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Review Article

Core needle biopsy of benign, borderline and in-situ problematic lesions of the breast: Diagnosis, differential diagnosis and immunohistochemistry

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ABSTRACT

Core needle biopsy (CNB) is the most common sampling technique for the histologic evaluation of breast abnormalities. Diagnosing benign proliferative, borderline and some in-situ lesions in CNB is challenging and subject to a significant degree of interobserver variability. In addition, due to the inherent limitations of CNB, "upgrading" to a more significant pathology at excision is an important consideration for some lesions. Pathologists carry a major responsibility in patient diagnosis, risk stratification and management. Familiarity with the histologic features and the clinical significance of these common and problematic lesions encountered in CNB is necessary for adequate treatment and patient follow-up. This review will focus on benign, atypical and in-situ epithelial proliferations, papillary lesions, radial sclerosing lesions, adenosis and cellular fibroepithelial lesions. Highlights of histologic features, useful strategies for accurate diagnosis, basic immunohistochemistry and management will be presented.

1. Introduction

The widespread use of screening radiologic modalities has increased the number of non-palpable, asymptomatic breast abnormalities being biopsied [1]. Each year, > 1 million breast biopsies are performed in the United States. Approximately 20% of these biopsies carry a diagnosis of malignancy and the rest are classified within the spectrum of benign, atypical and borderline breast disease [2]. Therefore, pathologists are increasingly confronted with an extensive variety of lesions sampled by minimally invasive procedures in which the small size, distortion, and fragmentation of the tissue may constitute a problem. Additionally, it is well-known that some of these benign, atypical and in-situ proliferative lesions are diagnostically challenging [1].

Pathologists carry an enormous responsibility in the management decision process. Over, under or misdiagnosis will lead to the wrong treatment and possibly unnecessary interventions. Understanding the clinical and pathological characteristics of breast lesions is necessary to ensure an adequate diagnosis. In this review, we provide a description of the clinical presentation, diagnostic features, immunohistochemical findings and differential diagnosis of some of the more frequent and challenging lesions in breast pathology.

2. Intraductal proliferations (usual and atypical ductal hyperplasias and ductal carcinoma in situ)

Proliferative lesions encompass a variety of lesions affecting the intraductal component of the major and terminal ducts of the breast. These changes may take multiple forms, ranging from benign entities, such as usual ductal hyperplasia (UDH), to lesions displaying atypical features, such as atypical ductal hyperplasia (ADH), to ductal carcinoma in situ (DCIS) [3-5]. Whether benign or atypical, ducts affected by these hyperplastic changes are lined by a layer of myoepithelial cells (MEC) [6]. Adequate identification and diagnosis of proliferative lesions are of utmost importance in the evaluation of core needle biopsies (CNB) because each entity is associated with a different risk for the development of invasive carcinoma [7].

2.1. Usual ductal hyperplasia

UDH can be found in patients of any age, but rarely occur before puberty [8]. The mean age at diagnosis is 53 years and is rare in patients older than 60 years of age [3,8]. UDH does not have any specific clinical features [9] and the reason for biopsy is usually due to stromal alterations such as pseudo-angiomatous stromal hyperplasia (PASH), fibrocystic changes or radial scars (RS)/complex sclerosing lesions in the adjacent mammary tissue [8].

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The microscopic changes in UDH are variable and range from a focal to a multifocal proliferation. The epithelial cells are irregularly located, with indistinct cell borders and variable nuclear size [9]. The nuclei are often overlapping and may be distributed in a "streaming" fashion, that is, the cells are oriented parallel to their long axes [10]. The degree of proliferation is variable and ranges from only a few epithelial cell layers to a solid proliferation that completely fills the lumen (florid ductal hyperplasia) resulting in ductal dilatation and expansion [11]. The presence of secondary lumens and micropapillary structures are possible (Fig. 1-A). Calcifications, squamous metaplasia and foamy histiocytes, as well as rare mitotic figures, can be found within the ducts involved by UDH. However, the presence of necrotic debris within the involved duct is rare. A variety of other proliferative changes such as sclerosing adenosis, apocrine metaplasia, and atypical lobular hyperplasia can be seen in association with UDH [8,12].

2.2. Atypical ductal hyperplasia

ADH is an intraductal proliferation of evenly spaced monomorphic epithelial cells with histologic and cytologic features resembling, but not fulfilling all the criteria for the diagnosis of low grade DCIS [13]. ADH is recognized as a risk marker for the development of breast cancer and a precursor lesion that shares molecular similarities with DCIS and invasive carcinoma [14,15]. On average, patients diagnosed with ADH are slightly older than patients with UDH, with a mean age of 58 years [3]. ADH is seen in approximately 4–9% of image guided CNB [16,17]. However, with the availability of population-based screening programs and advancement of imaging modalities, ADH has become more prevalent in biopsies performed for radiographic abnormalities. Approximately 31% of CNB performed for screen-detected microcalcifications contain ADH [16,18-21].

A diagnosis of ADH should not be rendered unless low grade DCIS is in the differential diagnosis [9]. The atypical cells may focally involve the TDLU and be admixed with a hyperplastic population of cells without atypia [22]. The cell borders are distinct, with moderately enlarged, hyperchromatic nuclei, and prominent nucleoli [8]. The cells lack the swirling, streaming and overlapping seen in UDH [9]. Mitotic figures are rare. Architecturally, ADH may show solid, cribriform and micropapillary patterns, therefore, distinguishing it from low grade DCIS is mostly based on quantitative criteria (Fig. 1-B). Accordingly, when morphologic changes of low-grade DCIS involve < 2 separate duct spaces or measure < 2 mm in maximum dimension, the diagnosis of ADH is rendered. Conversely, low-grade DCIS is diagnosed when the abnormal proliferation exceed these quantitative criteria [3,9,23,24]. However, in CNB specimens, the extent of the disease is often difficult to ascertain. Therefore, in lesions with borderline features, categorization as ADH or "atypical intraductal proliferation" is recommended until evaluation of the entire excisional specimen is possible [9].

2.3. Ductal carcinoma in situ

DCIS is a highly heterogeneous, non-obligate precursor of a proportion of invasive breast carcinomas [25-27]. The incidence of DCIS has increased over the years, largely due to increased life expectancy and improvements in diagnostic radiographical modalities [25-29]. DCIS accounts for 20–25% of newly diagnosed breast cancer in the USA [9,30]. The mean age at diagnosis is reported to be from 50 to 59 years [8,31-34]. After the development of population-based screening programs, 80–85% of DCIS cases are detected radiographically [9], typically by screening mammogram [8,35]. Nearly 10–15% of DCIS are discovered as incidental lesions in CNB performed for other indications, including palpable abnormalities [8,35].

Histologically, DCIS is characterized by an intraductal proliferation of malignant cells that involves and distends the lumens of the TDLU. An intact myoepithelial cell layer and basement membrane distinguishes DCIS from invasive carcinoma. Classification can be done based on nuclear grade, presence of necrosis, and architectural pattern [8]. Grading consists of three-tier category, based on the nuclear characteristics of the neoplastic cells [36]. DCIS is classified on the basis of the highest grade present [37]. Secretion, punctuate necrosis and calcifications may occur. The presence or absence of mitotic figures is not a definitive feature in the diagnosis of DCIS, because mitoses may also be found in normal and hyperplastic areas [8].

Low-nuclear grade DCIS is characterized by a proliferation of monomorphic, evenly spaced cells with roughly spherical, centrally located nuclei and inconspicuous nucleoli [6]. The most accepted diagnostic criteria for low-grade DCIS has been discussed above. Necrosis is uncommon, but its presence, including when of "comedo-type" does not preclude the diagnosis of low-grade DCIS [9]. Diagnosing intermediate and high-nuclear grade DCIS is often straightforward since these diagnoses do not require specific size criteria and are based in architectural and cytological features. Intermediate-nuclear grade DCIS lacks the monomorphic nuclear characteristics of low grade DCIS and typically shows mild to moderate pleomorphism (Fig. 1-C) [6]. High-nuclear grade DCIS has pleomorphic cells with irregularly spaced and usually large nuclei, exhibiting marked anisonucleosis, irregular nuclear contours, coarse chromatin and prominent nucleoli [6].

Architecturally, DCIS may show different patterns. The solid pattern is characterized by a proliferation of neoplastic cells that partially or completely fills the intraductal space. Cribriform DCIS consists of microlumina surrounded by the neoplastic cells [8]. Micropapillary DCIS consists of ducts lined by a layer of neoplastic cells giving rise to micropapillary fronds, arcades, or roman bridges, protruding into the duct lumen [8]. The lack of a fibrovascular core distinguishes micropapillary from the papillary architectural pattern. Other less common variants of DCIS include apocrine, signet ring, clear cell, neuroendocrine and spindle cell [8,9]. Rarely, intermixed ductal and lobular carcinoma in situ may involve the same TDLU [8,38].

2.4. Differential diagnosis and immunohistochemistry

The distinction between UDH and ADH on CNB is straightforward in the majority of cases. Usual ductal hyperplasia can be distinguished from ADH by the presence of fenestrations, streaming and absence of atypical nuclear features. However, when architectural changes such as secondary lumens, bridges or micropapillary fronds are present, this distinction may be more difficult. Typically, the lumens in moderate or florid UDH are irregular with a peripheral or random distribution within the duct. In contrast, the lumens in ADH are well formed with a more even distribution and the epithelial cells polarized around the spaces [8,9]. When epithelial bridges are present in UDH, the cells are stretched and twisted, contrary to the structural rigidity identified in ADH [9]. The micropapillary structures in UDH are characterized by a broader base with a thin, delicate apex lacking a true fibrovascular core [8,9]. The distinction between ADH and low-grade DCIS is much more complicated on CNB because is predominantly based on homogeneous involvement of the ducts using the quantitative criteria discussed above. At low-magnification, the solid and spindle cell patterns of DCIS can mimic the streaming present in UDH. However, careful examination of the proliferation at a higher magnification reveals the monomorphism and cytologic atypia characteristics of DCIS [3,9,23,24].

Usually, IHC stains are not required in the routine diagnosis of UDH, ADH and low-grade DCIS. In difficult cases, high-molecular weight cytokeratins (HMW-CK), such as CK5/6, are useful markers in distinguishing UDH from ADH or low-grade DCIS (Fig. 1-D) [39,40]. UDH has a mosaic pattern of CK5/6 expression, whereas ADH and low-grade DCIS tend to be negative or have only focal, weak positivity [41-44]. Another useful marker is estrogen receptor (ER), which expression is variable in UDH, showing scattered heterogeneous positivity, similar to the benign breast glandular epithelium [45-48]. ADH and low-grade DCIS tend to show diffuse and strong ER expression [45-48]. ER is positive in approximately 75–80% of DCIS, while progesterone receptor

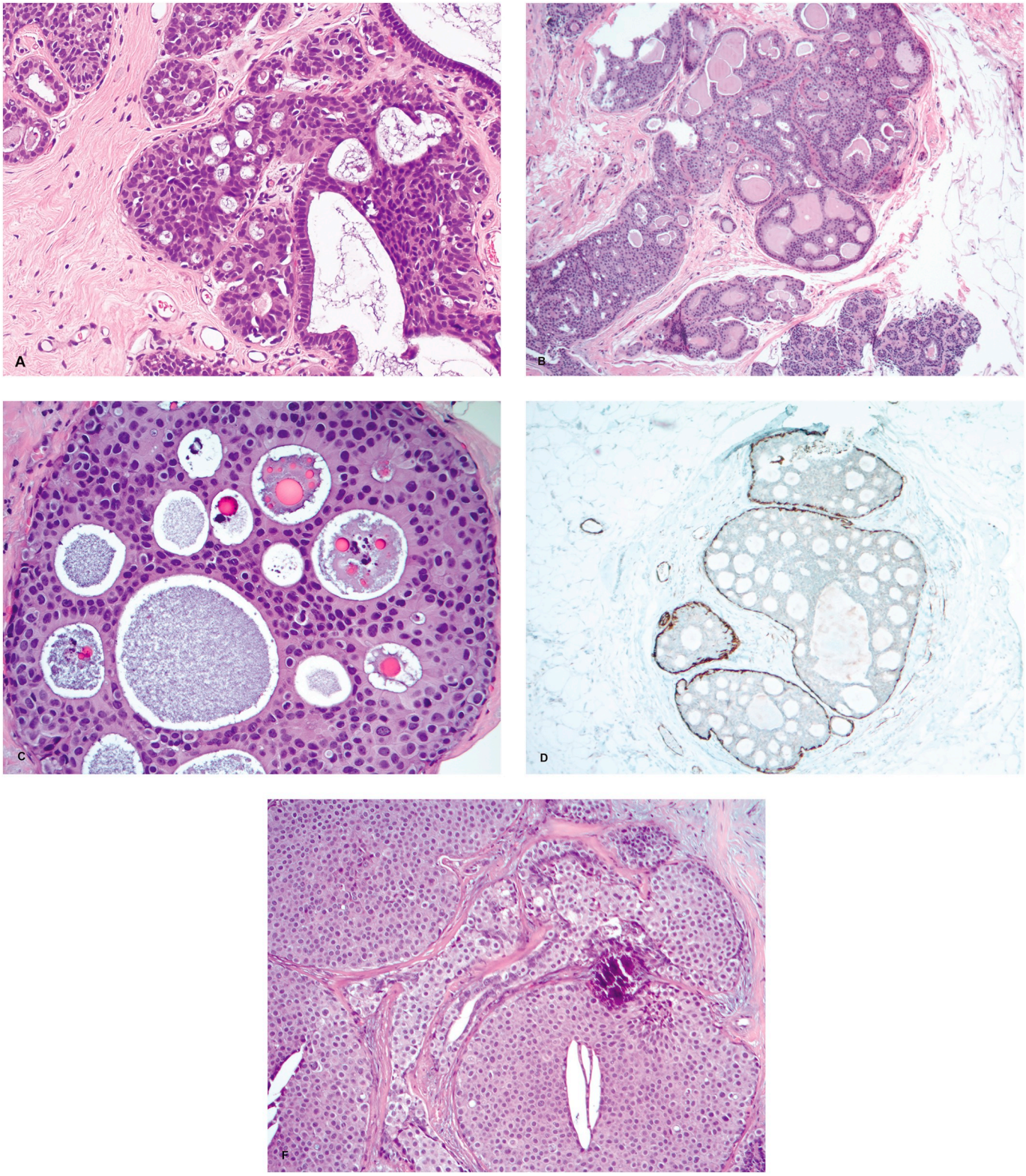

Fig. 1. A, Intraductal proliferation displaying streaming and focal secondary lumens with lack of polarization, best classified as usual ductal hyperplasia (hematoxylin-eosin, original magnification ×100).
B, Atypical ductal hyperplasia characterized by an intraductal proliferation with mild cytologic atypia seen as cellular monotony as well as focal cribriform pattern (hematoxylin-eosin, original magnification ×50).
C, Intermediate nuclear grade ductal carcinoma in situ, displaying moderate nuclear pleomorphism and cribriform architecture with nuclear polarization around the lumens (hematoxylin-eosin, original magnification ×200).
D, Cytokeratin 5/6 shows loss of staining in the intraductal proliferation in a case of DCIS and highlights the presence of myoepithelial cells around the periphery (×50).
E, Lobular carcinoma in situ with focal microcalcifications exhibits morphological similarities to the solid pattern of ductal carcinoma in situ (hematoxylin-eosin, original magnification ×100).

(PR) has a slightly lower expression [9]. *HER2/neu* immunoreactivity has been reported in 42% to 61% of DCIS, usually in high-grade DCIS [8,49,50].

ADH and low-grade DCIS should be distinguished from collagenous spherulosis. The round spaces of collagenous spherulosis may be mistaken for the cribriform pattern of ADH or low-grade DCIS. In contrast to ADH and DCIS, in collagenous spherulosis the cells surrounding these pseudolumina are not epithelial but myoepithelial cells and the spherules contain basement membrane-like material [8,9]. IHC stains for MEC, such as p63, calponin, smooth muscle actin (SMA) and smooth muscle myosin- heavy chain (SMM-HC) are positive not only at the periphery but also around the pseudolumina [51].

Other entities such as adenoid cystic carcinoma (ACC), invasive ductal and cribriform carcinomas are also part of the differential diagnosis of DCIS. ACC may present with a solid, tubular and cribriform architecture with true glandular and pseudoglandular spaces lined by a layer of basal-myoepithelial cells [9,52,53]. ACC is positive for CD117 (c-kit) and negative for ER, while low-grade DCIS shows an inverse staining pattern [9,54]. Similarly to DCIS, the glandular spaces in invasive ductal and cribriform carcinomas are surrounded by luminal cells [9]. However, in contrast, invasive ductal and cribriform carcinomas lack a surrounding MEC layer. Stromal reaction and myoepithelial cell attenuation may prevent adequate assessment of MEC on routine hematoxylin and eosin (H&E) sections and immunohistochemical (IHC) stains may be required to confirm the presence or absence of invasion [8,9].

Lobular carcinoma in situ (LCIS) is another lesion to consider in the differential diagnosis of DCIS. Distinction of LCIS from solid, low-grade DCIS can be difficult on morphologic grounds alone (Fig. 1-E) [9]. Distinction between pleomorphic LCIS and high-grade DCIS may also be difficult. Immunohistochemical stains may be necessary for a definitive characterization, especially when “comedo-type” necrosis is present [55]. Distinction between DCIS and LCIS can be made using e-cadherin and/or p120 immunostains [8]. DCIS has a strong e-cadherin and p120 membranous expression, while LCIS shows negative or weak aberrant expression of e-cadherin with a cytoplasmic staining pattern for p120 [9].

2.5. Prognosis and treatment

UDH confers a slight increase in subsequent breast cancer risk in either breast of about 1.5- to 2-fold. The risk is slightly higher among women with a family history of breast cancer [56-59]. The diagnosis of ADH is associated with an increased relative risk of 3–5 fold of subsequent development of invasive carcinoma [56]. When ADH is diagnosed on a core needle biopsy, it can be associated with an upgrade rate to non-invasive and invasive breast carcinoma of 18–31% in subsequent surgical excision [14,60,61]. This high frequency of upgrade from ADH to carcinoma warrants surgical excision for patients diagnosed with ADH on CNB [8,20,21].

The exact molecular behavior of DCIS, in particular, how it progresses to invasive breast carcinoma, is not well understood [25]. Low-grade DCIS is considered to be a precursor of low-grade invasive breast carcinoma and high-grade DCIS is a precursor of high-grade invasive breast carcinoma [25,62,63]. The interval between DCIS and the development of invasive carcinoma is shorter for high-grade DCIS, averaging 5 years, than for low-grade DCIS, which takes a mean period of > 15 years [8,64,65]. Larger tumor size and higher nuclear grade are correlated with time-to-tumor recurrence rate in patients treated with breast conservation surgery alone for DCIS [25,66]. Other reports suggest that DCIS with *HER2/neu* overexpression is associated with early invasive foci at a relatively higher rate [25,67,68].

Surgical treatment for DCIS includes mastectomy versus conservative breast excision, i.e. lumpectomy, wide local excision or partial mastectomy, with or without radiation [69]. Chemoprevention therapy for patients with ADH and receptor positive DCIS significantly reduces the risk of in-situ and invasive carcinoma in this high-risk population [70,71].

3. Papillary lesions (intraductal papilloma, atypical papilloma and in-situ papillary carcinomas)

Papillary lesions (PLs) of the breast encompass a diverse and broad spectrum of lesions ranging from benign to malignant. PLs account for approximately 1–4% of core needle biopsy diagnosis [72,73]. These lesions are notoriously difficult to diagnose on samples obtained by minimally invasive techniques as well as on excisions. In addition, a wide range of terminology and diagnostic criteria used over the years has complicated things further. Although the number of lesions included in this group is ample, most common papillary lesions encountered on CNB are intraductal papillomas, atypical papillomas (ADH and low-grade DCIS within papillomas), intracystic/encapsulated or solid papillary carcinomas, and ductal carcinoma in situ with a papillary pattern [1]. When evaluating a CNB with a morphologic diagnosis of a PL, knowledge of clinical and radiological features is important. Information about the location of the lesion (s) is crucial to narrow the differential diagnosis and to guide management since the clinical significance of these lesions may vary according to their location.

3.1. Intraductal papilloma

Intraductal papilloma (IP) is a benign, well-circumscribed, intraductal proliferative lesion. According to location, papillomas can be central or peripheral. Central papillomas present more commonly as palpable masses or nipple discharge whereas peripheral papillomas tend to less frequently cause symptoms or may also present as a palpable mass [73]. On mammography, small papillomas can be occult. Larger lesions usually appear as round or oval masses with well-circumscribed borders. Up to 25% of solitary papillomas are associated with calcifications [74]. On ultrasound (US), papillomas may appear as distinct solid nodules or as mural nodules within a dilated duct [75,76]. On magnetic resonance imaging (MRI), small papillomas may be occult, present as an opacity or as a dilated duct with an intraductal mass [73]. Although US seems to be superior to other techniques, radiologically, there are no features that can reliably distinguish benign from malignant papillary lesions [76,77].

Central papillomas are frequently solitary, whereas peripheral papillomas are usually multiple. The term “papillomatosis” has been used by many to describe the presence of multiple peripheral microscopic papillomas [78]. Women with multiple papillomas tend to be younger than those with solitary papillomas and are at increased risk for concurrent or subsequent carcinoma [79]. Central papillomas without atypia are associated with a two-fold increase in the risk for invasive carcinoma; whereas this risk is threefold for peripheral papillomas [9].

Histologically, papillomas are composed of 2 layers of cells, 1 ductal epithelial and 1 myoepithelial cell layer supported by a fibrovascular core (Fig. 2-A) [1]. Papillomas can also be involved by a variety of proliferative non-atypical and atypical processes such as apocrine changes, usual ductal hyperplasia, adenosis and columnar cell changes, among others [79]. Variable degrees of atypia can be found in papillomas and the diagnostic criteria vary among pathologists. The distinction among the spectrum of non-atypical, atypical proliferative changes and DCIS involving a papilloma may be difficult. In the differentiation between atypical ductal hyperplasia from low-grade DCIS within a papilloma, Page et al. [80] used criteria based on the extent of the abnormal population. Accordingly, ADH is diagnosed if the extent of the atypical population within the papilloma is < 3 mm and DCIS if the lesion is > 3 mm in size [81]. This criteria has also been recommended by the World Health Organization working group to pursue diagnostic consistency [9]. Tavassoli [82], in contrast, used the term “atypical papilloma” when less than a third of the papilloma

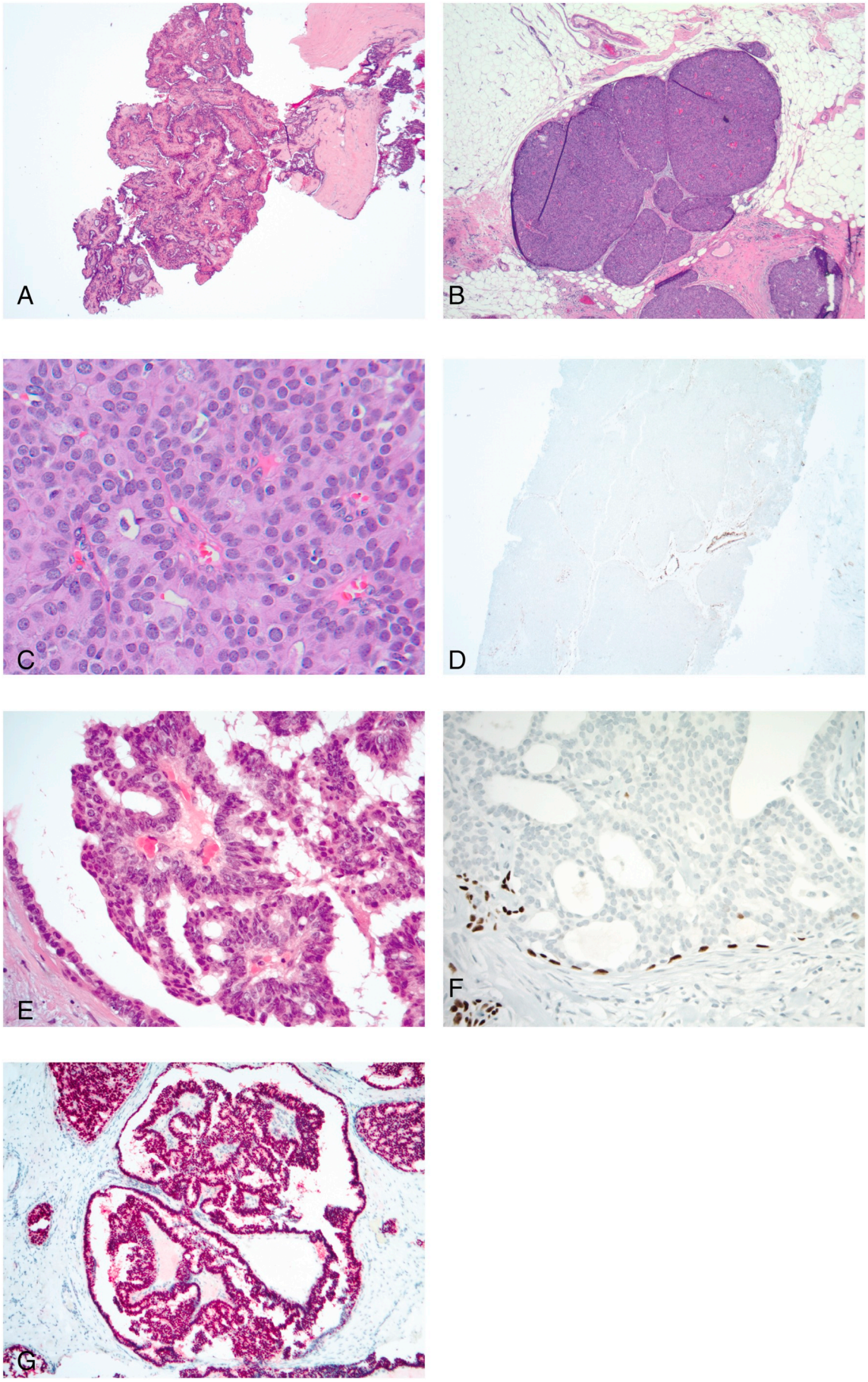

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Fig. 2. A, Intraductal papilloma with prominent fibrovascular cores lined by a benign epithelial, and a myoepithelial cell layer, seen at low-magnification (hematoxylin-eosin, original magnification ×20).
B, Solid papillary carcinoma composed of several tightly-packed nodules of neoplastic epithelium. The expansile nodules and the lack of an evident papillary network give the impression of invasive carcinoma (hematoxylin-eosin, original magnification ×200).
C, Higher magnification of a case of solid papillary carcinoma depicting delicate fine vessels with surrounding pseudorosettes (hematoxylin-eosin, original magnification ×400).
D, Calponin immunohistochemistry (IHC) is negative in solid papillary carcinoma. Although SPC are still considered in-situ tumors, IHC for myoepithelial cell markers may show some or all of the nests lacking a myoepithelial cell layer, making this a predominantly "H&E" diagnosis (original magnification ×20).
E, Papillary ductal carcinoma in-situ is composed of delicate papillary cores covered by one or two layers of columnar cells with variable degrees of stratification (hematoxylin-eosin, original magnification ×200).
F, The presence of myoepithelial cells in a case of papillary ductal carcinoma in situ is demonstrated using p63 immunohistochemistry (original magnification ×200).
G, Estrogen receptor is strongly positive in low-grade papillary ductal carcinoma in situ (original magnification ×100).

shows atypical features, and the term "carcinoma arising in a papilloma" when more than a third but < 90% of the papilloma is involved. Others diagnose papilloma with DCIS if the atypical proliferation in the papilloma shows all of the combined architectural and cytological features of DCIS regardless of its extent [83,84]. Of note, if high-grade atypia is present, the diagnosis of carcinoma is made regardless of the extent [9].

3.2. In-situ papillary carcinoma

Currently, the term "in situ papillary carcinoma" encompasses multiple histologic diagnoses including cystic and solid lesions (encapsulated papillary carcinoma, solid papillary carcinoma and papillary DCIS). Encapsulated papillary carcinoma (EPC), also known as intracystic papillary carcinoma and encysted papillary carcinoma, is morphologically composed of a solid mass within a surrounding cystic space and a fibrotic capsule. EPC has been traditionally considered an in-situ carcinoma; however, immunohistochemical studies have revealed that in some EPCs a myoepithelial cell layer cannot be demonstrated at the periphery of the lesion [85,86]. This finding has raised the concern that EPC may represent low-grade carcinomas with expansile growth pattern, or be in the spectrum of progression from in-situ to invasive disease [85].

Solid papillary carcinomas (SPC) are also currently considered as a variant of DCIS [83,87]. These tumors appear as multiple nodules, each representing a duct filled by a neoplastic, low to intermediate grade proliferation. The cells grow in a solid pattern with intermingled fibrovascular network and no apparent papillary structures. Similarly to EPC, SPC lack myoepithelial cells at the periphery in the majority of cases, raising questions regarding its "in-situ" nature (Fig. 2-B,C,D) [85,87,88].

Papillary DCIS is a multifocal neoplastic process that frequently coexists with other variants of DCIS such as cribriform, micropapillary and solid [78,88]. Papillary DCIS is usually composed of delicate papillary cores covered by one or two layers of columnar cells with variable degrees of stratification (Fig. 2-E) [83]. In contrast to DCIS arising within a papilloma, in papillary DCIS there is no evidence of a pre-existing papilloma [83]. Importantly, papillary DCIS retain a demonstrable peripheral MEC layer, a feature that is helpful in its differentiation from EPC and SPC in small biopsies (Fig. 2-F) [78].

3.3. Differential diagnosis and immunohistochemistry

Immunohistochemical stains (IHC) are often used in the diagnostic work-up of papillary lesions. Myoepithelial cell markers can be used to demonstrate the presence of MEC admixed with the ductal proliferation and throughout the papillary fronds. High-molecular-weight keratins, CK5/6 and 34βE12 (K903) in conjunction with estrogen receptor can help to establish the presence of atypia. Atypical proliferative lesions and DCIS lack staining with such keratins or show only occasional staining. In contrast, a strong and diffuse staining pattern indicates a benign process such as usual ductal hyperplasia. In normal breast tissue, ER is patchy positive in lobules and ducts. Conversely, in ADH or low-grade DCIS, ER is usually diffusely and strongly positive [40]. SPC and papillary DCIS are often of low to intermediate nuclear grade and therefore diffusely positive for ER and negative for CK5/6 (Fig. 2-G) [9].

The diagnosis of invasion arising from an in-situ papillary carcinoma (other than DCIS) in CNB may be challenging due to the fibrotic nature of the surrounding capsule, the presence of a sclerotic stroma and the limited tissue available for evaluation. In addition, due to the absence of a peripheral MEC layer in some of these lesions, MEC markers are often not useful in this setting. This is also especially problematic in SPC where a "papillary" network is often not evident. In cases of solid papillary carcinoma, the presence of a geographic jigsaw pattern with more ragged and irregular margins may be considered by some authors as invasive disease. Therefore, the H&E continues to be the most reliable stain and the diagnosis of frank invasion should only be made when malignant cells are clearly present beyond the fibrous capsule of the lesion [83,87].

3.4. Prognosis and treatment

The reported incidence of finding a more advanced lesion on follow-up excisional biopsy after the diagnosis of a benign papilloma on CNB ranges from 0% to 28% in the literature [72,83]. This incidence significantly increases to 30–67% when atypia is present [89,90]. Patient's age and size of the lesion has also been correlated with increased chances of finding a more severe lesion on excision [72,77,91]. Even though a substantial risk of upgrading exist, there is still controversy regarding the follow-up of "benign appearing" papillary lesions on CNB [72]. Several published studies advocate for excision of all papillary lesions, whereas others recommend radiological follow-up [72,79,92-94]. In our opinion, management should be based on a case by case approach taking into consideration the multiple factors mentioned before as well as the sampling technique. It has been reported that larger core biopsy needles, such as 8- to 11-gauge, and vacuum-assisted techniques may decrease the underdiagnoses of atypical or malignant PL and thus improve the negative predictive value [95-100]. Many studies reporting a high incidence of upgrading of PL after CNB, were done using data from biopsies performed under ultrasound or mammography guidance, using a 14 gauge or smaller needle [77]. Therefore, including all these variables in the clinical decision process is necessary.

4. Radial sclerosing lesions (radial scar and complex sclerosing lesion)

Radial sclerosing lesions (RSLs) are benign proliferative lesions displaying a stellate configuration radiologically and histologically [1]. Familiarity with these lesions is important because RSLs may have the radiological, gross and the histological appearance of invasive carcinoma. Similarly to other proliferative lesions, the diagnostic terminology used for RSLs has been variable, and terms such as sclerosing

papillary lesion, scleroelastotic scar, infiltrating epitheliosis, among others, have been used over the years [9]. Currently, most breast pathologists agree to use the term "radial scar" in "less complex" lesions measuring up to 1 cm. The term "complex sclerosing lesion" is used for lesions larger than 1 cm displaying "more complex" features [1,9,101-104].

Most RSLs are microscopic and not detectable by palpation or mammography and are diagnosed incidentally on biopsies/excisions performed for other reasons [8]. Larger lesions are usually detected by mammography and can become palpable [105]. With the use of widespread screening techniques, the incidence of RSLs has increased with reported rates of 0.03–0.09% [106]. Jacobs et al. recorded an incidence of 7.1% in their study of 1396 women who underwent open biopsies for benign breast disease [107], while others have reported an incidence of up to 28% [8]. The frequency of RSLs in mastectomies performed for carcinoma ranges from 4 to 26%. RSLs are often multiple and bilateral and most frequently affect women between 40 and 60 years of age [8,106].

Mammographically, RSLs present as an area of architectural distortion with the presence of a central radiolucency radiating long thin spicules [103]. On US, they appear as irregular hypoechoic masses with posterior shadowing [104]. However, radiological features alone are not sensitive or specific enough to distinguish between RSLs and invasive carcinoma and therefore CNB is recommended.

Histologically, RSLs are characterized by a central fibroelastotic core with the epithelial component radiating outward, giving the lesions its characteristic stellate appearance [8]. Usually, the ducts are compressed at the center and dilated at the periphery of the lesion. Calcifications have also been described [106]. RSLs are often populated by a variety of non-proliferative, proliferative, atypical, and malignant lesions, including cysts, apocrine metaplasia, UDH, ADH, adenosis, DCIS, lobular proliferations and invasive ductal or tubular carcinoma (Fig. 3-A, B). When carcinoma is present, it is usually of grade 1 or 2 [1].

4.1. Differential diagnosis and immunohistochemistry

The presence of compressed glands trapped at the center of the lesion may give the impression of invasive carcinoma, especially tubular carcinoma [1,8]. However, in contrast to invasive carcinomas, RSLs are lobulocentric proliferations and retain MEC and a basement membrane. In addition, the glands in tubular carcinoma tend to have a more defined angular shape [8,9].

A conspicuous myofibroblastic stromal reaction as part of the RSLs may raise the suspicion of low-grade fibromatosis like-metaplastic carcinoma or low-grade adenosquamous carcinoma arising from or in association with a RSL. Other problematic morphologic features in this setting include the presence of a prominent spindle cell component with variable degrees of atypia, areas of squamous metaplasia or "infiltrative" low-grade glands after CNB [108]. Although a mild degree of lymphocytic infiltration has been described towards the periphery in RSLs [106], the presence of a conspicuous lymphocytic infiltrate may indicate low-grade adenosquamous carcinoma [8,9]. The degree of stromal atypia seen in low-grade metaplastic carcinomas is usually subtle; therefore careful histologic examination and the use of IHC stains in this setting are crucial [109].

As with other proliferative breast lesions, immunohistochemical stains for MEC markers are frequently part of the work-up of RSLs. However, it has been reported by several authors that MEC markers demonstrate an altered staining pattern and intensity in a significant number of sclerosing lesions showing skipped areas of no staining and cross reactivity with fibroblasts which can be challenging to interpret [40,55,110,111]. Published studies have shown that using a panel of IHC to include CK5/6, 34βE12 and p63, among other CKs, is useful when low-grade metaplastic carcinomas are a consideration since these stains are often positive in metaplastic carcinomas and negative in "reactive" stroma. However, although rare, focal and usually weak, staining of stromal spindle cells of RSLs and phyllodes tumor can be seen with any of these markers; a finding that can be especially problematic in CNB [108,112].

4.2. Prognosis and treatment

Some authors have suggested that RSLs represent a natural model of carcinogenesis evolving from a proliferative lesion to atypia and ultimately to carcinoma [113]. However, there is currently no evidence to support this theory [9]. The relative risk of RSLs for the development of carcinoma appears low after adjustment for the presence of simultaneous proliferative lesions, estimated to be about 1.45–1.74 [9].

The management of RSLs diagnosed on CNB continues to be controversial and inconsistent [114]. A survey of breast surgeons revealed that only 50% would recommend excision [115]. Surgical upgrade of RSLs to atypia, in-situ or invasive carcinoma ranges from 0 to 40% in the literature [106,116-120]. A case by case approach is the best way to ascertain the management of RSLs diagnosed on CNB. It has been reported that lesions < 5 mm found incidentally on CNB do not pose a significant risk and therefore excision is not warranted [120]. Also, several published studies have demonstrated that the patient's age, radiological features, sampling technique and the association with other proliferative and atypical lesions impact the rate of atypia or malignancy present at excision [1,116,120,121]. Upgrading has been reported more commonly in patients over 50 years of age, lesions > 1.0 cm, when there is associated atypia, and when there is radiologic/pathologic discordance [113,116]. Others have suggested that thorough sampling (> 12 samples), the use of directional vacuum-assisted devices and sampling by a 9- or 11-gauge core needle substantially help in decreasing the risk of "missing" an associated atypical or malignant lesion [121,122].

5. Adenosis (sclerosing adenosis, apocrine changes involving adenosis and microglandular adenosis)

Adenosis is a benign proliferation of glandular elements lined by a layer of epithelial cells surrounded by myoepithelial cells. Adenosis is considered a lobulocentric proliferative lesion derived from the TDLU [123]. It has multiple histologic variants and the main significance is its potential mimicry of invasive carcinoma [9]. Adenosis may form a clinically palpable or radiographically detectable mass when the affected lobules merge together to create an adenosis tumor [8,124].

5.1. Sclerosing adenosis

Sclerosing adenosis (SA) is the most common histological variant of adenosis and typically affects premenopausal females [8]. SA is seen in approximately 12% of breast core needle biopsies [123,125]. The most common radiographic findings of SA is microcalcifications on mammogram and masses with or without calcifications on ultrasound [126]. On MRI, SA is detected as enhancing masses, non-mass enhancements or small enhancing focuses [127]. Histologically, SA is characterized by a proliferation of glands with preservation of the epithelial and myoepithelial cell layers [9]. The epithelial cell layer may occasionally be attenuated or almost completely obliterated. The basement membrane can be thickened and eosinophilic. The surrounding stroma is hyalinized or fibrotic (Fig. 3-C) [8]. In some instances, SA may show an irregular pattern with involvement of the adipose tissue, fibromammary tissue and even nerves, which can be mistaken for perineural invasion of invasive carcinoma [128,129]. SA can be identified adjacent or in association with other benign entities, such as, fibrocystic changes, RS/complex sclerosing lesions, fibroepithelial and papillary lesions [130]. Patients with SA are three times more likely to present with adjacent areas of atypical lobular hyperplasia and LCIS [9,131,132]. Atypical ductal hyperplasia, DCIS and invasive carcinoma can also involve or be

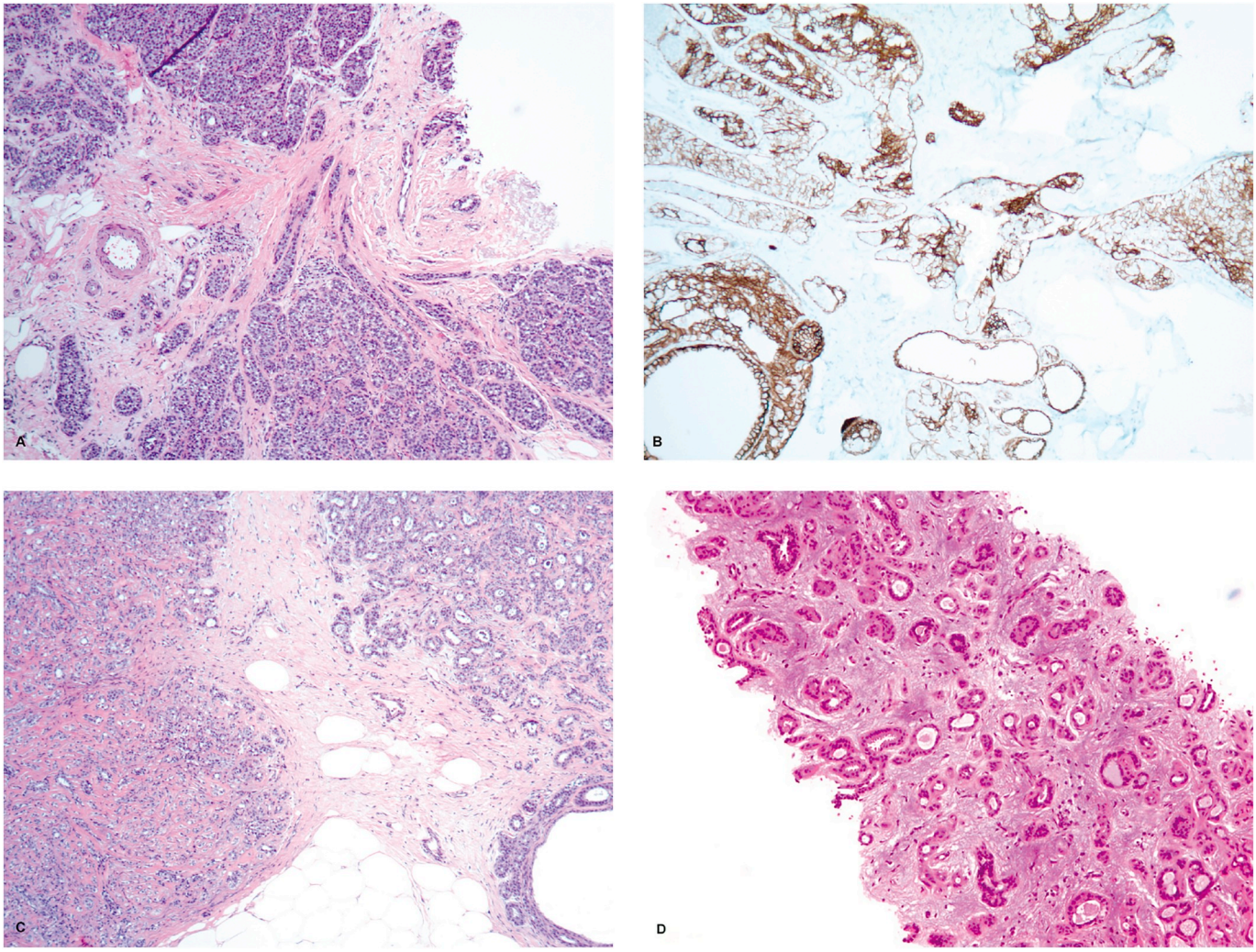

Fig. 3. A, Radial sclerosing lesion with associated atypical lobular hyperplasia (hematoxylin-eosin, original magnification x50).
B, E-cadherin immunohistochemistry is negative in the atypical lobular hyperplasia (original magnification ×200).
C, Sclerosing adenosis with a solid, lobulocentric area to the left and a looser, infiltrative pattern on the right (hematoxylin-eosin, original magnification ×50).
D, Apocrine adenosis with infiltrative pattern and stromal fibrosis. The differential diagnosis includes tubular carcinoma, although no desmoplastic response or cytologic atypia are noted. The use of immunostaining for myoepithelial cells would be of help in confirming the diagnosis (hematoxylin-eosin, original magnification ×50).

nearby areas of SA [133].

5.2. Apocrine adenosis

Apocrine metaplasia is estimated to be present in approximately 40% of benign breast biopsies. It is often seen in association with fibrocystic changes, adenosis, and papillary lesions, among others [134]. Apocrine adenosis (AA) refers to apocrine change involving SA and atypical apocrine adenosis (AAA) refers to apocrine atypia within SA [134-137]. There are no typical radiological features that distinguish apocrine adenosis from other forms of adenosis [138]. AAA is rare, with a reported incidence of approximately 0.4% [135,139]. Histologically, apocrine change is distinctly characterized by enlarged cells, with abundant granular, eosinophilic cytoplasm and well defined cellular borders [135]. Large round nuclei with vesicular chromatin and conspicuous nucleoli are typically present [135,140,141]. Similar to SA, stromal fibrosis may accompany the epithelial apocrine changes (Fig. 3-D). Variable criteria primarily based on architectural changes, nuclear features, and extent of the disease has been used to classify atypical apocrine proliferations. It is generally agreed that the term “cytologic atypia” in apocrine lesions refers to nuclear enlargement of at least 3 –fold increase in nuclear size compared to normal apocrine cells, prominent single or multiple nucleoli, increased nuclear to cytoplasmic ratio, nuclear hyperchromasia and focal mitosis [134,135,142]. Where to draw the line between apocrine atypia and apocrine DCIS is still a matter of debate among experts and is also beyond the scope of this article. Marked proliferation of atypical apocrine elements in SA is difficult to distinguish from apocrine DCIS and invasive carcinoma [8,137,143]. Disruption or focal loss of myoepithelial cell layer in apocrine lesions has been described [135,144], hence, caution should be exercised when evaluating CNB of sclerotic apocrine lesions in which the differential diagnosis of invasive carcinoma is being considered [134].

5.3. Microglandular adenosis

One of the most problematic lesions in breast CNB is microglandular adenosis (MGA). MGA is a glandular proliferative lesion that mimics and can give rise to invasive breast carcinoma. MGA can occur at any age, affecting women from 28 to 82 years [8,145]. It may clinically present as a palpable mass or as an incidental finding on CNB performed for other reasons [8]. No specific mammographic or

ultrasonographic findings have been described for MGA [8]. MRI may show a mass with moderate early and delayed enhancement [8].

In contrast with other forms of adenosis, the glands in MGA are distributed in a non-lobulocentric pattern and lack a myoepithelial cell layer. MGA is composed of small, round glands lined by a single layer of flat-to-cuboidal epithelial cells, with round nucleus and inconspicuous nucleoli [8]. Intraluminal periodic acid-fast (PAS) and mucicarmine positive secretions, and microcalcifications may be present [8,145]. In atypical MGA, the glandular pattern is retained; however, the cells display cytologic and architectural atypia [145,146]. Cartilaginous or chondroid metaplasia sometimes occurs in atypical MGA or in carcinoma arising in MGA [146].

The association between MGA and invasive carcinoma has been documented clinically and pathologically [147,148]. The morphologic features of the associated invasive carcinoma vary; invasive ductal carcinoma of no-special type, adenoid cystic carcinoma [147,149], or invasive carcinoma that recapitulates the morphology of MGA and atypical MGA, being the most common types [147,150]. The invasive carcinoma arising in MGA disrupts the basement membrane and typically shows necrosis, frequent mitotic figures and is surrounded by a lymphocytic reaction [8].

5.4. Differential diagnosis and Immunohistochemistry

The different forms of adenosis should be discriminated on CNB because the management may differ. For SA, the main consideration in the differential diagnosis is invasive carcinoma. As previously mentioned, SA is a lobulocentric proliferation in contrast to the haphazardly arranged glands seen in invasive carcinoma [9]. Also, in cases of SA, the basement membrane and a MEC layer are usually identified on H&E sections [8]. However, occasionally the degree of stromal sclerosis makes this identification difficult. Cytologic atypia, even in low-grade carcinomas, typically exceeds that seen in cases of sclerosing adenosis. Yet, on CNB, evaluation of all these features may be limited by the size of the biopsy and stains may be required [8]. Special stains for reticulin, laminin, PAS or collagen IV can be used to delineate the basement membrane around areas of SA. However, IHC stains for myoepithelial markers, including p63, calponin and SMA, are likely to provide more reliable results [8,110,151].

Lesions in the differential diagnosis of apocrine adenosis with or without atypia include apocrine DCIS involving SA, LCIS (pleomorphic variant), and invasive apocrine carcinoma. The presence of architectural patterns characteristics of DCIS, marked pleomorphism, necrosis or multiple mitotic figures favor a diagnosis of DCIS [8]. As with SA, the presence of stromal sclerosis compressing the atypical apocrine cells, may lead to its misinterpretation as invasive carcinoma [135]. Awareness of this possible diagnostic pitfall is the first step for a correct diagnosis. When in doubt, immunohistochemical stains with MEC markers can be used to confirm the diagnosis. In addition, apocrine adenosis with or without atypia stain positive for PAS (periodic acid-Schiff), EMA (epithelial membrane antigen), CK8, CK18, androgen receptor and GCDFP-15 (gross cystic disease fluid protein 15) but negative for ER and PR. The lack of cellular cohesion in pleomorphic LCIS is a helpful clue towards the correct diagnosis, since atypia and eosinophilic cytoplasm are shared by both entities. Pleomorphic LCIS is usually positive for GCDFP-15, a marker of apocrine differentiation, and negative for E-cadherin [152-154].

The histologic differential diagnosis of MGA includes well-differentiated invasive ductal carcinoma, tubular carcinoma and other forms of adenosis such as sclerosing adenosis [155]. Similarly to well-differentiated invasive carcinoma, MGA displays in infiltrative, disordered growth pattern and lacks myoepithelial cells. Tubular carcinoma is usually composed of glands with angular edges and variable size [8] whereas MGA is composed of small, uniformly open, and round glands in dense, hypocellular, fibrous or fatty mammary stroma. The absence of stromal desmoplasia and the presence of a thickened basement membrane help distinguish MGA from invasive carcinoma [155].

Distinction between other forms of adenosis and MGA is important to avoid undertreatment because, even though MGA is a benign lesion, it may recur if not completely excised. It is also advisable to excise MGA diagnosed on CNB to entirely evaluate the lesion and exclude areas of atypia or invasive carcinoma, whereas SA diagnosed on CNB does not require excision [148,155].

The epithelial cells of MGA, atypical MGA and carcinoma associated with MGA have a dual basal and luminal pattern by IHC. The lesions are positive for S100, CK8/18 and EGFR [145,148] and negative for ER, PR, HER2, GCDFP-15, CK5/6 and EMA [8,147,149]. This immunophenotype differs from low-grade invasive carcinoma that tends to be strongly positive for ER, PR and EMA [8,147]. In the distinction between MGA and invasive carcinoma, Ki-67 and p53 has proven to be helpful. In their study of 11 cases of MGA, Khalifeh et al., found that Ki-67 and p53 labeling indices were significantly increased in cases of invasive carcinoma arising within MGA ($< 3\%$ in all MGA, 5% to 10% in MGA with atypia and $> 30\%$ in carcinomas arising from MGA) [148].

5.5. Prognosis and treatment

Similarly to other proliferative lesions without atypia, SA is considered a low risk factor for the subsequent development of breast cancer, with an associated relative risk of 1.7–2.1 [3,12,123,131]. Surgical excision is not routinely recommended for cases of SA diagnosed on CNB, unless they are associated with other proliferative lesions such as RS/complex sclerosing lesion, atypia or there is radiological/pathological discordance [8,156].

The association between apocrine metaplasia and invasive breast carcinoma has been questioned in the literature. The presence of molecular alterations in some benign proliferative apocrine lesions had raised the idea that a group of these lesions may be clonal; though there is currently not enough data to draw a definitive conclusion [134]. However, it is of current consensus that apocrine metaplasia is not a precursor of carcinoma [135]. Because AAA is rare, long term follow-up studies that include large number of cases are not available. Some authors have found an increased risk when associated with proliferative lesions, whereas others have found no association [135,157,158]. Currently, it is believed that AAA may not be a precursor of invasive breast carcinoma and that, when in isolation, is not associated with increased breast cancer risk [135,139,159].

Several studies have reported the progression from MGA and atypical MGA to invasive carcinomas [146,148,160-162]. Carcinoma has been found in approximately 30% of patients with MGA [8]. Molecular analysis have suggested that these lesions are clonal neoplastic lesions and non-obligate precursors of high-grade triple-negative breast cancers, as synchronously diagnosed ipsilateral MGA, atypical MGA and invasive carcinomas display similar patterns of copy number alterations, mutation profiles and immunohistochemical expression patterns [145,147,160,163-165]. The prognosis and behavior of MGA, atypical MGA and carcinoma associated with MGA are difficult to determine because of their rarity; but it appears that underestimation of the tumor extent is not uncommon [148,166].

6. Cellular fibroepithelial lesions

Fibroepithelial lesions consist of a group of biphasic neoplasms that demonstrate both, epithelial and stromal proliferation [9]. The most common entities included in this group are fibroadenoma (FA) and phyllodes tumor (PT). The latter is sub-classified into benign, borderline and malignant categories based on several stromal features such as cellularity, atypia, overgrowth, and presence of mitosis as well as the nature of the tumor margins [9]. Diagnosis of these lesions on CNB remains a challenging task, mainly due to their histological heterogeneity and overlapping features.

6.1. Fibroadenoma

FA occurs frequently in women of childbearing age [9], with a mean age of 30 years [167]. The most common presenting symptom is a painless, solitary, firm or rubbery, well-circumscribed mass [8,9]. Radiographically, FA presents as a nodular, well-circumscribed lesion [9].

FA is a hyperplastic lesion of the specialized intralobular stroma with the adjacent glandular structures secondarily distorted by the stromal proliferation [8,168]. There are two distinct histologic growth patterns; intracanalicular and pericanalicular [8,9]. The pericanalicular pattern is observed when the stromal cells proliferate around the ducts in a circumferential fashion [9]. The intracanalicular pattern is observed when the stromal growth compresses the ducts and causes slit-like spaces [8,9]. These two patterns are clinically irrelevant; however, the intracanalicular growth pattern in FA may be mistaken for a PT, especially on CNB.

The stroma of FA is typically homogeneous and may range from hypocellular to hypercellular. In the usual type of FA the proportion between stroma and epithelium are evenly balanced throughout the tumor [8]. Cellular FA is defined by prominent cellular stroma and may show overlapping histologic features with PT [9]. Nevertheless, stromal heterogeneity is rare in FA. Juvenile FA is also characterized by prominent stromal cellularity, in addition to a pericanalicular growth pattern and epithelial hyperplasia [8,9]. This type of FA can show a higher mitotic count and grow large, especially in adolescent patients [8,9]. Complex FA is defined as fibroadenomas with associated fibrocystic changes, including cysts larger than 3 mm, papillary apocrine hyperplasia, sclerosing adenosis and calcifications [9]. Myxoid changes and calcifications may be observed in FA; however, lipomatous, smooth muscle and osteochondroid metaplasia are much more rare [9]. In lesions with prominent myxoid stroma, the term myxoid FA can be used (Fig. 4-A) [9]. Myxoid FA have been associated with Carney syndrome [169]. ADH, ALH, DCIS, LCIS and invasive carcinoma may arise from or involve a FA (Fig. 4-B) [9]. Atypia found within a FA cannot predict for the presence of atypia within the adjacent mammary tissue and does not seem to result in a clinically meaningful risk of future development of breast carcinoma [170].

6.2. Phyllodes tumor

PT account for 2–3% of fibroepithelial tumors of the breast and 0.3–1% of all primary tumors of the breast [9,171–173]. PT typically occurs in patients between 35 and 55 years [171], approximately 15–20 years older than the median age of patients with FA [9,174]. Radiologically, PT also present as a nodular mass [9]. Uncommonly, suspicious findings such as irregular margins and heterogeneous appearance are present [8,175]. However, clinically and radiologically, there are not reliable features that can distinguish FA from PT [8,176], although PT may be suspected in lesions larger than 4 cm and with rapid growth [8].

PT is characterized by expansion and increased cellularity of the stromal component. The enhanced intracanalicular growth pattern creates clefts lined by a layer or epithelial and MEC [9]. Areas of stromal condensation with associated increased mitotic activity may be identified near the epithelial components [8]. Benign PT are characterized by well-defined tumor borders, mild stromal cellularity, none to mild atypia, < 5 mitotic figures per 10 high power field (HPF) and lack of stromal overgrowth or malignant heterologous components [9]. Borderline PT is characterized by typically well-defined or focally permeative tumor borders, moderate stromal cellularity, mild or moderate stromal atypia, absent or focal stromal overgrowth and no malignant heterologous components [9]. Mitotic activity is in the range of 5–9 per 10 HPF. Stromal overgrowth, defined as the absence of epithelial elements in at least one low power microscopic field [9] (4× lens and ×10 ocular objective) is more common in high-grade malignant PTs, but can also occur in borderline PT [8,177]. Malignant PTs usually reveal abundant mitotic activity (> 10 per 10 HPF), significant stromal cellularity and atypia, permeative tumor borders and may have malignant heterologous elements (Fig. 4-C) [8,178].

Like in FA, the epithelial cells in PT can give rise to atypia and carcinoma, however, this finding is uncommon [179,180].

6.3. Differential diagnosis and Immunohistochemistry

When classical features are present, the diagnosis of fibroadenoma and malignant phyllodes tumor on CNB is not difficult. The real problem arises when trying to differentiate cellular FA from benign and occasionally borderline PT. Phyllodes tumors commonly have stromal heterogeneity with areas resembling FA [8]. Pseudoangiomatous stromal hyperplasia (PASH) can be a prominent feature of PT [8] but can also be seen in FA. Lipomatous, cartilaginous and osseous metaplasia may occur in benign PT, but are more common in borderline and malignant cases [8,9]. Presence of giant cells in the stroma of FA and PT has been reported [181-184]. These giant cells may show multinucleation, pleomorphism, hyperchromasia and even floret-like nuclear arrangement [8]. Stromal cellularity and pleomorphism, increased mitotic activity and stromal overgrowth also favor the diagnosis of PT [185,186]. Infiltrative versus pushing tumor borders is also a useful diagnostic feature. However, in limited CNB samples, the evaluation of these morphologic characteristics is often not possible. In such cases, the diagnosis of “cellular fibroepithelial lesion” is recommended with deferral of final classification to the excisional specimen (Fig. 4-D) [9,185-187].

Lesions that may be considered in the differential diagnosis of fibroadenomas include fibroadenomatoid changes and hamartomas. Fibroadenomatoid changes or hyperplasia shares histologic features with FA but lacks the well-defined borders [188]. Hamartomas are well demarcated neoplasms composed of varying proportions of normal breast tissue components [9]. Differentiation of hamartomas from FA is difficult on CNB and the diagnosis is typically made on surgical excisions [189]. On CNB, fibromatosis may mimic benign and borderline PT. The presence of epithelial-lined clefts and CD34 IHC expression are useful features for the diagnosis of PT [187]. The main differential diagnosis of malignant PT includes metaplastic carcinomas and primary sarcoma of the breast. IHC stain with p63 is helpful in differentiating malignant PT versus metaplastic carcinoma. The distinction between malignant PT and primary breast sarcoma relies on the identification of residual epithelial structures in the former [9].

The use of Ki-67 proliferation marker to assess the degree of proliferation of the stromal cells has been used by some. Published studies show that Ki-67 index is increased in borderline and malignant PT [190]. However, no cutoff Ki-67 value has been established for the differentiation of different types of fibroepithelial lesions, and therefore, in our practice we do not use Ki-67 for this purpose.

The stromal cells of FA show variable positivity for CD34, actin, and PR [8]. CD34 is consistently expressed in benign and borderline PT, but it is reduced in malignant PT [191-194]. Similarly, stromal nuclear β-catenin staining can be seen in fibroadenomas, benign and borderline PT with decreased expression in malignant PT. This significantly limits the use of β-catenin in the differential diagnosis between fibroepithelial lesions and other spindle cell lesions such as fibromatosis on CNB [190,195]. Although typically focal and patchy, CK staining can be observed in PT [8]. This is significant when metaplastic carcinoma is in the differential diagnosis. P63 IHC stain is helpful in this setting since it is positive in metaplastic carcinoma and most of the time negative in PT [194].

6.4. Prognosis and treatment

Most fibroadenomas diagnosed on CNB do not require excision and do not recur if excised [9] The relative risk of developing invasive

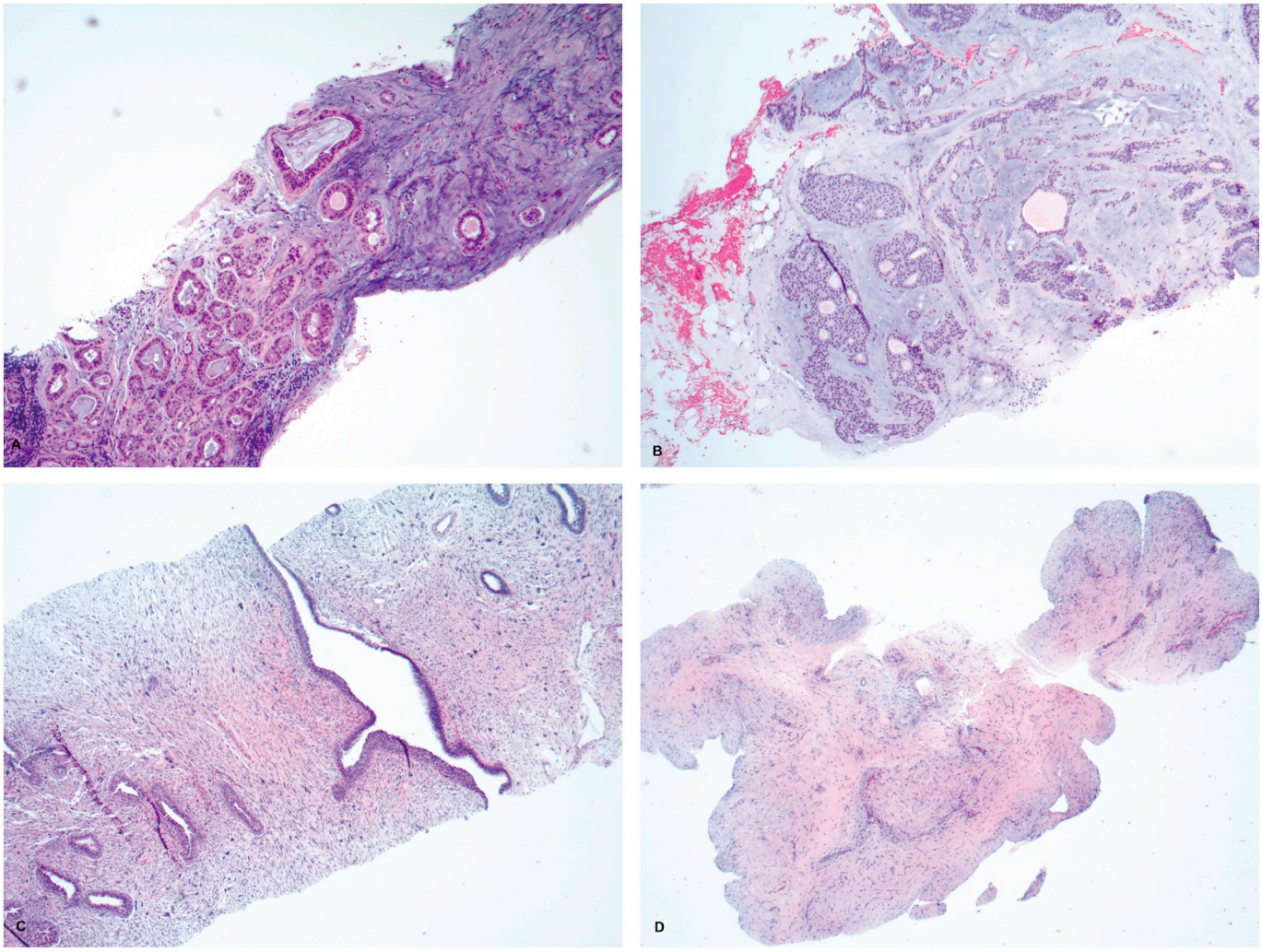

Fig. 4. A, Fibroadenoma with myxoid stroma, small cysts and apocrine changes (hematoxylin-eosin, original magnification ×50).
B, Fibroadenoma involved by atypical ductal hyperplasia seen as an intraductal proliferation of monotonous glands with cribriform architecture, measuring < 2 mm (hematoxylin-eosin, original magnification ×50).
C, Fibroepithelial lesion revealing significant stromal cellularity and pleomorphism diagnosed as malignant phyllodes tumor on core needle biopsy. The diagnosis was later confirmed on excision (hematoxylin-eosin, original magnification ×20).
D, Core needle biopsy of a fibroepithelial lesion composed predominantly of stromal elements with moderate cellularity and compressed epithelial slits. There was no atypia of mitosis in the stroma. This case was diagnosed as "fibroepithelial lesion, favor benign phyllodes tumor". This diagnosis was later confirmed on excision (hematoxylin-eosin, original magnification ×20).

breast carcinoma in patients diagnosed with FA has been reported to range from 1.6 to 2.6 and may be related to the presence of complex features [8,9,196-198].

Currently, there is no definitive evidence to support that FA can undergo malignant transformation. Rare reports in the literature appear to be poorly documented cases of PT initially misdiagnosed as FA on minimally invasive procedures or PT tumors diagnosed in patients with a past history of FA [199,200–202].

Surgical excision of cellular fibroepithelial lesions diagnosed on CNB has been associated with upstaging to PT in 18–42% of reported series [203-207]. Currently, the National Comprehensive Cancer Network guidelines (NCCN) recommends that palpable masses suspicious for PT due to rapid growth and a size > 3 cm be evaluated for surgical excision [203,208]. Reported local recurrence rates for PT range from 3 to 27% for benign, 18 to 42% for borderline, and 13 to 53% for malignant PT [209]. Therefore a wide surgical margin (at least 1 cm) is recommended for these tumors [178,210]. Recurrence usually occur within 2–3 years and distant metastasis, almost exclusively seen in malignant PT, may involve nearly any internal organ, but the lungs and bones are the most common sites [9].

7. Conclusions

The diagnosis of some benign, borderline and in-situ lesions of the breast is without doubt one of the most challenging areas in surgical pathology. These lesions are especially difficult when only small areas are sampled by core needle biopsy. Nevertheless, the histologic diagnosis dictates the patient management and ultimately the prognosis and follow-up. Pathologists' familiarity with the histologic features, possible pitfalls and inherent diagnostic limitations of CNB is essential. Yet, in some cases, a definitive diagnosis cannot be reached on CNB and surgical excision should be recommended.

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