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# Overview of Pathology Evaluation of Breast Lesions and Quality Assurance

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Michael O. Idowu, Jaime A. Singh,  
and Margaret M. Grimes

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## Masses/Densities/Distortions: General Considerations

Radiologic evaluation of breast masses or architectural distortion generally requires assessment of shape, margin, density, orientation, echogenicity pattern, asymmetry, and enhancements, as defined by Breast Imaging-Reporting and Data System (BI-RADS), depending on the imaging modalities used (mammogram, ultrasound, or magnetic resonance imaging [MRI]). Both benign and malignant breast conditions may present as masses, densities or distortions with or without associated calcifications. Progressive asymmetry of the breast, so-called shrinking breast, may be seen in association with invasive lobular carcinoma. Radiologically identified lesions require biopsies for pathologic evaluation.

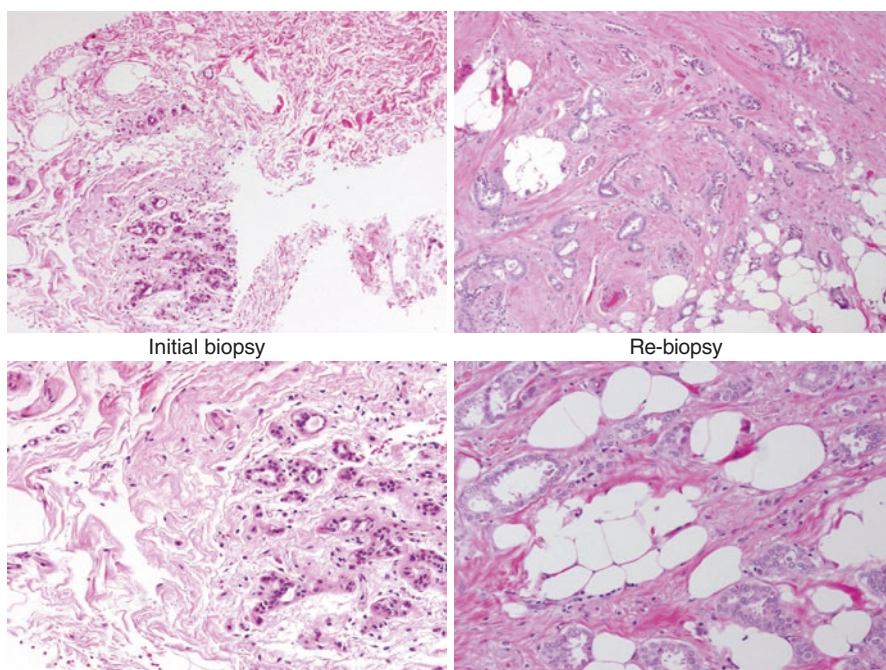
Core needle biopsy performed with ultrasound or with stereotactic guidance is often the first approach to tissue diagnosis. While palpable lesions lend themselves to diagnosis by means of fine needle aspiration (FNA) biopsy, core needle biopsy is preferred for primary breast lesions, because the intact tissue specimen and generally larger sample obtained via core needle biopsy usually allows for a more definitive diagnosis compared with FNA biopsy. In the case of invasive carcinoma, a core needle biopsy more often allows for ancillary testing, such as, estrogen receptor (ER), progesterone receptor (PGR commonly known as PR) and human epidermal growth factor receptor 2/erb-b2 receptor tyrosine kinase 2 (ERBB2 commonly known as HER2). While FNA was a component of the original “triple approach” (physical examination, mammography, and FNA) for initial

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M.O. Idowu, MD, MPH (✉) • J.A. Singh, MD • M.M. Grimes, MD, MEd  
Department of Pathology, Virginia Commonwealth University Health (VCU HEALTH),  
Richmond, VA, USA  
e-mail: [michael.idowu@vcuhealth.org](mailto:michael.idowu@vcuhealth.org); [margaret.grimes@vcuhealth.org](mailto:margaret.grimes@vcuhealth.org);  
[jaime.singh@vcuhealth.org](mailto:jaime.singh@vcuhealth.org)

diagnosis of breast masses, it is currently less commonly used for this purpose in the United States [1–3]. However, when core needle or surgical specimens are not available, cytology specimens are acceptable especially in cases of metastasis [4, 5].

From a pathology standpoint, it is critical to ensure that the radiographically targeted lesion can be explained by the histologic findings [6]. Of utmost importance in assessing core needle biopsies of breast lesions is correlation of the mammographic or clinical findings with the pathology. The pathologist should communicate with the radiologist or clinician if there is apparent radiologic–pathologic discordance, and the pathology report should include a comment to that effect. In cases where clinical/radiologic information is not available to the pathologist, the determination of radiologic–pathologic concordance becomes challenging, and such correlation will depend solely on the radiologists or clinicians. Discordant radiologic–pathologic correlation on core needle biopsies should trigger additional evaluation, re-biopsy, or an excision. For example, a spiculated mass on breast imaging (BI-RADS 4 or 5) diagnosed as benign breast tissue with no specific lesion on histopathology (discordant findings) requires additional evaluation, re-biopsy, or excision to ensure that the targeted lesion has been adequately sampled (Fig. 2.1). The negative discordant findings on histology may be due to sampling or technical difficulties with the biopsy. While the importance of radiologic–pathologic



**Fig. 2.1** Spiculated mass with only benign breast tissue on initial biopsy (*left images*). Re-biopsy performed because of radiologic–pathologic discordance showed invasive ductal carcinoma (*right images*)

correlation cannot be overemphasized, it must be pointed out that correlation and accuracy are not synonymous.

Widely acceptable pathologic diagnostic criteria should be strictly applied to minimize suboptimal management. Accurate assessment of pathologic changes seen in core biopsies performed for mass lesions or distortions requires not only knowledge of pathologic criteria required for diagnosis, but also of the potential pitfalls related to sampling. False-positive and false-negative histologic diagnoses could lead to suboptimal management. Equivocal diagnoses, although occasionally unavoidable, should be minimized [7]. For example, a large, centrally located papilloma will be sampled only partially by a core needle biopsy; absence of atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS) involving the papilloma on core needle biopsy cannot exclude these possibilities on surgically excised specimens. Similarly, it is possible for only DCIS to be present on core needle biopsy, but for invasive carcinoma to be associated with the DCIS on surgical excision. Therefore, optimal management often depends not only on the pathological diagnoses on biopsies but also on clinical and imaging considerations.

The probability of having invasive carcinoma on surgical specimens after a diagnosis of DCIS in core needle biopsies may inform the decision to perform sentinel lymph node sampling. Although controversial, performance of sentinel lymph node(s) samplings following a diagnosis of DCIS on core needle biopsies may eliminate the need for second surgery should invasive carcinoma be identified on surgical excision specimens. Higher probability of invasive carcinoma on surgical excision (with only DCIS on core needle biopsies) may be associated with any one of the following [8]:

1. Extensive calcifications on imaging
2. Palpable mass or solid mass on imaging
3. Lesion larger than 25 mm on imaging
4. High-grade DCIS on histology

Sentinel lymph node mapping is significantly affected following total mastectomy. In view of this, sentinel lymph node sampling is often performed in the setting of total mastectomy, even if the diagnosis on core needle biopsy is DCIS. Currently, sentinel lymph node sampling following DCIS diagnosed on needle core biopsy in the setting of breast conservation surgery is controversial and discouraged, given the potential complications [8, 9].

While there are several breast lesions that may present as masses, distortion, or densities, some of the more common lesions with potential diagnostic challenges and pitfalls will be considered in this chapter.

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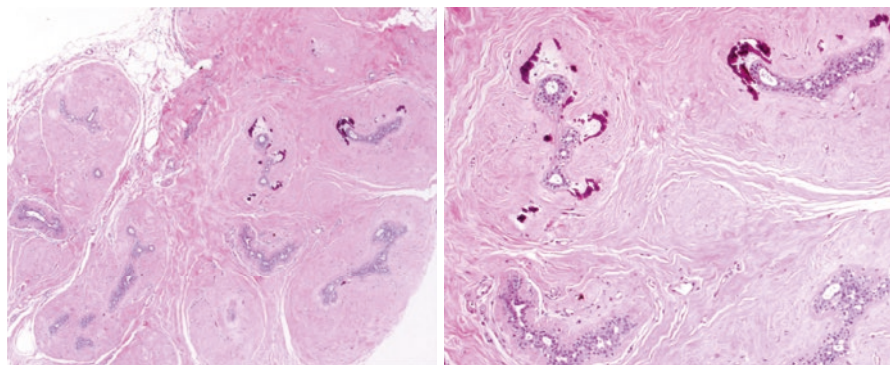
## **Fibroepithelial Lesions: Fibroadenoma and Phyllodes Tumor**

Fibroepithelial tumors are biphasic tumors characterized by both epithelial (ductal) and mesenchymal (stromal) components and consist predominantly of fibroadenoma and phyllodes tumor. Fibroadenoma is more commonly seen in adolescent or young adult women, but may be seen in older or postmenopausal women as well. The stromal component of fibroadenoma can be highly collagenized, myxoid or cellular, but

generally appears homogenous in any given case. In older women, the stroma may be sclerotic and calcified. The stromal component typically compresses the ducts to slit-like “intracanalicular” structures or open and rounded “pericanalicular” structures. There is no evidence that these patterns have biological significance.

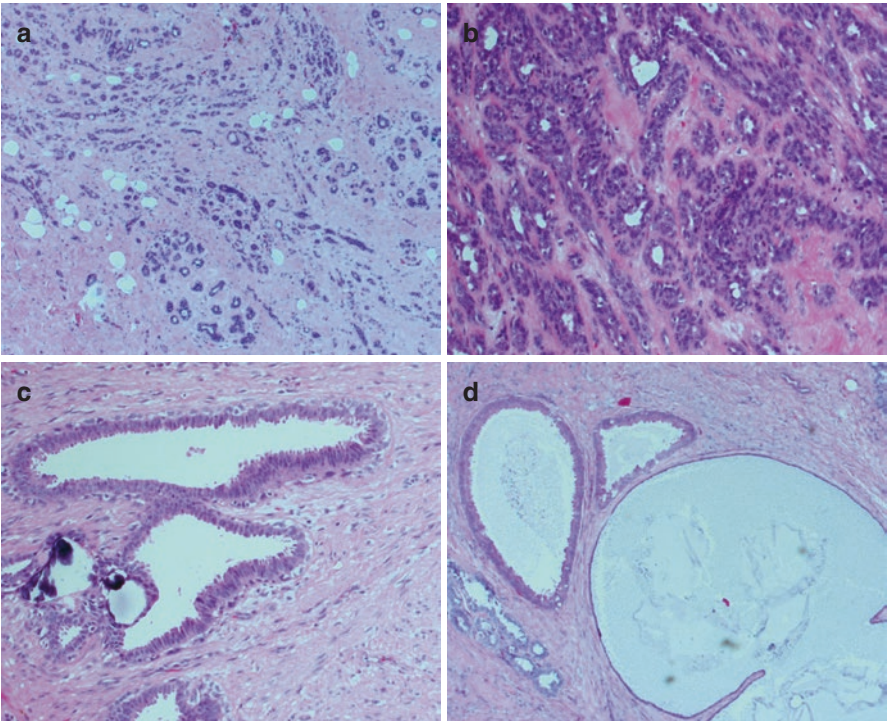
Fibroadenomas are generally mobile lesions with smooth, well circumscribed borders on physical examination. However, they may also present as nodular densities or calcified lesions on breast imaging. Fibroadenomas are benign tumors and excision is usually curative. Rarely incomplete excision of a fibroadenoma may be followed by recurrence. Diagnosis of fibroadenoma on core needle biopsy usually is straightforward because of the classic appearance of a biphasic tumor with an intracanalicular or less likely pericanalicular patterns (Fig. 2.2). If the edge of the fibroadenoma is present in the core biopsy, there is a distinct tissue plane (circumscribed) between the lesion and the adjacent normal breast tissue; in the event that the lesional tissue appears to be infiltrating the adjacent breast or adipose tissue, the possibility of phyllodes tumor should be entertained. Fibrocystic changes including papillary apocrine metaplasia, sclerosing adenosis, cystic spaces and epithelial calcifications may be present within the lesion (Fig. 2.3). Sometimes the term “complex fibroadenoma” is applied to fibroadenomas having these changes [10]. The ductal epithelium of a fibroadenoma in the majority of cases is completely benign. However there are exceptions, and the pathologist must evaluate the epithelium of a fibroadenoma with the same criteria used in any breast biopsy. Rarely, atypical hyperplasia or ductal or lobular carcinoma in situ may be found within a fibroadenoma (Fig. 2.4); even more rarely, invasive carcinoma may be present.

Stromal cellularity and atypia are evaluated in fibroepithelial lesions. While such assessment is somewhat subjective, it has been suggested that the stroma of adjacent uninvolved breast lobules be used to determine degree of cellularity and atypia in a fibroepithelial lesion to minimize subjectivity (Table 2.1). One of the diagnostic difficulties facing pathologists in evaluation of core needle biopsies in fibroepithelial lesions is interpretations of lesions with apparently increased stromal cellularity. Young women may have fibroadenomas that are more cellular than those found in older women. There is overlap between so-called cellular fibroadenoma and low-grade (histologically benign) phyllodes tumor on core needle biopsy [11–13], and differentiating between these two can be challenging. The major criterion

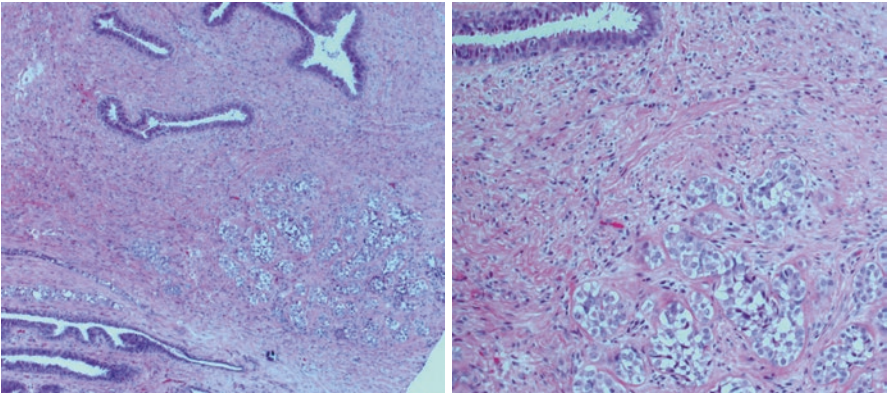


**Fig. 2.2** Fibroadenoma. The stroma is sclerotic or collagenized and the ducts are compressed. Calcifications are sometimes associated with fibroadenoma





**Fig. 2.3** So-called complex fibroadenoma. A fibroadenoma having the following: (a, b) sclerosing adenosis, (c) epithelial calcifications, (d) apocrine metaplasia and cyst



**Fig. 2.4** Fibroadenoma with lobular neoplasia

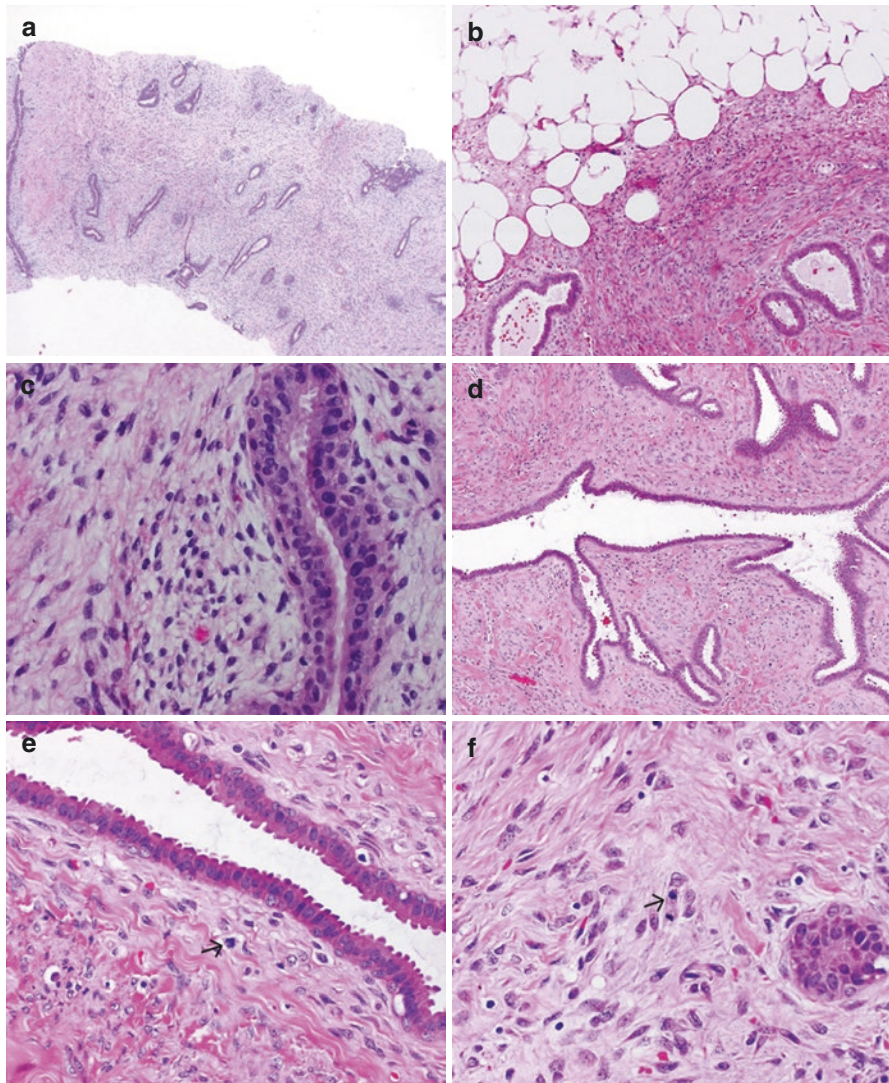
differentiating phyllodes tumor from fibroadenoma is the degree of stromal cellularity and stroma atypia. Table 2.2 highlights some clinical, radiologic, and pathologic features requiring evaluation in fibroepithelial lesions [14–16]. The diagnosis of phyllodes tumor (Fig. 2.5) requires a constellation of features to be present, as no single feature is entirely specific.

**Table 2.1** Suggested criteria for evaluating stroma cellularity and atypia in fibroepithelial lesions focusing on the most cellular zones of the tumor compared to normal perilobular stroma if available [14–16]

Grade	Cellularity (compared to normal perilobular stroma)	Atypia
Mild	Slight increase (up to twice that of normal perilobular stroma) of evenly spaced nuclei with no overlap or touching	Nuclei with smooth nuclear contours and little variation in size similar to normal perilobular stroma
Moderate	Intermediate findings with some overlapping nuclei	Some variation in nuclear size with wrinkled nuclear membrane
Marked	Confluent areas of densely overlapping nuclei	Marked variation in nuclear size, coarse chromatin/hyperchromasia, and irregular nuclear membranes with discernible nucleoli at 10× objective and 10× eyepiece (100×)

**Table 2.2** Features of fibroadenoma and phyllodes tumor

Clinical, pathology, and imaging features	Fibroadenoma	Phyllodes tumor
Mass	Palpable lesion or mammographic density	Typically palpable
Age	Usually <30 years; may be seen in older women	Typically 40 years or older, premenopausal, uncommon in young adults
Shape	Rounded, circumscribed	Circumscribed or infiltrative
Size	Usually ≤3 cm; pediatric cases may be larger	Variable but typically large (>3 cm)
Growth rate	Slow (over months to years)	Typically rapid (over weeks to months)
Epithelial pattern	Intracanalicular or pericanalicular	Exaggerated intracanalicular pattern is typical
Stromal cellularity	Typically low; stromal cells do not overlap	Moderate to high; stromal cells overlap in higher grades Heterologous differentiation may be present in malignant phyllodes tumors
Stromal mitoses (mitoses are counted at 40× objective and 10× eye-piece; that is, 400× high power field [hpf])	Absent or rare	Benign: ≤4/10 hpf Borderline: 5–9/10 hpf Malignant: 10 or more/10 hpf [5]
Stromal overgrowth (stroma without epithelium in at least one 40× low power field, i.e. 4× objective and 10× eye-piece)	No	No, in benign and borderline; yes, in malignant
Stromal heterogeneity	Usually not	Variable
Tissue fragmentation on core biopsy	No	Typical but not observed in all cases
Tumor margin	Circumscribed	Circumscribed or infiltrative into adjacent fat or breast tissue
Recurrence	Not usual	Benign: 10–15% Borderline: 20–25% Malignant: 25–30% [17]

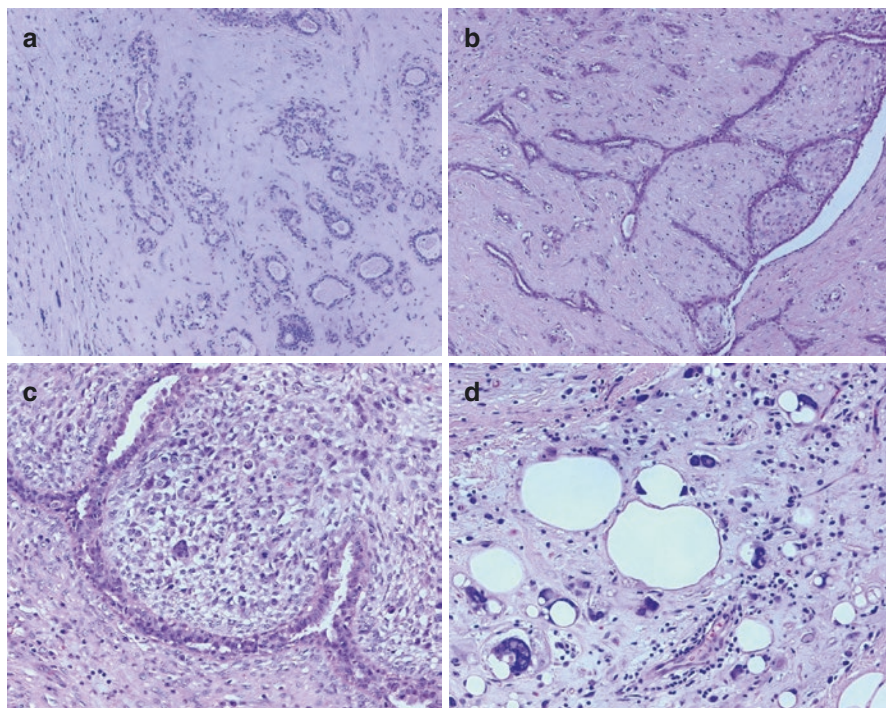


**Fig. 2.5** Phyllodes tumor with (a) increase stroma cellularity, (b) invasion into surrounding adipose tissue, (c) periductal cuffing, (d) clover leaf appearance/exaggerated intracanalicular pattern, (e, f) increased mitosis (arrows)

In phyllodes tumor, there is increased cellularity with increased stroma cells around ductal epithelium (referred to as periductal condensation/accentuation), but this pattern is not observed in all cases or may not be evident in a core biopsy. Complicating the assessment of stromal cellularity is the variable degree and distribution of cellularity that may exist within a single phyllodes tumor (stromal heterogeneity). The stroma heterogeneity contributes to the difficulty encountered in making a definitive diagnosis or grading of a phyllodes tumor on core needle biopsy [17].



Aside from the degree of cellularity, the presence of increased mitotic activity in the stroma, and stromal cell nuclear atypia, may allow the diagnosis of phyllodes tumor on core needle biopsy. An additional feature that has been noted is the tendency for some phyllodes tumors to fragment on core needle biopsy, a feature related to the exaggerated ductal lumens typically seen in these tumors [11]. While some low-grade (benign) phyllodes tumors can be identified with confidence on core needle biopsy, cases that are equivocal are often called “cellular fibroepithelial lesion (or tumor),” a term intended to convey the uncertainty in excluding phyllodes tumor. High-grade (malignant) phyllodes tumors (Fig. 2.6) have a very high degree of cellularity, marked nuclear atypia, and mitotic activity, and in some cases histologically sarcomatous and heterologous stroma. The diagnosis of high grade phyllodes is usually not challenging on core needle biopsy as long as the epithelial component (in a typical exaggerated intracanalicular pattern) is also present. When the ductal component is not present in the biopsy, the differential diagnosis of high-grade (malignant) phyllodes tumor will include metaplastic carcinoma (mesenchymal type) or the rare stromal sarcoma of the breast, potentially leading to immunohistochemistry work-up. In both metaplastic carcinoma or stromal sarcoma, normal breast ducts may become surrounded or entrapped by the tumor; this should not be mistaken for evidence of a biphasic neoplasm. Metaplastic carcinoma in many cases can be excluded by the absence of diffuse staining with



**Fig. 2.6** Malignant phyllodes. The same tumor showing stroma heterogeneity. Less cellular (a, b) and more cellular area with malignant cells having liposarcomatous differentiation (c, d)



antibodies to cytokeratin; exclusion of stromal sarcoma may require examination of the excised lesion. If a diagnosis of phyllodes tumor is made on core needle biopsy, the lesion should be excised with a margin of normal tissue, since recurrence of incompletely excised phyllodes tumor may occur. Recurrence in low-grade (benign) lesions has been reported in as many as 10–15% compared to 30% or more for malignant cases [15, 17, 18]. Recurrent phyllodes tumors are sometimes higher grade than the original lesion; it is uncertain whether this is due to progression or to heterogeneity in the tumor [15, 19]. Metastases may occur in cases of phyllodes tumors; the majority of these occur in cases of histologically malignant phyllodes tumors, but rarely metastasis of borderline and, even more rarely, of histologically benign phyllodes tumors has been reported [17].

Once diagnosed, a phyllodes tumor is graded (low versus high) or categorized as benign, borderline, or malignant, based on histological parameters. A recent consensus statement outlines the grading scheme: benign phyllodes tumors have minimal nuclear atypia, pushing borders, and four or fewer mitoses per ten high-power fields (hpf); malignant phyllodes tumors have marked stromal cellularity and atypia, infiltrative margins, and ten or more mitoses per ten hpf and usually have areas of *stromal overgrowth* (stroma without epithelium in at least one 40× microscopic field: 4× objective and 10× eye-piece); borderline phyllodes tumors have features intermediate between benign and malignant [5].

In some cases, definitive classification of a fibroepithelial lesion into fibroadenoma or phyllodes tumor may require examination of surgically excised nodule or mass, which would allow assessment of overall architecture, stromal cellularity, nuclear features, and mitotic activity. In addition to stromal hypercellularity, the typical phyllodes tumor has an exaggerated intracanalicular pattern producing “leaf-like” invaginations, a pattern that may not be evident on core needle biopsy.

Fibroepithelial tumors are rare in the male breast because these tumors arise from intralobular stroma; lobules are normally absent or rare in the male breast. Fibroadenomas may however be seen in males taking androgen suppression therapy, estrogen hormonal treatments, or male-to-female transsexual [20–22].

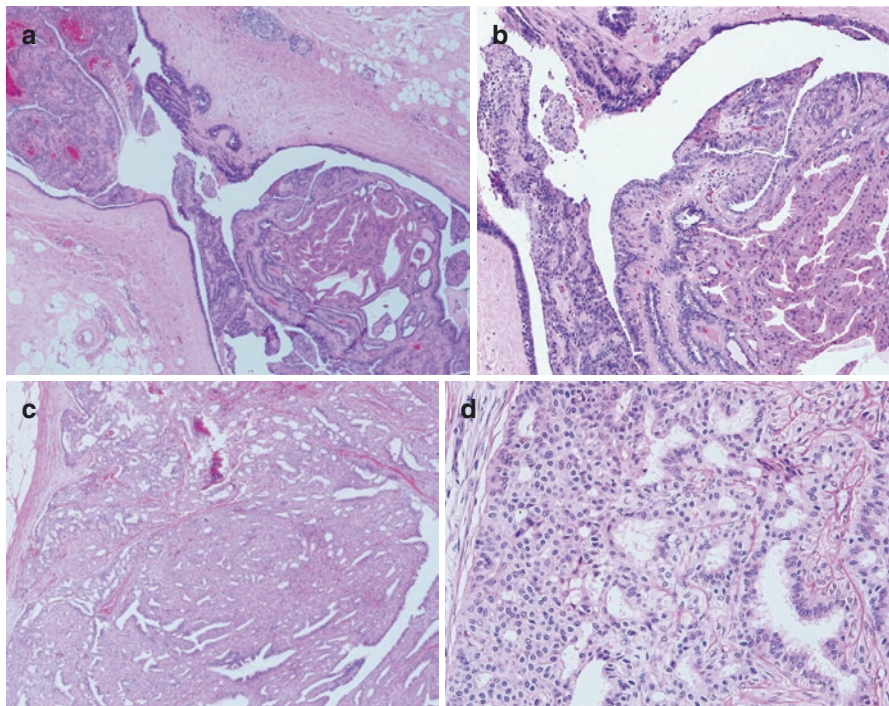
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## Papillary Neoplasms

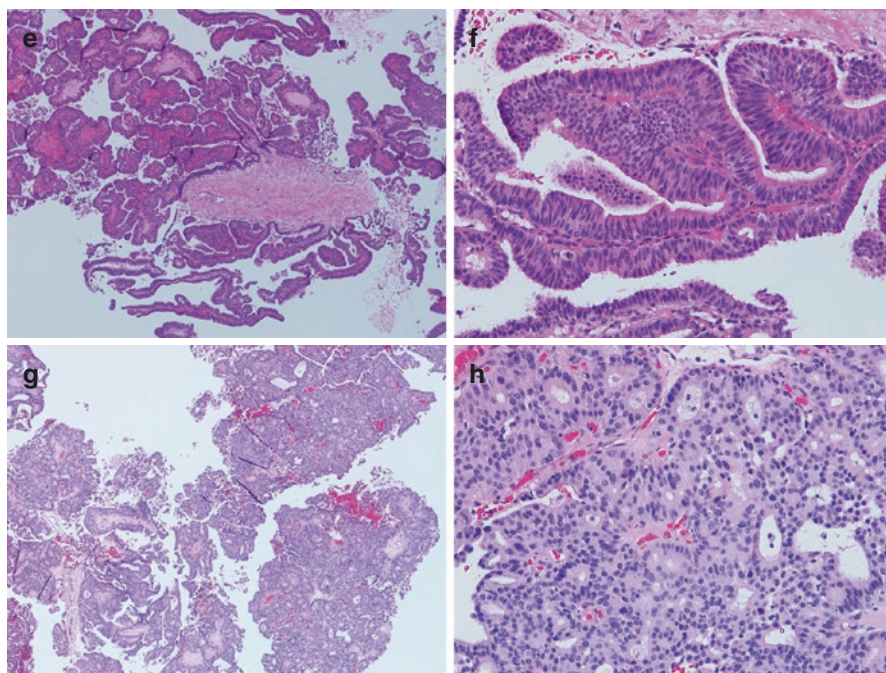
Papillary lesions or neoplasms of the breast consist of a spectrum of entities which include, papillary hyperplasia, juvenile papillomatosis, nipple adenoma (florid papillomatosis of the nipple), intraductal papilloma, sclerosing papilloma, “atypical papilloma” (ADH or DCIS involving papilloma), encapsulated papillary carcinoma, solid papillary carcinoma, papillary DCIS, and invasive papillary carcinoma. A comprehensive review [23–26] of these entities is beyond the scope of this text. The approach to interpretation and the pitfalls in the evaluation of selected papillary lesions will be highlighted. Intraductal papillomas (Fig. 2.7a, b) are lesions composed of epithelial proliferations supported by fibrovascular cores (papillary architecture), and confined to a duct; they may be single or multiple. Solitary papillomas usually occur in the large central (subareolar) ducts, while multiple papillomas typically are located in terminal ductal lobular units (TDLU) of the peripheral breast.

Papillomas range in size from microscopic to macroscopic; the larger lesions may be identified on mammography as a density or mass. Papillomas may occasionally be described on ultrasound as a mass that disappears after the first biopsy; this radiologic description may also be associated with apocrine metaplasia. For a partially cystic mass/lesion, it is often prudent to drain the fluid before biopsy of the solid component, if any. Microscopic papillomas almost always are incidental findings in biopsies or excisions performed for other reasons. Occasionally, however, papillomas, even microscopic ones, become sclerosed and calcified and are identified on the basis of mammographic calcifications.

The epithelial component of a papilloma may be nonproliferative or proliferative. The same histologic criteria used to evaluate non-papillary proliferative ductal epithelial lesions are used to assess papillomas. Papillomas may exhibit varying degrees of usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH) and ductal



**Fig. 2.7** Papillary lesions. (a, b) Intraductal papilloma. Notice the growth of the tumor in the duct. The duct has broad papillary fronds and apocrine metaplasia. (c, d) Intraductal papilloma with atypical ductal hyperplasia (aka atypical papilloma). (e, f) Intraductal papillary carcinoma. Note the monomorphic population of neoplastic cells consisting of one or more layers of hyperchromatic columnar cells surrounding fibrovascular stalk with no myoepithelial cells. (g, h) Intraductal papillary carcinoma - cribriform architectural pattern. Intraductal papillary carcinoma may also have cribriform, solid, or micropapillary architectural pattern, obscuring the spaces between the fibrovascular or papillary fronds. Myoepithelial cells are absent. Myoepithelial markers may be useful to highlight the absence of myoepithelial cells



**Fig. 2.7** (continued)

carcinoma in situ (DCIS). The term “atypical papilloma” is often used for papillomas in which a portion of the epithelial component is consistent with atypical ductal hyperplasia (ADH) or low-grade DCIS (Fig. 2.7c, d). The 2012 WHO categorization of papillomas recommended the use of the terms “papilloma with atypical ductal hyperplasia (ADH)” and “papilloma with ductal carcinoma in situ (DCIS)” instead of atypical papilloma in the context of low-grade lesions. High-grade DCIS in a papilloma is diagnosed as such regardless of the extent of involvement of the papilloma [27]. According to the WHO, papilloma with ADH and papilloma with DCIS are defined as a papilloma with a monotonous population of low-grade cells with architectural and cytologic features of ADH (<3 mm) or DCIS (3 mm or more), respectively [5, 23, 27]. Note that the size or extent cutoff of 3 mm is different from the cutoff used for de novo (i.e., non-papillary) ADH and DCIS which has a cutoff of 2 mm. It must also be pointed out that the current WHO size criteria for ADH and DCIS in papilloma is slightly different from the original criteria proposed by Page et al., whose criteria were:  $\leq 3$  mm for ADH in papilloma and  $>3$  mm for DCIS in papilloma [28]. The use of CK5/6, CK14, and estrogen receptor (ER) may be useful in distinguishing ADH from hyperplasia without atypia (or UDH), with ER having strong homogenous positivity in ADH/DCIS in papilloma and heterogeneous positivity or outright negativity in papilloma without atypia; CK5/6 and CK14 have opposite staining pattern to ER—they are positive in UDH in papilloma but negative or weakly positive in ADH/DCIS in papilloma [5, 23, 27]. The management of non-atypical



papillary lesions on core needle biopsy is controversial. Risk assessment of association with carcinoma should probably inform the decision to surgically excise or not. For example, a central papilloma is associated with a twofold increase in the risk of subsequent carcinoma [29, 30], which is similar to the risk of de novo UDH [5, 31, 32]. While atypical papilloma (ADH/DCIS in papilloma) is associated with a risk of associated invasive carcinoma ranging from 5 to 7.5 [28, 30]; this is slightly higher than the risk associated with de novo ADH [5, 31, 32]. It is generally accepted that atypical papillomas and papillary DCIS on core needle biopsies should be surgically excised [25]. However, there are ongoing controversies on the management of central papilloma on core needle biopsy [33–39]. We do not subscribe to “a one-size-fits-all approach” and believe that a prudent approach should involve optimal radiologic–pathologic correlation and clinical presentation. For example microscopic papillomas with no evidence of atypia that are completely encompassed in a core needle biopsy, especially in young patients, probably do not need to be excised [39]. On the other hand, central papilloma may need to be excised to ease patient’s symptoms.

Papillomas may undergo sclerosis, with marked alteration of the papillary architecture; epithelial cells that are “pinched off” by the sclerosis may be present in stroma adjacent to the involved duct. Care should be taken not to mistake entrapped epithelium for invasive carcinoma. Clues include the low-power histologic pattern and the cytologic features. Entrapped epithelium usually is directly adjacent to the involved duct within fibroblastic or sclerotic connective tissue. At high magnification, attention to the cytologic features and the presence of myoepithelial cells (identified on H&E or immunohistochemical stain) is helpful in the distinction from invasive carcinoma.

## Papillary Carcinomas

**Intraductal papillary carcinoma** (also known as papillary ductal carcinoma in situ or noninvasive papillary carcinoma) is an in situ carcinoma with no evidence of underlying benign papilloma. It may present as blood-stained nipple discharge, a mass, or mammographic calcifications. The neoplastic cells (usually low to intermediate nuclear grade, rarely high nuclear grade) are arranged as one or more columnar epithelium lining a fibrovascular stalk (Fig. 2.7e, f). Intraductal papillary carcinoma may also have micropapillary, solid, or cribriform architectural patterns (Fig. 2.7g, h). Myoepithelial cells are absent in the papillary fronds within the duct but present in the periphery of the main duct with the papillary growth. Often multiple ducts are involved. Adjacent stroma should be assessed for evidence of invasive carcinoma. *The main differentiating feature of intraductal papillary carcinoma and papilloma with DCIS is that the entire lesion in intraductal papillary carcinoma is comprised of monotonous neoplastic cell population, while in papilloma with DCIS, there is a background of nonneoplastic cells with focal areas of low grade DCIS.*

**Encapsulated papillary carcinoma**, a variant of papillary carcinoma, usually presents as a circumscribed mass with or without nipple discharge. The “encapsulated” nomenclature is apparently due to a thick fibrous capsule or wall surrounding the mass, which consists of histologic features similar to those of intraductal papillary carcinoma. However, encapsulated papillary carcinoma generally has cribriform or solid architectural patterns. The controversies surrounding encapsulated papillary carcinoma

revolve around the fact that it usually lacks myoepithelial cells within and at the periphery of the tumor. This has led to the notion that encapsulated papillary carcinoma may in fact be a low-grade indolent invasive papillary carcinoma. Rarely, metastasis has been reported in encapsulated papillary carcinoma [40, 41]. While this absence of myoepithelial cells raises the possibility of an invasive process histologically, encapsulated papillary carcinoma typically behaves in an indolent fashion and should probably be managed like DCIS [24]. We stage pure encapsulated papillary carcinoma as an in situ carcinoma (Tis), unless there is frank invasion. The size of the invasive component is used for staging, not the size of entire encapsulated papillary carcinoma. DCIS may be present in adjacent breast tissue with potential higher risk of recurrence.

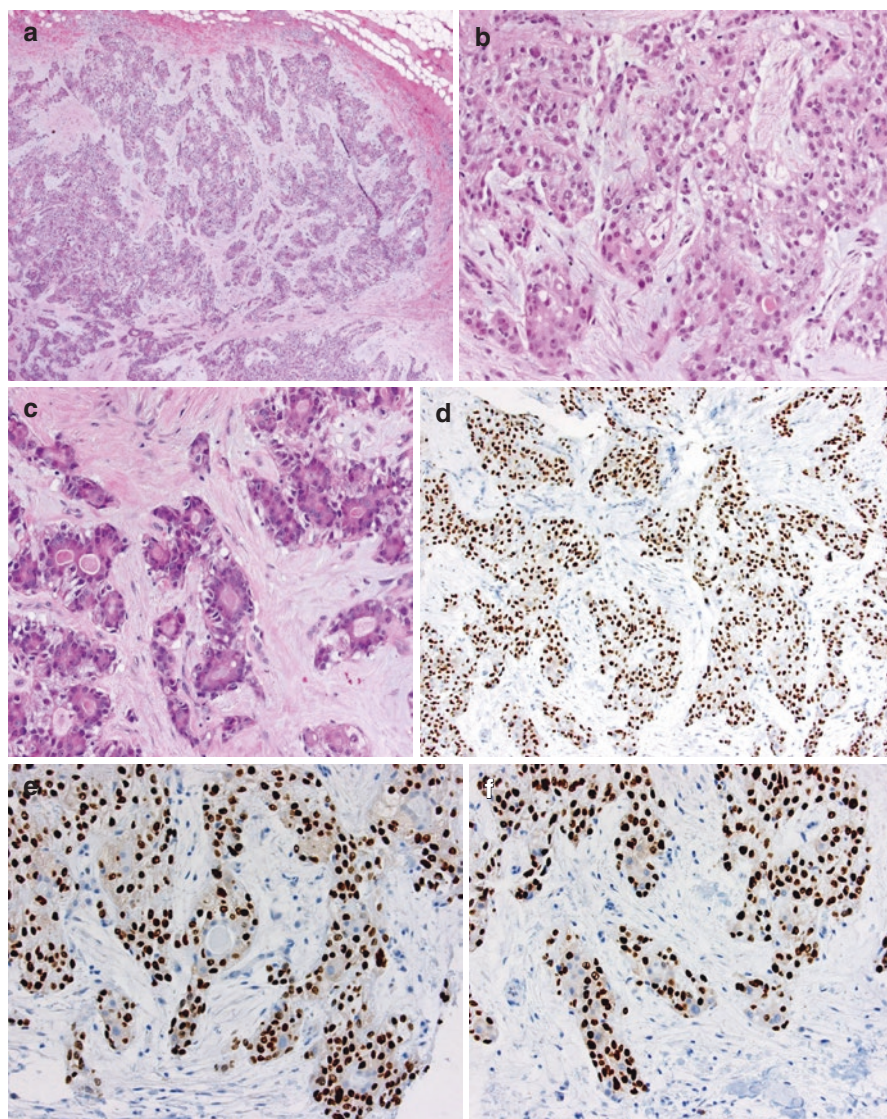
**Solid papillary carcinoma** usually presents histologically at low power as one or more well-defined *solid* nests of cells. *At higher magnification, the presence of fine fibrovascular cores can be identified among the solid rounded or geographic duct-like structure, which usually are of low or intermediate grade.* Neuroendocrine differentiation and mucinous features may be present. Myoepithelial cells usually are absent within and at the periphery of the lesion. When they are present focally in lesions of low nuclear grade, distinction from intraductal papilloma with epithelial hyperplasia may be difficult. In such cases, immunohistochemical staining may be helpful: solid papillary carcinoma should be negative for high molecular weight cytokeratin and positive for estrogen receptor (ER). Similar to encapsulated papillary carcinoma, these tumors are typically indolent, and are treated as DCIS, unless there is definitive evidence of frank invasion. Although it may be difficult to determine in situ and invasive components, it has been suggested that irregular/jagged areas lacking myoepithelial cells be considered invasive carcinoma; we subscribe to this notion.

**Invasive papillary carcinoma**, generally, refers to an invasive carcinoma, in which >90% of the tumor is papillary. This is rare and difficult to diagnose because of its resemblance to nests of solid papillary carcinoma. The tumor has an irregular crowded papillary architecture with invasive or infiltrating borders. Metastatic papillary carcinoma from extramammary sites, especially the ovary and lung, should be considered and excluded. The invasive component of solid papillary carcinoma and encapsulated papillary carcinoma is by convention not invasive papillary carcinoma.

Invasive papillary carcinoma also should be distinguished from **invasive micropapillary carcinoma**, which has an entirely different morphology, namely, small clusters of tumor cells with absent fibrovascular cores and in empty spaces (retraction artifact). *Invasive micropapillary carcinoma has reverse polarity (so-called inside-out pattern), which can be demonstrated by epithelial membrane antigen (EMA) staining on the periphery rather than the lumen.*

## Adenomyoepithelioma

Adenomyoepithelioma is a biphasic tumor comprised of myoepithelial cells and ductal/luminal cells. There is usually proliferation of the myoepithelial cells around small ductal epithelium-lined spaces (Fig. 2.8). Adenomyoepithelioma can occur at any age, but more frequently in postmenopausal women. It may rarely be seen in men. It usually presents as a solitary centrally located mass



**Fig. 2.8** Adenomyoepithelioma. Note the proliferation of the myoepithelial cells around small ductal epithelium lined spaces (a–c), myoepithelial cells highlighted by p63 (d–f)

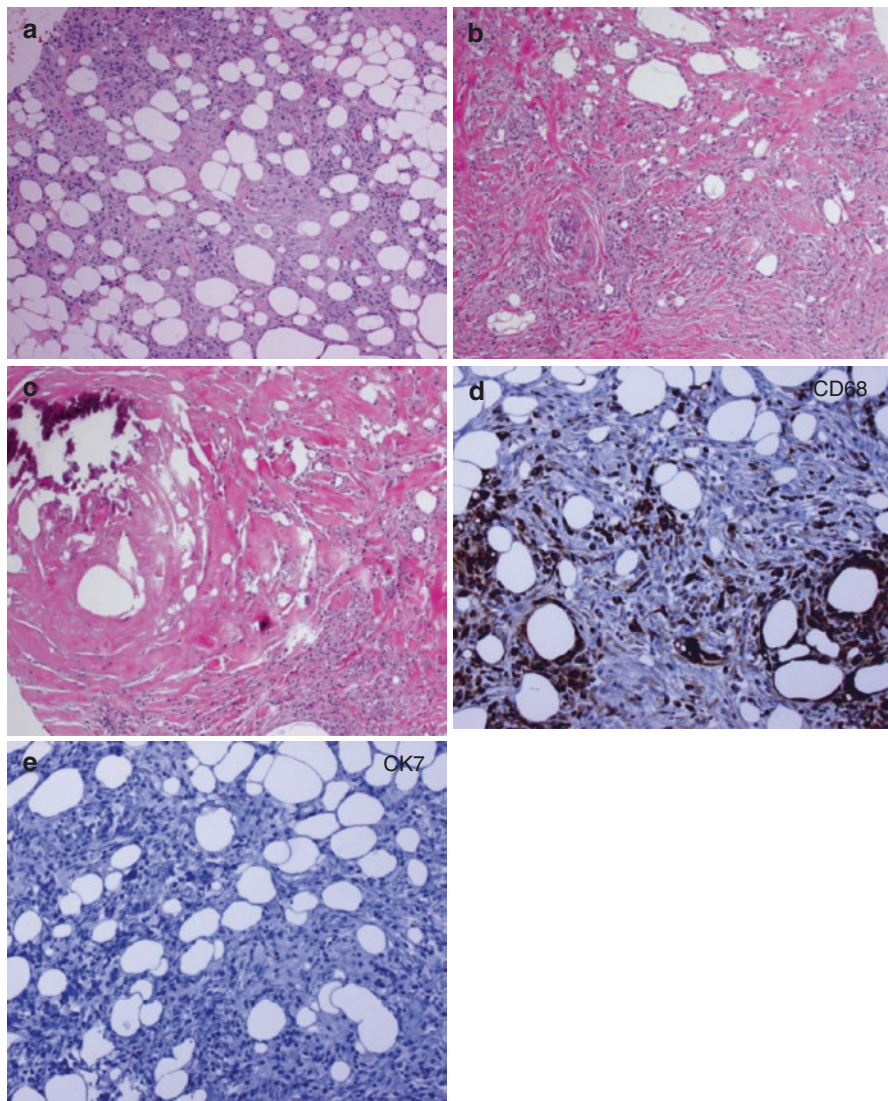
lesion with or without calcifications. It is often considered to be a variant of papillary neoplasms. The myoepithelial component may be spindled, epithelioid, plasmacytoid, or myoid, sometimes with clear cytoplasm, forming nests or sheets of cells. The myoepithelial component which stains with normal myoepithelial markers (p63, calponin, smooth muscle myosin heavy chain, smooth muscle actin, and CD10) may sometimes compress and obscure luminal epithelium. There have been reports of malignant transformation [42–44] and excision is the recommended management [5].



## Fat Necrosis

Fat necrosis (Fig. 2.9) is a common incidental finding in the breast, most often evidence of a biopsy that preceded excision of a target lesion. Fat necrosis may present as a palpable lump or mammographic density.

Fat necrosis may also be secondary to blunt trauma, a ruptured cyst or ectatic duct, breast infection, anticoagulation, hyperparathyroidism, and connective tissue disorders (e.g., polyarteritis nodosa, Weber-Christian disease, granulomatous angiopanniculitis). In some cases the etiology is unknown.

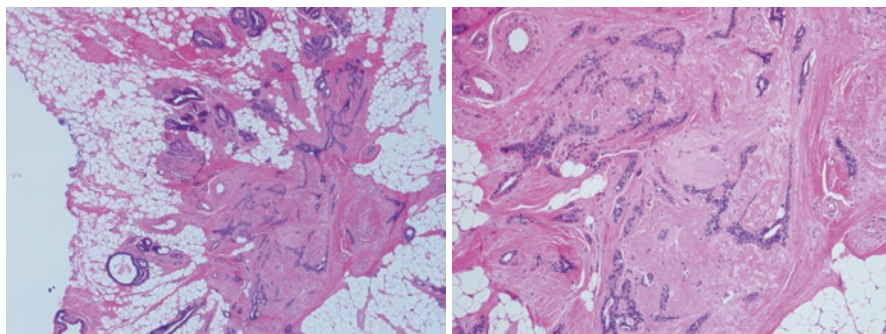


**Fig. 2.9** Fat necrosis showing foamy macrophages, varying degree of fibrosis and calcifications (a–c), foamy macrophages highlighted by CD68 (d), cytokeratin is negative (e)

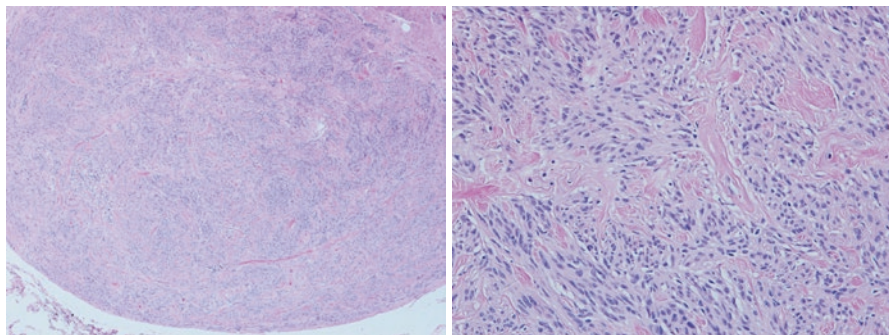
Necrotic adipocytes and lipid-laden histiocytes may elicit fibrosis, making areas of fat necrosis firm to palpation. These lesions are nonencapsulated, and the mammographic and gross appearance may be suspicious for carcinoma. On imaging, fat necrosis may present as spiculated mass, mixed density mass, distortion, or calcifications (some of these calcifications may be linear with linear orientation). Histologically, there are necrotic adipocytes with foamy macrophages infiltration and varying degree of calcifications and fibrosis. The presence of histiocytes infiltrating fat rarely may be mistaken for infiltrating carcinoma on histologic examination, but careful analysis of the cytologic features and the absence of cytokeratin staining for epithelial cells and positive CD68 staining for histiocytes by immunohistochemistry should help in making the diagnosis.

## Radial Scar

Radial scars (Fig. 2.10) may be small incidental findings or larger lesions that are detected mammographically. Larger lesions are sometimes termed “complex sclerosing lesion.” Radial scars are nonencapsulated proliferations of ductal structures in and around a central zone of fibrosis/sclerosis and elastosis. Typically the centrally located ductal structures are small and compressed, while the outermost ducts are dilated and hyperplastic, lending a “radial” appearance on histologic examination at low magnification. A radial configuration may not be evident in the larger complex sclerosing lesions. Within the central sclerotic zone, the entrapped ducts may mimic invasive carcinoma. Careful attention to the presence of an outer layer of myoepithelial cells around these structures assists in differentiating them from carcinoma. However, radial scars may be associated with carcinoma, either in situ or invasive. The hyperplastic ducts in the peripheral zones should be examined for evidence of architectural and cytologic atypia. Invasive carcinoma may be present in the outer zones or periphery of the lesion. Conversely, some cases of invasive carcinoma may mimic a pattern of radial scar. For these reasons, the finding of radial scar on core needle biopsy often triggers surgical excision to exclude the presence of carcinoma.



**Fig. 2.10** Radial scar. Note the central elastotic stroma with compressed ducts in the center and more dilated ducts at the periphery. It is important to ensure that the compressed duct has myoepithelial cells



**Fig. 2.11** Myofibroblastoma. Note the bland spindle cells arranged in short, haphazard fascicles or nests separated by eosinophilic keloid-like fibers

## Hamartoma

Hamartoma of the breast is a mass lesion, usually circumscribed or encapsulated, composed of benign breast ducts and lobules, connective tissue stroma, and adipose tissue, without an organized architecture [45]. A palpable hamartoma may be mistaken clinically for fibroadenoma. Fibrocystic changes may be present in the hamartoma and, rarely, carcinoma may be present. Because of the histologic resemblance of hamartoma to normal breast tissue, diagnosis on core needle biopsy may be difficult and requires close correlation with the mammographic findings and the targeted lesion. Recurrence after excision is rare.

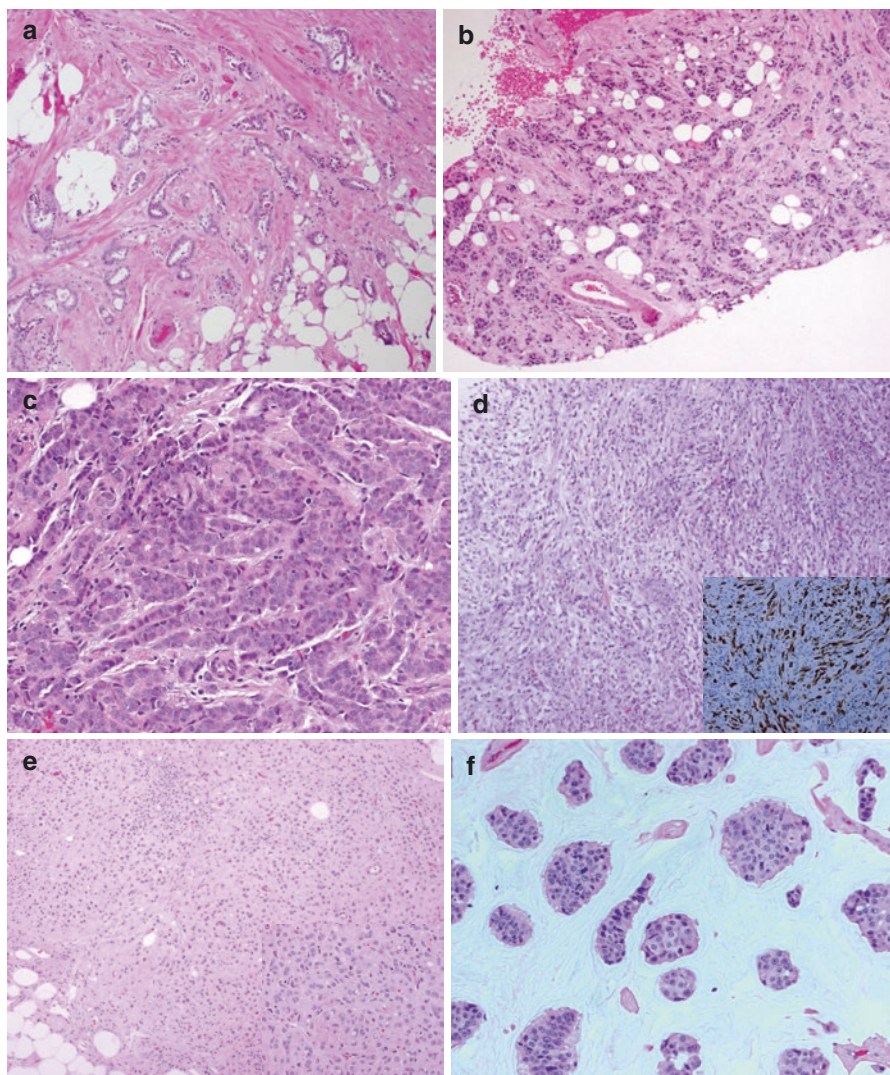
## Myofibroblastoma

Myofibroblastic proliferations in the breast range from incidental foci of pseudoangiomatous hyperplasia (PASH) to mass lesions known as myofibroblastoma (Fig. 2.11). Myofibroblastomas may be seen at any age, but are more commonly seen in postmenopausal women. Classically myofibroblastomas are circumscribed but nonencapsulated tumors with pushing borders. Myofibroblastoma consists of bland spindle cells arranged in short, haphazard fascicles or nests separated by eosinophilic keloid-like fibers. However, several histologic variants have been described, including epithelioid variant which may mimic invasive lobular carcinoma [46, 47]. Familiarity with these variants will minimize misdiagnosis as invasive carcinoma. The myofibroblasts are identified by positive immunohistochemical staining for desmin, CD34, and vimentin; smooth muscle actin, BCL2, CD99, CD10, ER, and PR are variably positive. Cytokeratins, EMA, S100, HMB45, and CD117 (ckit) are consistently negative.

## Invasive Breast Carcinomas

Invasive breast carcinomas are the most common carcinomas in women accounting for almost a quarter of all breast cancers in women. Invasive breast carcinomas (Fig. 2.12) denote primary malignant epithelial neoplasm in the breast with





**Fig. 2.12** Invasive carcinomas. (a–c) Invasive carcinoma NOS (invasive ductal carcinoma), (d) metaplastic carcinoma (inset shows cytokeratin positivity in spindle cells), (e) invasive lobular carcinoma (inset shows higher power), and (f) mucinous carcinoma

stromal invasion. Vascular invasion, useful when present, is not required for a diagnosis of invasive carcinoma. Morphologically, invasive carcinoma may have apparent glandular differentiation, single-cell infiltration, targetoid features, or other morphologic types. Invasive carcinomas are heterogeneous and consist of different histologic types. The most common type (40–75% of mammary carcinomas) used to be called *invasive/infiltrating “ductal” carcinoma* because it was originally thought to arise from the ductal rather than the terminal ductal lobular unit (TDLU) which was thought to be the origin of invasive lobular carcinoma.

TDLU is now known as the entity where all breast carcinomas originates, not just invasive lobular carcinoma [48]. In view of this, the WHO recommends a preferred term *invasive carcinoma of no special type* instead of invasive ductal carcinoma [5]. In addition to *invasive carcinoma of no special type*, the other subtypes of invasive breast carcinoma include, but are not limited to the following: invasive lobular carcinoma, tubular carcinoma, cribriform carcinoma, carcinoma with medullary features, metaplastic carcinoma, invasive papillary carcinoma, invasive micropapillary carcinoma, adenoid cystic carcinoma, secretory carcinoma, and others.

Of note, it is important to exclude *metaplastic carcinoma* when a spindle cell neoplasm is encountered in the breast whether atypical or fibromatosis-like spindle cells. Non-spindle cell histomorphology may also be seen in metaplastic carcinoma including low-grade adenosquamous and squamous cell carcinoma. Metaplastic carcinoma may occasionally have mesenchymal differentiation (osseous, chondroid, rhabdomyoid, and even neuroglial) mixed with the carcinoma component [5].

There are well-known criteria to help differentiate the different subtypes. Table 2.3 highlights some features of invasive carcinomas. However, comprehensive discussion of the different histologic criteria of the different subtypes of invasive breast carcinomas is beyond the scope of this text.

**Table 2.3** Histologic features of common invasive breast carcinomas

Type of invasive carcinoma	Epidemiology	Histologic features
Invasive carcinoma of no special type (aka invasive ductal carcinoma, invasive carcinoma not otherwise specified, or infiltrating ductal carcinoma)	Most common invasive breast carcinoma (40–75%)	Diagnosed when other types of breast carcinoma have been excluded. There is stromal invasion and a variety of architectural patterns ranging from solid, glandular, to single-cell infiltrates with variable cytoplasm. It may be mixed with other types of invasive carcinoma
Invasive lobular carcinoma	5–15% of invasive breast cancer	Classic variant consists of proliferation of non-cohesive small neoplastic cells with invasion into the stroma in single file or in a concentric pattern around normal ducts. There is generally no desmoplastic stromal reaction. There is often associated intracytoplasmic lumen. Other histologic variants include solid, alveolar, pleomorphic, and tubulolobular variant. Generally negative for E-cadherin <i>Invasive lobular carcinoma more frequently metastasizes to the gastrointestinal tract, uterus, ovary, meninges, and bone</i> , compared to invasive carcinoma of no special type, which frequently metastasizes to the lung
Tubular carcinoma	~2%	Characteristically consists of tubules with oval/rounded and angulated shape haphazardly arranged (>90% of the tumor). The nuclei are generally low grade (high nuclear grade would argue against tubular carcinoma). Apical snouts may be present, but are not required for diagnosis

(continued)

**Table 2.3** (continued)

Type of invasive carcinoma	Epidemiology	Histologic features
Mucinous carcinoma (aka colloid carcinoma)	~2%	Characterized by nests of tumor cells floating in mucin in >90% of the tumor for pure mucinous carcinoma. It may however be mixed with other carcinoma especially invasive carcinoma of no special type, in which case “mucinous features” is commonly used
Carcinoma with medullary features (aka medullary carcinoma, atypical medullary carcinoma, invasive carcinoma with medullary features)	<1%	The tumor shows some or all of the following criteria: syncytial architecture (>75% of tumor mass), pushing margins, no tubular differentiation, pleomorphic tumor cells with vesicular nuclei, and at least one nucleolus, prominent and diffuse lymphoplasmacytic stroma. Most are triple negative. Relatively good outcome, possibly due to prominent lymphoplasmacytic infiltrate
Metaplastic carcinoma	0.2–0.5%	Heterogeneous morphology, namely, <i>adenosquamous</i> (tubuloglandular architecture admixed with squamous cells), <i>fibromatosis-like</i> (bland spindle cells arranged in fascicles infiltrating breast parenchyma, reminiscent of fibromatosis, positive for cytokeratins) <i>Squamous cell carcinoma</i> (like squamous cell carcinoma in other parts of the body) <i>Spindle cell carcinoma</i> (atypical spindle cells arranged in variable architectural patterns [which are positive for high molecular weight cytokeratins] often admixed with inflammatory cells) <i>Metaplastic carcinoma with mesenchymal differentiation</i> (metaplastic carcinoma having osseous, chondroid, rhabdomyoid, etc. components which may appear bland or overtly malignant) <i>Mixed metaplastic carcinoma</i> (mixture of the different metaplastic carcinoma morphology) The rule of thumb is that metaplastic carcinoma must be excluded in any spindle cell lesion in the breast. Often triple negative

## Surgical Excision of Mass Lesion/Density/Distortion

It is important for the pathologist to describe carefully and in detail the gross measurements of the specimen and the location of the imaged target lesion. Information on the presence or absence of biopsy clips is important. Attention should be paid to the margins of the specimen; it is common to use ink to identify the surgical margin on histologic sections. The use of different colors of ink to correspond to different margins may be helpful. To minimize the possibility of ink tracking in the fatty crevices, thereby complicating margin evaluation, attention to the following steps is important: ensure that the specimen is dry by patting with paper towels; gently and carefully apply the ink(s) on the specimen's margin(s); gently pat the specimen to remove excessive ink; allow the specimen to dry for about 30 s; and apply 5% acetic acid (vinegar) as mordant [49]; some use Bouin solution as mordant. The pathologist or



other qualified personnel should then serially section the tissue and record the presence of any gross lesions, including the size and distance from the surgical margins.

In some cases, the gross measurements are different from measurements made on histologic examination of the tissue sections. Nonneoplastic changes such as fibrosis- or biopsy-related changes may not be distinguishable from invasive carcinoma at the macroscopic level. Conversely, microscopic areas of invasive carcinoma may extend beyond the limits of the lesion identified grossly. In both circumstances, the histologic measurement supersedes the gross impression and is the basis for pathologic tumor staging (pT). Similarly, the grossly measured distance of lesion from margins must be compared with the histologic findings, and the latter should take precedence.

It may be difficult to accurately assess margins in breast excision specimens due to the following [50]:

1. Artifactual narrowing after extirpation due to lack of supporting tissue normally present in vivo.
2. The artifactual narrowing is further compounded by radiologic manipulation of surgical specimens. Specimens excised with wire localization usually are imaged prior to receipt in the pathology laboratory, and the compression of the specimen may distort the tissue planes and the suture-designated margins.
3. Ink that is used in the pathology laboratory to mark the margins, if not properly fixed to the tissue and dried prior to sectioning the specimen, often tracks into the deeper portion of tissue making assessment of the true inked margin difficult on histology.
4. Generally, only a portion of the whole specimen or margin is examined histologically.
5. Inadequate pathologic sampling of the closest margin.
6. Perpendicular versus en face margin evaluation may have different margin status.

Uncommonly, inadequate markings by the surgeon may make accurate orientation of margins impossible; in such cases assistance of the surgeon(s) to orient the specimen should be sought.

Further complicating the issue is the question of what constitutes a “clear” margin for in situ and invasive carcinomas [51–53]. Perpendicular versus “en face” (pathology radial shaved margin) evaluation of margin introduces variability in margin assessment. It has been reported that pathologic en face margins may overestimate positive margins [50, 54] as positive en face margin may still have a clearance of up to 2 mm to inked margin depending on the thickness of the sections. Perpendicular inked margin is more commonly used in the pathologic evaluation of margins for breast-conserving surgery specimen. Recent consensus guidelines for invasive carcinoma and DCIS in patients undergoing breast-conserving surgery with whole-breast irradiation indicated that “ink on tumor” is considered a positive margin [50, 55] and that clinical judgment should be used in determining whether a negative margin of less than 1.0 mm requires re-excision; re-excision should not be routinely performed for “no ink on tumor.” Factors to consider on whether to re-excite or not include residual calcifications on post-excision mammography and extent of DCIS in proximity to the margin [55]. In view of these, our practice is to take sections of margins perpendicular to the edge of the lesion, and we report both the distance of tumor from excision margins and the extent of disease closest to the margin(s), when less than 1.0 mm to the margin(s).

## **Lymph Nodes**

Excision of biopsy-proven invasive carcinoma is usually accompanied by sentinel lymph nodes. In some cases, excision of pure DCIS diagnosed on core needle biopsy may be accompanied by sentinel lymph node biopsy, especially in the setting of total mastectomy. There are controversies on the performance of sentinel lymph node biopsy for pure DCIS on needle core biopsy, in the setting of breast-conserving surgery as indicated earlier in this chapter [8, 9].

Sentinel and non-sentinel lymph node(s) should be sectioned at 2 mm intervals and entirely submitted, unless there is gross evidence of metastatic carcinoma in the node, in which case a single representative section is appropriate. Since metastatic tumor deposits can vary in size and macrometastasis is metastasis greater than 2.0 mm, cutting the node at 2 mm intervals theoretically should allow identification of small foci that might escape detection with only partial submission of the node or thicker sectioning of the node. There are controversies regarding the number of histologic hematoxylin and eosin (H&E)-stained sections and whether nodes that are negative on H&E should be further examined with immunohistochemical staining for cytokeratin. Since isolated tumor cells in a lymph node do not impact nodal status for pathologic staging, the benefit of this additional testing appears to be of little value; therefore, it has been suggested that routine cytokeratin immunohistochemistry should be discouraged [56]. We subscribe to this practice, if the sentinel lymph nodes are sectioned at 2.0 mm intervals. However, this cannot always be assumed. Furthermore, invasive lobular carcinoma may sometimes be particularly difficult to identify in the lymph nodes. In these particular instances, we believe that the use of cytokeratin immunohistochemistry in the evaluation of sentinel lymph nodes is not unreasonable. Size of nodal metastasis have implications on whether axillary dissection is performed or not. Contiguous tumor deposit less than 0.2 mm or less than 200 tumor cells in a lymph node is referred to as isolated tumor cells (ITC); contiguous tumor deposit between 0.2 mm and 2.0 mm is referred to as micrometastasis; while contiguous tumor deposit with at least one nodal metastasis greater than 2.0 mm is referred to as macrometastasis. Nodes with ITC are not counted as positive nodes, even if there is another lymph node with macrometastasis. Axillary dissection is generally performed for macrometastasis.

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## **Prognostic and Predictive Markers in Invasive Carcinoma**

### **Estrogen and Progesterone Receptors**

Testing for estrogen receptor (ER) and progesterone receptor (PR) status and for HER2 (ERBB2) overexpression or amplification is standard in the pathologic assessment of invasive breast carcinoma. These tests are generally performed on formalin-fixed, paraffin-embedded tissue sections of biopsies or of excision specimens. Patients with invasive carcinomas that express ER and/or PR are candidates for antihormonal therapies. ER and PR are assessed by immunohistochemical staining. The proportion of positive tumor cells and the intensity of staining typically are reported. Assessment of positive staining may be performed manually (semiquantitative assessment) or quantified via image analysis. Certain caveats pertain to hormone receptor testing. The College of

American Pathologists (CAP) in collaboration with other professional societies, has determined that the minimum length of formalin fixation time for tissues stained for ER and PR (and for HER2) is 6 h. Additionally, cold ischemic time (length of time between removal of the tissue from the patient and placement in formalin) should be 1 h or less. Prolonged cold ischemic time or inadequate formalin fixation may produce false results. Fixation for more than 72 h may also interfere with the staining reaction. Cases falling outside these guidelines and in which negative results are obtained should prompt repeat testing on a subsequent specimen (repeat biopsy or excision specimen). The recommended scoring guidelines should be strictly followed [57–59].

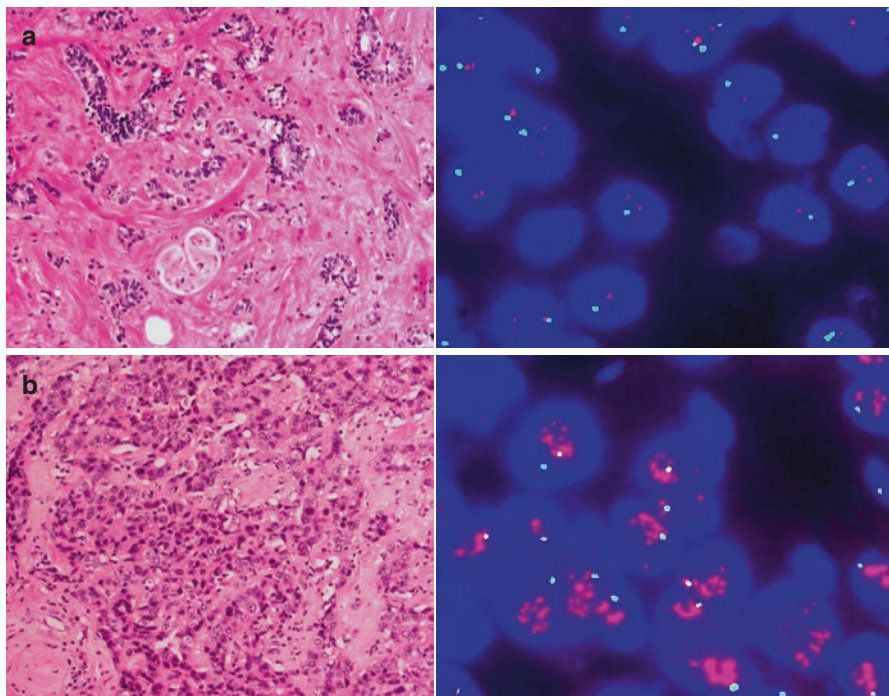
## Proliferative Index

It is increasingly of clinical interest to determine the proliferation rate of the malignant cells in invasive carcinomas. This typically is performed by immunohistochemical staining for a proliferation antigen such as Ki-67. The percentage of positive malignant cells can be assessed either manually (semiquantitative estimation of percent positive cells) or with automated quantitative measurement. High and low proliferation rates portend, respectively, a more or less aggressive potential behavior of a carcinoma and may factor into clinical decision-making. Specific guidelines for assigning low, intermediate, or high proliferation ranges have not yet been determined.

## HER2

HER2 (ERBB2, human epidermal growth factor receptor) is a tyrosine kinase protein that is encoded by the *HER2 (ERBB2)* gene. The overexpression of the protein, and/or the amplification of the gene, in invasive breast carcinoma, is associated with poor prognosis but also identifies patients who are candidates for HER2 targeted therapy. HER2-positive invasive carcinomas (which comprise approximately 15–20% of all invasive breast carcinomas) tend to respond well, to anti-HER2-targeted therapies, providing considerable survival benefit. The effectiveness of this treatment makes identification of such cases of paramount importance. HER2 protein overexpression is determined by immunohistochemical staining; *positive HER2 status is based on more than 10% of tumor cells staining with intense, complete membranous staining. Less complete staining, weak staining, or intense staining of less than 10% of cells is considered equivocal.* Amplification of the *HER2* gene typically is determined by in situ hybridization, either fluorescent (FISH) or chromogenic (CISH). *In testing that uses a control probe, amplification is based on a HER2 to control signal ratio of >2 or a HER2 copy number of 6 or greater (even if the ratio is less than 2). Cases with a ratio less than 2 and an average HER2 copy number of at least 4 but less than 6 are considered equivocal.* Because of the clinical importance of identifying HER2-positive cases, equivocal results in either testing modality (immunohistochemistry or ISH) should trigger reflex or repeat testing, either by the alternate modality (ISH or immunohistochemistry) or using a different or subsequent tissue sample because of tumor heterogeneity [57]. *It is critical, however, to use the most current HER2 scoring guidelines because these guidelines undergo periodic review and update.* If a tumor





**Fig. 2.13** Two masses in the same breast. (a) H&E of mass 1 invasive carcinoma NOS, low nuclear grade, and corresponding non-amplified HER2 FISH. (b) Mass 2 H&E of invasive carcinoma NOS, high nuclear grade, and corresponding amplified HER2 FISH, same patient as in Fig. 2.13a

has morphologically different areas, it may be prudent to perform HER2 on the different tumors in view of tumor heterogeneity, because one morphologic type may be negative, while the other may be positive (Fig. 2.13a, b).

## Reporting

Use of a synoptic reporting template in cases of surgically excised breast carcinomas and DCIS is a requirement for laboratory accreditation by the College of American Pathologists (CAP). The CAP has deemed status with the Centers for Medicare and Medicaid Service (CMS), so that accreditation by the CAP qualifies a laboratory for payment for pathology services through Medicare and Medicaid. In the case of invasive carcinomas, the elements of the template include the specimen site, type of procedure, histologic type of carcinoma, histologic scoring and grading, size of the carcinoma, margin status, lymph node status, and hormone receptor and HER2 status, followed by the pathologic TNM staging. Synoptic reporting ensures the reporting of elements that are important for clinical management. The use of synoptic report also ensures that the required elements in the quality category of the merit-based incentive payment system (MIPS), previously known as physician quality reporting system (PQRS), are always included in breast cancer reports.

## Breast Calcifications

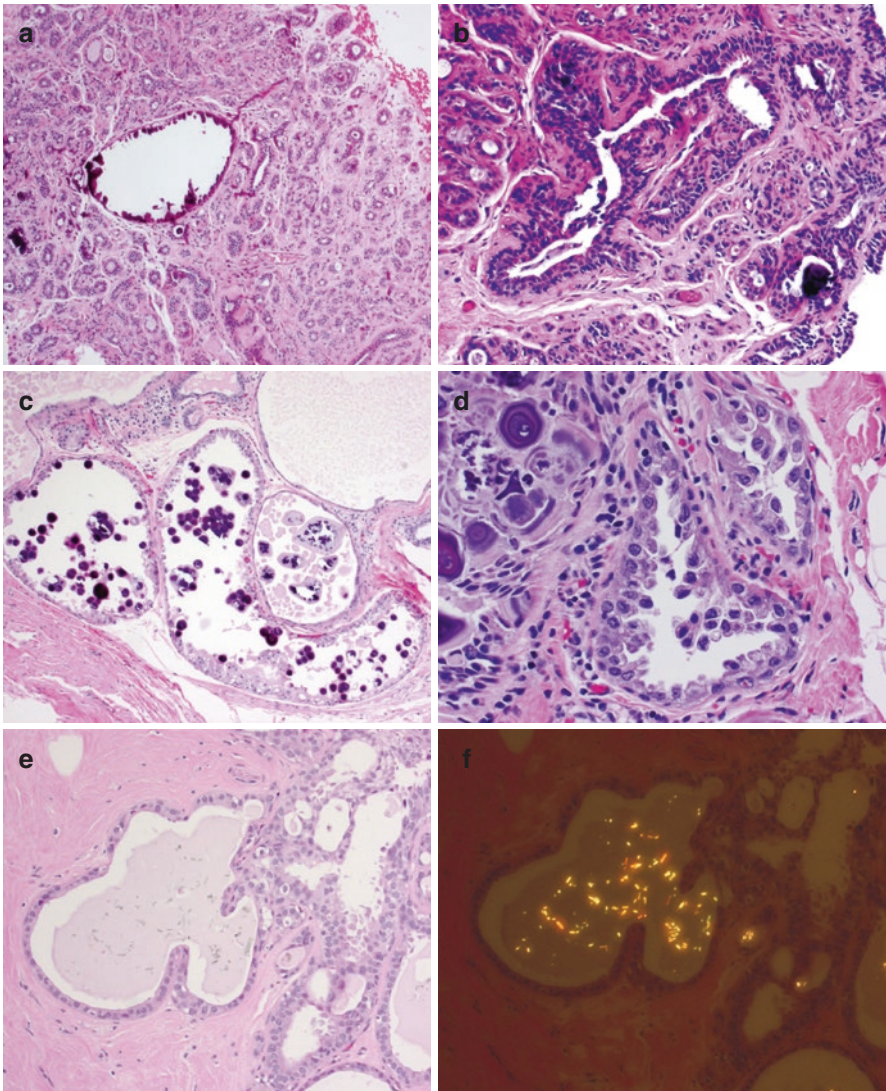
Breast calcifications are not created equal. Some radiologic calcifications are more commonly associated with benign processes than others. The evaluation of breast calcifications in radiology and pathology is distinctly different but converges with the overarching goal of detecting precursor lesions (e.g., ductal carcinoma in situ [DCIS]) that are potentially curable. Radiology determines which calcifications require biopsy and further histological evaluation. Pathology on the other hand identify the radiologically targeted calcifications in histology specimens and determine the histologic association of such calcifications.

The initial evaluations of breast calcifications fall on the breast radiologist. At least half of the biopsies performed for non-palpable breast abnormalities are due to mammographically detected calcifications, and about half of these may have ductal carcinoma in situ (DCIS). The evaluations of breast calcifications by radiologists, which have evolved over time, are to identify, characterize (morphology and distribution patterns, location), and determine which calcifications or groups of calcifications may be associated with a precursor lesion or cancer and therefore require biopsy. The reporting of such evaluation by the radiologists has now been standardized by the BI-RADS (Breast Imaging Reporting and Data System). *BI-RADS categories generally divide calcifications into typically benign or suspicious morphology*; the BI-RADS categories are discussed further in the radiologic section of this text [60–68].

The pathogenesis of these calcifications is unclear [69]. There are controversies on whether such calcifications are formed by cellular degeneration, an active cell-mediated process or both [68, 69]. It has been suggested that it may be secondary to membrane-bound vesicles (extracellular/intracellular) of degenerating cells, extracellular matrix, apoptotic bodies, or from the mitochondria of dying cells that have lost their ability to regulate intracellular calcium [68, 70]. Regardless of the mechanism or pathogenesis, *from a pathology standpoint, breast calcifications are mostly dystrophic*, forming in an abnormal local environment rather than calcifications secondary to systemic metabolic derangements like hypercalcemia, which is referred to as metastatic calcifications in pathology [70].

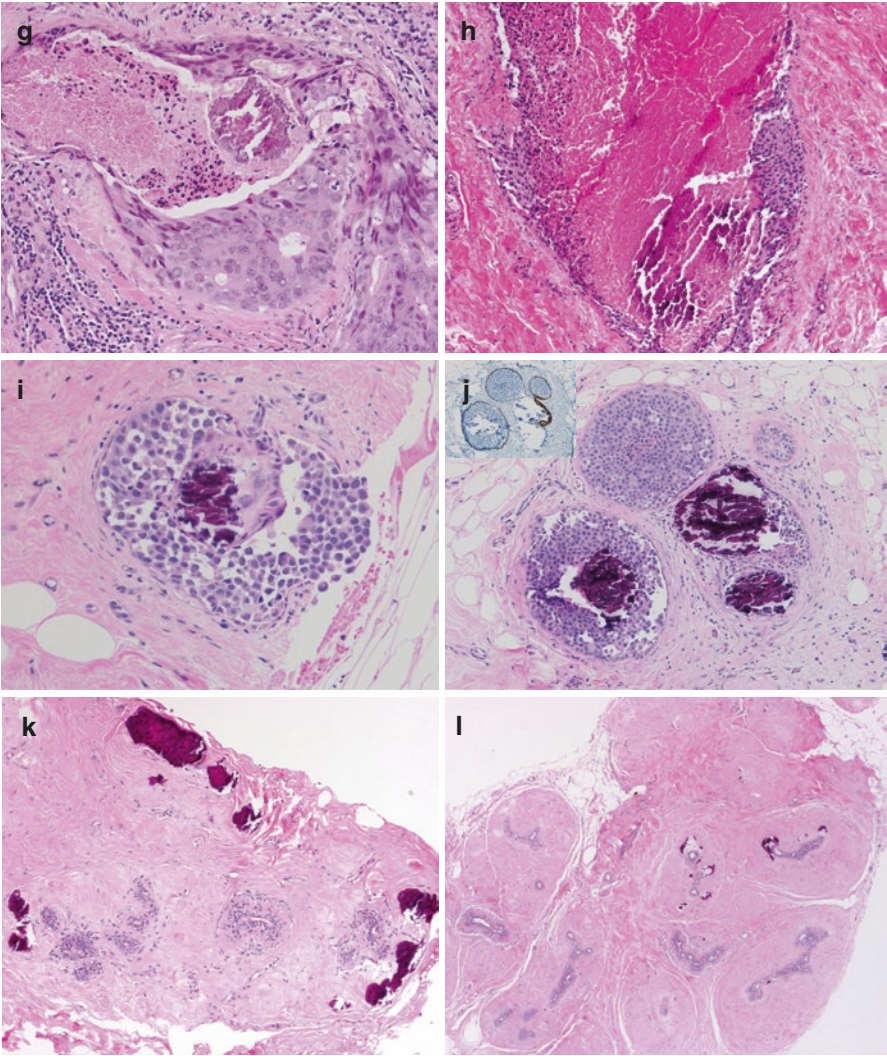
It is worth mentioning that “dystrophic calcifications” as described mammographically have different connotation from the dystrophic type calcifications in pathology. Mammographically, dystrophic calcifications are coarse, irregularly shaped calcifications, which are variable in size, shape, and densities because they do not form in preformed spaces; they may be bilateral. Bilaterally significantly increased radiologic dystrophic calcifications may raise the possibility of metabolic disorders like renal disease, autoimmune disorders, chest wall trauma, or burns. From a radiology standpoint, mammographically detected “dystrophic calcifications” are considered “typically benign” in BI-RADS lexicon and are generally not biopsied [62, 71]. Clinically, pathogenesis of calcifications is not important; the significance lies in whether the detected calcifications are associated with lesion(s) that require surgical intervention to prevent or at least minimize the future occurrence of invasive carcinoma.

Breast calcifications detected on histology may be morphologically different (Fig. 2.14a–p). The morphologic differences though interesting are of no clinical significance; pathologists evaluate breast biopsies performed for calcifications to

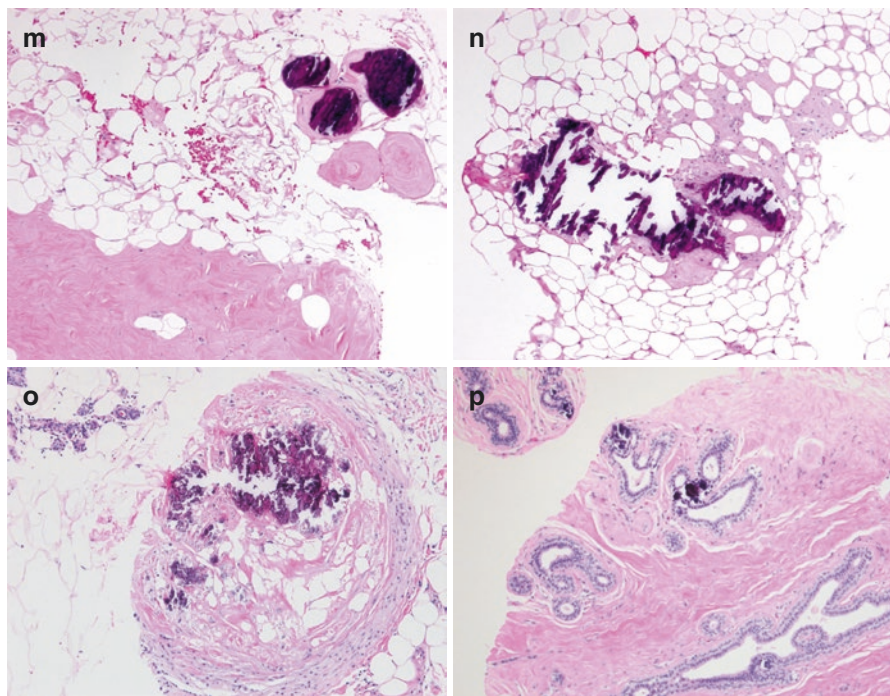


**Fig. 2.14** Calcifications and associated lesions. Calcifications associated with benign adenosis (a) and intraductal papilloma (b). Calcifications (psammomatous calcifications with round and laminated calcifications) associated with cystic hypersecretory hyperplasia (c) and cystic hypersecretory carcinoma (d). Calcifications (calcium oxalate) associated with apocrine metaplasia (e), best seen with polarization (f). Calcifications associated with ductal carcinoma in situ (DCIS) with comedonecrosis (g, h). Calcifications associated with lobular carcinoma in situ (LCIS), though uncommon may be seen. Inset shows negative E-cadherin immunohistochemical stain (i, j). Calcifications associated with fibroadenoma (k, l). Stromal calcifications. (m, n). Calcifications associated with fat necrosis (o) and benign ductal epithelium (p)





**Fig. 2.14** (continued)



**Fig. 2.14** (continued)

determine the presence or absence of calcifications and more importantly its associations—benign or malignant lesions or lesions with higher relative risk of malignancy [72]. It is useful for pathologists to have a basic understanding of radiologic evaluation and description of calcifications to foster meaningful radiologic–pathologic correlation and minimize false-negative diagnosis due to sampling which may lead to delayed diagnosis [73–75]. To facilitate such correlation, it is necessary for pathologists to have appropriate information regarding the distribution or types of calcifications and the specimen/biopsy radiographs [76]. However, in most cases needle core biopsy specimens are often not accompanied by specimen radiographs, and the requisition sheets often simply indicates “calcifications” without describing the type or distribution of such calcifications, essentially leaving the responsibility for such correlation to radiologists. Although the radiologic–pathologic correlation should ideally be performed by the radiologist who obtain the biopsy, it is important for pathologists to attempt such correlation to minimize cases “falling through the cracks.”

It cannot always be assumed that radiologic–pathologic correlation is performed by radiologists because of the following: (a) radiologists’ workload, (b) *a radiologist different* from the one who performed the initial radiologic interpretation and biopsy may get the pathology report, (c) lack of specific regulatory requirement for such correlation, (d) breast biopsies for calcifications may be performed by surgeons (not radiologists), and (e) breast biopsy pathology reports may end up with the primary care physicians or surgeons, some of whom may rely solely on the pathology report

without radiologic–pathologic correlation, especially for negative histology. Given that there may be up to 8% radiologic–pathologic discordance of breast biopsies and almost a quarter of these discordant cases may harbor carcinoma, the need for radiologic–pathologic correlation for optimal patient care cannot be overemphasized [77]. Hence, *pathologists should attempt to determine whether the pathologic findings provide reasonable and acceptable explanation of the breast imaging findings* from an optimal patient care standpoint.

## Adequate Evaluation of Breast Calcifications by Pathologists

For biopsies performed for calcifications, there is at least some radiologic suspicion of a premalignant or malignant lesion. Ideally x-rays of the biopsied tissues are performed by breast radiologists to ensure that the biopsies indeed contain the targeted calcifications [76]. It has been suggested that separation of the cores with and without calcifications by radiologists enhances identifications of calcification histologically; others do not find this practice necessary [6, 78, 79]. We have not found such separation particularly useful in our practice.

Pathologic evaluation of breast calcifications can be considered adequate as long as the following questions are appropriately considered and addressed:

(a) *If there are calcifications:*

What is the estimated size of the largest calcifications? Are these the calcifications targeted by the radiologists?

What types of calcifications are there?

What are the calcifications associated with?

(b) *If there are no calcifications:*

Is there a lesion (e.g. DCIS or invasive carcinoma) than can be treated?

Is there a standard institutional approach to search for calcifications?

Are deeper levels obtained? Fixed number of levels or cutting through the block?

Are x-rays obtained? Have steps been taken to ensure exhaustive search for calcifications?

*If there are calcifications, the following should be considered:*

**Size of calcifications:** The resolution of mammography matters in determination of calcifications seen on histology. The resolution of full-field digital mammography is 50 to 100 microns [80, 81]. This means that digital mammography (tomosynthesis) can detect calcifications as small as 50 microns or approximately the size of seven red blood cells. It is likely that the resolutions may significantly improve in the future. Currently, histopathologic evaluation of calcifications must be informed by the resolution of mammography to ensure that the calcifications seen on histology are indeed what was targeted. Tiny speck(s) of calcifications the size of one (7–8 microns) or two red blood cells are unlikely to be seen with the current resolution of mammogram and may not be the calcifications targeted on mammography, especially if a precursor lesion is not seen. This knowledge should help determine



whether to pursue additional steps to search for more calcifications (e.g., deeper levels, leveling through the block or x-ray of the paraffin tissue block), if no specific lesion is found.

*Type of calcifications:* Subtyping calcifications seen histologically is usually not necessary in pathology since the importance of such calcifications in the breast is the associated lesions. However, it is generally known that there are two types of breast microcalcifications [67]: type I (composed of calcium oxalate) and type II (composed of calcium phosphate, mainly hydroxyapatite); most breast calcifications are calcium phosphates/hydroxyapatite. Therefore, breast evaluation for calcifications is not complete unless the possibility of calcium oxalate, which is often associated with apocrine lesions, is considered and addressed [68, 82].

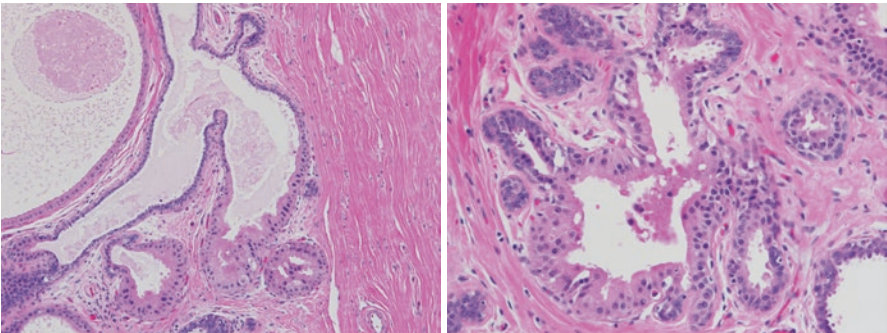
*Calcification and associated lesions:* Indicating the location or associations of calcifications was recommended by the joint task force of the American College of Radiology (ACR), American College of Surgeons (ACS), and College of American Pathologists (CAP) in 1997 [76] and is therefore a good pathology practice. For example, certain lesions are more commonly associated with some calcifications (e.g., high-grade DCIS is often associated with linear or pleomorphic calcifications with linear or segmental orientation) and must therefore be excluded [66]. *However, different lesions may be associated with similar types of radiologic calcifications.* Similarly, different types of calcifications may be associated with the same lesion. For example, fat necrosis may rarely be associated with pleomorphic or linear calcifications; linear calcifications may also be associated with sutures especially in the context of postsurgical evaluation of residual or recurrent disease; and filarial calcifications may be linear and should be considered in patients who are living in, who have visited, or who have emigrated from endemic areas [66, 83]. The identification of radiologically targeted calcifications is critical histologically in order to provide satisfactory explanation for the radiologic findings (correlation/congruence).

The mechanisms of some of the associated lesions are mostly of academic not clinical or management interests. For example, mammary apocrine changes is similar to normal apocrine glands of axillary, areolar, or perineal apocrine cells with similar histochemical or immunohistochemical staining reaction (positive for PASD, cytokeratins 8 and 18, AR [Androgen Receptor], and GCDP15 [Gross Cystic Disease Fluid Protein 15; also known as BRST2], but negative for ER and PR) and secretion [84, 85]. Apocrine change in the breast is generally regarded as metaplastic as the gradual change from normal cuboidal epithelium to apocrine cells can be seen in breast sections (Fig. 2.15), however, this position is controversial [84]. Apocrine change in the breast is considered a benign lesion.

Table 2.4 highlights common lesions associated with calcifications in the breast.

*If there are no calcifications on initial evaluation and no precursor lesion is identified:* Additional efforts should be made to identify the radiologically targeted calcifications. The joint task force of the ACR (American College of Radiology), ACS (American College of Surgeons), and CAP (College of American Pathologists) recommended that deeper levels beyond the initial sections should be examined if no

calcifications are identified on the initial sections but calcifications are present in the specimen radiograph. The task force also recommended that radiograph of the paraffin blocks may be obtained and the specimen should be examined for calcium oxalate by polarizing [76]. The task force did not indicate the minimum number of levels. Hence, to find a balance between optimal patient management and cost containment,



**Fig. 2.15** Apocrine metaplasia developing in native duct, supporting a metaplastic rather than de novo lesion

**Table 2.4** Summary of diagnostic criteria for common lesions associated with various calcifications [5, 31, 32]

Common breast lesions associated with calcifications	Diagnostic criteria	Mimics
Ductal carcinoma in situ (DCIS), high grade	Proliferation of pleomorphic, poorly polarized cells with irregular contours, coarse, clumped chromatin and prominent nucleoli. Single-cell layer of similar cells is sufficient for a diagnosis of high-grade DCIS. Mitoses and comedonecrosis (though often associated) are not required for diagnosis. No quantitative criteria needed for high-grade DCIS—any high-grade DCIS should be considered DCIS High-grade DCIS is generally surgically excised with or without sentinel lymph node sampling	DCIS involving lobules or sclerosing adenosis may mimic invasive carcinoma. Myoepithelial markers are useful in such cases
Ductal carcinoma in situ (DCIS), low grade	Uniform size or monomorphic, round (i.e., atypical), evenly spaced cell population with distinct cell borders. May be solid, cribriform, papillary, or micropapillary in architecture. If cribriform, the spaces/hole should be almost cookie cutter in appearance (not slit-like or irregular). Risk for development of invasive carcinoma is 8–10 times that of the reference population. Quantitative criteria: at least 2.0 mm or involving at least two ducts/spaces (controversial) Low-grade DCIS is generally surgically excised	Invasive carcinoma (when involving sclerosing adenosis), invasive cribriform carcinoma, LCIS, atypical ductal hyperplasia, usual ductal hyperplasia, collagenous spherulosis

(continued)

**Table 2.4** (continued)

Common breast lesions associated with calcifications	Diagnostic criteria	Mimics
Atypical ductal hyperplasia (ADH)	<p>The proliferation in ADH as in low-grade DCIS is monotonous; however, in ADH there may be a second population of cells admixed with the monotonous population or only partially involving the TDLU spaces. Quantitative criteria are useful in distinction of ADH and DCIS. Two common quantitative criteria are involvement of at least two membrane-bound spaces or a size &gt;2.0 mm for low grade DCIS</p> <p>Risk for development of invasive carcinoma is 3–5 times that of the reference population The risk applies to either breast.</p> <p>ADH is generally surgically excised</p>	Collagenous spherulosis usual ductal hyperplasia, low grade DCIS
Flat epithelial atypia (FEA)	<p>While the cells may be cuboidal/columnar, the nuclei (similar to low-grade DCIS or ADH) are round, uniform with inconspicuous nucleoli. The involved acini are variably distended with smooth contours having secretory materials and calcifications.</p> <p>Associated with coexistence of ALH, LCIS, ADH, DCIS, and invasive carcinoma.</p> <p>FEA is not equivalent to ADH or ALH in spite of “atypia” in the name. Radiologic-pathologic correlation to determine whether all targeted calcifications have been removed, in which case close follow-up rather than excision, is recommended</p>	Fibrocystic change, columnar cell change
Columnar cell change and columnar cell hyperplasia	<p>Variably dilated acini lined by columnar cells with oval nuclei with inconspicuous nucleoli. Lesions with one or two cell layers of columnar cell change; those with more than two cell layers are referred to as columnar cell hyperplasia. May be associated with other lesions including ALH and LCIS. Relative risk of 1.5 for subsequent development of cancer</p> <p>No surgical excision necessary for pure columnar cell change/hyperplasia in the absence of concomitant proliferative lesions</p>	FEA
Ductal hyperplasia without atypia (or usual ductal hyperplasia)	<p>Filling and distension of spaces with haphazardly oriented epithelial cells with variability in shape which may occasionally show streaming or syncytial growth in the center of the involved spaces and slit-like unevenly distributed fenestrations at the periphery in contrast to rigid ridges in ADH and DCIS.</p> <p>Risk for developing invasive carcinoma is 1.5–2 times that of reference population. Risk conferred on either breast</p> <p>No surgical excision necessary for ductal hyperplasia without atypia in the absence of concomitant proliferative lesions</p>	ADH

a good starting point should probably be ensuring that there are indeed calcifications in the specimen radiographs. Such radiographs may not be readily available to pathologists, but efforts should be made to at least review the radiology report or have a discussion with the radiologist. Some obtain an *initial 3–5 deeper levels and obtain more levels if the initial levels still show no calcifications; others simply exhaust the block to minimize turnaround time*; while others x-ray the paraffin blocks before deciding whether further evaluation is needed, as the calcifications may have been dislodged and fallen out of the tissue [6]. It is important to point out that exhaustive search for calcifications has been associated with low yield and high cost [86]. Therefore, each institution should determine appropriate protocol with emphasis on adequate and effective communications between pathologists and radiologists.

*If there are no calcifications on initial evaluation and a precursor lesion is identified:* If no calcifications are identified, but there is a specific diagnosis of a potentially treatable or precursor lesion, the question as to whether to embark on an exhaustive search of calcifications in this case will depend on the type of lesions. For example, if the lesion identified is DCIS or ADH, even in the absence of calcifications, it is probably unnecessary to continue to look for calcifications, since the purpose of the mammographic screening and biopsy has been achieved, namely, identification and management of treatable precursor lesions. Further search for calcifications in this scenario is likely an academic exercise which may not be cost-effective. On the other hand, if the lesion identified is the so-called flat epithelial atypia (FEA) in the absence of calcifications, it may be prudent to search for calcifications by obtaining deeper levels, since it would be useful to determine if there is a worse lesion, namely, ADH or DCIS. In the absence of lesions worse than FEA, the current recommendation is to closely watch the patient rather than excise pure FEA, especially if there are no residual calcifications on breast imaging, given the low positive predictive value of FEA for malignancy [87–90]. Additionally, if the only lesion identified is atypical lobular hyperplasia (ALH) or lobular carcinoma in situ (LCIS), which is not commonly associated with calcifications, it may be prudent to search for additional lesions known to be commonly associated with calcifications.

Finally, in the event that it is determined that the histologic findings do not provide satisfactory explanation of the breast imaging findings, further actions need to be taken for optimal patient care. Such actions include, but are not limited to: re-biopsy, recommendation of excision based on level of radiologic suspicion, or closer follow-up. Having a system in place for routine correlation of radiologic and pathologic findings, and for open communication with other members of the breast health team is critical.

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## References

1. Steinberg JL, Trudeau ME, Ryder DE, Fishell E, Chapman JA, McCready DR, et al. Combined fine-needle aspiration, physical examination and mammography in the diagnosis of palpable breast masses: their relation to outcome for women with primary breast cancer. *Can J Surg.* 1996;39(4):302–11.
2. Morris A, Pommier RF, Schmidt WA, Shih RL, Alexander PW, Vetto JT. Accurate evaluation of palpable breast masses by the triple test score. *Arch Surg.* 1998;133(9):930–4.



3. Kaufman Z, Shpitz B, Shapiro M, Rona R, Lew S, Dinbar A. Triple approach in the diagnosis of dominant breast masses: combined physical examination, mammography, and fine-needle aspiration. *J Surg Oncol*. 1994;56(4):254–7.
4. Kocjan G, Bourgain C, Fassina A, Hagmar B, Herbert A, Kapila K, et al. The role of breast FNAC in diagnosis and clinical management: a survey of current practice. *Cytopathology*. 2008;19(5):271–8.
5. WHO classification of tumours of the breast. 4th ed. Lyon: International Agency for Research on Cancer; 2012.
6. Idowu MO, Hardy LB, Souers RJ, Nakhleh RE. Pathologic diagnostic correlation with breast imaging findings: a College of American Pathologists Q-Probes study of 48 institutions. *Arch Pathol Lab Med*. 2012;136(1):53–60.
7. Idowu MO, Wiles A, Wan W, Wilkinson DS, Powers CN. Equivocal or ambiguous terminologies in pathology: focus of continuous quality improvement? *Am J Surg Pathol*. 2013;37(11):1722–7.
8. van Roozendaal LM, Goorts B, Klinkert M, Keymeulen KB, De Vries B, Strobbe LJ, et al. Sentinel lymph node biopsy can be omitted in DCIS patients treated with breast conserving therapy. *Breast Cancer Res Treat*. 2016;156(3):517–25.
9. Coromilas EJ, Wright JD, Huang Y, Feldman S, Neugut AI, Hillyer GC, et al. Axillary evaluation and lymphedema in women with ductal carcinoma in situ. *Breast Cancer Res Treat*. 2016;158(2):373–84.
10. Dupont WD, Page DL, Parl FF, Vnencak-Jones CL, Plummer WD Jr, Rados MS, et al. Long-term risk of breast cancer in women with fibroadenoma. *N Engl J Med*. 1994;331(1):10–5.
11. Bandyopadhyay S, Barak S, Hayek K, Thomas S, Saeed H, Beydoun R, et al. Can problematic fibroepithelial lesions be accurately classified on core needle biopsies? *Hum Pathol*. 2016;47(1):38–44.
12. Tsang AK, Chan SK, Lam CC, Lui PC, Chau HH, Tan PH, et al. Phyllodes tumours of the breast – differentiating features in core needle biopsy. *Histopathology*. 2011;59(4):600–8.
13. Lawton TJ, Acs G, Argani P, Farshid G, Gilcrease M, Goldstein N, et al. Interobserver variability by pathologists in the distinction between cellular fibroadenomas and phyllodes tumors. *Int J Surg Pathol*. 2014;22(8):695–8.
14. Jacobs TW, Chen YY, Guinee DG Jr, Holden JA, Cha I, Bauermeister DE, et al. Fibroepithelial lesions with cellular stroma on breast core needle biopsy: are there predictors of outcome on surgical excision? *Am J Clin Pathol*. 2005;124(3):342–54.
15. Tan BY, Acs G, Apple SK, Badve S, Bleiweiss IJ, Brogi E, et al. Phyllodes tumours of the breast: a consensus review. *Histopathology*. 2016;68(1):5–21.
16. Jara-Lazaro AR, Akhilesh M, Thike AA, Lui PC, Tse GM, Tan PH. Predictors of phyllodes tumours on core biopsy specimens of fibroepithelial neoplasms. *Histopathology*. 2010;57(2):220–32.
17. Giri D. Recurrent challenges in the evaluation of fibroepithelial lesions. *Arch Pathol Lab Med*. 2009;133(5):713–21.
18. Cowan ML, Argani P, Cimino-Mathews A. Benign and low-grade fibroepithelial neoplasms of the breast have low recurrence rate after positive surgical margins. *Mod Pathol*. 2016;29(3):259–65.
19. Grimes MM. Cystosarcoma phyllodes of the breast: histologic features, flow cytometric analysis, and clinical correlations. *Mod Pathol*. 1992;5(3):232–9.
20. Kanhai RC, Hage JJ, Bloemena E, van Diest PJ, Karim RB. Mammary fibroadenoma in a male-to-female transsexual. *Histopathology*. 1999;35(2):183–5.
21. Lemmo G, Garcea N, Corsello S, Tarquini E, Palladino T, Ardito G, et al. Breast fibroadenoma in a male-to-female transsexual patient after hormonal treatment. *Eur J Surg Suppl*. 2003;588:69–71.
22. Karihtala P, Rissanen T, Tuominen H. Male malignant phyllodes breast tumor after prophylactic breast radiotherapy and bicalutamide treatment: a case report. *Anticancer Res*. 2016;36(7):3433–6.
23. Agoumi M, Giambattista J, Hayes MM. Practical considerations in breast papillary lesions: a review of the literature. *Arch Pathol Lab Med*. 2016;140(8):770–90.

24. Wei S. Papillary lesions of the breast: an update. *Arch Pathol Lab Med.* 2016;140(7):628–43.
25. Collins LC, Schnitt SJ. Papillary lesions of the breast: selected diagnostic and management issues. *Histopathology.* 2008;52(1):20–9.
26. Ueng SH, Mezzetti T, Tavassoli FA. Papillary neoplasms of the breast: a review. *Arch Pathol Lab Med.* 2009;133(6):893–907.
27. Tan PH, Schnitt SJ, van de Vijver MJ, Ellis IO, Lakhani SR. Papillary and neuroendocrine breast lesions: the WHO stance. *Histopathology.* 2015;66(6):761–70.
28. Page DL, Salhany KE, Jensen RA, Dupont WD. Subsequent breast carcinoma risk after biopsy with atypia in a breast papilloma. *Cancer.* 1996;78(2):258–66.
29. Dupont WD, Page DL. Risk factors for breast cancer in women with proliferative breast disease. *N Engl J Med.* 1985;312(3):146–51.
30. Lewis JT, Hartmann LC, Vierkant RA, Maloney SD, Shane Pankratz V, Allers TM, et al. An analysis of breast cancer risk in women with single, multiple, and atypical papilloma. *Am J Surg Pathol.* 2006;30(6):665–72.
31. Page DL, Dupont WD. Benign breast disease: indicators of increased breast cancer risk. *Cancer Detect Prev.* 1992;16(2):93–7.
32. Jensen RA, Dupont WD, Page DL. Diagnostic criteria and cancer risk of proliferative breast lesions. *J Cell Biochem Suppl.* 1993;17G:59–64.
33. Laval M, Delangle R, Ndoye A, Sylvestre E, Laviolle B, Lavoue V, et al. The role of percutaneous biopsy and prognostic factors of malignancy in solitary breast papilloma: a retrospective multicenter study of 259 cases. *Anticancer Res.* 2015;35(12):6881–6.
34. Wyss P, Varga Z, Rossle M, Rageth CJ. Papillary lesions of the breast: outcomes of 156 patients managed without excisional biopsy. *Breast J.* 2014;20(4):394–401.
35. Yamaguchi R, Tanaka M, Tse GM, Yamaguchi M, Terasaki H, Hirai Y, et al. Management of breast papillary lesions diagnosed in ultrasound-guided vacuum-assisted and core needle biopsies. *Histopathology.* 2015;66(4):565–76.
36. Shamonki J, Chung A, Huynh KT, Sim MS, Kinnaird M, Giuliano A. Management of papillary lesions of the breast: can larger core needle biopsy samples identify patients who may avoid surgical excision? *Ann Surg Oncol.* 2013;20(13):4137–44.
37. Fu CY, Chen TW, Hong ZJ, Chan DC, Young CY, Chen CJ, et al. Papillary breast lesions diagnosed by core biopsy require complete excision. *Eur J Surg Oncol.* 2012;38(11):1029–35.
38. Tseng HS, Chen YL, Chen ST, Wu YC, Kuo SJ, Chen LS, et al. The management of papillary lesion of the breast by core needle biopsy. *Eur J Surg Oncol.* 2009;35(1):21–4.
39. McGhan LJ, Pockaj BA, Wasif N, Giurescu ME, McCullough AE, Gray RJ. Papillary lesions on core breast biopsy: excisional biopsy for all patients? *Am Surg.* 2013;79(12):1238–42.
40. Rakha EA, Gandhi N, Climent F, van Deurzen CH, Haider SA, Dunk L, et al. Encapsulated papillary carcinoma of the breast: an invasive tumor with excellent prognosis. *Am J Surg Pathol.* 2011;35(8):1093–103.
41. Mulligan AM, O'Malley FP. Metastatic potential of encapsulated (intracystic) papillary carcinoma of the breast: a report of 2 cases with axillary lymph node micrometastases. *Inter J Surg Pathol.* 2007;15(2):143–7.
42. Hayes MM. Adenomyoepithelioma of the breast: a review stressing its propensity for malignant transformation. *J Clin Pathol.* 2011;64(6):477–84.
43. McLaren BK, Smith J, Schuyler PA, Dupont WD, Page DL. Adenomyoepithelioma: clinical, histologic, and immunohistologic evaluation of a series of related lesions. *Am J Surg Pathol.* 2005;29(10):1294–9.
44. Yoon JY, Chitale D. Adenomyoepithelioma of the breast: a brief diagnostic review. *Arch Pathol Lab Med.* 2013;137(5):725–9.
45. Wahner-Roedler DL, Sebo TJ, Gisvold JJ. Hamartomas of the breast: clinical, radiologic, and pathologic manifestations. *Breast J.* 2001;7(2):101–5.
46. Magro G. Mammary myofibroblastoma: an update with emphasis on the most diagnostically challenging variants. *Histol Histopathol.* 2016;31(1):1–23.
47. Magro G. Mammary myofibroblastoma: a tumor with a wide morphologic spectrum. *Arch Pathol Lab Med.* 2008;132(11):1813–20.

48. Wellings SR, Jensen HM, Marcum RG. An atlas of subgross pathology of the human breast with special reference to possible precancerous lesions. *J Natl Cancer Inst.* 1975;55(2):231–73.
49. Williams AS, Hache KD. Recognition and discrimination of tissue-marking dye color by surgical pathologists: recommendations to avoid errors in margin assessment. *Am J Clin Pathol.* 2014;142(3):355–61.
50. Moran MS, Schnitt SJ, Giuliano AE, Harris JR, Khan SA, Horton J, et al. Society of Surgical Oncology-American Society for Radiation Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in stages I and II invasive breast cancer. *J Clin Oncol.* 2014;32(14):1507–15.
51. Sigal-Zafrani B, Lewis JS, Clough KB, Vincent-Salomon A, Fourquet A, Meunier M, et al. Histological margin assessment for breast ductal carcinoma in situ: precision and implications. *Mod Pathol.* 2004;17(1):81–8.
52. Silverstein MJ, Lagios MD, Groshen S, Waisman JR, Lewinsky BS, Martino S, et al. The influence of margin width on local control of ductal carcinoma in situ of the breast. *N Engl J Med.* 1999;340(19):1455–61.
53. Dunne C, Burke JP, Morrow M, Kell MR. Effect of margin status on local recurrence after breast conservation and radiation therapy for ductal carcinoma in situ. *J Clin Oncol.* 2009;27(10):1615–20.
54. Wright MJ, Park J, Fey JV, Park A, O'Neill A, Tan LK, et al. Perpendicular inked versus tangential shaved margins in breast-conserving surgery: does the method matter? *J Am Coll Surg.* 2007;204(4):541–9.
55. Morrow M, Van Zee KJ, Solin LJ, Houssami N, Chavez-MacGregor M, Harris JR, et al. Society of Surgical Oncology-American Society for Radiation Oncology-American Society of Clinical Oncology consensus guideline on margins for breast-conserving surgery with whole-breast irradiation in ductal carcinoma in situ. *Ann Surg Oncol.* 2016;23(12):3801–10.
56. Weaver DL. Pathology evaluation of sentinel lymph nodes in breast cancer: protocol recommendations and rationale. *Mod Pathol.* 2010;23(Suppl 2):S26–32.
57. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, et al. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. *Arch Pathol Lab Med.* 2014;138(2):241–56.
58. Fitzgibbons PL, Murphy DA, Hammond ME, Allred DC, Valenstein PN. Recommendations for validating estrogen and progesterone receptor immunohistochemistry assays. *Arch Pathol Lab Med.* 2010;134(6):930–5.
59. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer (unabridged version). *Arch Pathol Lab Med.* 2010;134(7):e48–72.
60. Bassett LW. Mammographic analysis of calcifications. *Radiol Clin North Am.* 1992;30(1):93–105.
61. Monsees BS. Evaluation of breast microcalcifications. *Radiol Clin North Am.* 1995;33(6):1109–21.
62. Lazarus E, Mainiero MB, Schepps B, Koelliker SL, Livingston LS. BI-RADS lexicon for US and mammography: interobserver variability and positive predictive value. *Radiology.* 2006;239(2):385–91.
63. Gallagher R, Schafer G, Redick M, Inciradi M, Smith W, Fan F, et al. Microcalcifications of the breast: a mammographic-histologic correlation study using a newly designed path/rad tissue tray. *Ann Diagn Pathol.* 2012;16(3):196–201.
64. Hofvind S, Iversen BF, Eriksen L, Styr BM, Kjelleveold K, Kurz KD. Mammographic morphology and distribution of calcifications in ductal carcinoma in situ diagnosed in organized screening. *Acta Radiol.* 2011;52(5):481–7.
65. Kopans D, Gavenonis S, Halpern E, Moore R. Calcifications in the breast and digital breast tomosynthesis. *Breast J.* 2011;17(6):638–44.

66. Demetri-Lewis A, Slanetz PJ, Eisenberg RL. Breast calcifications: the focal group. *AJR Am J Roentgenol*. 2012;198(4):W325–43.
67. Scimeca M, Giannini E, Antonacci C, Pistolesi CA, Spagnoli LG, Bonanno E. Microcalcifications in breast cancer: an active phenomenon mediated by epithelial cells with mesenchymal characteristics. *BMC Cancer*. 2014;14:286.
68. Cox RF, Morgan MP. Microcalcifications in breast cancer: lessons from physiological mineralization. *Bone*. 2013;53(2):437–50.
69. Morgan MP, Cooke MM, McCarthy GM. Microcalcifications associated with breast cancer: an epiphenomenon or biologically significant feature of selected tumors? *J Mammary Gland Biol Neoplasia*. 2005;10(2):181–7.
70. Tse GM, Tan PH, Cheung HS, Chu WC, Lam WW. Intermediate to highly suspicious calcification in breast lesions: a radio-pathologic correlation. *Breast Cancer Res Treat*. 2008;110(1):1–7.
71. Michaels AY, Birdwell RL, Chung CS, Frost EP, Giess CS. Assessment and management of challenging BI-RADS category 3 mammographic lesions. *Radiographics*. 2016;36(5):1261–72.
72. Page DL, Dupont WD. Anatomic markers of human premalignancy and risk of breast cancer. *Cancer*. 1990;66(Suppl 6):1326–35.
73. Dahlstrom JE, Sutton S, Jain S. Histologic-radiologic correlation of mammographically detected microcalcification in stereotactic core biopsies. *Am J Surg Pathol*. 1998;22(2):256–9.
74. Dahlstrom JE, Jain S. Histological correlation of mammographically detected microcalcifications in stereotactic core biopsies. *Pathology*. 2001;33(4):444–8.
75. Tse GM, Tan PH, Pang AL, Tang AP, Cheung HS. Calcification in breast lesions: pathologists' perspective. *J Clin Pathol*. 2008;61(2):145–51.
76. Bassett L, Winchester DP, Caplan RB, Dershaw DD, Dowlatsahi K, Evans WP 3rd, et al. Stereotactic core-needle biopsy of the breast: a report of the Joint Task Force of the American College of Radiology, American College of Surgeons, and College of American Pathologists. *CA Cancer J Clin* 1997;47(3):171–190.
77. Liberman L, Menell JH. Breast imaging reporting and data system (BI-RADS). *Radiol Clin North Am*. 2002;40(3):409–30, v.
78. Margolin FR, Kaufman L, Jacobs RP, Denny SR, Schrumpf JD. Stereotactic core breast biopsy of malignant calcifications: diagnostic yield of cores with and cores without calcifications on specimen radiographs. *Radiology*. 2004;233(1):251–4.
79. Easley S, Abdul-Karim FW, Klein N, Wang N. Segregation of radiographic calcifications in stereotactic core biopsies of breast: is it necessary? *Breast J*. 2007;13(5):486–9.
80. Pisano ED, Zuley M, Baum JK, Marques HS. Issues to consider in converting to digital mammography. *Radiol Clin North Am*. 2007;45(5):813–30, vi.
81. Pagliari CM, Hoang T, Reddy M, Wilkinson LS, Poloniecki JD, Given-Wilson RM. Diagnostic quality of 50 and 100 µm computed radiography compared with screen-film mammography in operative breast specimens. *Br J Radiol*. 2012;85(1015):910–6.
82. Tornos C, Silva E, el-Naggar A, Pritzker KP. Calcium oxalate crystals in breast biopsies. The missing microcalcifications. *Am J Surg Pathol*. 1990;14(10):961–8.
83. Lai KC, Slanetz PJ, Eisenberg RL. Linear breast calcifications. *AJR Am J Roentgenol*. 2012;199(2):W151–7.
84. Wells CA, El-Ayat GA. Non-operative breast pathology: apocrine lesions. *J Clin Pathol*. 2007;60(12):1313–20.
85. Zagorianakou P, Zagorianakou N, Stefanou D, Makrydimas G, Agnantis NJ. The enigmatic nature of apocrine breast lesions. *Virchows Arch*. 2006;448(5):525–31.
86. Grimes MM, Karageorge LS, Hogge JP. Does exhaustive search for microcalcifications improve diagnostic yield in stereotactic core needle breast biopsies? *Mod Pathol*. 2001;14(4):350–3.
87. Dialani V, Venkataraman S, Frieling G, Schnitt SJ, Mehta TS. Does isolated flat epithelial atypia on vacuum-assisted breast core biopsy require surgical excision? *Breast J*. 2014;20(6):606–14.
88. Calhoun BC, Sobel A, White RL, Gromet M, Flippo T, Sarantou T, et al. Management of flat epithelial atypia on breast core biopsy may be individualized based on correlation with imaging studies. *Mod Pathol*. 2015;28(5):670–6.



89. Maeda I, Kanemaki Y, Tozaki M, Koizumi H, Oana Y, Okanami Y, et al. Positive predictive value for malignancy of pure flat epithelial atypia diagnosis by percutaneous needle biopsy of the breast: management of FEA in ultrasonography. *Breast Cancer*. 2015;22(6):634–40.
90. Said SM, Visscher DW, Nassar A, Frank RD, Vierkant RA, Frost MH, et al. Flat epithelial atypia and risk of breast cancer: a Mayo cohort study. *Cancer*. 2015;121(10):1548–55.

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