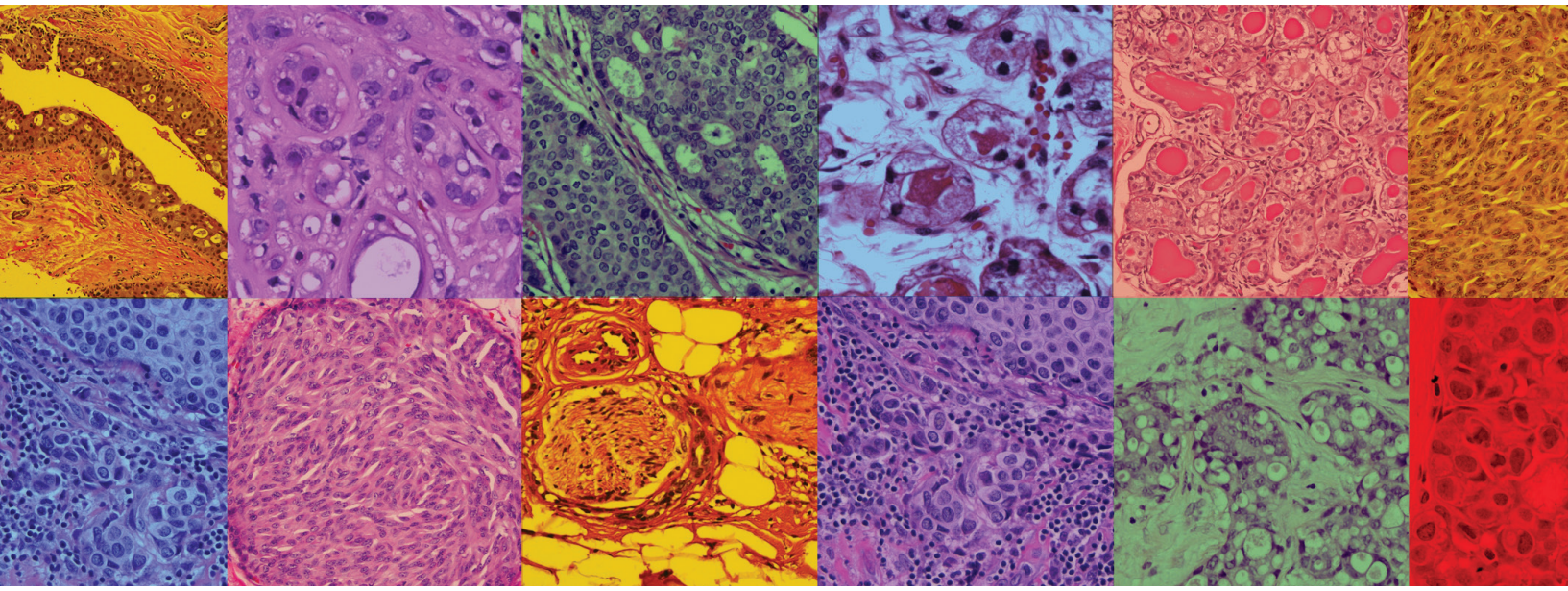
DIFFICULT DIAGNOSES IN BREAST PATHOLOGY



Juan P. Palazzo

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New York

ISBN: 978-1-933864-79-2
eBook ISBN: 978-1-935281-30-6

Acquisitions Editor: Richard Winters
Production Editor: Dana Bigelow
Compositor: Manila Typesetting Company
Printer: SCI

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Library of Congress Cataloging-in-Publication Data
Difficult diagnoses in breast pathology / edited by Juan P. Palazzo.
p. ; cm.
Includes bibliographical references and index.
ISBN 978-1-933864-79-2
1. Breast—Diseases—Diagnosis. 2. Tumor markers. I. Palazzo, Juan P.
[DNLM: 1. Breast—pathology. 2. Biopsy, Fine-Needle. 3. Breast Diseases—diagnosis.
4. Tumor Markers, Biological. WP 840]
RG493.D547 2011
618.1'9—dc22

2011008921

Made in the United States of America
11 12 13 14 15 5 4 3 2 1

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Preface

The goal of this book is to provide pathologists with a reference guide to use in the diagnosis and differential diagnosis of common and uncommon breast diseases.

The role of the pathologist has become very important in the diagnosis and management of patients with breast diseases. Pathologists are frequently asked to make diagnosis in small samples and are faced with difficult decisions in their daily practice.

The book is organized into chapters devoted to the challenges in the diagnosis of breast diseases using core biopsies and chapters dedicated to specific epithelial and mesenchymal lesions, lymphoid proliferations, and immunohistochemistry.

This is a book that primarily emphasizes the diagnostic morphologic features. The text highlights the most important aspects of each entity with a particular focus in the diagnostic criteria, differential diagnosis, immunohistochemical findings, and management. Tables and key points are included in each chapter to summarize the most important findings.

I was very fortunate to have worked with such an outstanding group of experts in the field. 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 problem cases from their own perspective.

My hope is that this book provides information that will help pathologists with the interpretation of breast biopsies and will also be a source of education for residents and fellows, as well as other physicians interested in breast disorders.

I want to thank all my colleagues from the Department of Pathology of Jefferson University for sharing breast cases with me. Mr. Richard Winters from Demos Medical Publishing for his patience and valuable advice and Christopher Braster from Jefferson University for help with the photographs. My entire family for the relentless support in all my endeavors.

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Difficult Diagnoses in Breast Pathology

1

The Diagnostic Challenges of Core Needle Biopsy Interpretation

AYLIN SIMSIR
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 magnetic resonance imaging, 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 two-fold. 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) and lobular carcinoma in situ (LCIS), fibroepithelial lesions, radial scars, and mucinous lesions.

■ ATYPICAL DUCTAL HYPERPLASIA

Atypical ductal hyperplasia 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 usual duct hyperplasia 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, 3 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

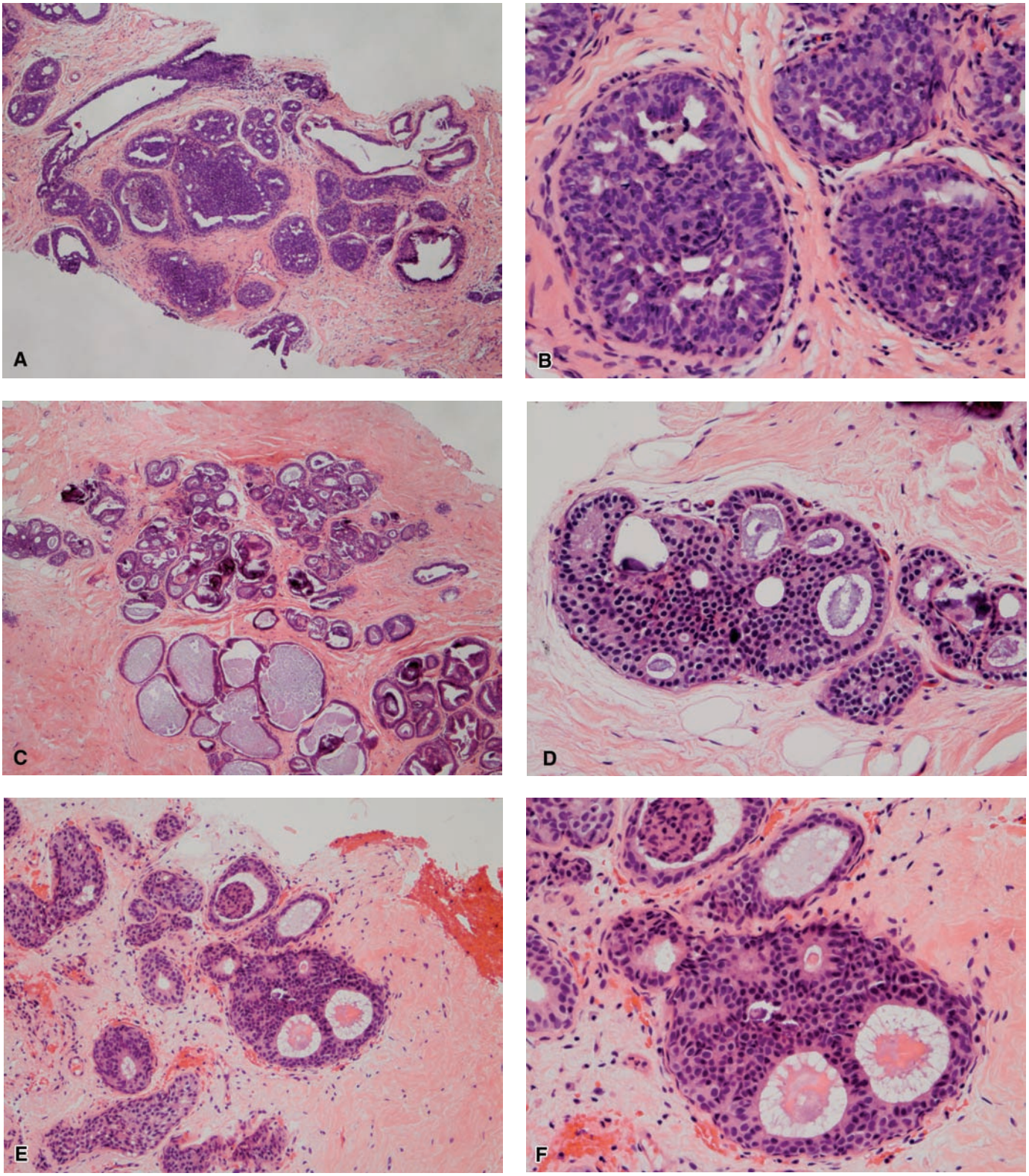

FIGURE 1.1 Spectrum of proliferative breast lesions in CNB. (A) Florid ductal hyperplasia. A proliferation of epithelial cells within ductal spaces leading to the formation of irregular slit-like spaces is noted. (B) Florid ductal hyperplasia. Higher magnification shows a heterogeneous population of cells with streaming and irregular, peripheral secondary lumens. (C) Ductal carcinoma in situ, cribriform type. A cribriform proliferation is noted with evenly placed, rounded "punched-out" spaces. (D) Ductal carcinoma in situ, 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. (E) Atypical ductal hyperplasia. Atypical ductal hyperplasia meets some, but not all, of the criteria of DCIS. The proliferation involves only 1 duct, and the spaces appear more regular than that seen in florid ductal hyperplasia. (F) Atypical ductal hyperplasia. 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.

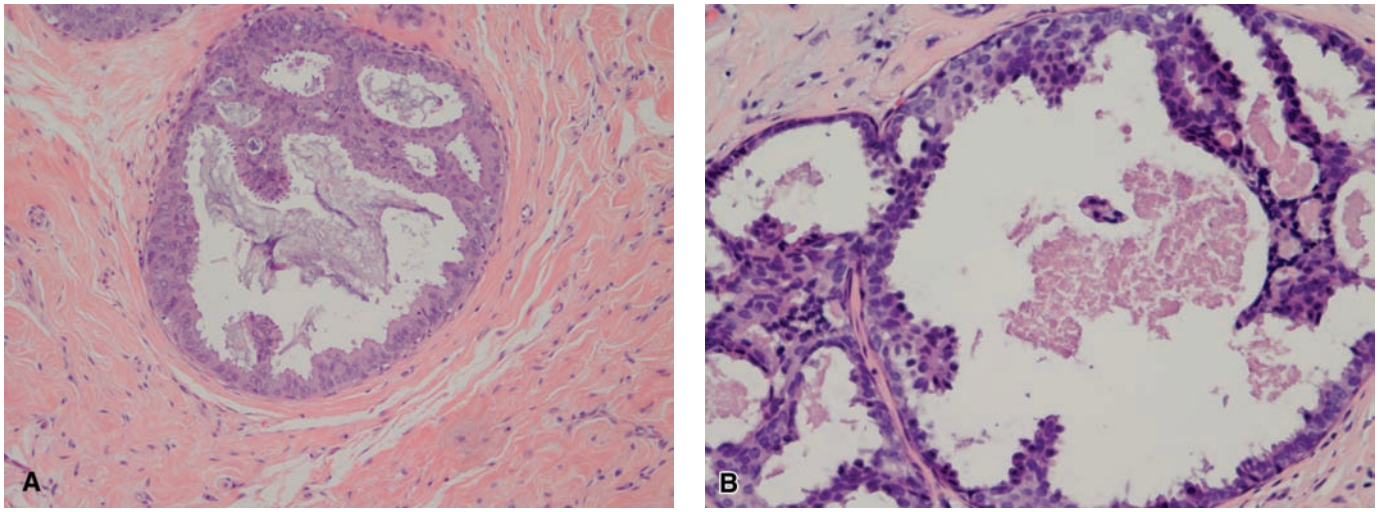

FIGURE 1.2 Difficulty in distinguishing ADH from DCIS in core biopsy. In core biopsy, the small amount of tissue obtained can make distinguishing ADH from DCIS challenging. Proliferations shown here that involve only 1 duct but show tufts (A) and micropapillae (B) are especially challenging.

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. Usual ductal hyperplasia 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, B). In DCIS, spaces are round and regular with a monotonous cell population (Figure 1.1C, D). Atypical ductal hyperplasia falls in the middle, with either uniform cells with irregular cell spaces or regular spaces

■ **Table 1.1** Comparative pathologic features among florid ductal hyperplasia, ADH, and low-grade DCIS

	Florid Ductal Epithelial Hyperplasia	ADH	Low-Grade DCIS
Definition	Increase in the number of cells above the normal 2 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 6–7 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		Involvement of only 1 duct that meets the criteria of low-grade DCIS	Involvement of 2 or more ducts
Size		<2 mm	2 mm

with heterogeneous cells (Figures 1.1E-F and 1.2A-B). The pathologic features distinguishing florid hyperplasia, atypical ductal carcinoma, and DCIS are summarized in Table 1.1.

Immunohistochemistry

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 interpretation of this stain because apocrine metaplasia and columnar alterations also show a negative reaction.

Management Issues

Atypical ductal hyperplasia is encountered in percutaneous CNB in only 2% to 15% (6,7) of core biopsies. Surgical excision is the recommended management because 7% to 56% (8,9) of the cases diagnosed as ADH in CNB will be upgraded to DCIS or invasive carcinoma after excision. 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%) (10,11) as compared with 14-gauge automated CNB (44%–56%) (12,13) 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.

■ **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)
No. of foci of ADH (2 or more associated with greater underestimation)
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)
Presence of a mass by palpation or on ultrasound
Personal history of breast cancer

Key Points

- The pathologic diagnosis of ADH in CNB is difficult due to an inability to distinguish these lesions from low-grade 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 UDH and ADH, discussion of the cases at an intradepartmental conference or review by a second pathologist is also helpful, as surgical excision will not be recommended for diagnoses 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.

■ 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 2 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 (14).

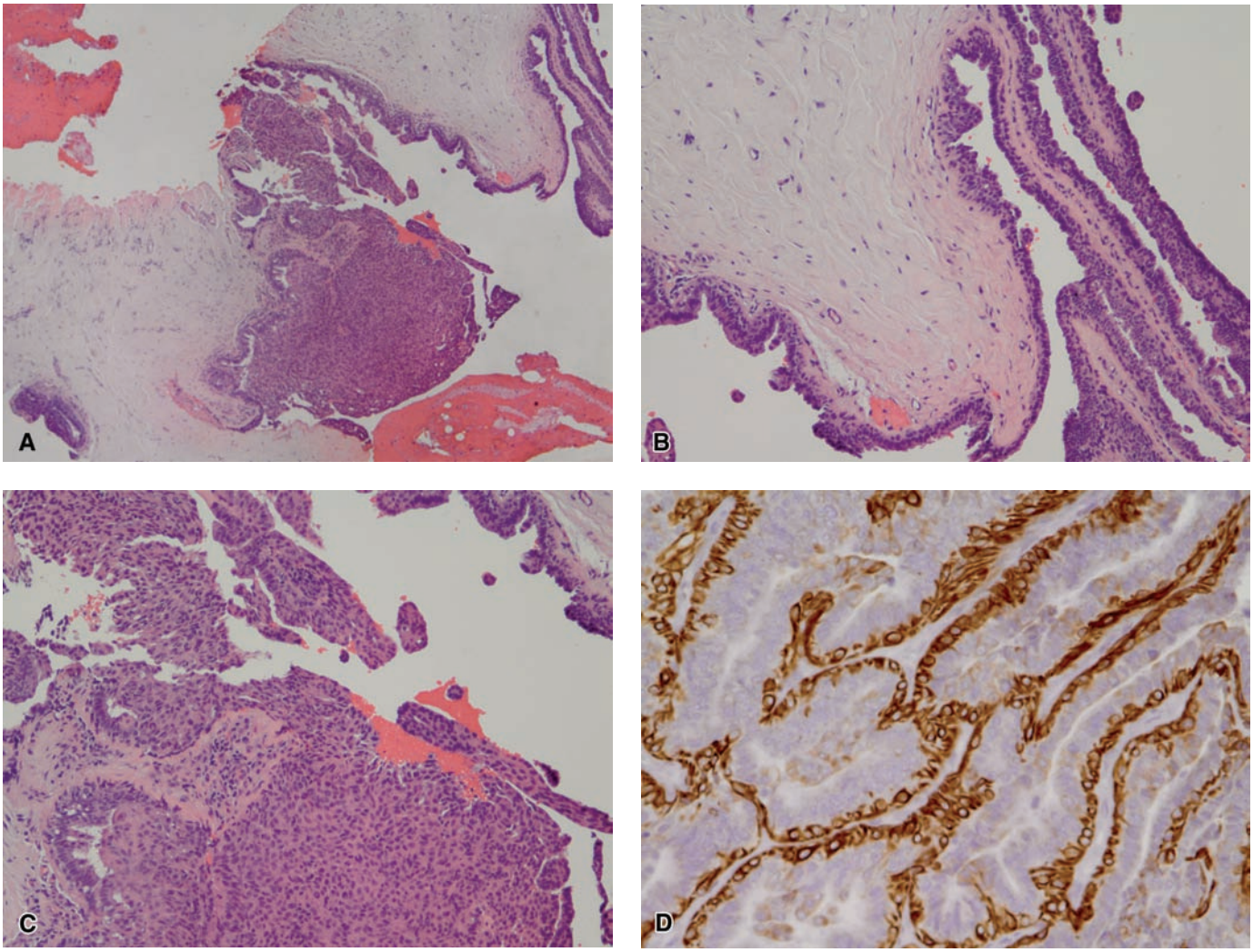

FIGURE 1.3 Papilloma. (A) Papilloma. Core biopsy shows fibrovascular cores lined by epithelial and myoepithelial cells. (B) Papilloma. A typical fibrovascular core is noted. (C) Papilloma with hyperplasia. Areas of hyperplasia become more complex and crowded; however, the cells are heterogeneous and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

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. Ductal carcinoma in situ involving a papilloma is usually low grade and of the solid, cribriform, or micropapillary types (Figure 1.4A, B). Distinguishing a papilloma with ADH from one with DCIS can be demanding. 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 (14). 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 (15) (Figure 1.5A, 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

■ **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	
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
Necrosis	Absent	Usually absent	May be present	May be present
				Single cell population with a uniform appearance; columnar cells with degrees of stratification; uniform cells in solid, cribriform or micropapillary patterns
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

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 (16). 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.

Immunohistochemistry

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 (17) is summarized in Table 1.5.

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

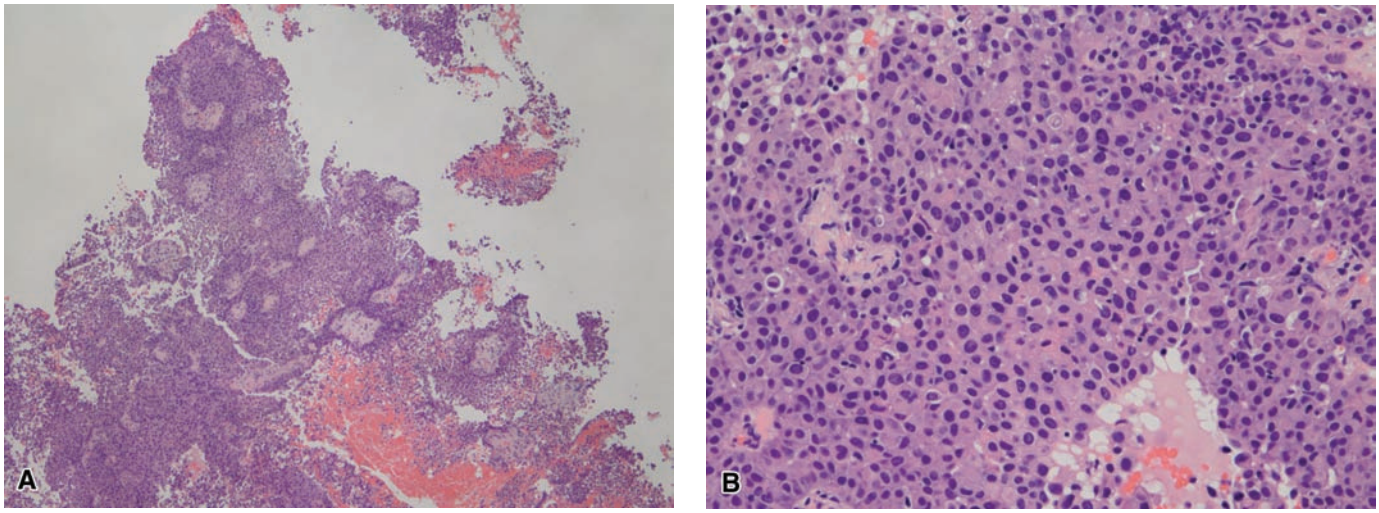

FIGURE 1.4 Papilloma with DCIS. (A) Papilloma with DCIS. A papillary proliferation is seen by the presence of fibrovascular cores. The epithelial proliferation shows a solid pattern of growth. Fragmentation of the cores is evident. (B) Papilloma with DCIS. Higher magnification shows the presence of fibrovascular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

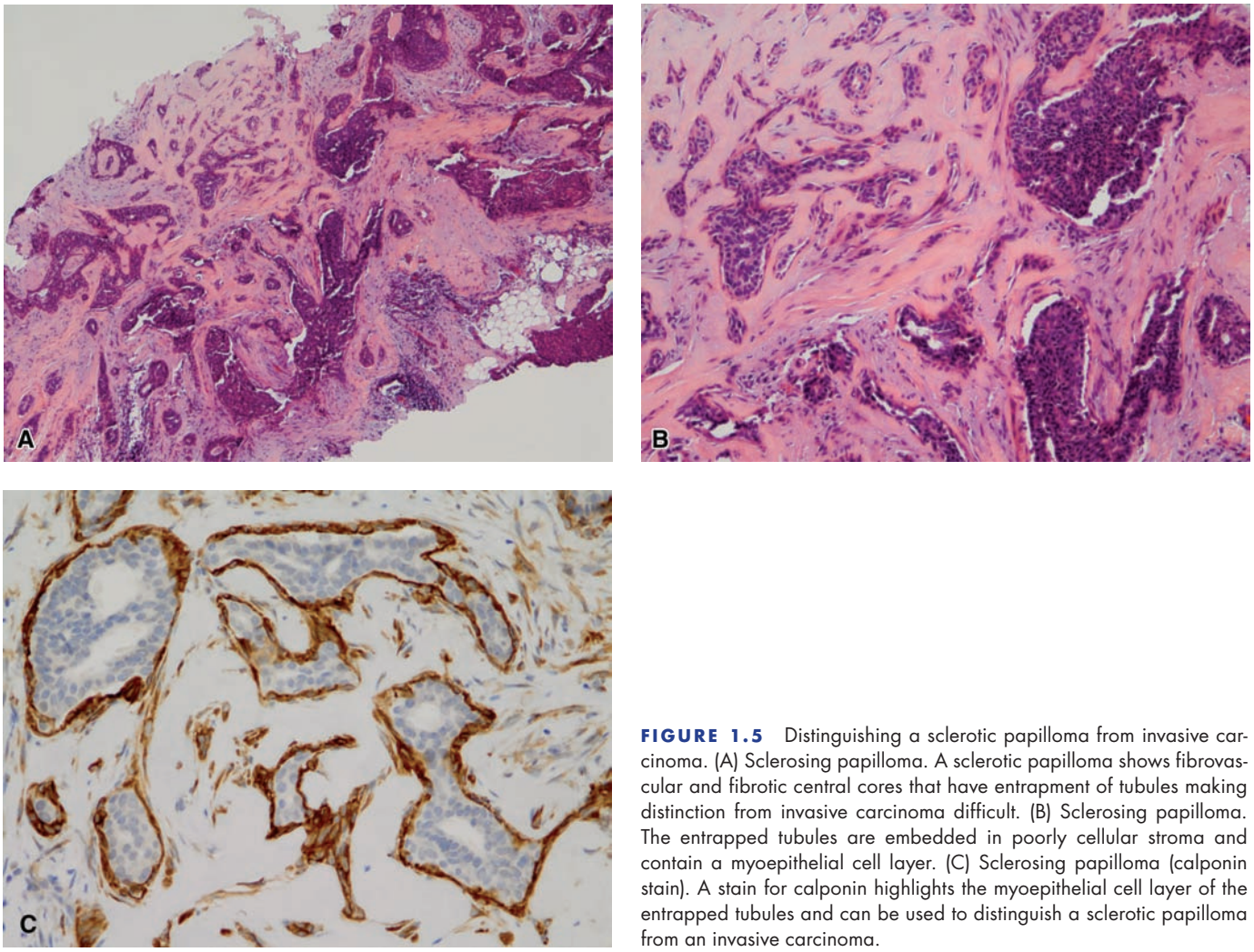

FIGURE 1.5 Distinguishing a sclerotic papilloma from invasive carcinoma. (A) Sclerosing papilloma. A sclerotic papilloma shows fibrovascular and fibrotic central cores that have entrapment of tubules making distinction from invasive carcinoma difficult. (B) Sclerosing papilloma. The entrapped tubules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