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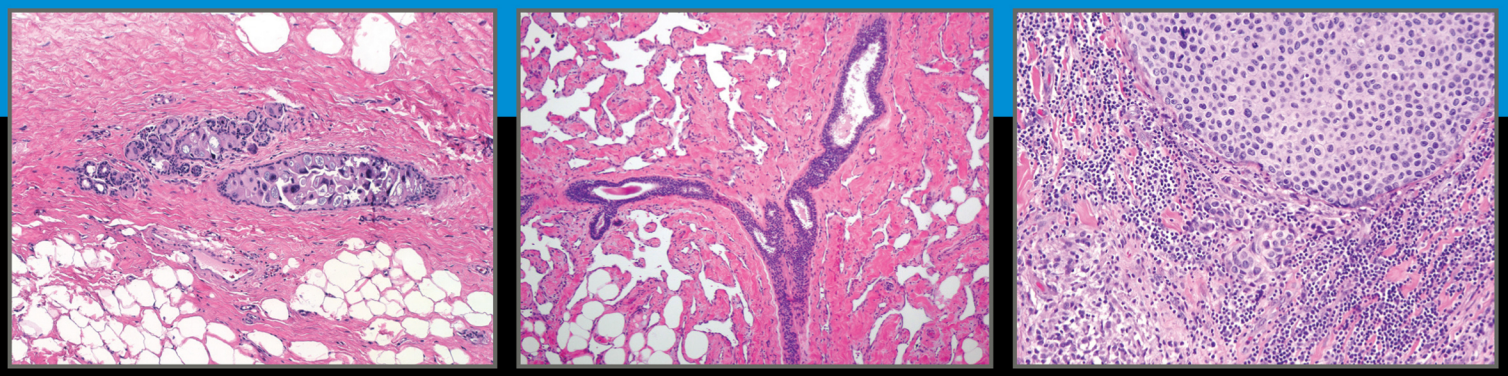
PRACTICAL SURGICAL PATHOLOGY OF THE BREAST



JUAN P. PALAZZO

Practical Surgical Pathology of the Breast

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To My Parents, Laura and Domingo

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PREFACE

The goal of this book is to provide pathologists and residents with a reference guide and tools to use in the diagnosis of breast diseases. It is an evolution of my previous text, *Difficult Diagnoses in Breast Pathology*, and it highlights the most important aspects of each entity with a focus on diagnostic criteria, differential diagnosis, and management. The text, topics, illustrations, tables, and references have been greatly expanded, and detailed descriptions have been improved to cover a wider spectrum of breast diseases.

The book consists of 14 chapters devoted to all aspects of breast pathology. The chapters include specific discussions such as the interpretation of core biopsies; the full spectrum of epithelial lesions, mesenchymal tumors, lymphoproliferative lesions; and the changes seen in the breast following neoadjuvant therapy. A thorough description of the spectrum of triple-negative tumors and adenosis and hypersecretory changes is included. The application of immunohistochemistry to interpret prognostic markers, as well as the most common markers applied to breast pathology and the molecular pathology of breast tumors, are discussed.

Each chapter includes tables, boxes containing common pitfalls, and helpful tips, as well as key points, which highlight the essential concepts of each section. High-quality color illustrations and a comprehensive number of references complement the text.

I was very fortunate to have worked with such an outstanding and unique group of experts in the field, who despite their busy schedules agreed to help me with this project. Without their great dedication and effort, this book would not have been possible. Each chapter reflects the authors' own experience in practice and the best guide to solve problematic cases from their perspective.

My hope is that this book provides information that will help pathologists in the interpretation of breast biopsies and will also be a source of education for residents and fellows.

I want to thank all my colleagues from the Department of Pathology of the Sidney Kimmel Medical College at Thomas Jefferson University, and I also thank Mr. David D'Addona and Ms. Young Kim from Demos Medical Publishing for their support, encouragement, and patience. The contribution of Dr. Esteban Gnass with the quality of the photos and editing is greatly appreciated. Lastly, I would like to thank my family for their relentless support in all my endeavors.

Juan P. Palazzo

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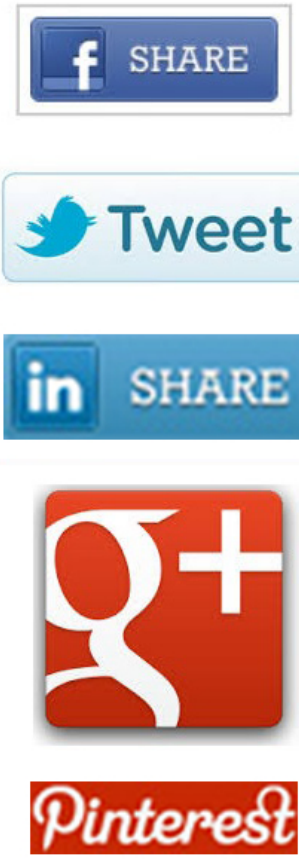

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THE DIAGNOSTIC CHALLENGES OF CORE NEEDLE BIOPSY INTERPRETATION

Aylin Simsir and Joan F. Cangiarella

Percutaneous core needle biopsy (CNB) is a safe, accurate, and cost-effective diagnostic method. Over the last few decades, there has been a marked growth in its use for the diagnosis of palpable and nonpalpable mammary lesions. Radiologic guidance, including stereotactic guidance, ultrasonography, and MRI, has significantly enhanced the ability to sample lesions by CNB. With the introduction of vacuum-assisted biopsy (VAB) and the use of larger needles, the amount of tissue obtained by CNB has also increased. Despite these advances, diagnostic challenges in the pathologic interpretation and controversies in the management of certain lesions diagnosed by percutaneous CNB still remain.

A key component to the success of a CNB program is the mandatory use of the triple test with effective communication among members of the multidisciplinary team. There must be knowledge of the clinical and radiologic findings and confidence that the lesion targeted for biopsy is adequately sampled and that the pathologic results are concordant with the imaging and clinical findings. Discordance among the clinical, radiologic, or pathologic findings warrants excision. Pathologists must be effective communicators and should not interpret a CNB without knowledge of the clinical and radiologic findings.

The challenges for pathologists in the interpretation of percutaneous core biopsies are twofold. First, there exists a variety of lesions that are diagnostically difficult to interpret in CNB due to an overlap of pathologic features with other entities. These lesions are uncommon in CNB, and the small amount of tissue obtained by percutaneous CNB makes classification of these lesions diagnostically difficult. The second issue is that some lesions, when identified in percutaneous CNB, often create uncertainty with regard to proper clinical management. These lesions include atypical ductal hyperplasia (ADH), papillary lesions, atypical lobular hyperplasia (ALH), lobular carcinoma in situ (LCIS), fibroepithelial lesions, radial scars (RSs), and mucinous lesions.

ATYPICAL DUCTAL HYPERPLASIA

ADH is a proliferative lesion of the breast epithelium that fulfills some, but not all, of the criteria of a low-grade, non-comedo-type ductal carcinoma in situ (DCIS). Microcalcifications are the most common mammographic presentation of ADH. When ADH is encountered in CNB, one must consider whether the radiologic findings correlate with the pathologic findings. Sampling error by core remains a potential problem. In many cases of DCIS identified at surgical excision, DCIS is found in the central portion of the lesion, and foci of ADH are found at the periphery (1). If the CNB samples the peripheral areas only, ADH will be present on the core specimen, but DCIS may be identified at surgical excision. Although the diagnostic features of ADH in a CNB are similar to those of a surgical excision specimen, one should not overinterpret the findings in small CNB samples. When debating between a diagnosis of usual ductal hyperplasia (UDH) and ADH in core, the impact of the diagnosis must be considered since only a diagnosis of ADH warrants surgical excision. If debating between ADH and DCIS, preference is given to diagnosing the lesion as an ADH and rendering a definitive diagnosis on the excision specimen.

PATHOLOGIC FEATURES

One of the most difficult challenges for the pathologist in the interpretation of breast biopsies is distinguishing ADH from UDH and DCIS. Distinguishing ADH from low-grade DCIS or from florid ductal epithelial hyperplasia is even more challenging in the limited tissue sample obtained by CNB. Microscopically, three components to the diagnosis of ADH include architectural pattern, cytology, and extent (2,3). These components may be difficult to evaluate in small samples.

Interobserver variability in the pathologic diagnosis of ADH is widely recognized (4). The pathologic findings in UDH to DCIS occur on a spectrum with patterns that may overlap. UDH has a heterogeneous population of cells, with cells streaming and secondary lumina that are irregular, slit-like, and often arranged at the periphery (Figure 1.1A and B). In DCIS, spaces are round and regular with a monotonous cell population (Figure 1.1C and D). ADH falls in the middle, with either uniform cells with irregular cell spaces or regular spaces with heterogeneous cells (Figures 1.1E and F and 1.2A and B). The pathologic features distinguishing florid hyperplasia, atypical ductal carcinoma, and DCIS are summarized in Table 1.1.

IMMUNOHISTOCHEMICAL AND MOLECULAR MARKERS

The routine distinction of ADH from UDH and DCIS relies on the microscopic study of hematoxylin and eosin (H&E) stains without the use of immunohistochemistry. Although immunohistochemical staining may distinguish florid hyperplasia from ADH or DCIS, it has not been shown to be useful in distinguishing ADH from DCIS. Immunohistochemical staining with cytokeratin 5/6 (high-molecular-weight cytokeratin) shows positivity in the luminal epithelial cells in the majority of UDH (88%) but negativity in ADH (92%) (5). Caution must be exercised in the

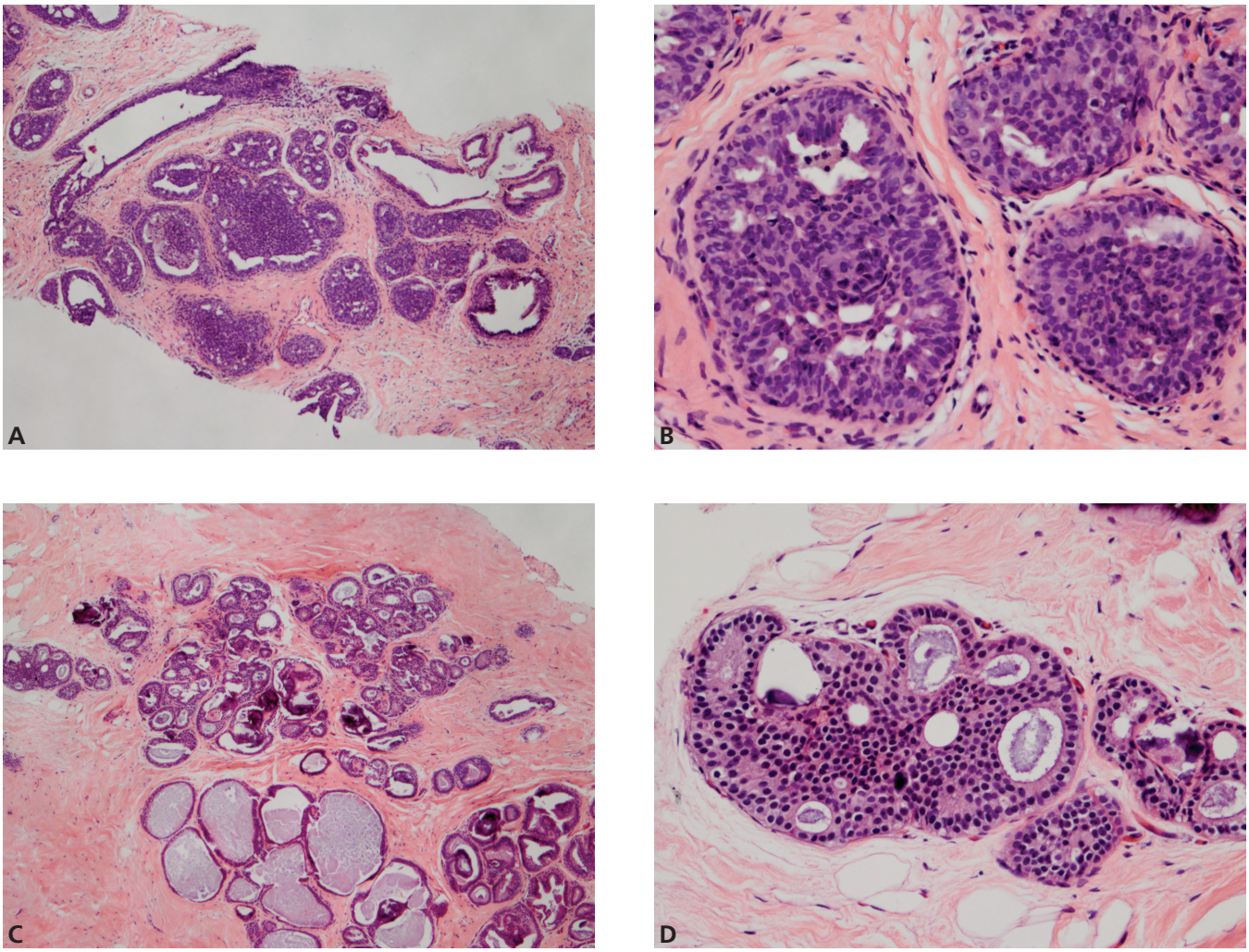

FIGURE 1.1 Spectrum of proliferative breast lesions in CNB. (A) Florid ductal hyperplasia. A proliferation of epithelial cells within ductal spaces leading to the formation of irregular slit-like spaces is noted. (B) Florid ductal hyperplasia. Higher magnification shows a heterogeneous population of cells with streaming and irregular, peripheral secondary lumens. (C) DCIS, cribriform type. A cribriform proliferation is noted with evenly placed, rounded "punched-out" spaces. (D) DCIS, cribriform type. Higher magnification shows cells with distinct cell membranes and minimal overlapping. There is cytologic monotony and uniformity. The spaces are round and uniform.

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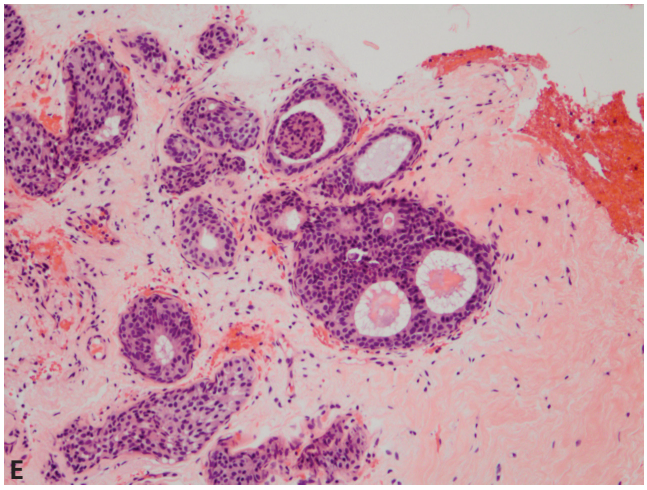


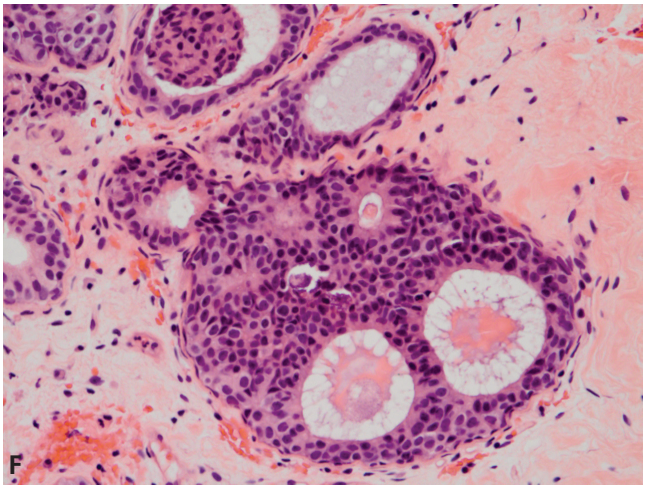
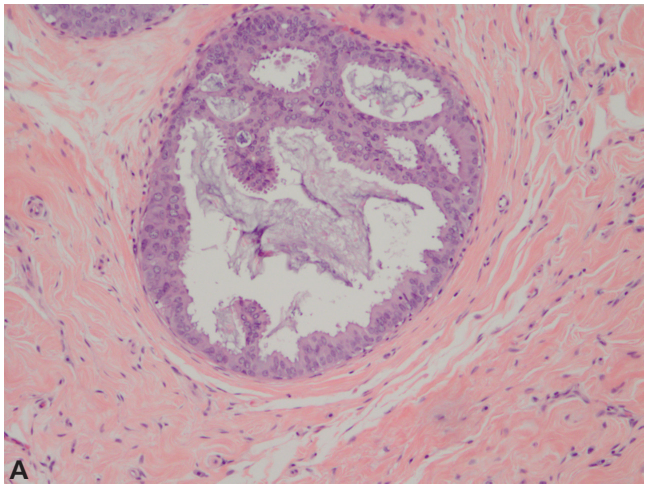


FIGURE 1.1 (*continued*) (E) Atypical ductal hyperplasia. ADH meets some, but not all, of the criteria of DCIS. The proliferation involves only one duct, and the spaces appear more regular than that seen in florid ductal hyperplasia. (F) ADH. Higher magnification shows some cells with nuclear enlargement at the periphery, but the cells in the central portion of the duct show streaming of nuclei.
ADH, atypical ductal hyperplasia; CNB, core needle biopsy; DCIS, ductal carcinoma in situ.



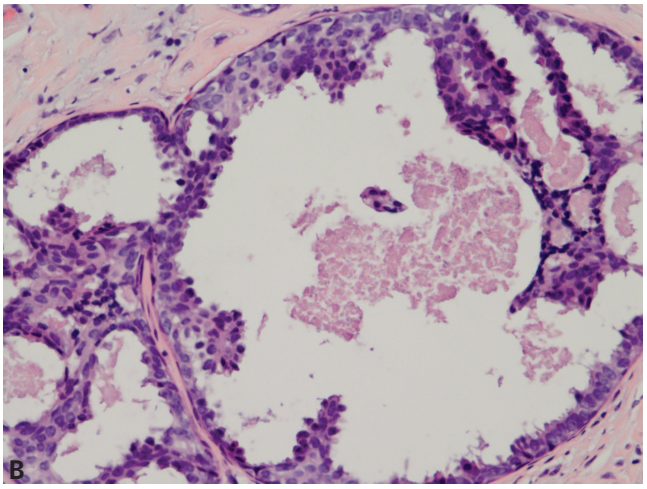


FIGURE 1.2 Difficulty in distinguishing ADH from DCIS in core biopsy. In core biopsy, the small amount of tissue obtained can make distinguishing ADH from DCIS challenging. Proliferations shown here that involve only one duct but show tufts (A) and micropapillae (B) are especially challenging.
ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ.

interpretation of this stain because apocrine metaplasia and columnar alterations also show a negative reaction. To date, there are no molecular markers that can predict the risk of development of breast cancer in patients with atypia (6). The atypical cell population in ADH shows a low proliferation rate, high levels of estrogen receptor positivity, and shares genetic and molecular features with low-grade DCIS and low-grade, estrogen-receptor-positive invasive breast carcinoma, suggesting that ADH is an early lesion in the formation pathway of low-grade breast cancer (7).

MANAGEMENT ISSUES

ADH is encountered in percutaneous CNB in only 2% to 15% (8,9) of core biopsies. Surgical excision is the recommended management because 7% to 56% (10,11) of the cases diagnosed as ADH in CNB will be upgraded to DCIS or invasive carcinoma after excision. A recent nomogram was developed to calculate the likelihood of upgrading a diagnosis of ADH at excision and ultimately to predict which patients diagnosed with ADH on core biopsy could be

TABLE 1.1 Comparative Pathologic Features Among Florid Ductal Epithelial Hyperplasia, ADH, and Low-Grade DCIS

	Florid Ductal Epithelial Hyperplasia	ADH	Low-Grade DCIS
Definition	Increase in the number of cells above the normal two-cell layer	Meets some but not all of the criteria of low-grade, non-comedo-type DCIS	Meets all of the criteria of low-grade, non-comedo-type DCIS
Architectural pattern	Streaming of nuclei, solid, papillary, bridging, and fenestrated patterns	Cribriform, micropapillary, papillary, columnar cell	Solid, cribriform, micropapillary
Cell placement	Uneven nuclear spacing, irregular peripherally placed spaces in a duct, parallel arrangements	Evenly spaced; second cell population of polarized columnar cells adjacent to the basement membrane	Evenly spaced; rigid bars with long axis of cells perpendicular to the long axis of the bar
Characteristic of spaces	Peripherally placed, irregular spaces in a duct	Bar crossing an entire space or six to seven cells across	Rigid bars, secondary lumina with rounded, "punched out" spaces
Cytology	Irregularly shaped nuclei, nuclear overlap, inconspicuous nucleoli, infrequent mitotic figures, indistinct cell membranes	Uniform, regular oval, and round nuclei; cytologic uniformity and monotony or cytologic atypia with nuclear enlargement, hyperchromasia, and the presence of nucleoli; more prominent cell membranes	Cytologic uniformity and monotony, minimal overlapping of nuclei, distinct cell membranes
Extent	Any extent	Involvement of only one duct that meets the criteria of low-grade DCIS	Involvement of two or more ducts
Size	Any size	<2 mm	≥2 mm

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ.

spared surgery but unfortunately this tool predicted an upgrade rate to carcinoma of 8%, a rate too high to spare a patient surgery (12). Underestimation is related to sampling error and is directly associated with the amount of tissue removed at biopsy. Underestimation rates are lower for 11-gauge VAB (10%–27%) (13,14) as compared with 14-gauge automated CNB (44%–56%) (15,16) due to the significant increase in volume of tissue obtained by using larger needles and vacuum assistance. Most cases of carcinoma found at excision are DCIS, with invasive carcinoma representing approximately 30%. Factors related to the underestimation of carcinoma in cases diagnosed as ADH in CNB are summarized in Table 1.2.

COMMON PITFALLS AND HELPFUL TIPS

- The pathologic diagnosis of atypical ductal hyperplasia (ADH) in core needle biopsy (CNB) is difficult due to an inability to distinguish these lesions from low-grade ductal carcinoma in situ (DCIS) in a limited sample obtained by core.
- Strict criteria should be followed to accurately diagnose ADH in CNB and avoid underdiagnosis or overdiagnosis.
- In a CNB in which the diagnosis falls between usual ductal hyperplasia (UDH) and ADH, discussion of the case at an intradepartmental conference or review by a second pathologist is also helpful, as surgical excision will not be recommended for diagnosis of UDH.
- The finding of ADH in CNB warrants surgical excision, as the underestimation rate of carcinoma at surgical excision ranges from 7% to 56%.
- Immunohistochemical stains may be applied to differentiate these lesions in some cases; however, the diagnosis should be based primarily on the features identified on H&E stains.

TABLE 1.2 Factors Related to the Underestimation of Carcinoma at Surgical Excision in Cases Diagnosed as ADH on Percutaneous CNB

Size of core needle (smaller size needles [larger gauge] associated with greater underestimation)
Method of biopsy (automated vs. VAB; automated biopsy associated with greater underestimation)
Number of foci of ADH (two or more associated with greater underestimation)
Size of largest foci of ADH greater than or equal to 1.1 mm (associated with greater underestimation) (12)
Incomplete removal of lesion by VAB
Larger lesion size (inadequate sampling due to large lesion size leads to greater underestimation)
Lower number of cores obtained at biopsy (inadequate sampling leads to underestimation)
Patient's age younger than 55 and greater than 70 years (associated with greater underestimation) (12)
Presence of a mass by palpation or on ultrasound
Personal history of breast cancer

ADH, atypical ductal hyperplasia; CNB, core needle biopsy; VAB, vacuum-assisted biopsy.

PAPILLARY LESIONS

There are numerous challenges for the pathologist in diagnosing papillary lesions in general and specifically in CNB. Papillary lesions represent a spectrum of changes ranging from benign papillomas to atypical papillomas, to intraductal papillary carcinoma, and to invasive papillary carcinoma. Papillomas are often easily recognized by pathologists due to their fibrovascular cores lined by two cell layers: the inner myoepithelial cell layer and the outer layer of cuboidal or columnar epithelial cells (Figure 1.3A–D). Papillomas are single in approximately 50% of cases and present with nipple discharge in about 30%. Papillomas appear radiographically as an architectural distortion, as a density, or as a mass with or without associated microcalcification. Papillomas with atypia have an increased risk for the development of invasive breast cancer, similar to or even greater than those with ADH within the parenchyma of the breast (17).

PATHOLOGIC FEATURES

Core biopsies frequently represent a limited sample of the entire lesion. Difficulties arise in the categorization of papillary lesions as benign, atypical, or malignant. The pathologic features of the spectrum of papillary lesions are summarized in Table 1.3. Some papillomas have epithelial proliferations that fulfill the cytologic and architectural features of ADH or DCIS. Atypical papillomas show a monotonous cell population usually with a cribriform architecture. DCIS involving a papilloma is usually low grade and of the solid, cribriform, or micropapillary types (Figure 1.4A and B). Distinguishing a papilloma with ADH from one with DCIS can be challenging. Size and extent are used to distinguish atypical papillomas from papillomas with DCIS. On a sample obtained by core, size and extent are difficult to evaluate. Papillary lesions frequently fragment in CNB, making interpretation difficult. Another issue is related to sampling; does the lesion diagnosed in core represent the most worrisome area in a papillary lesion? In papillomas with ADH, the foci of ADH comprise less than 25% of the papilloma, and thus, sampling by CNB is a concern (17). This is also true for DCIS, where a risk of sampling error on core biopsy is 25% for cases of DCIS associated with a papilloma due to the low proportion of DCIS within the papilloma or the eccentric distribution of the DCIS (18). Another interpretative problem in papillary lesions in CNB is the potential confusion with invasive carcinoma, which can occur in both sclerosing and infarcted papillomas. In sclerosing papillomas, the fibrovascular cores may undergo sclerosis and distortion, leading to entrapment of the epithelium that mimics a pseudoinvasive pattern (19) (Figure 1.5A and B). The presence of a myoepithelial layer (Figure 1.5C), a lack of cytologic atypia in the entrapped tubules, and the absence of invasion into interlobular fat help to distinguish this lesion from a carcinoma. In infarcted papillomas, fibrosis at the periphery of the lesion can also simulate invasive carcinoma. The presence of clusters of squamous metaplastic cells surrounded by fibrotic tissue can also mimic an infiltrative process. The preservation of the papillary architecture in the areas of ischemic necrosis (necrosis in carcinomas usually lacks underlying architectural detail) and the lack of cytologic atypia within the entrapped ductules help in making the correct diagnosis (20). The careful attention to the histologic features and the use of myoepithelial cell markers aid in distinguishing these lesions from a carcinoma. Pathologic features distinguishing sclerotic and infarcted papillomas from invasive carcinomas are presented in Table 1.4.

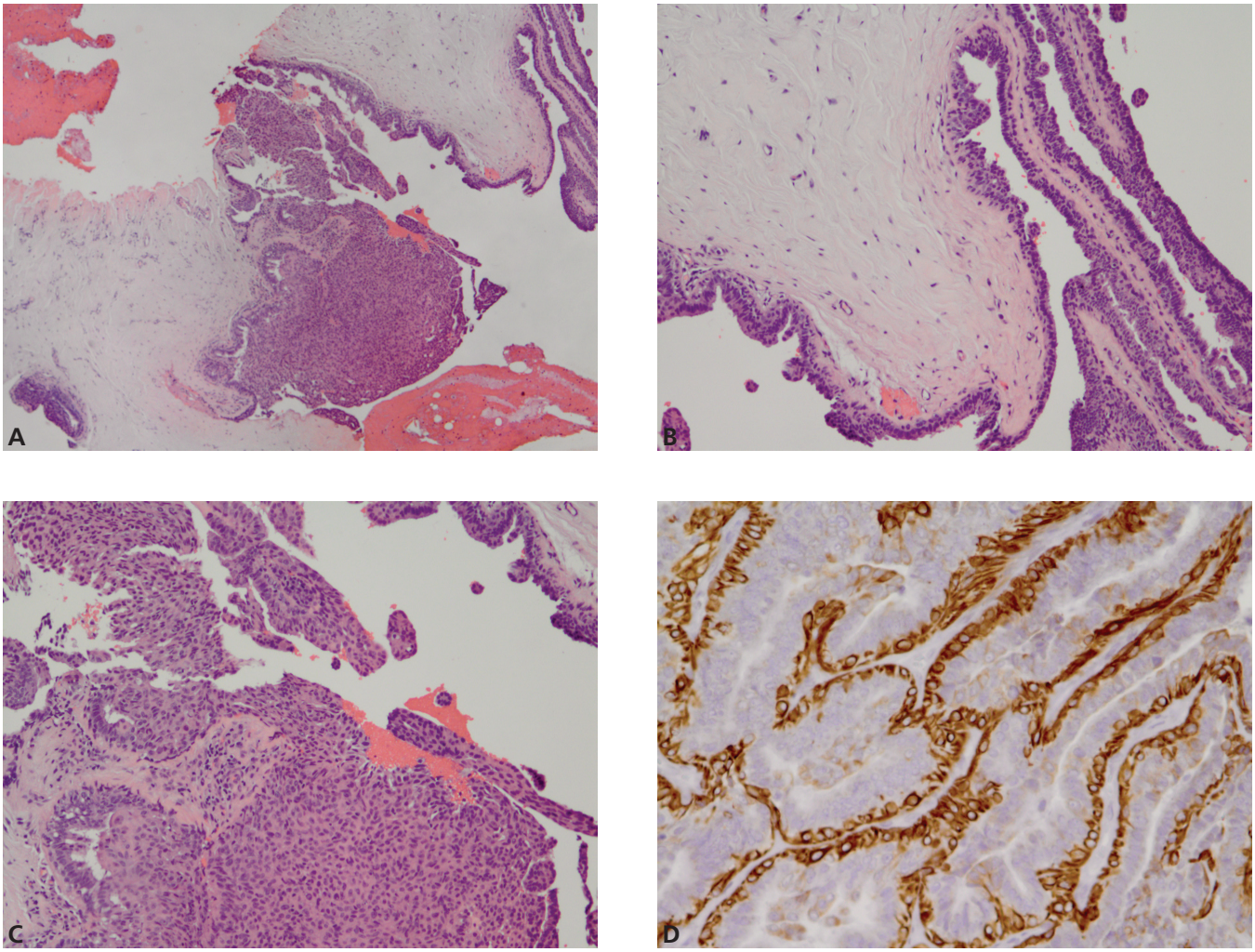


FIGURE 1.3 Papilloma. (A) Papilloma. Core biopsy shows fibrovascular cores lined by epithelial and myoepithelial cells. (B) Papilloma. A typical fibrovascular core is noted. (C) Papilloma with usual hyperplasia. Areas of hyperplasia become more complex and crowded; however, the cells are heterogeneous and lack atypia. (D) Papilloma (cytokeratin 5/6 stain). Immunohistochemical stain for cytokeratin 5/6 highlights the epithelial proliferation in this benign papilloma.

TABLE 1.3 Comparative Pathologic Features Among Benign Papilloma, Atypical Papilloma, Papilloma With DCIS, and Papillary DCIS

	Benign Papilloma	Atypical Papilloma	Papilloma With DCIS	Papillary DCIS
Architectural pattern	Papillary	Architectural pattern of ADH or DCIS (≤3 mm in size) or atypical population comprises between 10% and <33% of the lesion	Architectural pattern of DCIS (>3 mm in size) or atypical population involves at least a third but <90% of the lesion	Papillary, cribriform, solid, or spindled
Presence of fibrovascular cores	Yes	Yes	Yes	Yes; may be obscured
Cellular components	Epithelial and myoepithelial; epithelial hyperplasia may be present	Epithelial; myoepithelial layer may be lost; focal ADH with monotonous cell proliferation	Epithelial; typically loss of myoepithelial cell layer	Epithelial only; no evidence of a preexisting benign papilloma
Atypia	Absent	Present; can be focal	Usually present; varying degrees	Usually present

(*continued*)

TABLE 1.3 Comparative Pathologic Features Among Benign Papilloma, Atypical Papilloma, Papilloma With DCIS, and Papillary DCIS (*continued*)

	Benign Papilloma	Atypical Papilloma	Papilloma With DCIS	Papillary DCIS
Necrosis	Absent	Usually absent	May be present	May be present
Cytology	Heterogeneous	Monotonous	Monotonous	Monotonous
Myoepithelial cell layer	Present	Present in area of benign papilloma; reduced or absent in atypical area	Usually absent	Usually absent
Immunohistochemistry	CK5/6 positive (Figure 1.3D)	Usually CK5/6 negative in ADH	Usually CK5/6 negative	CK5/6 negative

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ.

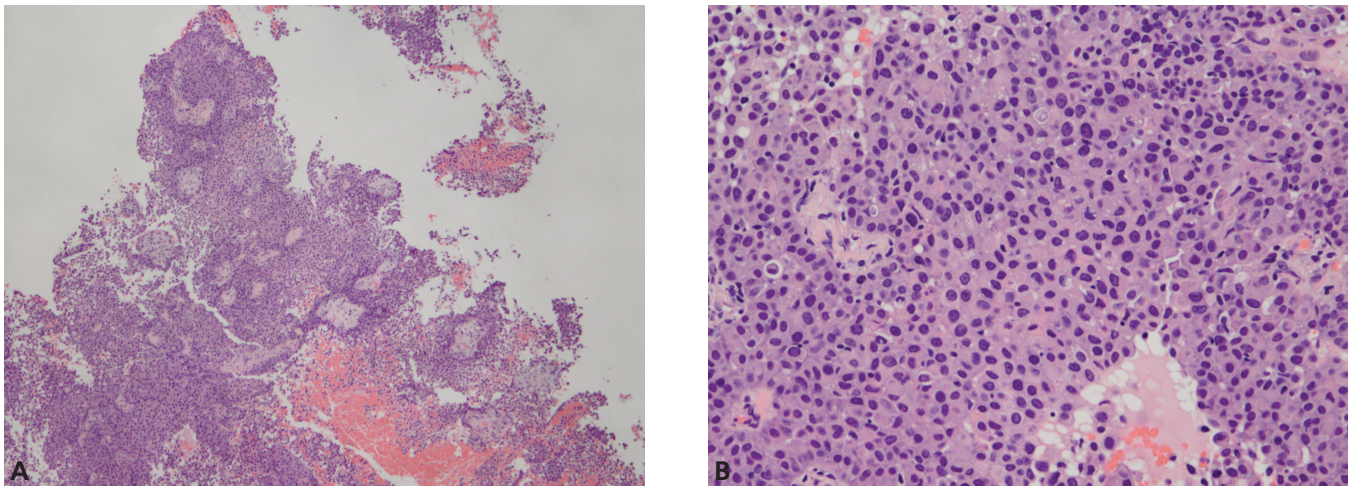


FIGURE 1.4 Papilloma with DCIS. (A) Papilloma with DCIS. The papillary proliferation is characterized by the presence of fibrovascular cores. The epithelial proliferation shows a solid pattern of growth. Fragmentation of the cores is evident. (B) Papilloma with DCIS. Higher magnification shows the presence of fibrovascular cores surrounded by a solid proliferation of epithelial cells with nuclear atypia.
DCIS, ductal carcinoma in situ.

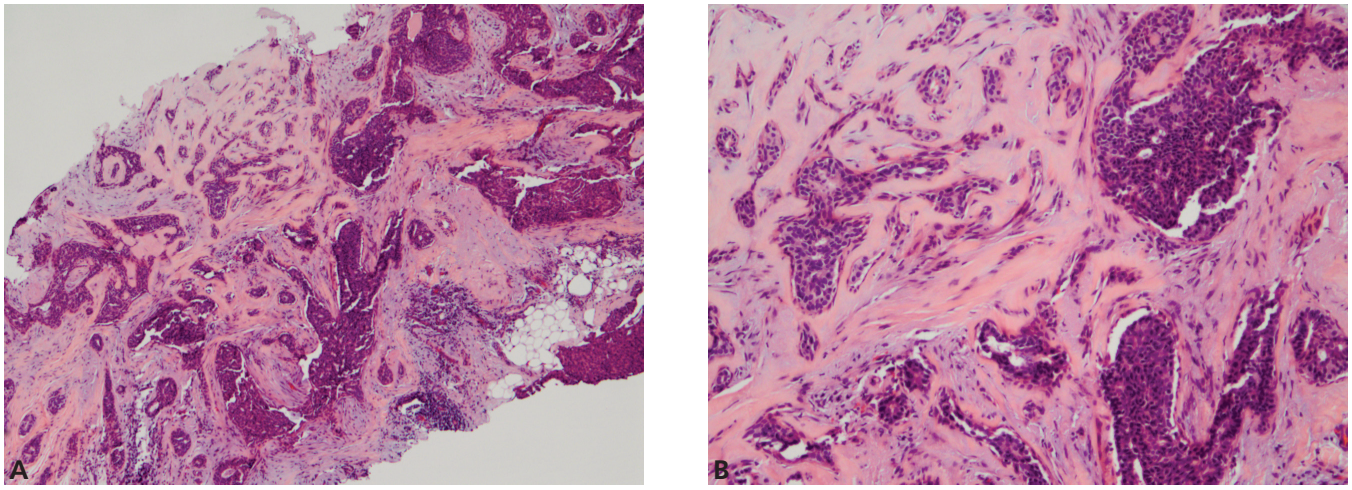


FIGURE 1.5 Distinguishing a sclerotic papilloma from invasive carcinoma. (A) Sclerosing papilloma. A sclerotic papilloma shows fibrovascular and fibrotic central cores that have entrapment of tubules, making distinction from invasive carcinoma difficult. (B) Sclerosing papilloma. The entrapped tubules are embedded in a poorly cellular stroma and contain a myoepithelial cell layer.

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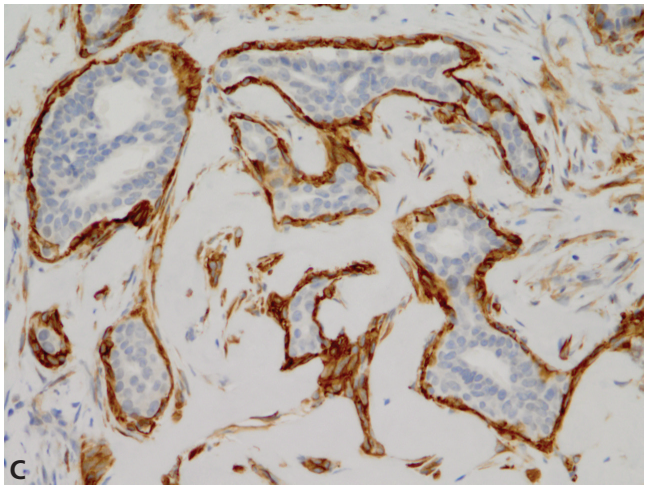

FIGURE 1.5 (*continued*) (C) Sclerosing papilloma (calponin stain). A stain for calponin highlights the myoepithelial cell layer of the entrapped tubules and can be used to distinguish a sclerotic papilloma from an invasive carcinoma.

TABLE 1.4 Comparative Features to Distinguish Sclerosing Papillomas and Infarcted Papillomas

	Sclerosing Papilloma	Infarcted Papilloma
Architecture	Central fibrotic core with entrapment of distorted ductules; at the periphery, the sclerotic process merges with a benign papillary process	Ischemic necrosis is seen; however, outlines of the papilloma are preserved; peripheral area usually spared from ischemia
Stroma	Poorly cellular, sclerotic, hyalinized stroma; hemosiderin-laden macrophages and mononuclear cells may be present	Fibroblastic and collagenous proliferation with entrapment of compressed and distorted ductules
Ductules	Entrapped ductules contain a myoepithelial cell layer and lack atypia; ductules are confined to the core of the papilloma and extension of ductules into fat is not seen	Epithelium may show squamous metaplasia; hyperchromatic nuclei may be present but usually lacks cytologic atypia or mitotic figures
Myoepithelial cell marker	Positive in entrapped ductules	Positive in entrapped ductules

COMMON PITFALLS AND HELPFUL TIPS

- Papillary lesions in core biopsies are difficult to diagnose due to the tissue fragmentation and the sampling limitations.
- The presence of infarction and sclerosis should be considered before making a diagnosis of carcinoma.
- A panel of immunohistochemical stains utilizing myoepithelial markers, high-molecular-weight cytokeratins, and neuroendocrine markers can be used in the classification of papillary lesions.
- Atypical papillary lesions and papillary carcinoma in core needle biopsy (CNB) warrant excision.
- Management of benign papillomas in CNB is controversial; while most studies recommend surgical excision, radiologic follow-up may be allowed in concordant cases.

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The use of a panel that includes myoepithelial cells markers, high-molecular-weight cytokeratins, and neuroendocrine markers that have been shown to distinguish benign from malignant papillary proliferations (21) is summarized in Table 1.5. The absence of expression of CD44s and CD133 has been shown to be useful in identifying malignant papillary lesions (22,23).

TABLE 1.5 Immunohistochemical Stains That Aid in Distinguishing Benign From Malignant Papillary Lesions

Cell Type	Cell Marker	Use
Myoepithelial cell marker	Smooth muscle actin, p63, calponin, S-100 protein, CD10	Highlights myoepithelial cell layer in benign papillomas; decreased or absent in atypical papillomas and papillary carcinomas
Epithelial cell marker	High-molecular-weight cytokeratin, CK5/6, 34bE12, CK14	Positive in epithelial proliferations in benign papillomas; lacking in atypical papillomas and papillary DCIS
Neuroendocrine marker	Chromogranin A and synaptophysin	Negative in benign papillomas

DCIS, ductal carcinoma in situ.

MANAGEMENT ISSUES

The risk of the development of carcinoma has been shown to be largely local, in the region of the original papilloma supporting the recommendation of excision of all atypical papillomas. Multiplicity also increases the risk. Papillary lesions are encountered in percutaneous CNB, ranging from 0.01% to 8.1% of all core biopsies. Although the accepted recommendation for atypical papillary lesions and papillary carcinoma diagnosed in percutaneous CNB is excision, the management of benign papillary lesions remains controversial. The concern is that if excision is not performed, focal areas of ADH or DCIS may be missed in the small sample obtained by CNB. The literature pertaining to the diagnosis of benign papillary lesions in percutaneous CNB is limited; however, the incidence of carcinoma found after biopsy of a benign papillary lesion is wide, ranging from 0% to 33% (24–28). Although most studies recommend excision of all papillary lesions diagnosed at percutaneous CNB due to the small but definite risk of malignancy at excision, more recent studies are considering radiologic follow-up in some instances (29). Although one study recommended radiologic follow-up rather than surgical excision for benign incidental papillomas less than 2 mm in size (30), another study of 15 mm or smaller benign papillomas showed an upgrade rate of 4.7% and recommended surgical exision (31). Others have shown that more tissue at core biopsy, as indicated by sampling with a 12-gauge needle or larger, by 11-gauge VAB, or by greater than 7 cores or greater than 96 mm^2 of tissue, may allow patients with a benign papilloma diagnosis by core biopsy to avoid surgical exision (32,33).

LOBULAR LESIONS

INTRODUCTION

Both ALH and LCIS are considered risk factors for the development of carcinoma. The risk for the development of breast cancer is four to five times that of the general population for ALH and approximately 11 times for LCIS (34,35). LCIS is often bilateral and multifocal and associated with an increased risk of invasive carcinoma of either breast. Recent genetic and molecular evidence have challenged the notion of LCIS as a risk factor but suggested that ALH and LCIS may be indolent precursors. Since most cases of LCIS are discovered as an incidental finding with no associated clinical or radiologic findings, the presence of LCIS rarely accounts for the primary histologic diagnosis after CNB. A multidisciplinary approach with radiologic correlation is critical when a diagnosis of LCIS or ALH is made in percutaneous CNB.

PATHOLOGIC FINDINGS

LCIS consists of an intralobular proliferation of small uniform cells in which the abnormal cells must comprise all of the cells in the lobular unit with no intercellular spaces between cells, and at least 50% of the acini in the lobular unit are distorted or expanded (Figure 1.6A and B). ALH has less than 50% of the affected lobule with the cytologic appearance of LCIS (Figure 1.6C). Classical and pleomorphic forms of LCIS are described in Table 1.6. The main difficulty for the pathologist is to distinguish pleomorphic LCIS from DCIS and to distinguish low-grade DCIS with cancerization of lobules from LCIS. Marked cellular pleomorphism in pleomorphic LCIS, along with the presence of necrosis and calcification, makes distinction from DCIS difficult. Radiographic correlation does not help in the distinction because the pleomorphic LCIS can be indistinguishable from DCIS. Cancerization of lobules, or spread of DCIS into lobules, creates lobular expansion and confusion with LCIS. The cells in LCIS are usually more dyscohesive and lack any microacinar pattern. The presence of intracytoplasmic vacuoles, although not specific, may be a clue to the diagnosis of LCIS. Pathologic features that can be used to distinguish low-grade DCIS from LCIS are summarized in Table 1.7. The distinction of LCIS from DCIS is critical because management of the patient with regard to the need

to obtain negative margins at surgical excision (important for DCIS but not for LCIS) and the use of radiotherapy differs. Distinguishing DCIS from LCIS by microscopy alone can be extremely challenging, however, the use of E-cadherin immunohistochemistry (DCIS positive, LCIS negative) resolves most cases (Figure 1.6D).

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The use of E-cadherin, a transmembrane glycoprotein involved in cell adhesion, is useful to distinguish DCIS from LCIS, as loss of expression is noted in LCIS and invasive lobular carcinomas. Although this marker has been shown to be extremely useful in distinguishing LCIS from DCIS in most cases, aberrant expression in LCIS has been described in up to 15% of the cases (36).

MANAGEMENT ISSUES

A diagnosis of ALH or LCIS in percutaneous CNB accounts for less than 2% of core biopsies in most series. Although ALH and LCIS identified at surgical excision are managed conservatively by clinical and radiologic follow-up, management guidelines for ALH and LCIS diagnosed at percutaneous CNB remain more controversial. Some studies find excision to be unnecessary, whereas others recommend surgical excision. The current National Comprehensive Cancer Network guidelines recommend excision for all cases of LCIS diagnosed at core biopsy (37). Many studies show a significant risk of approximately 13% for ALH and 20% for LCIS for finding carcinoma at surgical excision after a diagnosis of either ALH or LCIS in CNB (38). Most retrospective studies comparing CNB diagnosis of ALH or LCIS and subsequent excision

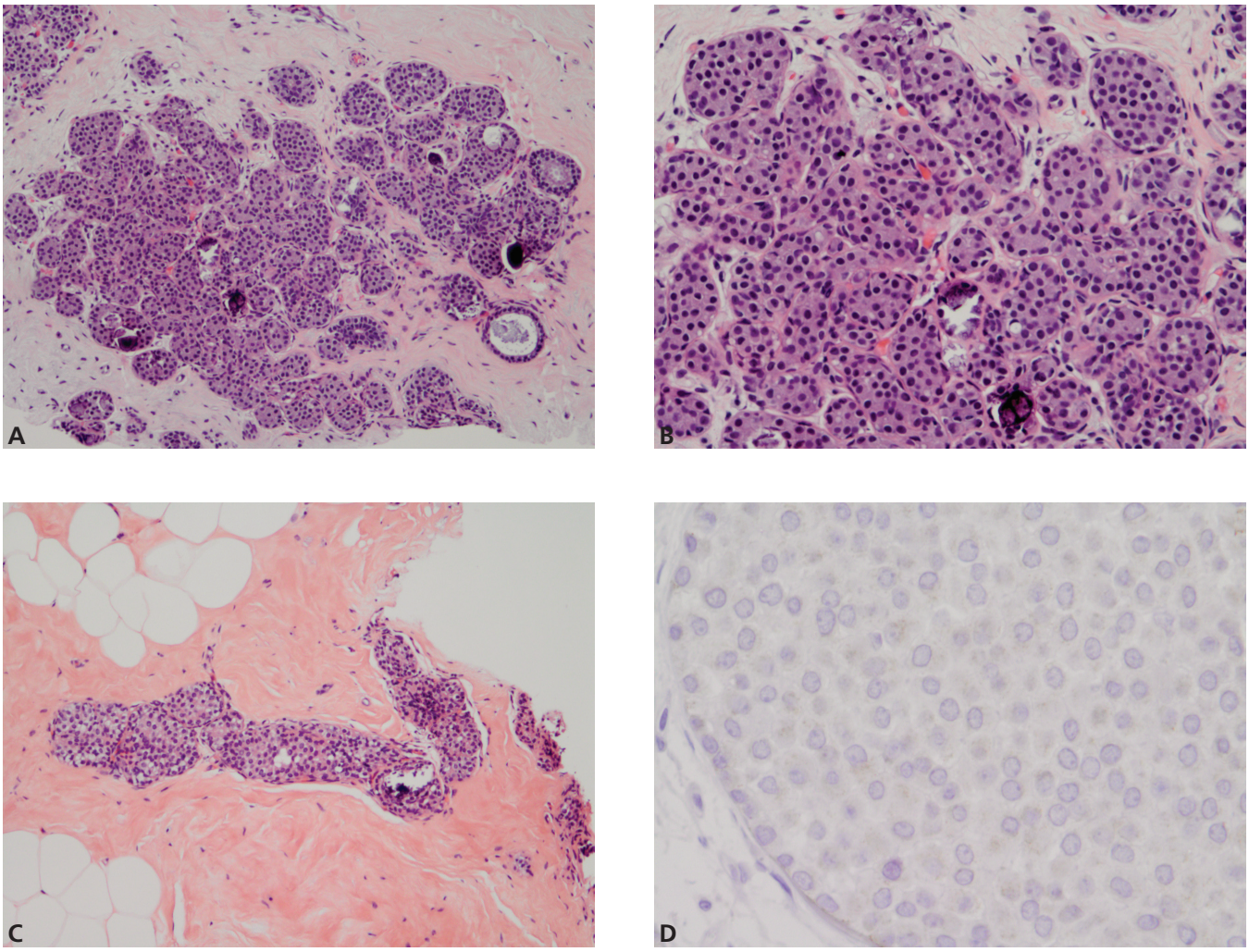

FIGURE 1.6 (A) Lobular carcinoma in situ. Core biopsy shows an intralobular proliferation that expands greater than 50% of the acini in the lobular unit. (B) LCIS. The intralobular proliferation is composed of small uniform cells with round nuclei and eosinophilic cytoplasm. (C) Atypical lobular hyperplasia. ALH shows a similar proliferation, but less than 50% of the acini in the lobular unit are distorted or expanded. (D) LCIS (E-cadherin stain). E-cadherin is negative in LCIS.
ALH, atypical lobular hyperplasia; LCIS, lobular carcinoma in situ.

TABLE 1.6 Comparative Pathologic Features Between Classical LCIS and Pleomorphic LCIS (see Figure 1.7)

	Classical LCIS	Pleomorphic LCIS
Cell size	Small	Large
Nuclei	Uniform; round to oval	Pleomorphic; atypical
Cytoplasm	Small amount of clear to lightly eosinophilic	Abundant; eosinophilic, granular
Nucleoli	Inconspicuous	Conspicuous and large
Necrosis	Absent	Present
Microcalcification	Usually absent	Present
E-cadherin reactivity	Negative	Negative

LCIS, lobular carcinoma in situ.

TABLE 1.7 Comparative Features Between LCIS and Low-Grade DCIS (see Figure 1.8)

	LCIS	Low-Grade DCIS
Pattern	Mainly involves lobules; can involve ducts in a pagetoid fashion	Mainly involves ducts; can involve lobules (cancerization of lobules)
Cohesiveness of cells	Discohesive	Cohesive
Architecture	Mosaic pattern; solid	Microacinar pattern; cribriform, micropapillary, solid
Cellular characteristics	Monotonous; intracytoplasmic vacuoles common	Monotonous; more variability as compared with LCIS
Immunohistochemistry	E-cadherin negative	E-cadherin positive

DCIS, ductal carcinoma in situ; LCIS, lobular carcinoma in situ.

COMMON PITFALLS AND HELPFUL TIPS

- A diagnosis of atypical lobular hyperplasia (ALH) or lobular carcinoma in situ (LCIS) in most core biopsies is an incidental finding. Radiologic correlation with the pathologic findings is necessary to avoid missing a significant lesion.
- Distinguishing LCIS from ALH can be subjective because these lesions represent a continuum. This is less problematic in core needle biopsy (CNB) because the management is the same.
- Pathologists must be able to distinguish LCIS with pagetoid spread from DCIS with cancerization of lobules in percutaneous CNB because management differs. Dyscohesive cells in a mosaic pattern and the presence of intracytoplasmic vacuoles should point toward a diagnosis of LCIS. E-cadherin immunohistochemistry can be particularly helpful in this distinction.
- Pleomorphic LCIS can be confused with ductal carcinoma in situ (DCIS). It is important to recognize this variant due to its more aggressive course and differing treatment. Distinguishing DCIS from pleomorphic LCIS may be impossible by microscopy alone and may require E-cadherin staining for definitive diagnosis.
- Immunohistochemical staining with E-cadherin can be used to help distinguish DCIS (positive) from LCIS (negative).
- While older studies recommend surgical excision after a diagnosis of ALH or LCIS in CNB in all cases due to an underestimation rate of carcinoma of 13% and 20%, respectively (mean), recent studies are not advocating excision in all cases. Radiologic-pathologic concordance, mammographic and MRI findings, family and personal history, and number of terminal duct lobular units (TDLUs) involved play an important role in determining the need for excision. It should be noted that these women, whether they have surgical excision or not, require close ongoing follow-up due to the risk of developing a subsequent carcinoma in the contralateral or ipsilateral breast after a diagnosis of lobular neoplasia on core biopsy.