



Precision pathology as applied to breast core needle biopsy evaluation: implications for management

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Abstract

With the shift to de-escalation of therapy for some breast cancers and fewer surgical excisions for high-risk lesions identified on breast imaging studies at one end of the spectrum, and the greater use of neoadjuvant systemic therapy at the other end, pathologists are ever more critical in guiding management decisions for women with breast disease following core needle biopsy. One important consequence of this shift in management paradigms is the elimination of the opportunity for a “second-look” with the excision specimen to confirm or refine the diagnosis rendered on core needle biopsy. Thus, not only is there the imperative for accuracy and precision of core needle biopsy diagnoses, increasingly it is the only opportunity for that diagnosis.

Introduction

Core needle biopsy is firmly established as the gold standard for tissue acquisition for pathologic evaluation following identification of a palpable or radiologic abnormality of the breast. The large majority of core needle biopsy specimens are readily diagnosed as the pathologic correlate of a palpable or image-detected mass, such as fibroadenoma or invasive ductal carcinoma, or lesions associated with microcalcifications, such as ductal carcinoma in situ (DCIS) or sclerosing adenosis. The focus of this article will be diagnostic challenges encountered on core needle biopsy, particularly given the shift to fewer surgical excisions for benign and some atypical lesions; and in an era of greater use of neoadjuvant systemic therapy (NAST), where there is an imperative to consider non-breast primaries prior to the initiation of treatment, mimics of invasive breast carcinomas will be discussed.

Radiologic–pathologic correlation

In order to appropriately interpret any breast core needle biopsy specimen, the pathologist must have knowledge

about the imaging target; that is, whether the target lesion is a mass, an area of microcalcifications or an area of non-mass enhancement (NME) or architectural distortion. It is also helpful to know the imaging modality with which the lesion was detected, or is best seen, which frequently correlates with the type of lesion detected. Masses are often best seen on ultrasound, calcifications, and architectural distortion/asymmetry on mammographic studies and NME on MRI studies. The BIRADS (Breast Imaging Reporting and Data System) is used by breast imagers to categorize mammographic findings into degree of suspicion for malignancy (Table 1) [1]. Most specimens procured will be from lesions categorized as BIRADS 4B or higher. The onus for determination of radiologic–pathologic concordance lies with the radiologist performing the biopsy, but the pathologist bears the responsibility for ensuring every effort has been made to correlate the pathologic findings with the imaging studies, which may include obtaining additional levels to identify calcifications not present on the initial sections, or to rule in/out a mass-forming lesion. Any discordant diagnosis requires reconciliation.

Radiologic–pathologic correlation conferences are a useful forum in which to review biopsies that appear to be discordant. Radiologic review of the imaging studies with colleagues may dispel initial concerns about an imaging finding permitting downgrading of the level of suspicion and thereby determination of concordance with non-specific benign pathologic findings. Cases where discordance between the imaging studies and the pathologic findings remains require further work-up, either with repeat core

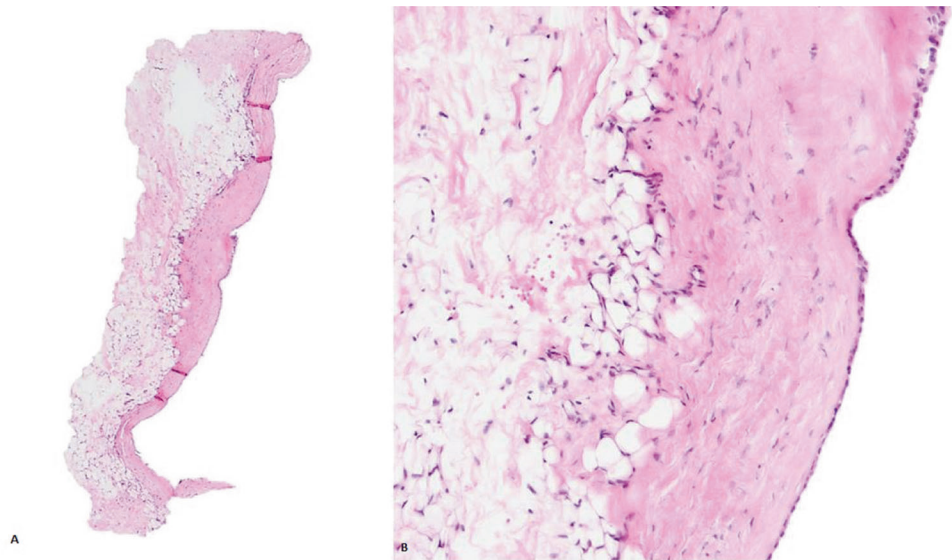
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Table 1 American College of Radiology BIRADS Assessment Categories [1].

BIRADS category	Management and likelihood of malignancy
0—Incomplete	Need additional imaging evaluation and/or comparison with prior images
1—Negative	Routine screening; essentially 0% likelihood of malignancy
2—Benign	Routine screening; essentially 0% likelihood of malignancy
3—Probably benign	6-month follow-up or continued surveillance; >0 to ≤2% likelihood of malignancy
4—Suspicious	4A: low suspicion for malignancy, >2 ≤ 10% 4B: moderate suspicion for malignancy, >10 to ≤50% 4C: high suspicion for malignancy, >50% <95%
5—Highly suspicious	≥95% likelihood of malignancy
6—Known malignancy	Biopsy proven malignancy

Fig. 1 Cyst wall. **a** On low power, this fragment of fibroadipose tissue is not immediately striking; however, notice the denser fibrous tissue and attenuated epithelial lining at the edge of the tissue core. **b** On higher power, the attenuated epithelial lining is better appreciated. In the appropriate radiologic context, these features may be a sufficient correlate for an image-detected breast mass.



needle biopsy, surgical excision, or short interval imaging follow-up.

Microcalcifications

Mammographically-detected microcalcifications are a common indication for core needle biopsy. The most radiologically suspicious lesions are biopsied because of concern for DCIS, but there are many other pathologic entities that may be associated with microcalcifications including microcysts and apocrine cysts—the latter usually associated with translucent, polarizable calcium oxalate crystals as opposed to the more commonly encountered hematoxylinophilic calcium phosphate-, fibroadenomas, adenosis, columnar cell lesions, and atypical ductal hyperplasia (ADH).

Masses

Breast masses are another common indication for core needle biopsy, with the most frequent benign diagnosis

being fibroadenoma. Invasive carcinomas also present as breast masses, either as a clinically palpable mass, or as a screen-detected breast mass. Other pathologic entities that may present as a mass include intraductal papilloma, phyllodes tumor, sclerosing adenosis, cyst or clusters of microcysts/apocrine cysts, lymphocytic mastopathy, and pseudoangiomatous stromal hyperplasia (PASH).

Biopsy of a breast cyst may reveal only tissue cores of apparently fibrous breast parenchyma. Careful review may reveal an attenuated layer of epithelium on the edge of the tissue core that permits diagnosis (Fig. 1). Scattered chronic inflammatory cells may also be present. Recognition of these findings in an otherwise nonspecific biopsy may avoid the need for an excisional biopsy.

Lymphocytic mastopathy is easily overlooked as the pathologic correlate for an image-detected breast mass because the histologic findings are subtle. Clues to the correct diagnosis include recognition of the stromal change, which is best described as having a “waxy” appearance (Fig. 2). Tight clusters of lymphocytes may also be seen around the terminal duct lobular units and blood vessels.

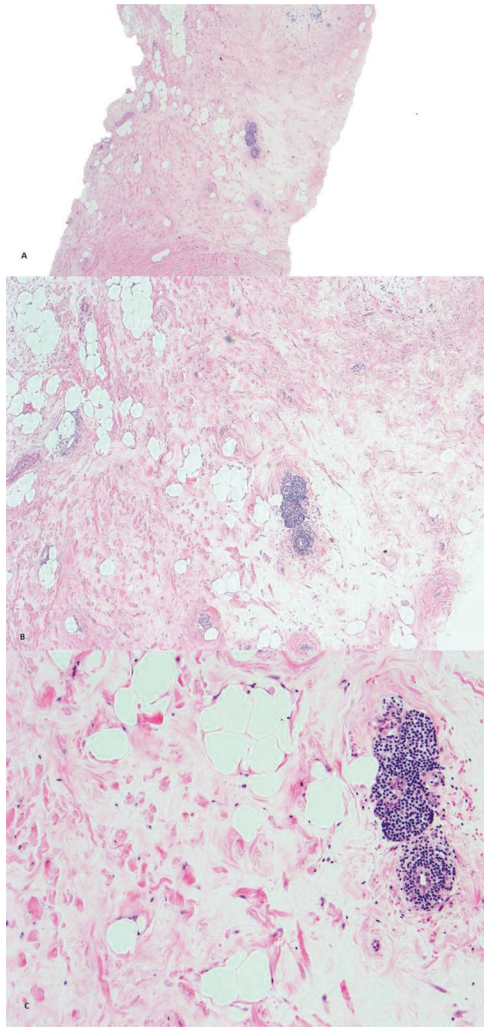


Fig. 2 Lymphocytic mastopathy. **a** On scanning magnification, this core biopsy may appear to be normal. However, the stroma has an unusual appearance. **b, c** On higher power, the presence of lymphocytes clustered around acini and small vessels is apparent, as well as keloidal-like collagen fibers. In this case, epithelioid myofibroblasts are not as obvious. A descriptive diagnosis is appropriate.

Once these two features have been observed, recognition of the epithelioid myofibroblasts and keloidal-like collagen bundles that complete the constellation of features characteristic of this lesion becomes easier [2, 3]. A descriptive diagnosis that raises the possibility of lymphocytic mastopathy is advisable in this setting. Again, if clinically and radiologically concordant, pathologic recognition means surgical excision can be avoided.

Pseudoangiomatous stromal hyperplasia may be the pathologic correlate of an image-detected mass (Fig. 3), but it is important to remember that PASH is a common finding in benign breast biopsies [4]. As such, care should be taken not to give overly significant attribution to the presence of focal PASH in a core biopsy of a breast mass. Concordance

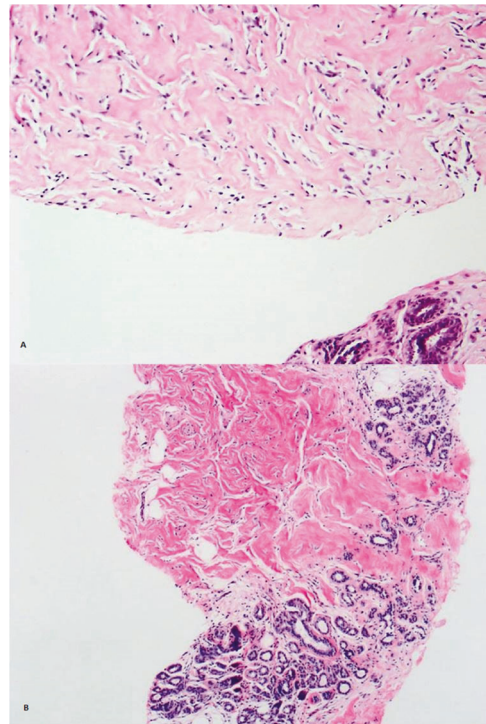


Fig. 3 Pseudoangiomatous stromal hyperplasia (PASH). **a** In this case, it is clear that PASH, is a dominant finding and as such is a good correlate for an image-detected mass. **b** In contrast, the PASH is rather focal in this case, and may not be the pathologic correlate of an image-detected mass. It is important that such focal changes are not overemphasized.

can often be resolved through discussion and review with the radiologist.

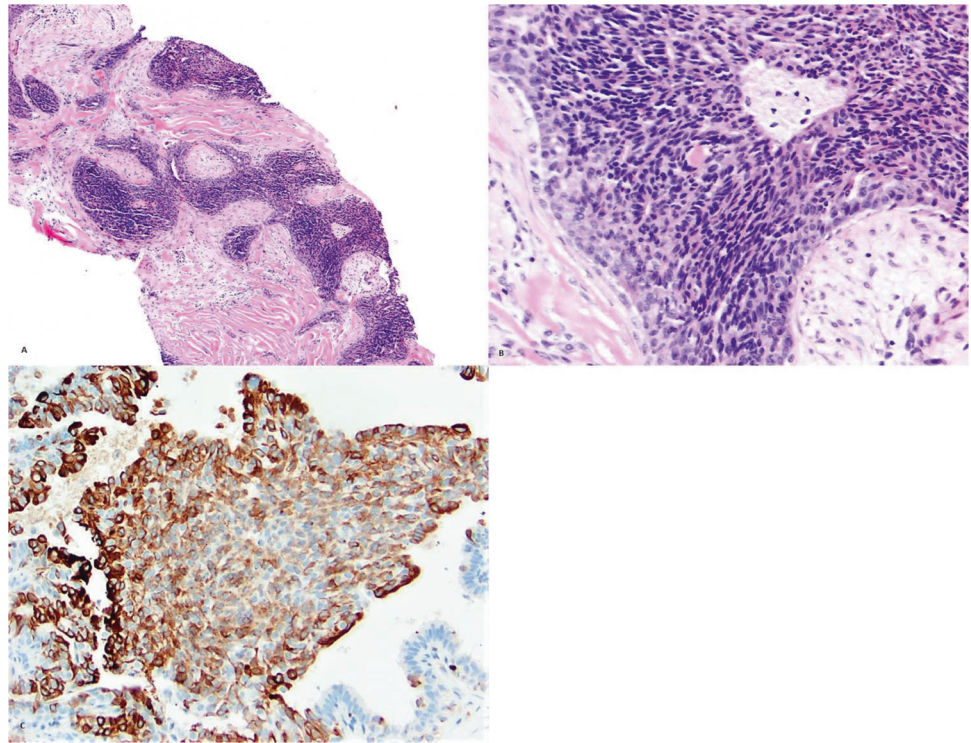
Any case in which histologic features of a mass-forming lesion are not identified following review of additional levels warrants a note in the pathology report to that effect.

Non-mass-like enhancement and architectural distortion

NME is a descriptive term applied to areas of enhancement detected on MRI studies that do not meet criteria for a mass [5]. Several studies have evaluated the pathologic correlates of NME lesions and identified a panoply of diagnoses that may account for this imaging finding including apocrine cysts, PASH, usual ductal hyperplasia (UDH), sclerosing adenosis, ADH, DCIS, and invasive carcinoma [6, 7].

Architectural distortion is also a descriptive term used when there is focal disruption in the normal radiologic pattern of the breast tissue on imaging studies with any modality. Invasive carcinoma is the principal diagnostic concern; other pathologic correlates include benign sclerosing lesions and fat necrosis [8].

Fig. 4 Usual ductal hyperplasia. **a** On low power, multiple spaces appear involved by a florid epithelial proliferation. The spaces are irregular and distorted in contour due to the fibrotic stroma. **b** On intermediate power, streaming of the epithelial cells and some slit-like spaces are appreciated; the epithelial proliferation appears heterogeneous with smaller cells with more hyperchromatic nuclei located in the center of the involved space and larger cells with paler nuclei more peripherally located. Intranuclear inclusions can also be seen. **c** Cytokeratin 5/6 immunostain shows a heterogeneous pattern of expression confirming the H&E impression of usual ductal hyperplasia.



There are a few good practice habits to observe in approaching any core needle biopsy of the breast: (1) it is important to be aware of the imaging findings and the radiologist's differential diagnosis, (2) always obtain additional levels in any case for which a mass lesion or NME lesion cannot be confidently identified, or in which biopsied calcifications are not present, (3) be judicious when ordering immunostains; select wisely a panel that will aid in difficult differential diagnoses (see later discussion); blanket panels as a routine can lead to confusion and are wasteful of resources, (4) finally, it is prudent to rereview the hematoxylin and eosin (H&E) stained slide at the time of hormone receptor and HER2 receptor signout, particularly for triple negative (ER, PR, and HER2 negative) breast cancers to ensure the histology is consistent with a breast primary.

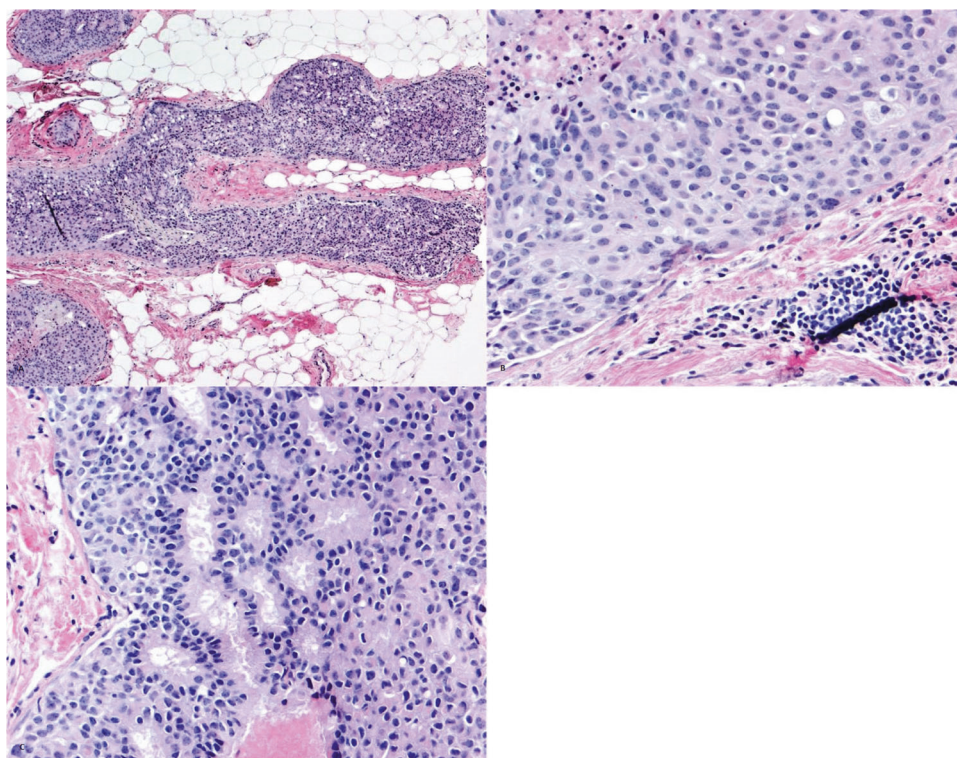
Commonly encountered diagnostic dilemmas

There are several recurring differential diagnoses that pose diagnostic challenges on core needle biopsy. These include distinguishing UDH from intermediate nuclear grade DCIS; lesions on the border of ADH and low nuclear grade DCIS; differentiating DCIS from lobular carcinoma in situ (LCIS), both classic and non-classic variants (refer to Lakhani article); benign sclerosing lesions from invasive carcinomas and distinguishing benign, atypical, and malignant papillary lesions from one another (refer to Brogi article).

Usual ductal hyperplasia vs. ductal carcinoma in situ (UDH vs. DCIS)

Arguably one of the most difficult differential diagnoses in breast pathology is the distinction of UDH from intermediate nuclear grade DCIS. Both are epithelial proliferations composed of sheets of round to ovoid cells with elongated nuclei that vary in size and shape. The cells may appear to stream or swirl within the involved duct or lobule. Slit-like spaces may be present within the epithelial proliferation; there may be little evidence of any cellular polarization. Features that facilitate distinction of UDH from intermediate nuclear grade DCIS include a greater degree of cytologic heterogeneity in UDH, particularly with regard to the nuclear features. In UDH, the nuclei not only vary in size and shape, but also in the degree of hyperchromasia, with some nuclei being darker and others having a clearer, more vesicular chromatin pattern (Fig. 4). In contrast, the chromatin pattern of nuclei in intermediate grade DCIS is very similar from one cell to the next, and the nuclei are larger than those seen in UDH (Fig. 5). The other morphologic feature that may aid in distinguishing these two lesions from one another is the presence of subtle areas of cellular polarization, either around any spaces that may be present or at the periphery of the involved duct or lobule [9]. Identification of this feature would favor a diagnosis of DCIS.

Fig. 5 Ductal carcinoma in situ, intermediate nuclear grade. **a** Low power view reveals an intraductal epithelial proliferation. **b** At higher magnification, the epithelial proliferation appears somewhat heterogeneous with respect to cell placement one to the next; there is variability in the size and shape of the nuclei and no obvious cellular polarization. However, the nuclei do appear rather atypical. **c** In other areas, cellular polarization is striking.



Some cases remain challenging and require adjunctive immunostains to aid diagnosis (Table 2). In this setting a high molecular weight keratin, such as CK5/6, and ER are most useful [10, 11]. UDH is composed of a mixed population of epithelial cells and thus demonstrates a heterogeneous pattern of expression with both CK5/6 and ER. DCIS, on the other hand, is a monoclonal proliferation of neoplastic epithelial cells that express low molecular weight keratin. Thus, DCIS is negative for CK5/6. The nuclei of intermediate grade DCIS typically show strong and diffuse expression with ER.

It is important to note that UDH in and of itself does not have a radiologic correlate and as such is not a frequent imaging target without secondarily involving a sclerosing lesion, for example, to produce an imaging abnormality. The radiologic correlates for DCIS include microcalcifications, architectural distortion, NME lesion, and less commonly a mass-forming lesion. Correlating the imaging findings with the pathology is always important, and may be of some help in guiding interpretation in this situation, though likely less so than in other differential diagnostic settings.

Potential pitfalls

There are two areas that merit special mention in the distinction of UDH from DCIS. The first has been alluded to

above; that is the involvement of benign sclerosing lesions by UDH. In this setting the contours of the ducts and lobules involved by UDH can be distorted by the stromal sclerosis present perhaps giving the impression of irregular nests of lesional cells. In addition, if the stroma is more cellular in this area than in the background breast parenchyma, it could be misinterpreted as being a desmoplastic stroma. Recognizing eosinophilic areas of stromal fibrosis and hyalinization as well as the lobulocentric architecture of the involved ducts and lobules on low power, will aid in identification of the underlying benign sclerosing lesion (see below for discussion of immunohistochemistry in benign sclerosing lesions). Once appreciated, evaluation of the epithelial proliferation can proceed as described above to determine whether the benign sclerosing lesion is involved by UDH or DCIS.

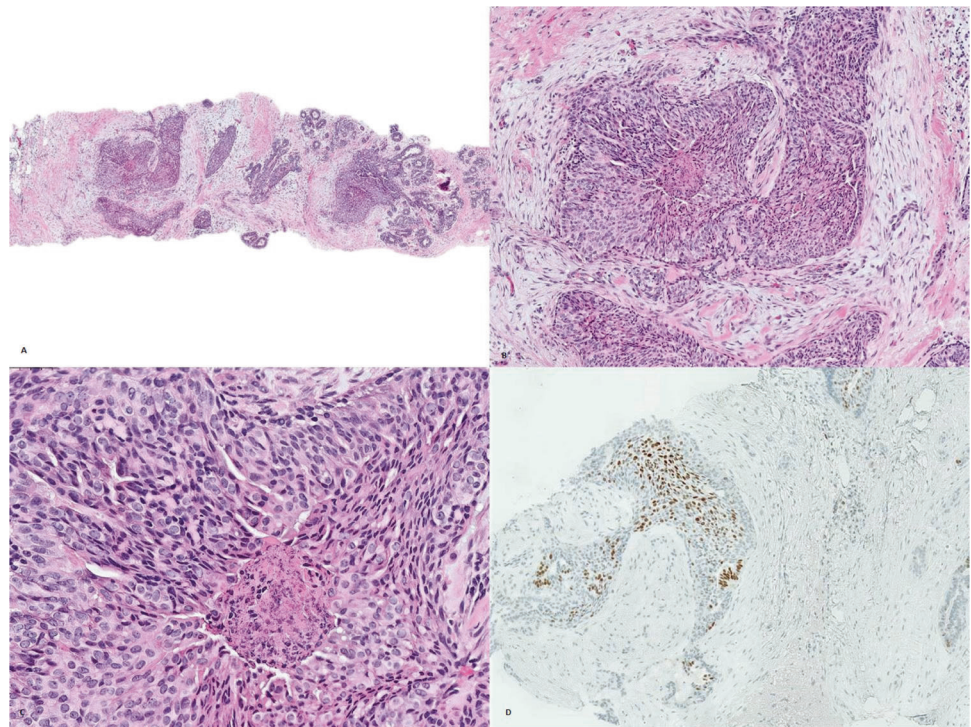
The second potential pitfall is the presence of necrosis in association with the epithelial proliferation (Fig. 6). It goes without saying that the presence of necrosis should heighten the index of suspicion for DCIS, however, it should be noted that necrosis may be seen in association with UDH. In challenging cases, it is good practice to evaluate the characteristics of the epithelial proliferation whilst mentally subtracting the necrosis to determine whether the cellular features of UDH or DCIS are present.

If an error in diagnosis has been made and UDH has been erroneously classified as DCIS, the ER stain performed as

Table 2 Adjunctive immunostains for challenging differential diagnoses on core needle biopsy.

Differential diagnostic challenge	Immunohistochemistry panel	Patterns of expression
UDH vs. DCIS (low and intermediate nuclear grade)	CK5/6 (HMW keratin) and ER	UDH: heterogeneous pattern of expression for both markers DCIS: CK5/6 negative; ER strongly and diffusely positive
ADH vs. DCIS (low grade)	N/A	
DCIS vs. LCIS	E-cadherin and p120 catenin	DCIS: membranous pattern of expression with both markers LCIS: absent or decreased/aberrant expression with E-cadherin; cytoplasmic expression with p120 catenin
Benign sclerosing lesion vs. invasive carcinoma	Myoepithelial cell markers, such as SMMHC, calponin, and p63	Benign sclerosing lesions: positive expression in the myoepithelial cells with all antibodies (though note that reduced or absent expression has been reported) Invasive carcinoma: myoepithelial cells are absent, hence there will be no staining (note the possibility of cross-reactivity with fibroblasts and myofibroblasts; interpret carefully)

Fig. 6 Usual ductal hyperplasia. **a** Scanning magnification view of a case of usual ductal hyperplasia involving a benign sclerosing lesion. **b** Medium power shows the distortion of the ducts created by the sclerotic stroma. Note the presence of necrosis in the center of the epithelial proliferation. **c** Higher power illustrates the cellular heterogeneity characteristic of usual ductal hyperplasia. The myoepithelial cell layer is readily identified. **d** An estrogen receptor (ER) immunostain shows variable positivity supporting the diagnosis of usual ductal hyperplasia.



part of the predictive marker work-up serves as a useful safety check. Any case classified as low or intermediate nuclear grade DCIS ought to demonstrate strong and diffuse nuclear expression with ER. Heterogeneous expression or weak ER expression merits review of the H&E slide to ensure that the lesion is not misclassified UDH.

Finally, it bears mentioning that the impact of misclassifying UDH as DCIS or vice versa has significant management consequences, with the former diagnosis permitting a return to routine breast cancer screening and the latter requiring surgical excision with or without radiation therapy or mastectomy (with some women opting for

bilateral mastectomy following a diagnosis of DCIS on core needle biopsy) [12].

Atypical ductal hyperplasia (ADH) vs. ductal carcinoma in situ (DCIS)

ADH and low nuclear grade DCIS are lesions composed of the same atypical epithelial cells sharing the same cytologic features and many of the same molecular alterations, but which are separated by degree, either qualitatively by degree of involvement of the affected acinus (i.e., incomplete) or quantitatively by linear extent of the ducts and

Table 3 Key features of ADH and low nuclear grade DCIS [13].

	Atypical ductal hyperplasia	Low nuclear grade DCIS
Architecture	Rigid cellular bridges/bars; bulbous micropapillae; round, punched out spaces	
Cytology	Cellular uniformity; even cell placement; distinct cell borders	
Extent	Partial involvement of multiple spaces (i.e., residual normally polarized cells present); complete involvement of <2 spaces or ≤2 mm in extent	Complete involvement of multiple spaces; involvement of ≥2 spaces or >2 mm in extent

lobules involved (≤ 2 mm) or the number of acini involved (< 2 acini) [13]. Lesions exceeding the aforementioned criteria are classified as low nuclear grade DCIS with those meeting or falling short being categorized as ADH. These criteria for ADH and low nuclear grade DCIS were established many decades ago in excision specimens and when accurately applied are associated with a three- to five-fold and an eight- to tenfold risk for the subsequent development of breast cancer, respectively [14–18]. The diagnostic criteria still apply today and are endorsed by the expert editorial board of the WHO Classification of Tumors of the Breast, with the caveat that a more cautious interpretation of the criteria for low-grade nuclear DCIS is appropriate in the limited tissue sampling afforded by core needle biopsy procedures [13]. Definitive categorization of lesions on the threshold can be deferred to an excision specimen.

The key features of ADH and low nuclear grade DCIS are summarized in Table 3. In brief, the cells comprising both of these lesions are round or cuboidal with moderate amounts of amphophilic to clear cytoplasm. The cell borders are distinct often imparting a mosaic pattern to the proliferation. The nuclei are round and monomorphic with even chromatin. Both ADH and DCIS may have a variety of architectural patterns including cribriform, solid, and micropapillary in which the cells polarize around spaces evenly distributed within the proliferation, are arranged in solid sheets within the acini, or form bulbous micropapillations, respectively. Even within the solid pattern, the cells attempt to polarize forming rosettes or microacini that may be appreciated when present [13]. The extent criteria separating ADH from DCIS are as described above.

The majority of cases of ADH and low-grade DCIS are readily distinguished from one another; it is the few lesions on the threshold of these diagnoses that present the most challenge (Fig. 7). Consistent application of criteria permits precision and reproducibility. In the setting of core needle biopsy specimens however, as noted above, a conservative approach is recommended. For lesions on the threshold of a diagnosis of ADH versus DCIS, it is advisable to provide a descriptive diagnosis, such as “severely atypical intraductal proliferation bordering on low-grade DCIS”, rather than a definitive diagnosis of DCIS. The reason for this guidance is that it is prudent to evaluate an excision specimen to ascertain whether the atypical proliferation is limited or

more extensive. ADH and borderline lesions are managed with a conservative surgical excision. Patients with a diagnosis of DCIS rendered on core needle biopsy may be managed with an excision, but for a variety of reasons patients are increasingly opting for mastectomy or even bilateral mastectomy [12]. If there were no further atypia at the time of the definitive surgical procedure, mastectomy would represent overtreatment of a low-grade lesion only a few millimeters in extent. Unequivocal cases of low-grade DCIS should be diagnosed on core needle biopsy. Extent criteria apply only to low-grade DCIS and not to intermediate or high nuclear grade DCIS. There are no clinically available adjunctive tests that aid in the distinction of ADH from low-grade DCIS.

Of note, several countries have initiated clinical trials evaluating the feasibility of a nonsurgical approach to management for women with low and intermediate grade DCIS diagnosed on core needle biopsy consistent with the current interest in de-escalating therapy where there is a low risk of progression to invasive breast cancer (refer to Schnitt article for further discussion of this topic).

Ductal carcinoma in situ (DCIS) vs. lobular carcinoma in situ (LCIS)

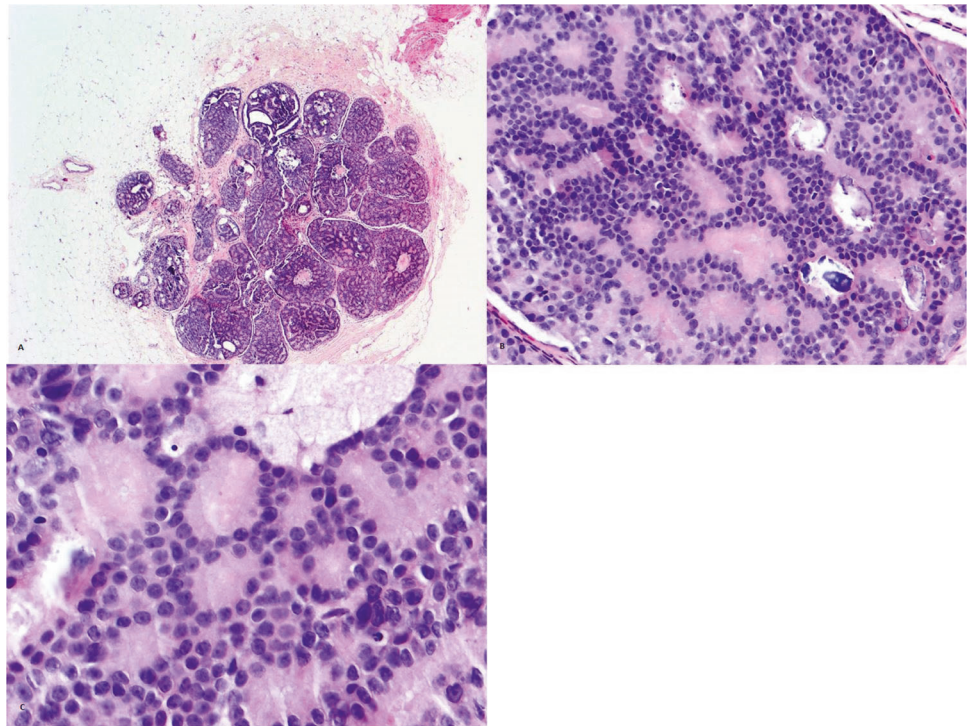
Another potentially challenging differential diagnosis is the distinction of DCIS from LCIS. This may include low nuclear grade DCIS, solid pattern from classic LCIS as well as high nuclear grade DCIS from pleomorphic LCIS, and DCIS with comedo necrosis from florid LCIS [19]. This topic is discussed in the article on Lobular Neoplasia by Dr. Lakhani.

Benign sclerosing lesions vs. invasive carcinoma

Core needle biopsy specimens present a particular challenge for this differential diagnosis as features that guide toward benignity may not be sampled.

In any core needle biopsy specimen with a small glandular proliferation, it is important to evaluate on low power for lobulocentricity: that is, does the proliferation appear to conform to the architecture of a terminal duct lobular unit. Benign sclerosing lesions, such as sclerosing adenosis and radial scar/complex sclerosing lesion, tend to maintain a rounded, lobulated contour that is more easily

Fig. 7 Severely atypical intraductal proliferation. **a** At scanning magnification an atypical intraductal proliferation involving multiple spaces and measuring 2.5 mm in extent is seen. **b, c** At higher magnifications the low-grade cytologic atypia and architectural atypia in the form of microacini and cribriform spaces is appreciated. This case meets criteria for a diagnosis of DCIS, but in the setting a core needle biopsy, a descriptive diagnosis, such as “severely atypical intraductal proliferation bordering on low-grade DCIS”, is advised. The patient elected to have a mastectomy; no residual disease was identified (refer also to figures in Schnitt article).



appreciated on low power. Invasive carcinomas have a more infiltrative border with malignant glands and nests percolating through the fibrous stroma and adipose tissue in a haphazard manner. This lobulocentricity or haphazard infiltration may be the feature that is most difficult to appreciate on core needle biopsy if the lesion is large and the biopsy does not sample the edge of the lesion, at the interface with the normal breast parenchyma.

Stromal fibrosis and hyalinization are more characteristic of benign sclerosing lesions. While some invasive carcinomas can have these features, most have a more cellular or desmoplastic stroma. After assessing for these low power features, the proliferation should be evaluated for the presence or absence of a myoepithelial cell layer. Often, however, this can be difficult to determine as the myoepithelial cells may become attenuated in benign sclerosing lesions, necessitating use of immunohistochemical stains, when there is a diagnostic dilemma. Finally, the epithelial cells should be evaluated to assess for atypia. Involvement of benign sclerosing lesions by carcinoma in situ (LCIS or DCIS) is a well-recognized pitfall in breast pathology for misclassification as invasive carcinoma (Figs. 8, 9).

Immunostains for myoepithelial cells can be extremely helpful in this differential diagnosis. Smooth muscle myosin heavy chain (SMMHC), calponin, and p63 make up a good panel, being suitably sensitive and specific [11]. Another potential pitfall for this differential diagnosis, or the potential for compounding an error in diagnosis, is the observation that there may be reduction in, or loss of,

expression of some myoepithelial cell markers in benign sclerosing lesions [20]. Thus, it is important that a panel of immunostains is used rather than a single marker, and results should be interpreted carefully taking into consideration the morphologic features as well as the staining pattern with the myoepithelial cell markers.

The management impact of an erroneous diagnosis here is also significant. Benign sclerosing lesions, even if involved by classic LCIS, may not require excision. As will be discussed below, there has been a shift away from routine excision for radiologically–pathologically concordant benign lesions, though this has yet to be widely adopted for benign sclerosing lesions. A diagnosis of invasive carcinoma prompts excision or mastectomy, usually with sentinel lymph node biopsy. Remember that evaluation of the ER stain is an opportunity for assuring accurate diagnosis; benign sclerosing lesions involved by UDH will show heterogeneous expression with ER. LCIS and DCIS will both show strong, diffuse expression, so in these situations, it will be the myoepithelial cell makers that will be of greater importance in reaching the correct diagnosis in challenging cases.

Lesions no longer routinely excised

There are several histologically benign lesions that are categorized as “high risk” by the field of breast imaging when identified on core needle biopsy due to the historically frequent association with an upgrade to a more significant

Fig. 8 Lobular carcinoma in situ, involving sclerosing adenosis. **a** At low power, nests of monomorphic epithelial cells are present somewhat haphazardly distributed within a fibrous stroma. It is difficult to determine with certainty whether or not the proliferation is lobulocentric in pattern. **b** At higher power, the atypia in the epithelial cells is appreciated. Cytologic features of a lobular phenotype are present with nuclei that are round and monomorphic and intracytoplasmic vacuoles being readily identified. Myoepithelial cells are difficult to discern, however. **c** A smooth muscle myosin heavy chain immunostain highlights the myoepithelial cell layer, confirming this as an in situ process.

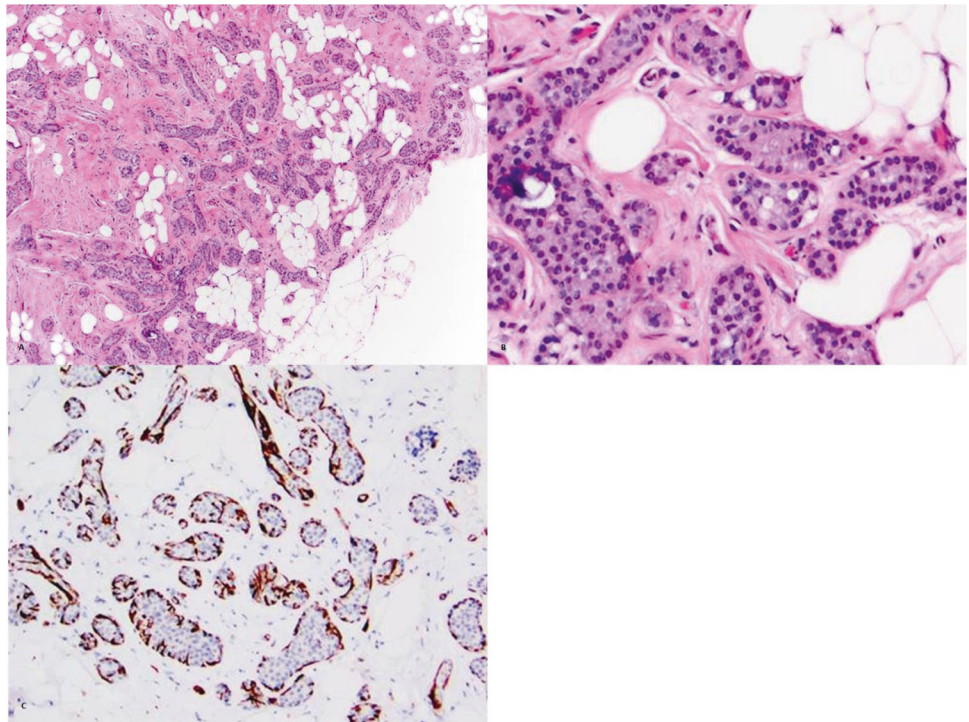
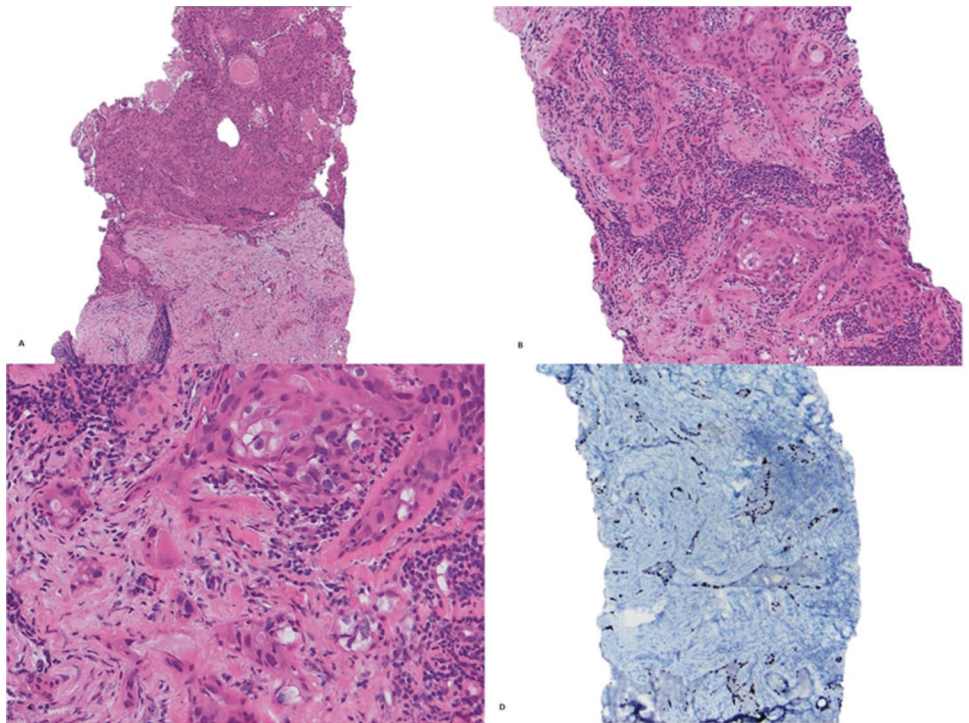


Fig. 9 Ductal carcinoma in situ, involving a complex sclerosing lesion. **a** On low power view a highly atypical epithelial proliferation is seen. Smaller nests appear to be infiltrating through a dense sclerotic stroma in the lower half of the image. **b** On intermediate power, the cytologic atypia of the epithelial cells is apparent. The epithelial cell nests are irregular in contour, which raise concern for an invasive process, however, the presence of stromal sclerosis should signal the need for caution. **c** Higher power view of the small nests present in the stroma. **d** A p63 immunostain confirms the presence of the myoepithelial cell layer around both the smaller and larger distorted epithelial cell nests supporting the impression of DCIS involving a benign sclerosing lesion.

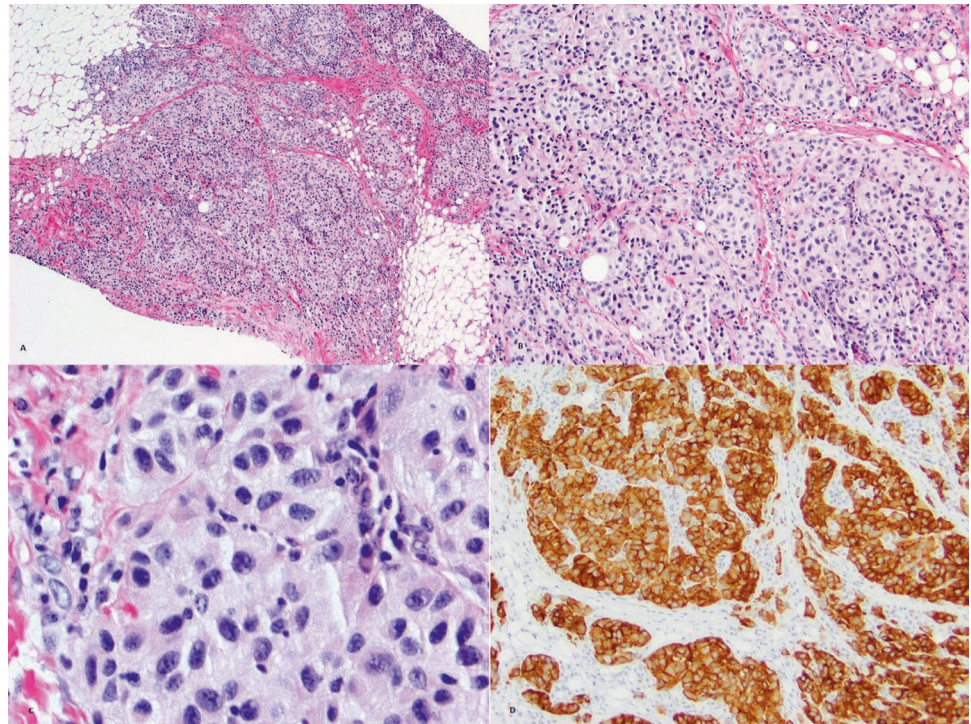


lesion at the time of surgical excision. Much of the data that generated these high upgrade rates was from small studies which included cases that were not always radiologically–pathologically concordant, or cases that were not always excised, or had not had pathologic rereview to

determine if the reported finding in the excision was adjacent to or remote from the target lesion. More contemporary data evaluating upgrade rates for columnar cell lesions, intraductal papillomas, radial scars and benign sclerosing lesions, mucocele-like lesions, and even incidental atypical

Fig. 10 Metastatic melanoma.

a At low power, malignant epithelioid cells are present as solid nests within the fibroadipose tissue. **b** At intermediate power, the abundant eosinophilic cytoplasm is notable. **c** At highest power, the nuclear atypia is readily apparent; however, features of melanocytic differentiation are not obvious. **d** MART-1 immunostain confirms the diagnosis of metastatic melanoma in a patient with known prior history.



lobular hyperplasia or LCIS have much lower upgrade rates of the order of 0–4% [21]. This has allowed for a shift in management, with many of these aforementioned lesions no longer requiring excision in radiologically–pathologically concordant cases. The paradigm shift in management for “high risk” lesions is still evolving [22], but with exploration of de-escalation of therapy for women with DCIS, it is likely that avoiding excision of benign and some atypical lesions must soon follow.

Cancers on core needle biopsy in an era of NAST

NAST is used increasingly for breast cancer patients with palpable tumors particularly if they are either ER, PR, and HER2 negative, or are HER2 positive. These groups of patients are most likely to achieve a complete pathological response and/or downstaging of disease which may convert an inoperable patient to an operable one or a patient who needed mastectomy to one who may be able to choose a conservative surgical excision. In such an environment, the opportunity for a second look to confirm the diagnosis of invasive breast carcinoma or refine histologic type or grade is postponed until completion of chemotherapeutic regimens. Thus, there is even greater imperative to ensure that the diagnosis rendered is the correct diagnosis. As pointed out above, it is always important to review the H&E slide when interpreting the ER, PR, and HER2 immunostains, but especially so when the biomarkers are negative. If there is patient history of a prior cancer, or if there are morphologic

features that raise consideration for a tumor other than breast carcinoma, further work-up is indicated. Breast carcinoma has a tremendous range of appearances, so suggesting further work-up with unusual morphology is not necessarily helpful. Additional clues that a cancer in the breast may not be breast carcinoma include absence of an in situ component, recognizing that sampling issues may be the reason there is no in situ component present or acknowledging that triple negative breast cancers often lack a significant component of DCIS, and extensive lymphovascular space invasion in the presence of a relatively small invasive component.

The tumors most commonly metastatic to the breast include malignant melanoma (Fig. 10), ovarian carcinoma (Fig. 11), lung carcinoma (Fig. 12), and lymphoma (Fig. 13) [23]. Checking the patient’s history is often the most helpful first step in patients with a tumor of unusual morphology and/or triple negative status. Immunostains are usually necessary either to confirm a breast primary or identify a metastasis; patient history will guide the panel ordered. Use of immunohistochemistry in breast pathology is discussed in the article by Dr. Cimino-Mathews in this issue of the journal. The key to reaching the correct diagnosis is to consider the possibility of metastasis in any unusual looking case or triple negative breast cancer.

Correlation of the biomarker status with the morphology of the breast tumor is another critical responsibility, and indeed is now part of the mandated CAP requirements for ER testing in breast carcinoma [24]. In many cases it is

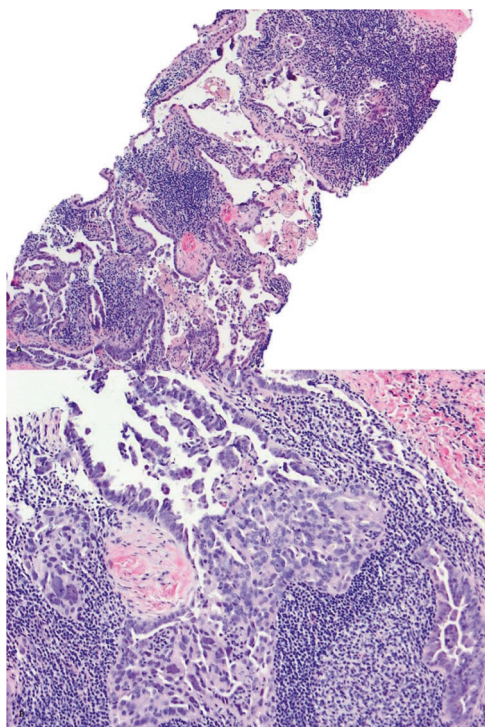


Fig. 11 Metastatic serous carcinoma. **a** Low power view of a malignant glandular and papillary proliferation with associated calcifications. **b** At higher power, marked nuclear atypia is apparent. Nuclear atypia of this degree is unusual in the absence of neoadjuvant chemotherapy.

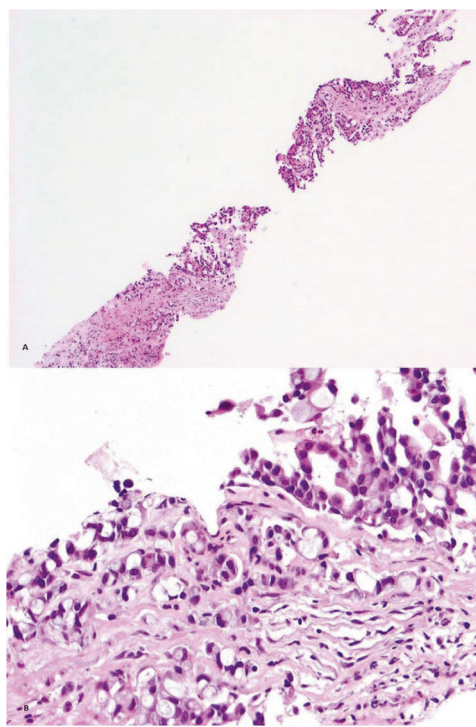


Fig. 12 Metastatic lung carcinoma. **a** Low power view shows an adenocarcinoma with some signet ring cell features. **b** At higher power the signet ring cell features are easier to appreciate. Without a high index of suspicion or knowledge of clinical and past medical history, this case could easily be misdiagnosed as primary breast carcinoma.

possible to anticipate the ER and HER2 expression based on the histologic type and grade of the tumor. Low-grade invasive ductal carcinomas and invasive lobular carcinomas are typically strongly ER positive (>95%). High grade breast carcinomas may be ER positive or negative. Several special histologic types, such as tubular carcinoma, invasive cribriform carcinoma and most mucinous carcinomas are ER positive, others such as adenoid cystic carcinoma are typically ER negative. If the biomarker results do not conform with those expected, review of the H&E slides, the patient history and the immunohistochemistry assay with repeat testing or further work-up is indicated [24]. Examples of situations in which this type of discordance may occur include focal, weak, or absence of ER expression in a well or moderately differentiated glandular proliferation which may be secondary to metastatic lung carcinoma or microglandular adenosis, respectively. Benign epithelial proliferations, such as UDH, sclerosing adenosis, or adenomyoepithelioma (Fig. 14), also fall into this category, as discussed above. With the exception of adenoid cystic carcinomas or some carcinomas arising in association with microglandular adenosis, ER negative breast carcinomas are usually high grade, which is particularly problematic as many of the mimics of hormone receptor negative (or triple

negative) breast carcinomas are also high grade; examples for this situation include metastatic melanoma (Fig. 10), epithelioid angiosarcoma and diffuse large B-cell lymphoma (Fig. 13). It bears mentioning at this juncture, that it is important to be accurate in scoring of ER-low positive breast carcinomas. The availability of highly sensitive ER antibodies has shifted some breast carcinomas from formerly ER negative to ER-low positive tumors. This observation has prompted the adjustment of thresholds for patient enrollment in some clinical trials for the treatment of triple negative breast cancers from <1% of tumor cell nuclei staining to up to 10% nuclear positivity. Thus, accuracy at the lower end of the spectrum has important treatment ramifications.

HER2 positive breast carcinomas are typically high grade, often with fairly abundant eosinophilic cytoplasm, or have apocrine features. Again, accuracy in scoring is critical to patient management. Patients with ER negative, HER2 positive (overexpressing or amplified) tumors may be candidates for neoadjuvant chemotherapy. Most laboratories determine HER2 status using immunohistochemistry. Tumors that are negative (0 or 1+) or positive (3+) do not require confirmatory testing using FISH. FISH testing is mandated for tumors

Fig. 13 Diffuse large B-cell lymphoma. At low power (a) and intermediate power (b), the breast parenchyma is seen to be diffusely involved by solid sheets of malignant epithelioid cells with an admixed lymphocytic infiltrate. High power (c) shows the large pleomorphic nuclei with abundant clear cytoplasm. Breast markers were negative in this case, prompting further work-up. d The tumor cells stain positively with CD20.

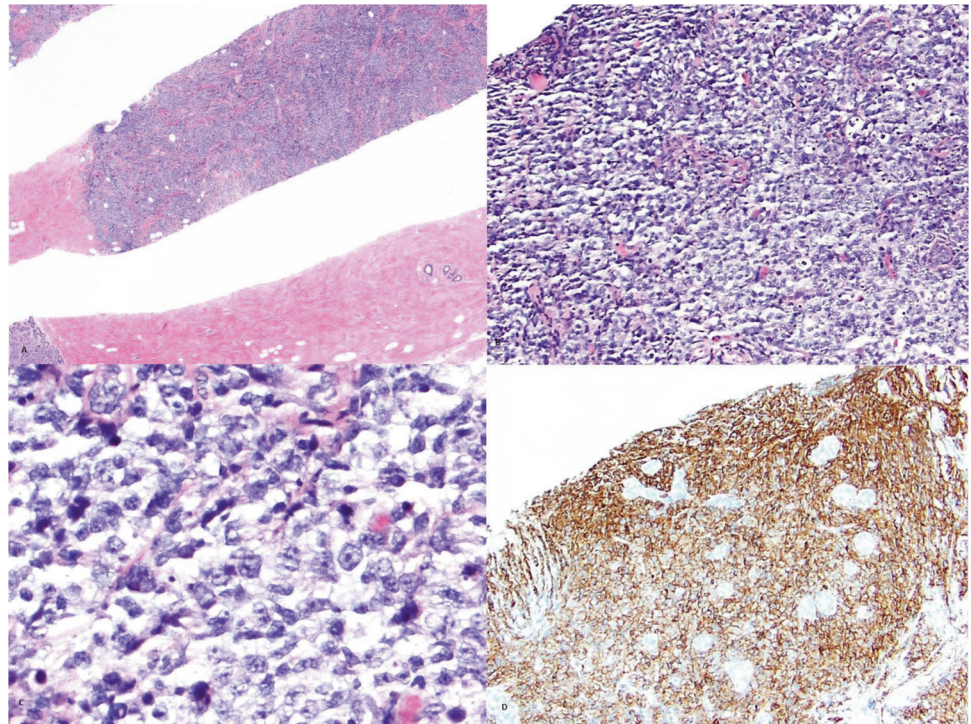
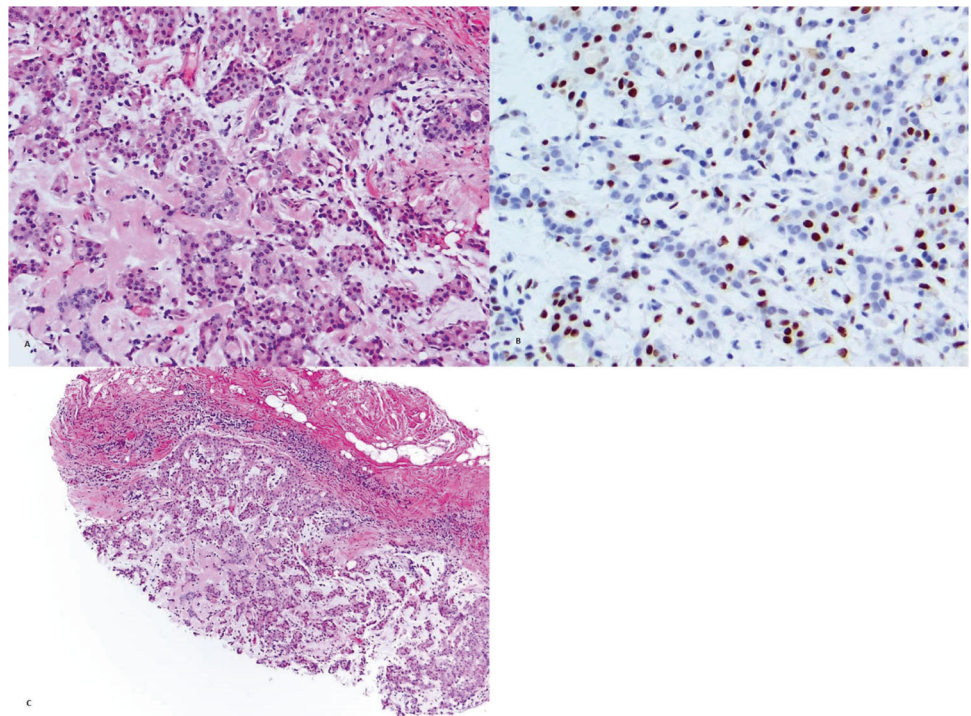


Fig. 14 Discordant estrogen receptor (ER) result. a The original diagnosis rendered for this case was invasive ductal carcinoma, grade 2. b The ER stain shows variable positivity, inconsistent with the original diagnosis. c Re-review of the H&E reveals a circumscribed lesion with myxoid appearing stroma. Further work-up confirmed the diagnosis to be adenomyoepithelioma.



showing 2+ expression on immunohistochemistry to identify cases with HER2 gene amplification and many laboratories follow this guidance, reflex testing only IHC equivocal (2+) cases (Fig. 15) [25]. Thus, ensuring morphology is compatible with HER2 3+ positivity at

the time of interpretation and signout is paramount as patients may receive systemic therapy prior to surgery given the chemosensitivity and frequent complete pathologic response in patients with HER2 positive tumors.

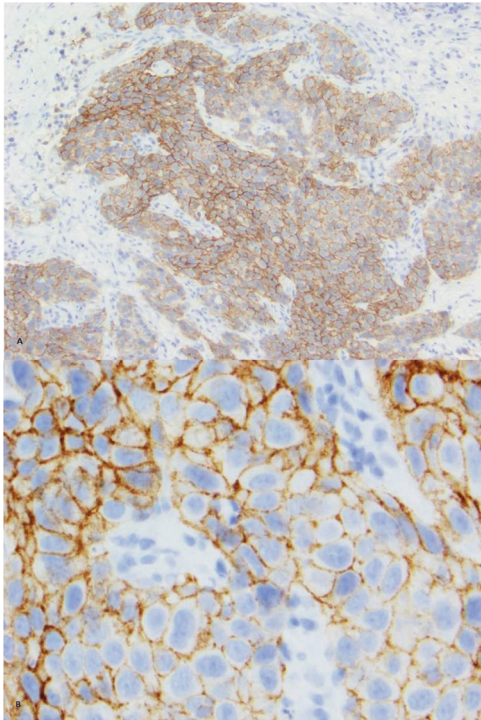


Fig. 15 HER2 immunostain. **a** At low power, it may appear that >10% of tumor cells are showing circumferential membranous staining. However, it should be noted that it is not strong and “crisp”. **b** High power review confirms that the membrane staining is neither intense nor complete and thus the case is better classified as 2+ as opposed to 3+. The tumor was not amplified upon reflex FISH testing.

Conclusion

Breast core needle biopsy is a minimally invasive procedure that provides adequate tissue for diagnosis and treatment decision making in the vast majority of cases. Better data has led to a shift away from surgical intervention for many benign and some atypical lesions formerly excised. For the most part, breast carcinomas are readily recognized and biomarker studies guiding treatment can be performed on these limited samples. There are, however, some pitfalls of which to be aware, particularly in an era of NAST where the opportunity for confirmation of the diagnosis rendered on core needle biopsy prior to treatment is eliminated.

Compliance with ethical standards

Conflict of interest The author declares that no conflict of interest.

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