin Oncol. 2007;37(10):730–6.
58. Wahner-Roedler DL, Sebo TJ, Gisvold JJ. Hamartomas of the breast: clinical, radiologic, and pathologic manifestations. Breast J. 2001;7(2):101–5.
59. Panikar N, Agarwal S. Sclerosing lobular hyperplasia of the breast: fine-needle aspiration cytology findings–a case report. Diagn Cytopathol. 2004;31(5):340–1.
60. Fisher CJ, Hanby AM, Robinson L, Millis RR. Mammary hamartoma–a review of 35 cases. Histopathology. 1992;20(2):99–106.
61. Anani PA, Hessler C. Breast hamartoma with invasive ductal carcinoma. Report of two cases and review of the literature. Pathol Res Pract. 1996;192(12):1187–94.
62. Rosen PP. Mucocele-like tumors of the breast. Am J Surg Pathol. 1986;10(7):464–9.
63. Glazebrook K, Reynolds C. Original report. Mucocele-like tumors of the breast: mammographic and sonographic appearances. AJR Am J Roentgenol. 2003;180(4):949–54.
64. Kim SM, Kim HH, Kang DK, et al. Mucocele-like tumors of the breast as cystic lesions: sonographic-pathologic correlation. AJR Am J Roentgenol. 2011;196(6):1424–30.
65. Fisher CJ, Millis RR. A mucocoele-like tumour of the breast associated with both atypical ductal hyperplasia and mucoid carcinoma. Histopathology. 1992;21(1):69–71.
66. Hamele-Bena D, Cranor ML, Rosen PP. Mammary mucocele-like lesions. Benign and malignant. Am J Surg Pathol. 1996;20(9):1081–5.
67. Weaver MG, Abdul-Karim FW, al-Kaisi N. Mucinous lesions of the breast. A pathological continuum. Pathol Res Pract. 1993;189(8):873–6.
68. Kim JY, Han BK, Choe YH, Ko YH. Benign and malignant mucocele-like tumors of the breast: mammographic and sonographic appearances. AJR Am J Roentgenol. 2005;185(5):1310–6.
69. Jaffer S, Bleiweiss IJ, Nagi CS. Benign mucocele-like lesions of the breast: revisited. Mod Pathol. 2011;24(5):683–7.
70. Leibman AJ, Staeger CN, Charney DA. Mucocelelike lesions of the breast: mammographic findings with pathologic correlation. AJR Am J Roentgenol. 2006;186(5):1356–60.
71. Carder PJ, Murphy CE, Liston JC. Surgical excision is warranted following a core biopsy diagnosis of mucocoele-like lesion of the breast. Histopathology. 2004;45(2):148–54.
72. Al-Nafussi A. Spindle cell tumours of the breast: practical approach to diagnosis. Histopathology. 1999;35(1):1–13.
73. Chan KW, Ghadially FN, Alagaratnam TT. Benign spindle cell tumour of breast–a variant of spindled cell lipoma or fibroma of breast? Pathology. 1984;16(3):331–6.
74. Begin LR. Intracisternal microtubular aggregates in classic (non chondroid) chordoma. J Submicrosc Cytol Pathol. 1995;27(3):295–301.
75. Damiani S, Miettinen M, Peterse JL, Eusebi V. Solitary fibrous tumour (myofibroblastoma) of the breast. Virchows Arch. 1994;425(1):89–92.
76. Eyden BP, Shanks JH, Ioachim E, Ali HH, Christensen L, Howat AJ. Myofibroblastoma of breast: evidence favoring smooth-muscle rather than myofibroblastic differentiation. Ultrastruct Pathol. 1999;23(4):249–57.
77. Vuitch MF, Rosen PP, Erlandson RA. Pseudoangiomatous hyperplasia of mammary stroma. Hum Pathol. 1986;17(2):185–91.
78. Ibrahim RE, Sciotto CG, Weidner N. Pseudoangiomatous hyperplasia of mammary stroma. Some observations regarding its clinicopathologic spectrum. Cancer. 1989;63(6):1154–60.
79. Wieman SM, Landercasper J, Johnson JM, et al. Tumoral pseudoangiomatous stromal hyperplasia of the breast. Am Surg. 2008;74(12):1211–4.
80. Gow KW, Mayfield JK, Lloyd D, Shehata BM. Pseudoangiomatous stromal hyperplasia of the breast in two adolescent females. Am Surg. 2004;70(7):605–8.
81. Degnim AC, Frost MH, Radisky DC, et al. Pseudoangiomatous stromal hyperplasia and breast cancer risk. Ann Surg Oncol. 2010;17(12):3269–77.
82. Powell CM, Cranor ML, Rosen PP. Pseudoangiomatous stromal hyperplasia (PASH). A mammary stromal tumor with myofibroblastic differentiation. Am J Surg Pathol. 1995;19(3):270–7.
83. Stanley MW, Skoog L, Tani EM, Horwitz CA. Nodular fasciitis: spontaneous resolution following diagnosis by fine-needle aspiration. Diagn Cytopathol. 1993;9(3):322–4.
84. Haggitt RC, Booth JL. Bilateral fibromatosis of the breast in Gardner's syndrome. Cancer. 1970;25(1):161–6.
85. Abraham SC, Reynolds C, Lee JH, et al. Fibromatosis of the breast and mutations involving the APC/beta-catenin pathway. Hum Pathol. 2002;33(1):39–46.

86. Rosen PP, Ernsberger D. Mammary fibromatosis. A benign spindle-cell tumor with significant risk for local recurrence. Cancer. 1989;63(7):1363–9.
87. el-Naggar A, Abdul-Karim FW, Marshalleck JJ, Sorensen K. Fine-needle aspiration of fibromatosis of the breast. Diagn Cytopathol. 1987;3(4):320–2.
88. Cederlund CG, Gustavsson S, Linell F, Moquist-Olsson I, Andersson I. Fibromatosis of the breast mimicking carcinoma at mammography. Br J Radiol. 1984;57(673):98–101.
89. Pettinato G, Manivel JC, Insabato L, De Chiara A, Petrella G. Plasma cell granuloma (inflammatory pseudotumor) of the breast. Am J Clin Pathol. 1988;90(5):627–32.
90. Sari A, Yigit S, Peker Y, Morgul Y, Coskun G, Cin N. Inflammatory pseudotumor of the breast. Breast J. 2011;17(3):312–4.

Website Cited in this Chapter

Concordance assessment of image-guided breast biopsies and management of borderline or high-risk lesions. https://www.breastsurgeons.org/statements/index.php. Approved 15 Aug 2011.
Management of fibroadenomas of the breast. https://www.breastsurgeons.org/statements/index.php. Revised 29 Apr 2008
https://www.nccn.org/professionals/physician_gls/f_guidelines.asp#breast_screening