DIFFERENTIAL DIAGNOSIS OF PROLIFERATIVE BREAST LESIONS

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KEYWORDS

• Epithelial proliferative disease • Ductal carcinoma in situ

ABSTRACT

The correct diagnosis of proliferations within the mammary terminal duct-lobular unit has paramount prognostic and therapeutic implications. Occasionally, the differential diagnosis of compact florid hyperplasia, atypical ductal hyperplasia, and low-grade ductal carcinoma in situ can be quite challenging, with seeming morphologic overlap. This article presents s conceptual and practical understanding of these processes and their impact on subsequent cancer risk, with the intention of assisting the practicing pathologist render accurate and clinically relevant diagnoses for this frequently encountered set of mammary epithelial lesions.

PROLIFERATIVE BREAST LESIONS

OVERVIEW

Epithelial proliferations within the terminal duct-lobular unit (TDLU), including usual patterns of hyperplasia and atypical ductal hyperplasia (ADH), are commonly encountered breast lesions. The correct classification of these proliferations carries significant implications for the subsequent risk of developing invasive cancer. Most examples of usual or ordinary patterns of hyperplasia, ADH, and ductal carcinoma in-situ (DCIS) pose little diagnostic challenge for practicing pathologists. For cases that seem to be borderline, careful application of diagnostic criteria allows assignment into the appropriate category. In general, the authors' approach for borderline cases is to favor the lesser diagnosis.

A general understanding of the formative elements of proliferative lesions is necessary for proper classification. These fundamental principles include location, pattern and extent of spread, and cellular morphology. Immunohistochemical studies have little application in this differential diagnosis. This article focuses on the diagnostic criteria for usual patterns of hyperplasia, ADH, and low-grade DCIS, with practical guidelines for diagnosing borderline lesions encountered either on core biopsy or in excision specimens.

GROSS FEATURES

In general, the proliferative breast lesions described in this article do not present grossly detectable alterations. Exuberant examples of ordinary hyperplasia as well as some examples of low-grade DCIS may, rarely, form a mass when the specimen is examined grossly. Far more information is gained by a careful review of the specimen imaging studies, with attention to correlating tissue sectioning with imaging findings. The regular absence of noticeable gross changes supports complete submission of the tissue when practical. For specimens too large for complete submission, an ex vivo radiograph of tissue slices can guide sampling.

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> ### *Key Features*
> #### Proliferative Breast Lesions
>
> Usual hyperplasia without atypia
>
> 1. Cellular features: variability, nuclear overlap, uneven cell placement, indistinct cell borders
>
> 2. Architecture: peripheral secondary spaces, cellular swirling patterns, thin tapering cellular bars
>
> 3. Extent: usually involves a single TDLU but may be more extensive
>
> Atypical ductal hyperplasia
>
> 1. Cellular features: cellular monotony and uniformity; even placement of small cells
>
> 2. Architecture: rigid secondary spaces, crisp cribriform spaces, and rigid arching bars
>
> 3. Extent: incomplete involvement of spaces, residual normal polarized epithelium
>
> DCIS (low grade)
>
> 1. Cellular features: cellular monotony and uniformity, even placement of small cells
>
> 2. Architecture: rigid secondary spaces, crisp cribriform spaces, and rigid arching bars
>
> 3. Extent: complete involvement of two adjacent spaces, often involves true duct, usually larger than 3 mm

> ### *Pitfalls*
> #### Pitfalls in the Diagnosis of Proliferative Breast Lesions
>
> ! Thick histologic sections create the appearance of cellular monotony.
>
> ! Gynecomastoid pattern of usual hyperplasia mimics micropapillary ADH or DCIS.
>
> ! Papillary apocrine change may mimic micropapillary ADH or DCIS.
>
> ! ADH involving enlarged lobular units may suggest DCIS because of its size.
>
> ! In collagenous spherules the crisp spaces mimic ADH.
>
> ! Solid pattern of ADH may mimic lobular neoplasia.
>
> ! The fragmented nature of core biopsy precludes assessment of the extent of disease.

MICROSCOPIC FEATURES

Usual patterns of hyperplasia as well as ADH and low-grade DCIS are located within the TDLU. Usual hyperplasia is often termed "ordinary" to underscore that this pattern is the one found most frequently in benign breast biopsies. Usual hyperplasia is characterized by a proliferation of bland, variably sized cells in a streaming, swirling, or jumbled arrangement with nuclear overlap. The cells lack distinct cell borders. The nuclei usually are oval or carrot-shaped instead of round, may contain grooves and "helioid" inclusions, but lack conspicuous nucleoli (**Fig. 1**). As the cells proliferate, the residual lumen of the involved space becomes peripheral and compressed (**Fig. 2**). The proliferating cells form irregular bridges, and tethered tufts are often present. The degree of involvement does not change the assignment of this pattern of proliferation to the usual or ordinary category. The architecture of the proliferation within the involved space is a result of the relationship that the proliferating cells have with one another. The overlapping cells of usual-pattern hyperplasia result in thin, irregularly tapered tufts and bridges (**Figs. 3–5**). Frequently, cellular bars seem to consist of strands of anuclear cytoplasm. One pattern of ordinary hyperplasia resembles that of gynecomastia, with mounds of pyknotic cells heaped on underlying luminal epithelium (**Fig. 6**).

ADH is defined in terms of its resemblance to low-grade DCIS, but a critical distinction is the extent of involvement. ADH is characterized by a proliferation of monomorphic cells that are evenly spaced. This even placement results in secondary spaces that appear "rigid" or static, rather than the "fluid" streaming and swirling of usual-pattern hyperplasia. ADH is composed of a uniform population of bland cells with round nuclei and distinct cell borders. Architecturally, ADH can be solid, cribriform, micropapillary, or a combination thereof. The cribriform spaces are crisply round and regular, and the cellular bridges are rigid (**Fig. 7**). The cells of micropapillary ADH form bulbous projections composed of the same monomorphic cells that partially line the involved space; the micropapillae have narrow stalks that interdigitate with the luminal cells.

The distinction between ADH and low-grade DCIS depends on the extent of involvement within

Fig. 1. Usual hyperplasia without atypia. Note the cellular variability, uneven cell placement, and irregular secondary spaces. Several "helioid" inclusions are present.
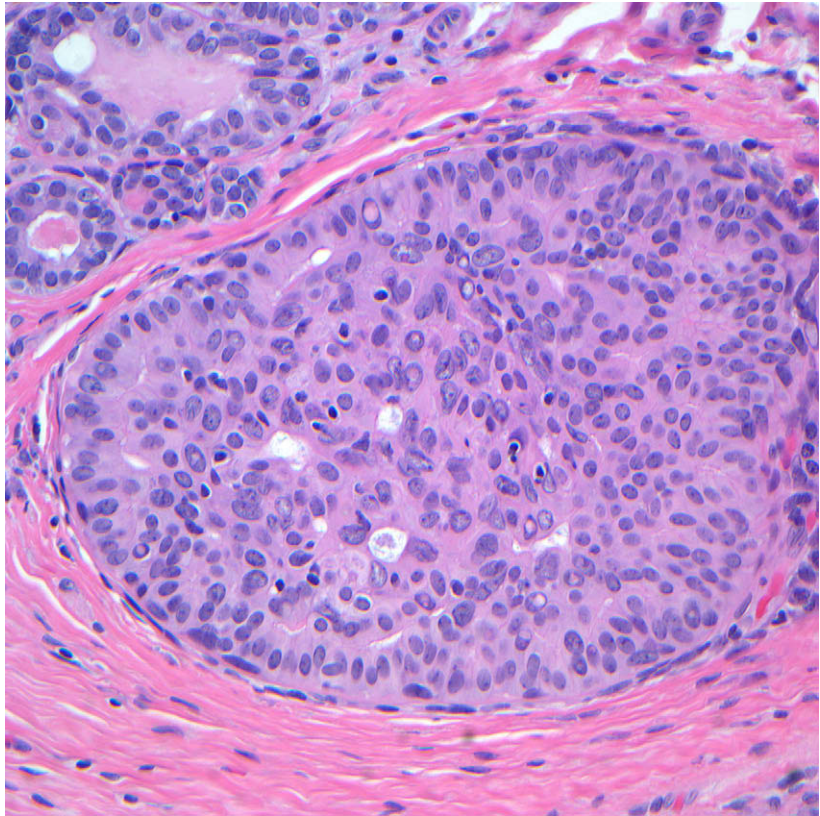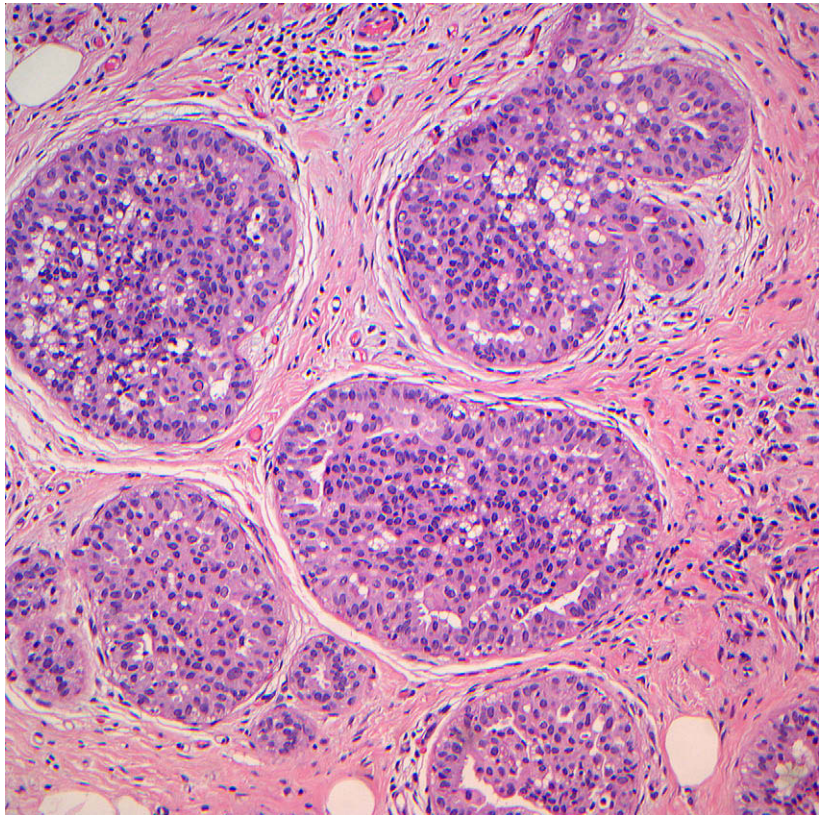

Fig. 2. Usual hyperplasia without atypia. This terminal ductal lobular unit contains usual-pattern hyperplasia. As the cells proliferate, the resulting secondary spaces are peripheral and slitlike. Note the swirling arrangement of the proliferating cells and their indistinct cell borders.
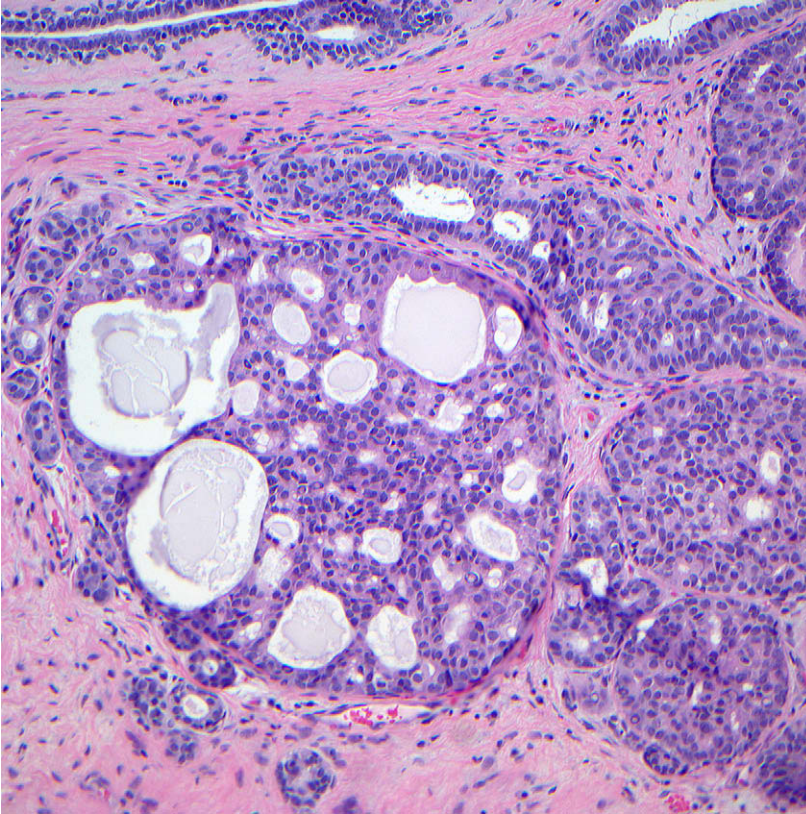
Fig. 3. Usual hyperplasia without atypia. At first glance, the secondary spaces appear regular, but close examination shows cellular bars composed of cells that are not uniform in appearance or in placement. Note the thin, tapering strand of cytoplasm that separates the two larger secondary spaces at left.
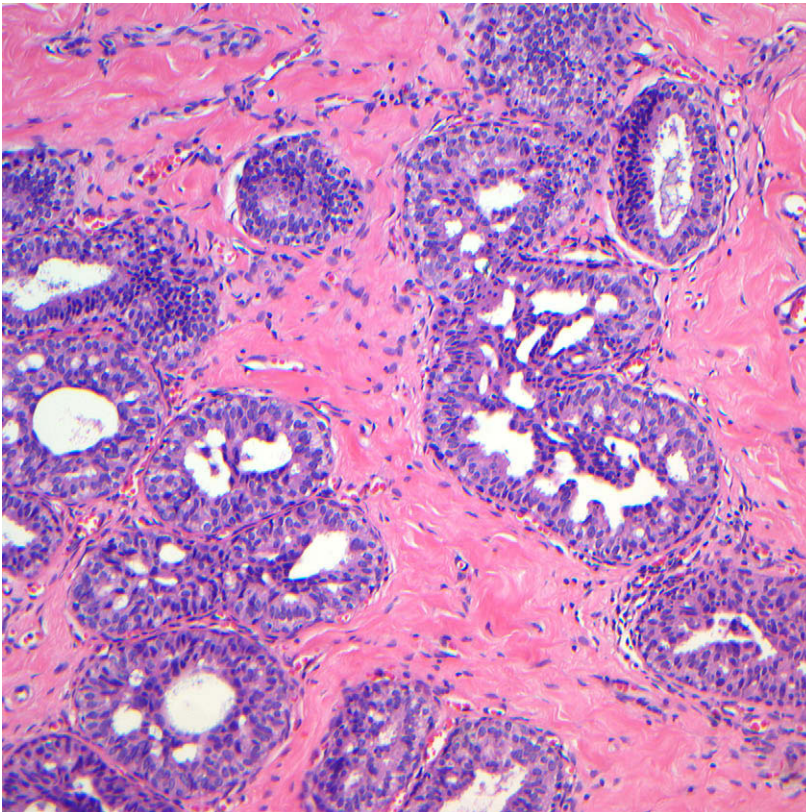

Fig. 4. Irregular cellular bars identify this example as usual hyperplasia without atypia.

Fig. 5. The cellular bars that define secondary spaces are thin, delicate, and tapering, all features of usual hyperplasia; some are composed of wisps of anuclear cytoplasm.
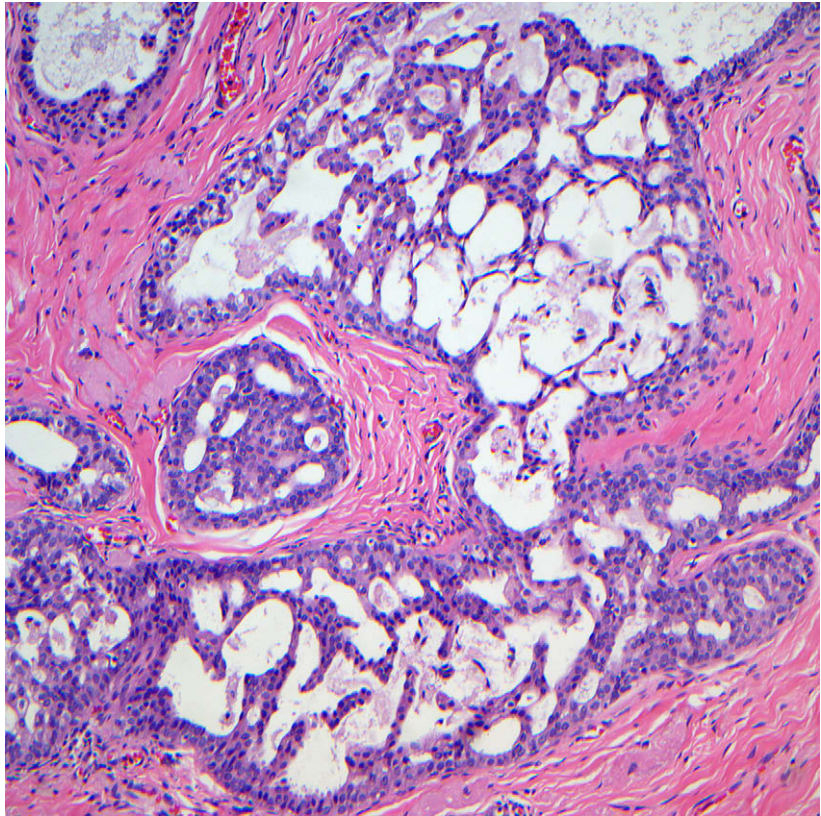

Fig. 6. This partially involved space contains tapering projections of proliferating cells that appear "stuck" on the underlying luminal epithelium. This pattern is seen in gynecomastia and in the female breast is part of usual hyperplasia without atypia.
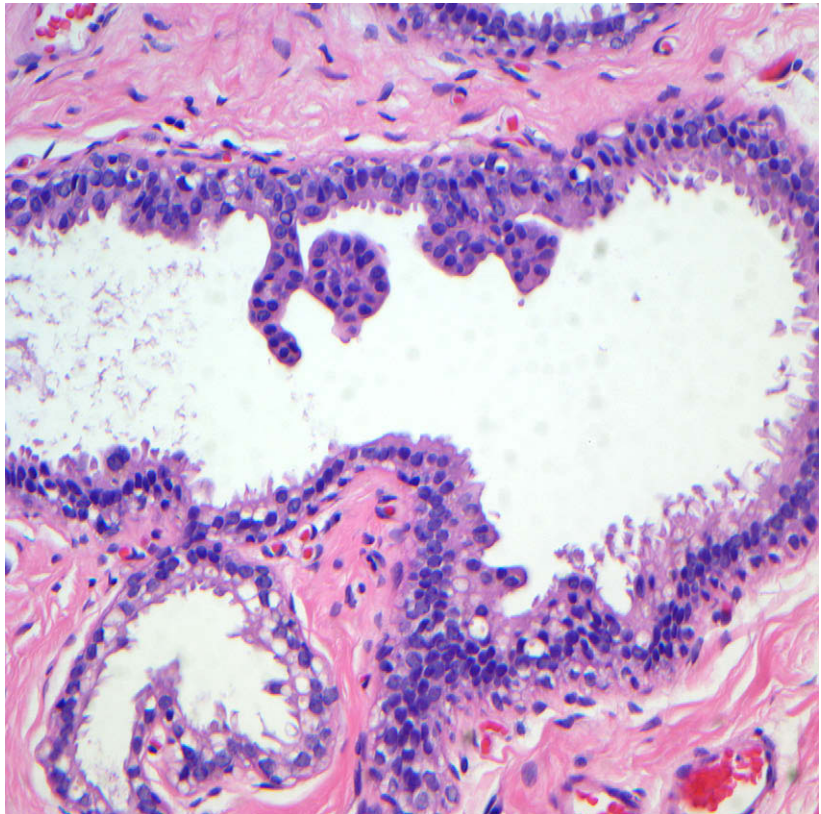
Fig. 7. Atypical ductal hyperplasia. This TDLU contains a population of uniform, evenly spaced cells that are arranged in rigid cellular bars. None of the spaces is replaced completely by the neoplastic cells, thus negating a diagnosis of DCIS.

the TDLU. DCIS is diagnosed when the characteristic uniform population of cells completely fills two adjacent spaces; any lesser involvement is, by definition, ADH (**Fig. 8**). As a matter of practicality, DCIS is usually at least 3 mm in extent; smaller lesions are better categorized as ADH. That statement, however, does not mean that any monomorphic proliferation larger than 3 mm is DCIS; partial involvement of unfolded, enlarged lobular units qualifies as ADH (**Fig. 9**). Another helpful feature is that DCIS usually involves true ducts (**Fig. 10**). Usually DCIS completely involves multiple spaces, namely expanded and unfolded lobular units and intervening ducts.

The diagnostic principles relating to low-grade lesions cease to apply when the neoplastic cell population shows advanced cytologic atypia. In the presence of advanced cytologic atypia (often in the presence of necrosis), a diagnosis of DCIS can be made on a single partially involved space, with the certainty that more extensive disease will be present in additional sections or in the excision specimen that follows the diagnostic biopsy. The salient diagnostic features of proliferative breast lesions are summarized in the key Features Box.

DIFFERENTIAL DIAGNOSIS

In general terms, the differential diagnosis for ordinary hyperplasia is ADH, which in turn must be distinguished from low-grade DCIS. The differential diagnosis for DCIS includes unusual patterns of invasive carcinoma known as "invasive cribriform carcinoma."

Usual patterns of hyperplasia, when presenting a solid growth pattern, can be confused with ADH or low-grade DCIS (see **Fig. 3**). Making the correct diagnosis is facilitated by thin microscopic sections. Thick sections give the illusion of cellular monotony. Attention to cellular variability and overlap will assure the correct diagnosis. When usual hyperplasia resembles the pattern present in gynecomastia, it can mimic micropapillary ADH or even DCIS. This pattern is characterized by mounds of cells with pyknotic nuclei that seem to be "stuck" on luminal cells (see **Fig. 6**).

Fig. 8. Low-grade DCIS, cribriform type. The changes are sufficient to diagnose DCIS because two adjacent spaces are completely populated by the neoplastic cell population. In this example, a smaller space at bottom is involved also. The overall size of this area is 3 mm.
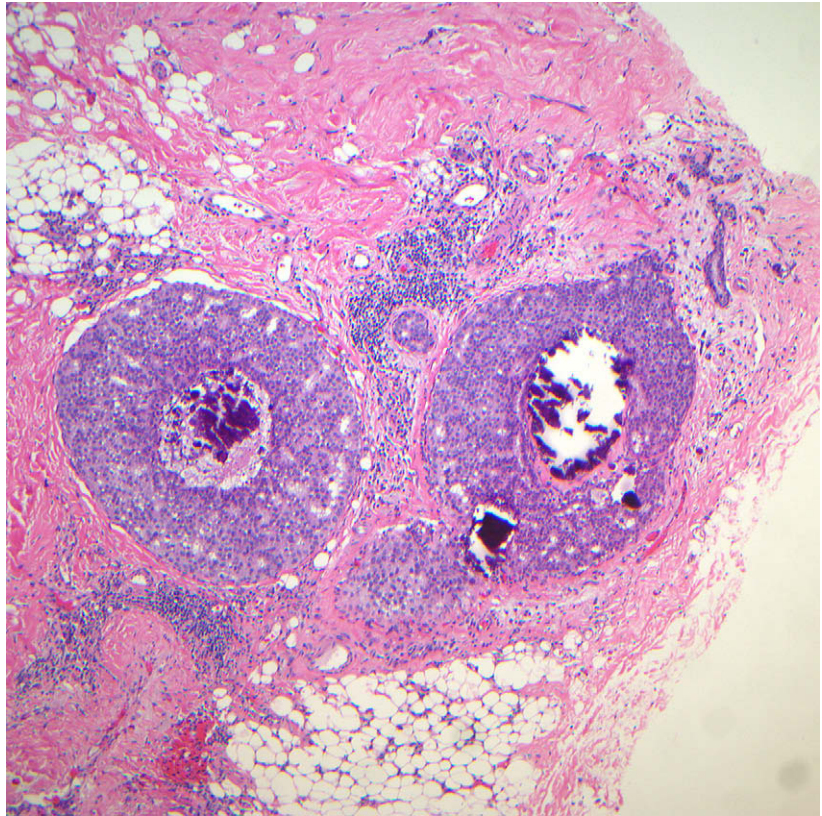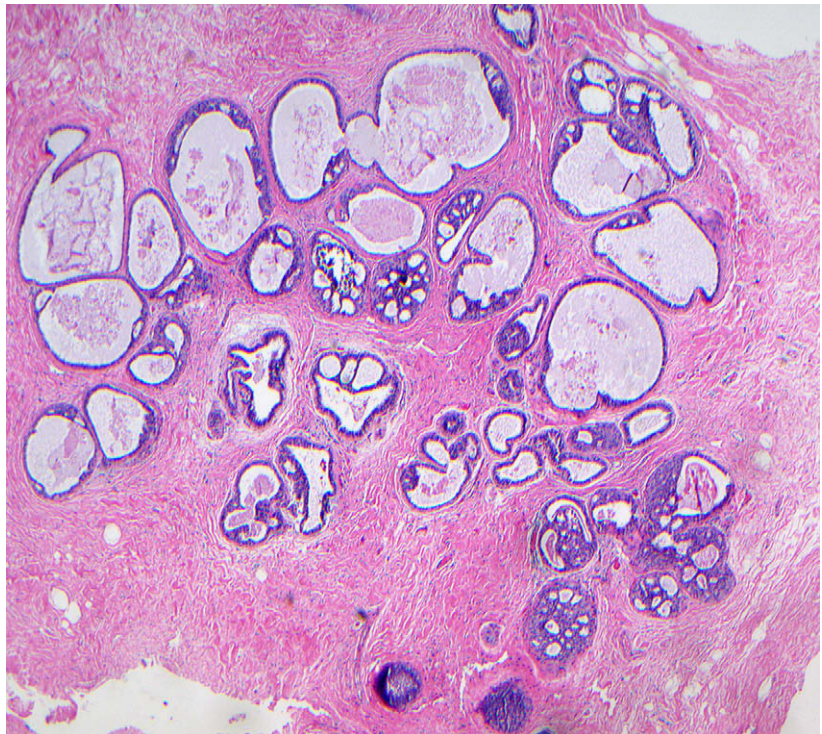

Fig. 9. Several spaces within this unfolded and enlarged lobular unit are partially involved by a uniform population of cells with rigid architecture. Although the overall size of this area is 5 mm, ADH is diagnosed because of partial involvement.
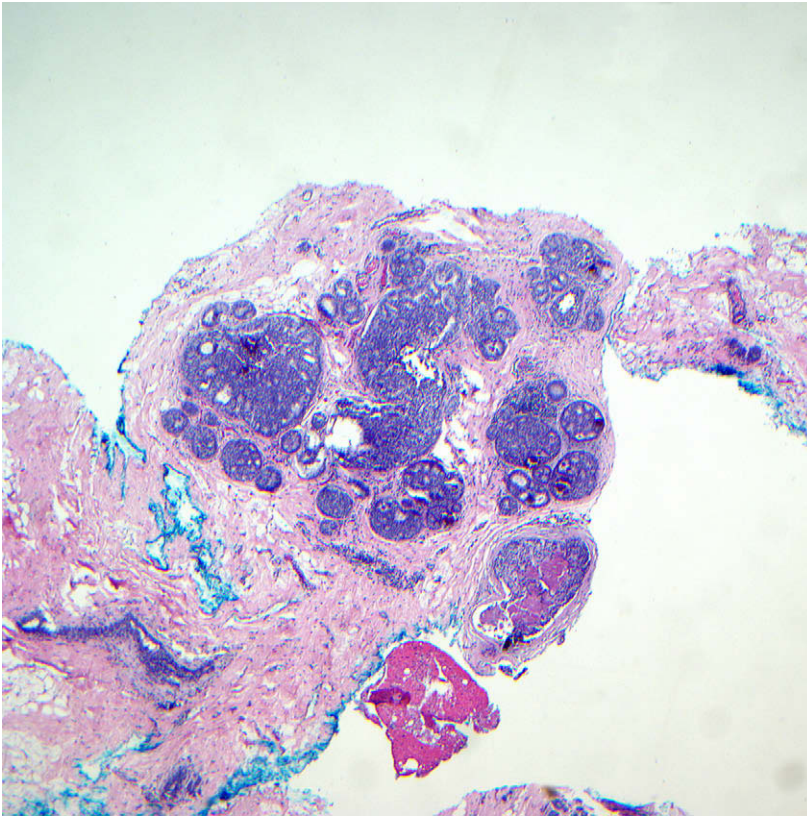
Fig. 10. Low-grade DCIS is diagnosed because neoplastic cells completely involve several adjacent spaces. This example spans several lobular units, with involvement of true ducts.

Cellular uniformity and crisp, regular secondary spaces are the diagnostic clues to ADH. ADH is a spatially limited, predominantly lobulocentric, low-grade and low-volume atypical proliferation that does not have the ability to involve and unfold a TDLU completely or to spread to other TDLUs across duct systems. When these features are completely present in two adjacent basement membrane–bound spaces, DCIS is diagnosed. DCIS usually involves true ducts and extends over an area of 3 to 4 mm (**Fig. 11**). It is important to remember that the differential diagnostic alternative for ADH is low-grade DCIS; intermediate- or high-grade DCIS is diagnosed even when present in lesser extent.

Some have advocated the use of immunohisto-chemical studies to distinguish ordinary patterns of hyperplasia from ADH. In an effort to improve diagnostic agreement in proliferative breast lesions, MacGrogan and colleagues[1] used immuno-histochemical analysis for CK5/6 and E-cadherin in a series of 105 cases. Generally speaking the diagnostic agreement based on morphologic grounds was moderate and was not improved significantly using these immunohistochemical markers.

Collagenous spherulosis is an uncommon finding within the breast, and its clinical signifi-cance is not known. The presence of true lumens and "pseudolumens" that contain basement membrane material occasionally can be confused with the crisp, rigid secondary spaces of ADH or DCIS (**Fig. 12**). Recognizing the two different types of spaces may be aided by the use of a periodic acid-Schiff alcian blue stain.

Occasionally lobular neoplasia (either atypical lobular hyperplasia or lobular carcinoma in situ) may be confused with TDLU involvement by solid pattern ADH or DCIS. A careful search for distinct cell–cell borders and microrosettes helps the clini-cian arrive at the proper diagnosis. Immunohisto-chemical expression of E-cadherin may be helpful in this distinction, with the realization that there may be aberrant expression.[2]

Invasive cribriform carcinoma is an uncommon form of breast carcinoma that occasionally can be confused with cribriform-type DCIS (**Fig. 13**). Careful attention to the lack of a lobulocentric

Fig. 11. Higher magnification of **Fig. 10**, showing involvement of a true duct at the bottom.
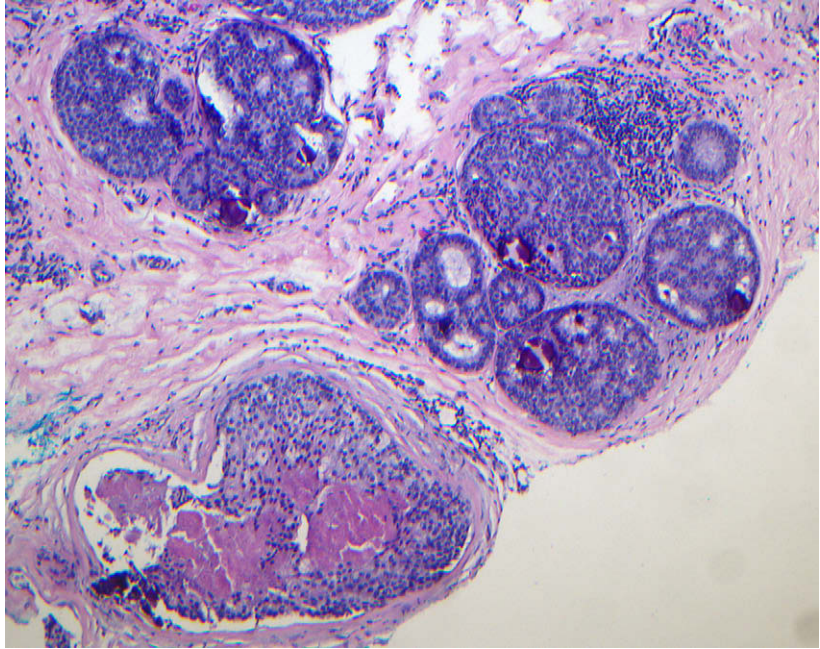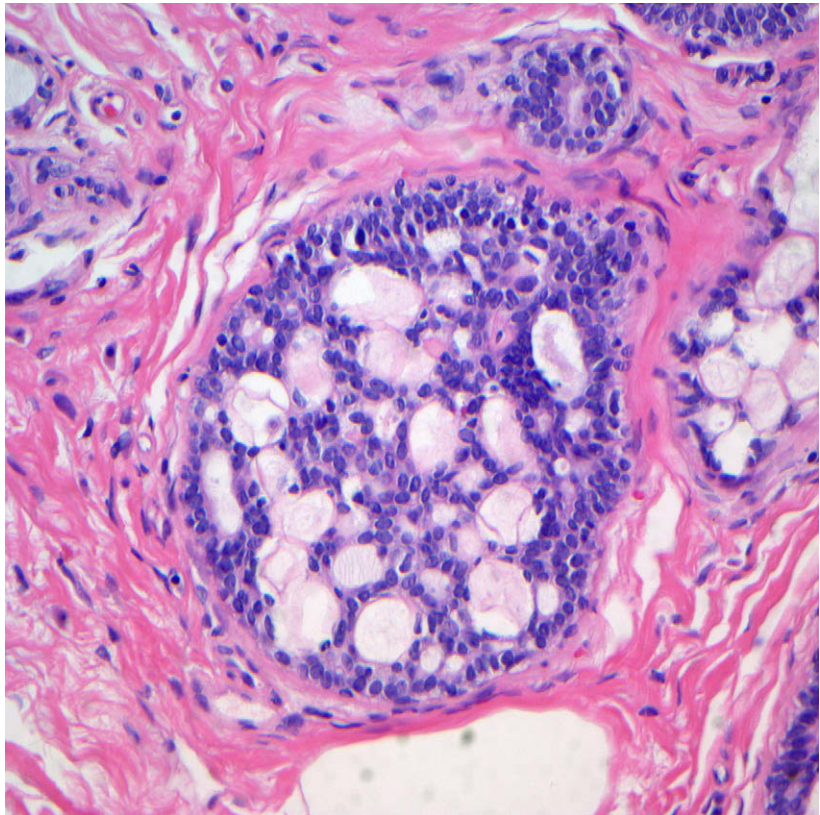

Fig. 12. Collagenous spherulosis mimics ADH with seeming crisp secondary spaces. Closer inspection shows the presence of true lumens and pseudolumens; the latter contain basement membrane material.
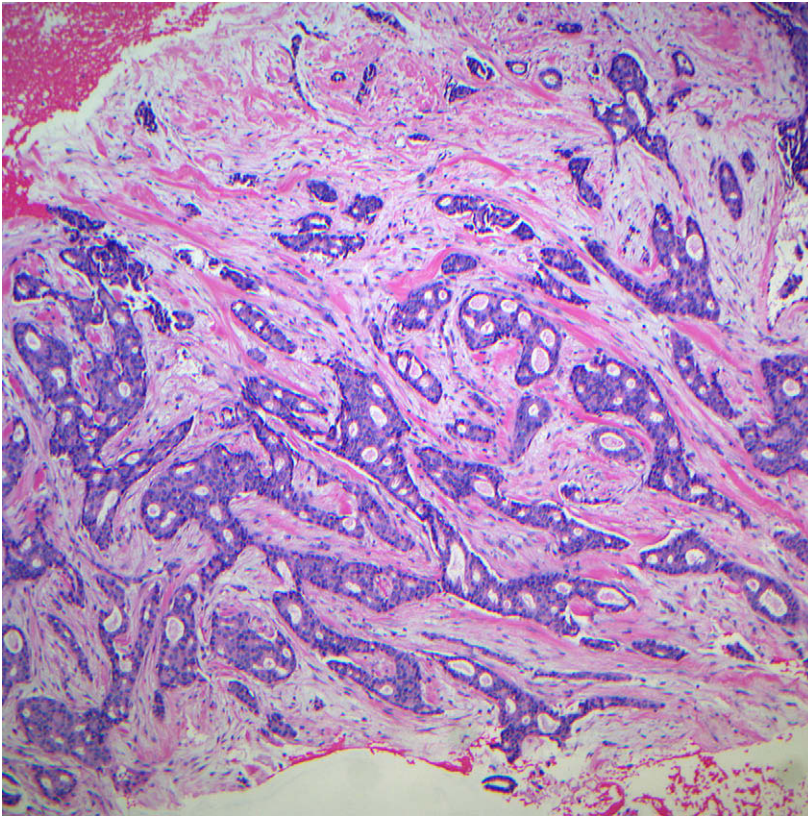
Fig. 13. Invasive cribriform carcinoma. Although the individual islands resemble cribriform DCIS, the infiltrative nature and lack of lobulocentricity characterize this lesion as an invasive carcinoma. Invasive cribriform carcinoma is biologically analogous to tubular carcinoma.

process and the absence of a myoepithelial cell layer helps identify the invasive nature of this form of invasive carcinoma, which has an excellent prognosis.

DIAGNOSIS ON CORE BIOPSY

If ordinary patterns of hyperplasia are diagnosed on core biopsy, and there is concordance with imaging studies, further excision is not necessary.

A number of studies report clinically significant diagnostic upgrades in the excisional biopsy specimen after a diagnosis of ADH on core biopsy, and thus excision is the usual recommendation in this setting. In an extensive review of the literature, the gauge of the biopsy device and the size of the lesion were the statistically significant factors that reduced underestimation at the time of core biopsy.[3] Using an 11-gauge vacuum-assisted device, Sohn and colleagues[4] were able to reduce by half the often-quoted upgrade rate of 36%. Even though needle core biopsies may excise the lesion completely, the nature of the procedure presents a fragmented specimen, precluding an assessment of the extent of

involvement, which is critical in the distinction between ADH and low-grade DCIS. Quantification of ADH within core biopsies has been attempted to predict the presence (or absence) of more advanced disease within the excisional biopsy specimen.[5] Upgrades are more likely if there are more than two foci of ADH, if the lesion is larger than 6 mm, or if the lesion is smaller than 6 mm but is not removed completely.[6] This finding is not surprising, because low-grade DCIS usually is at least 4 mm in extent. It does point out, however, that small, limited disease could be spared formal excision. It is likely that the practice of excising ADH detected on core biopsy will continue, based on the characteristics of the specimen obtained by the majority of needle biopsy devices currently in use. The authors maintain a conservative approach in borderline cases, diagnosing ADH and recommending excision to evaluate the full extent of the lesion. This approach allows the definitive diagnosis to be made on excision, without subjecting the patient to unnecessary additional therapy for a lesion amenable to cure by adequate surgery alone.

If ADH is present within an excisional biopsy specimen, no further surgical intervention is

Table 1
Relative risk associated with proliferative breast disease: Nashville Breast Cohort

Lesion	Increase in Relative Risk	Laterality of Risk
Usual patterns of hyperplasia	1.5–2 times	Bilateral risk
Atypical ductal hyperplasia	4–5 times	Bilateral risk
Low-grade DCIS	9–10 times	Ipsilateral risk

Data from Dupont W, Page D. Risk factors for breast cancer in women with proliferative breast disease. N Engl J Med 1985;312:146–51; and Page DL, Dupont WD, Rogers LW, et al. Continued local recurrence of carcinoma 15–25 years after a diagnosis of low grade ductal carcinoma in situ of the breast treated only by biopsy. Cancer 1995;76:1197–200.

necessary. In general, the finding of ADH at a margin of an excisional biopsy is of no consequence, unless it is at the periphery of an area of DCIS. The decision for re-excision should take the imaging findings into consideration: if no imaged abnormality remains, re-excision may not be necessary.

CLINICAL IMPLICATIONS AND PROGNOSIS

The relative risks associated with various proliferative lesions are shown in **Table 1**. Note that ordinary or usual hyperplasia and ADH are associated with bilateral risk, whereas low-grade DCIS carries a risk of ipsilateral breast cancer. A number of large epidemiologic studies[7–9] have confirmed the original work of Dupont and Page[10] (**Table 2**).

From a practical point of view, the risk associated with ordinary-pattern hyperplasia is insufficient (1.5 times increased risk) to affect patient management. The diagnosis of ADH is associated with an increased relative risk of subsequent breast cancer development 4 to 5 times that in age-matched controls.[10] Although ADH is a well-established risk indicator, the implications for an individual patient are less certain. Some women receive screening mammograms more frequently, but this approach is not proven or universally accepted.

The subsequent bilateral risk associated with ADH is significantly different from the risk associated with low-grade DCIS and is evidence that ADH is not an obligate precursor for in situ or invasive carcinoma. Thus, the diagnostic distinction of ADH from low-grade DCIS has important therapeutic implications. There is some molecular evidence indicating that ADH shares genetic alterations with more advanced lesions,[11] but long-term follow-up studies characterizing ADH at the molecular level in the absence of more advanced lesions are not available.

The natural history of low-grade non-comedo DCIS is one of progression to invasive cancer over a period that may extend over many years.[12] From the Nashville Breast Cohort, Page and colleagues[12] retrospectively identified 28 cases of low-grade DCIS initially diagnosed as benign. In long-term follow-up, nine women developed invasive carcinoma, all in the breast in which the original DCIS was found (and in same site, when documented). It is important to remember that these DCIS lesions were detected in the era before mammography and were present in specimens removed for some non-DCIS palpable abnormality. Furthermore, no attempt at clear margins was undertaken. It therefore is sound to consider DCIS a nonobligate precursor that has a significant likelihood of progression if not excised completely. The Nurses' Health Study has provided additional support for the understanding of the natural history

Table 2
Confirmatory studies of proliferative breast disease: increase in relative risk

Pathologic Finding	Nashville Breast Cohort (1985)[10]	Nurses' Health Study (1992)[7]	Breast Cancer Detection Demonstration Project (1993)[8]	Mayo Clinic (2005)[9]
Usual hyperplasia without atypia	1.5–2 times	1.6 times	1.3 times	1.9 times
Atypical ductal hyperplasia	4–5 times	3.7 times	4.3 times	4.2 times

of DCIS as a precursor to invasive carcinoma. In a review of 1877 cases, 13 cases originally diagnosed as benign were reclassified as DCIS.[13] Six women developed invasive carcinoma, all in the ipsilateral breast. Similar to the findings of Page and colleagues,[12] some of the cancers developed many (up to 18) years after the initial biopsy that, in retrospect, contained DCIS; this development was especially the case for low-grade DCIS.[13]

The objective of current therapeutic strategies is to curtail this natural evolution without sacrificing the whole breast. More recent studies have shown that the three most important determinants of recurrence/progression are the histologic characteristics of the DCIS, its size, and its margin status.[14] These three elements have been used to create the Van Nuys Prognostic Index (VNPI) that predicts the likelihood of disease recurrence. A recent review of 215 patients who underwent breast conservation surgery for DICS (without additional radiotherapy or hormonal therapy) showed that the presence of comedo necrosis and the VNPI were the only significant factors in predicting disease recurrence.[15]

In summary, specific histologic criteria for proliferative lesions of the breast have been linked to outcome through large epidemiologic studies. Careful application of these criteria will continue to identify women who are at an increased risk for later development of cancer and those whose risk is no greater than that in age-matched controls.

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