Current Concepts in Diagnosis, Molecular Features, and Management of Lobular Carcinoma In Situ of the Breast With a Discussion of Morphologic Variants

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• ***Context.***—**Lobular carcinoma in situ (LCIS) refers to a neoplastic proliferation of cells that characteristically shows loss of E-cadherin expression and has long been regarded as a risk factor for invasive breast cancer. Long-term outcome studies and molecular data have also implicated LCIS as a nonobligate precursor to invasive carcinoma. In the past few decades, pleomorphic and florid LCIS have been recognized as morphologic variants of LCIS with more-aggressive histopathologic features, less-favorable biomarker profiles, and more-complex molecular features compared with classic LCIS. There is still a lack of consensus regarding certain aspects of managing patients with LCIS.**

Objectives.—**To review recently published literature on LCIS and to provide an overview of the current morphologic classification of LCIS, recent molecular advances, and trends in patient management.**

Data Sources.—**Sources included peer-reviewed, published journal articles in PubMed (US National Library of Medicine, Bethesda, Maryland) and published guidelines from the National Comprehensive Cancer Network (Fort Washington, Pennsylvania).**

Conclusions.—**Lobular carcinoma in situ represents a marker for increased risk of breast cancer, as well as a nonobligate precursor to invasive carcinoma. Morphologic variants of LCIS—florid and pleomorphic LCIS—are genetically more-complex lesions and are more likely to be associated with invasive carcinoma. Further investigation into which molecular alterations in LCIS are associated with progression to invasive carcinoma is needed to help guide medical and surgical management.**

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Lobular carcinoma in situ (LCIS) was described by Foote and Stewart[1] more than 75 years ago as an in situ disease affecting multiple lobules and terminal ducts that is associated with a type of invasive carcinoma that is "peculiar and somewhat obscure." We have since gained a tremendous understanding about the natural history of LCIS and its relationship with the development of invasive carcinoma.

The original description by Foote and Stewart[1] of LCIS is what is now referred to as "classic" LCIS. The term *lobular neoplasia* has been applied to the spectrum of lesions comprising atypical lobular hyperplasia (ALH) and LCIS. The differences between classic LCIS and ALH are quantitative by definition and are somewhat subjective in practice. In this review, the term *lobular neoplasia* will be used when discussing studies that encompass *classic* LCIS and ALH. Pleomorphic LCIS and florid LCIS are morphologic variants of LCIS that have been identified and increasingly studied in the past few decades with the advent and routine use of E-cadherin immunohistochemistry (Table). Pleomorphic LCIS describes LCIS with high-grade cytologic features, whereas the designation *florid* is used to describe an architectural growth pattern in which LCIS causes marked expansion of ducts and lobules.

The purpose of this review is to provide an updated overview of clinical, morphologic, and molecular features of LCIS, with a focus on the current literature and how these data have a role in dictating patient management. The significance of LCIS variants in this context and their differences with classic LCIS will also be reviewed.

CLINICAL FEATURES AND INCIDENCE OF LOBULAR NEOPLASIA

Lobular neoplasia is most often diagnosed in premenopausal women, with a mean age of about 45 years and is diagnosed less frequently in postmenopausal women.[2,3] Patients with variant (florid and pleomorphic) types of LCIS have been shown to be older at presentation (50–60 years).[4–8] Lobular neoplasia is almost always an incidental finding and is typically associated with benign, proliferative lesions containing mammographically evident calcifications. Calcifications may also be seen in association with lobular neoplasia but are typically small and infrequently the source of calcifications targeted for stereotactic biopsy. In contrast, florid and pleomorphic LCIS (discussed below) often show

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Classic Lobular Carcinoma In Situ (LCIS) and Morphologic Variants of LCIS: Clinical and Morphologic Features and Biomarker Expression			
Characteristic	**Classic LCIS**	**Florid LCIS**	**Pleomorphic LCIS**
Age, y	Premenopausal, 40–50	Postmenopausal, 50–60	Postmenopausal, 50–60
Imaging	No findings; occasionally punctate calcifications	Calcifications, similar to DCIS; mass	Calcifications, similar to DCIS; mass
Morphology	Loosely cohesive cells fill and distend lobules and show pagetoid growth in ducts; occasional calcifications; no/rare mitoses; no necrosis; cytology: small, low-grade (type A); intermediate-grade (type B)	Marked ductal expansion by loosely cohesive cells; necrosis and calcifications common; cytology: small, low grade (type A); intermediate grade (type B)	Lobular and ductal expansion by loosely cohesive cells; necrosis and calcifications common; mitoses frequent; cytology: high grade, nuclear enlargement, pleomorphism; apocrine features: eosinophilic cytoplasm, granules, nucleoli
Biomarker expression	ER^+ and PR^+ (>95%); $HER2^-$	Most ER^+ and PR^+; rare HER2 overexpression	Most ER^+ and PR^+; decreased expression compared with classic LCIS; may be negative, particularly apocrine type; variable HER2 overexpression; more common in apocrine type

Abbreviations: DCIS, ductal carcinoma in situ; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; PR, progesterone receptor.

necrosis and calcifications and may show a pattern of calcifications on mammography similar to ductal carcinoma in situ (DCIS) or may even appear as mass-forming lesions on imaging.[6,8,9] Lobular neoplasia is frequently multicentric and bilateral.

Although the true incidence of LCIS is difficult to ascertain, studies have shown incidence rates of 0.07% to 3% in core biopsy samples[10,11] and 0.5% to 3.8% in open biopsies.[2,12] Epidemiologic studies from the late 1970s to early 2000s have demonstrated the incidence of LCIS has risen 2.6- to 4-fold.[13,14] These increases were most conspicuous in postmenopausal women.[13,14] More recent data continue to show an increase in the incidence of LCIS (from 2 per 100 000 women in 2000 to 2.75 per 100 000 women in 2009).[15] The increased incidence of lobular neoplasia is thought to be a reflection of the use of breast screening, increasing numbers of core biopsies, and better recognition by pathologists.

MORPHOLOGIC VARIANTS OF LCIS

Classic LCIS

Classic LCIS refers to a population of loosely cohesive, uniform neoplastic cells that fill and distend lobules (Figure 1, A). The classic teaching is that LCIS involves at least one-half of the acini within a lobule, whereas atypical lobular hyperplasia shows the same population of cells involving less than one-half of the acini. Classic LCIS cells have scant cytoplasm with small, monomorphic, round to ovoid nuclei that lack nucleoli (Figure 1, B and C). Haagensen et al[2] referred to these cells as *type A* cells. Type B cells exhibit slight pleomorphism with larger nuclei, nucleoli, and more-abundant cytoplasm (Figure 1, D). Intracytoplasmic mucin may impart a signet ring cell appearance to LCIS cells. Mitotic figures and necrosis are rarely seen. Calcifications may be present in classic LCIS but are not usually abundant. Lobular carcinoma in situ most often involves lobules but may also grow along the basement of extralobular ducts, that is, "pagetoid" growth, and may secondarily involve benign lesions, such as radial scars, papillomas, fibroadenomas, and collagenous spherulosis.

Pleomorphic LCIS

Pleomorphic LCIS refers to LCIS with high-grade cytologic features that often occur in association with invasive pleomorphic lobular carcinoma and can mimic high-grade DCIS.[16] Similar to classic LCIS, pleomorphic LCIS fills and distends lobules in a loosely cohesive manner, but it also tends to show a florid growth pattern (described below) and is frequently associated with central, comedo-type necrosis and calcifications (Figure 2, A through C). Cells of pleomorphic LCIS show enlarged, eccentrically placed nuclei that may have nucleoli (Figure 2, D). Binucleated and multinucleated cells are frequently seen.[17] The cytoplasm of pleomorphic LCIS is usually more abundant than that of classic LCIS and can also show intracytoplasmic mucin vacuoles with signet ring cell features. Apocrine differentiation may be seen in pleomorphic LCIS cells and is characterized by abundant eosinophilic cytoplasm, cytoplasmic granules, and prominent nucleoli (Figure 3, A through D).

Florid LCIS

Florid LCIS refers to a growth pattern of LCIS in which neoplastic cells fill and expand ducts in a solid architectural pattern, similar to the solid growth seen in DCIS (Figure 4, A). Florid LCIS has been referred to in the literature as *macroacinar lobular intraepithelial neoplasia*[18] and *LCIS with comedonecrosis*[19] The designation *florid* is applied to cases of LCIS with the marked ductal and lobular expansion by LCIS cells of low to intermediate nuclear grade (Figure 4, B). However, because *florid* describes an architectural, rather than a cytologic, feature, pleomorphic LCIS can also be described as growing in a florid pattern and having cells of varying nuclear grades commonly coexisting in florid LCIS.[20] There are currently no criteria for the degree to which the acini and ducts need to be expanded to label LCIS as *florid*. Necrosis and calcifications are frequently present (Figure 4, C) but are not always seen. Multiple foci of classic LCIS are frequently seen near florid LCIS, whereas florid LCIS itself may only be present as a discrete focus.

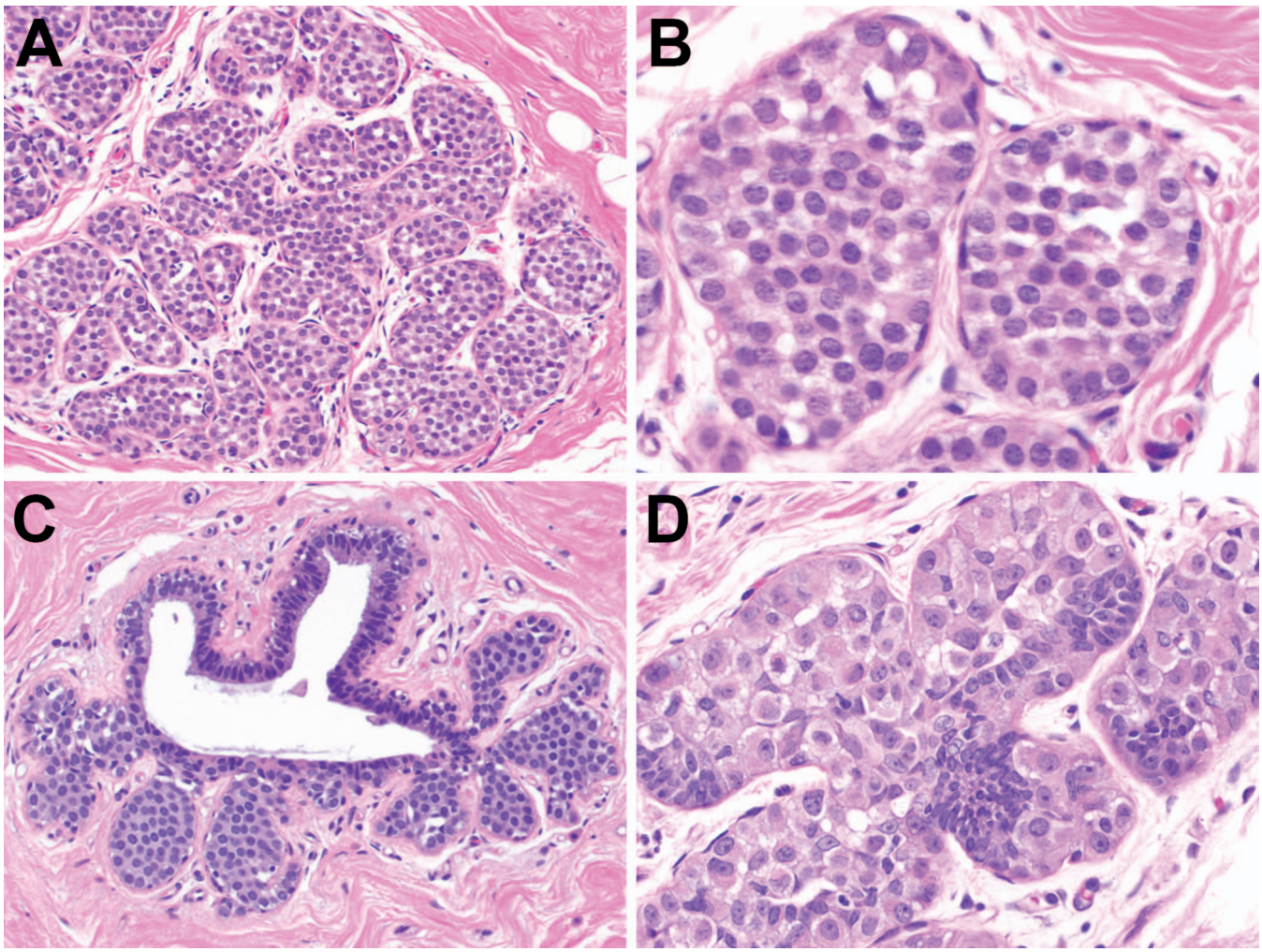

Figure 1. *Lobular carcinoma in situ, classic type. A, Classic lobular carcinoma in situ is composed of loosely cohesive cells that fill and distend lobules. B, Neoplastic cells are monomorphic with uniform, round nuclei. C, Lobular carcinoma in situ showing pagetoid growth beneath native ductal epithelium. D, So-called type B cells show enlarged nuclei, nucleoli, and more abundant cytoplasm compared with cells seen in (B) (hematoxylin-eosin, original magnifications ×100 [A], ×400 [B and D], and ×200 [C]).*

E-CADHERIN IMMUNOHISTOCHEMISTRY

Loss of membranous expression of E-cadherin is the defining immunohistochemical feature of lobular differentiation in breast carcinoma (Figure 5, A through C); consequently, E-cadherin is frequently employed by pathologists to make the distinction between LCIS and DCIS and between invasive lobular carcinoma and invasive ductal carcinoma. E-cadherin is a transmembrane glycoprotein that mediates cell-to-cell adhesion. The intracytoplasmic domain of E-cadherin binds to the actin cytoskeleton through interactions with catenin proteins p120, β-catenin, α-catenin, and δ-catenin in the cytoplasm.[21] p120 and β-catenin are normally expressed on the cell membrane by immunohistochemistry. Various molecular mechanisms inactivate or down-regulate E-cadherin and lead to disruption of cadherin-catenin complexes between cells, resulting in the loss of cellular cohesion characteristic of lobular lesions. Most commonly, E-cadherin is inactivated via deletions, mutations, or promoter methylation of the *CDH1* gene.[21–23] This inactivation of E-cadherin leads to loss of p120 and β-catenin expression on the cell membranes and accumulation of p120 in the cytoplasm (Figure 5, C).[21]

Almost all cases of LCIS, including florid and pleomorphic types, lack expression of E-cadherin protein, whereas DCIS and benign ducts have diffuse and strong membranous staining. Because of the widespread, routine use of E-cadherin, various "aberrant" staining patterns have been recognized that can be problematic for interpretation.[21,24] Lobular carcinoma in situ often exhibits weak, fragmented, membranous E-cadherin staining that is considerably less intense that in adjacent benign breast glandular tissue and is usually not diffuse in distribution (Figure 6, A and B). This pattern of aberrant staining does not usually cause interpretative issues. In rare instances, cases that are unambiguously classic LCIS by morphology show a diffuse pattern of membranous staining (Figure 6, C and D). This is typically a result of E-cadherin protein being inactivated but remaining on the cell surface as a dysfunctional protein. Disruption of the cadherin-catenin complex in such cases can be confirmed with p120, which will show cytoplasmic, but not membranous staining. A β-catenin immunostain will show loss of membranous staining. Less commonly, an

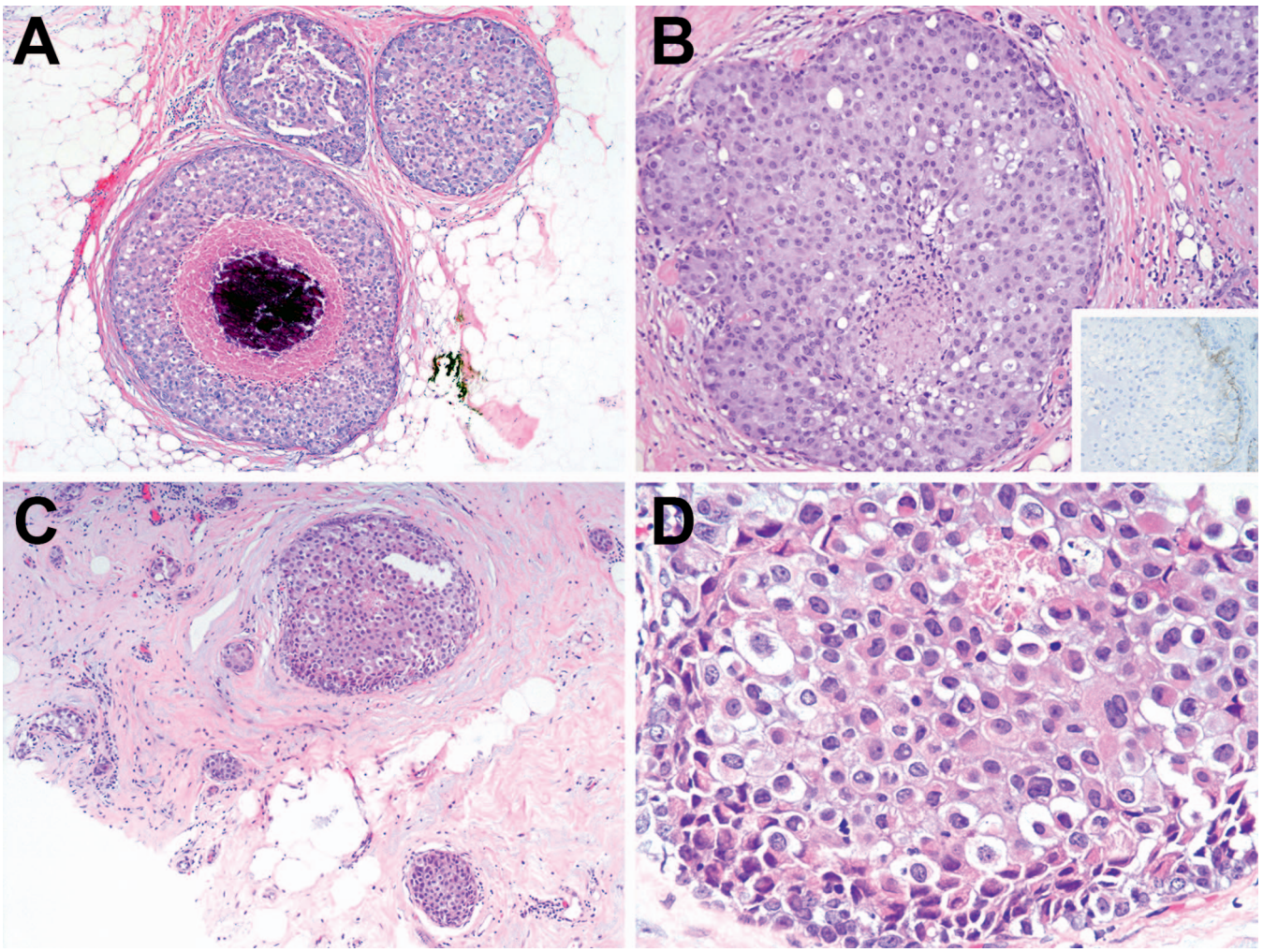

Figure 2. *Pleomorphic lobular carcinoma in situ. A, Multiple ducts are expanded by a population of loosely cohesive cells. Central necrosis and calcifications are present. B, Distended ducts are filled with a population of seemingly cohesive cells with abundant cytoplasm and prominent nucleoli. Necrosis is present. Inset, An E-cadherin immunostain is negative. C, Multiple ducts containing a population of loosely cohesive pleomorphic cells. D, Higher magnification shows the cells have abundant cytoplasm, prominent nucleoli, and irregular nuclear membranes. Some binucleate cells are also present. The cells were negative for E-cadherin (not shown) supporting lobular differentiation (hematoxylin-eosin, original magnifications ×100 [A through C] and ×400 [D]; original magnification ×200 [inset]).*

aberrant pattern of cytoplasmic expression of E-cadherin in LCIS may be observed (Figure 6, E and F).

Aberrant expression of E-cadherin is an uncommon occurrence, likely occurring in no more than 10% of cases; however, focal, patchy, and fragmented E-cadherin staining is seen more often.[25,26] Suboptimal antibody workup and "overstaining" can be the cause of aberrant E-cadherin staining, in some cases, and appropriate E-cadherin antibody optimization and validation is a critically important preanalytic step to ensure accurate diagnosis/classification.[27] In practice, E-cadherin is not necessary (or recommended) for cases in which the diagnosis is clear-cut, which helps to avoid encountering such cases with aberrant staining. From a management standpoint, E-cadherin is important in distinguishing classic LCIS from DCIS. The aim for treating DCIS is local eradication by surgical excision with negative margins, usually followed by adjuvant radiotherapy. Treatment of classic LCIS, in contrast, is less aggressive and usually includes clinical/imaging follow-up, with or without adjuvant endocrine therapy. The clinical implications of distinguishing high-grade DCIS from pleomorphic LCIS are uncertain.

HORMONE RECEPTOR AND HER2 EXPRESSION IN LCIS

Classic LCIS almost invariably expresses estrogen receptor (ER) and progesterone receptor (PR) and lacks human epidermal growth factor receptor (HER2) overexpression.[8,28] Compared with classic LCIS, pleomorphic LCIS exhibits greater variability in ER, PR, and HER2 expression. Chen et al[8] reported pleomorphic LCIS to be ER^- and PR^- in 44% and 48% of cases, respectively, and HER2 was overexpressed in 13% of cases. Furthermore, even in ER^+/PR^+ cases, pleomorphic LCIS showed lower levels of expression when compared with cases of classic LCIS.[8] Apocrine-type pleomorphic LCIS demonstrated even greater proportions of *HER2* amplification than did nonapocrine type (31% versus 0%).[8] Similar to classic LCIS, florid LCIS is commonly ER^+; however, unlike classic LCIS, florid LCIS occasionally demonstrates *HER2* amplification.[7,19]

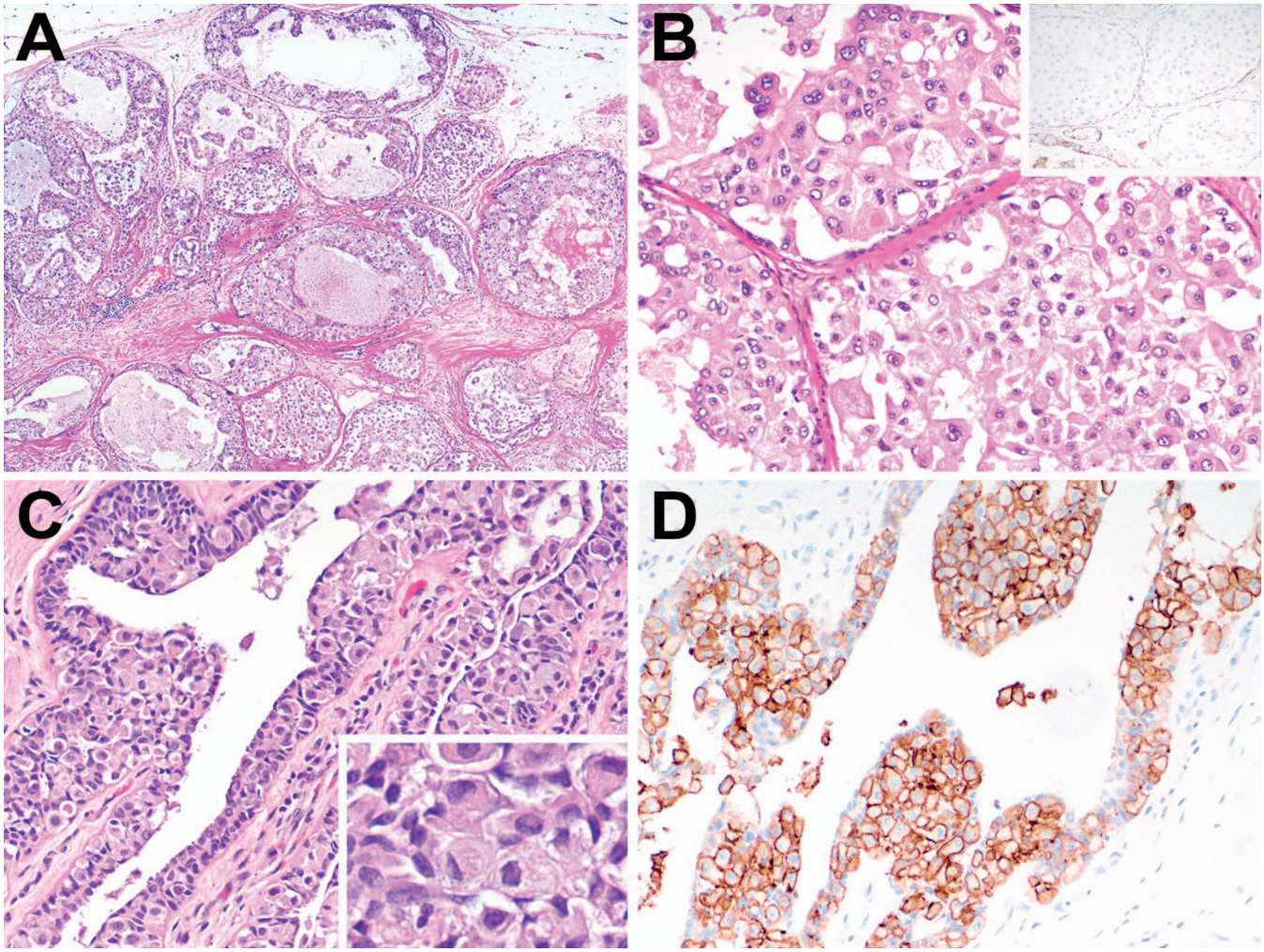

Figure 3. *Pleomorphic lobular carcinoma with apocrine differentiation and HER2 overexpression. A, Multiple ducts are markedly expanded by a population of enlarged cells with abundant eosinophilic cytoplasm. In some ducts, micropapillary growth is seen, a feature uncommonly seen in lobular carcinoma in situ (LCIS). Luminal necrosis is also seen in some ducts. B, Higher magnification of ducts shown in (A). Inset, An E-cadherin immunostain is negative, supporting lobular differentiation. C, Pleomorphic LCIS with apocrine differentiation growing in a pagetoid distribution in ducts. Inset, High magnification shows cells with abundant granular eosinophilic cytoplasm and enlarged hyperchromatic nuclei. D, HER2 overexpression is seen with diffuse membranous immunohistochemical staining of LCIS cells (hematoxylin-eosin, original magnifications ×40 [A], ×200 [B and C], and ×100 [D]; original magnification ×200 [B, inset], ×600 [C, inset]).*

MOLECULAR FEATURES OF LCIS

Classic LCIS and ALH

Most of our knowledge regarding genetic alterations in LCIS has been realized through comparative genomic hybridization and loss-of-heterozygosity studies. The most common, recurrent chromosomal changes identified in LCIS are loss of 16q and gain of 1q.[28–32] Losses of 16q and gains of 1q are also seen in other ER^+ proliferations, including columnar cell lesions and well-differentiated, invasive ductal carcinoma, including tubular carcinoma, low-grade DCIS, and atypical ductal hyperplasia, establishing the genetic homogeneity between these lesions.[29,31–36] This has led to an understanding of LCIS belonging to a group of lesions in a low-grade, ER^+ pathway of breast carcinogenesis.[35,37]

Mutations in the *CDH1* gene are almost entirely somatic and result from premature truncation of the translation, frequently accompanied by loss of the wild-type allele.[38,39] In addition to *CDH1* gene mutations, allelic loss and *CDH1* promotor methylation have also been implicated in the loss of E-cadherin expression.[40] Other tumor-suppressor genes located on chromosome 16 that have shown loss of expression in LCIS include the CCCTC-binding factor (*CTCF*) gene, a transcriptional regulator of several genes linked to tumorigenesis, as well as the dipeptidase 1 (*DPEP1*) gene, which is involved in the metabolism of an important glutathione that may have a role in the degradation of the surrounding extracellular matrix.[30] Other recurrent chromosomal alterations have been inconsistently seen in LCIS and include losses of 17q (home of *ERBB2* and *NF1*), 17p (home of *TP53*), 16p (home of *CCNF* [cyclin F]), 13q (home of *RB* [RB binding protein]), 12q, 11q (home of *CCND1* (cyclin D1), *MEN1* [multiple endocrine neoplasia 1], and *ATM* [ATM serine/threonine kinase]), 9p, and 8p and gains of 6p and 8p.[28,29,31,32,36]

Much of the molecular data regarding LCIS have focused on its relationship with invasive lobular carcinoma and its role as a potential precursor lesion. Comparative genomic hybridization studies of synchronous LCIS and invasive

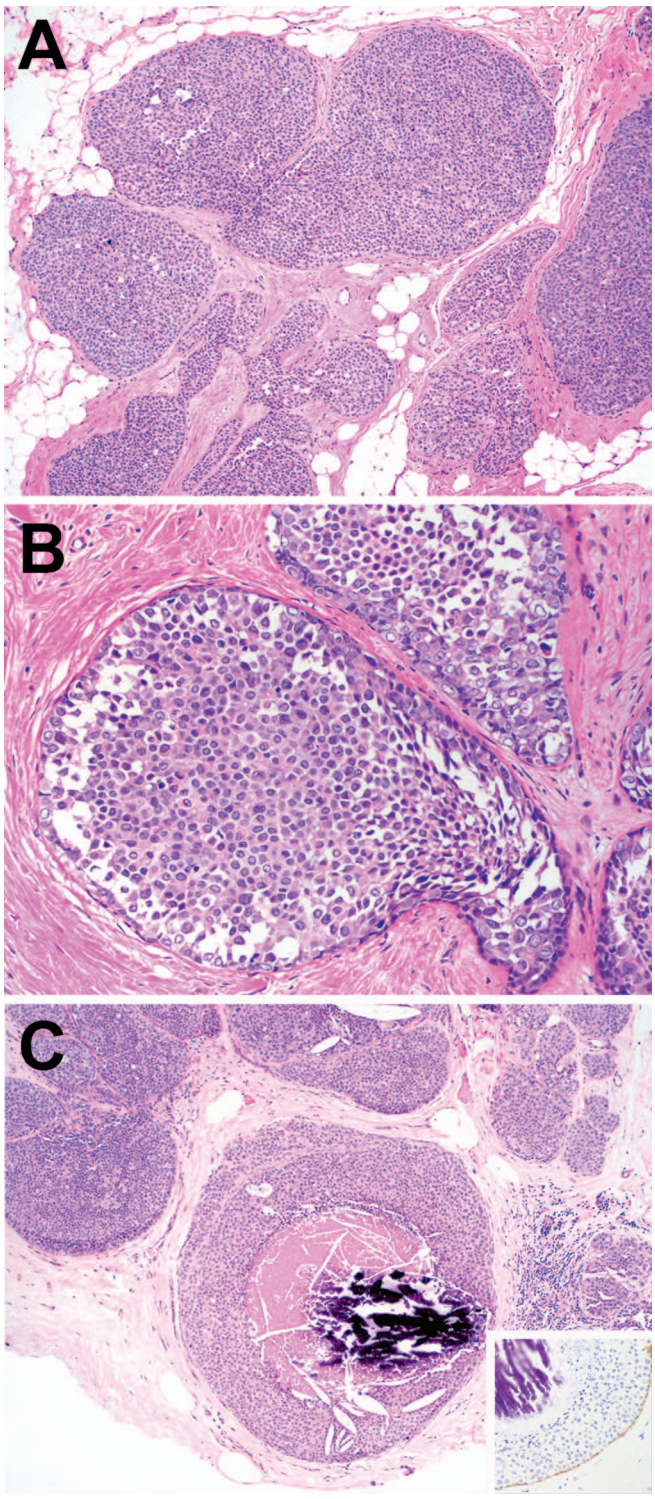

Figure 4. *Lobular carcinoma in situ, florid type. A, Multiple confluent ducts are filled and distended by a monotonous population of cells. B, Higher magnification of a duct filled with loosely cohesive, small- to medium-sized cells with intermediate-grade nuclei. The cells were negative for E-cadherin (not shown). C, Florid lobular carcinoma in situ with luminal necrosis and calcifications. Inset, An E-cadherin immunostain is negative, supporting lobular differentiation (hematoxylin-eosin, original magnifications ×100 [A and C] and ×200 [B]; original magnification ×200 [inset]).*

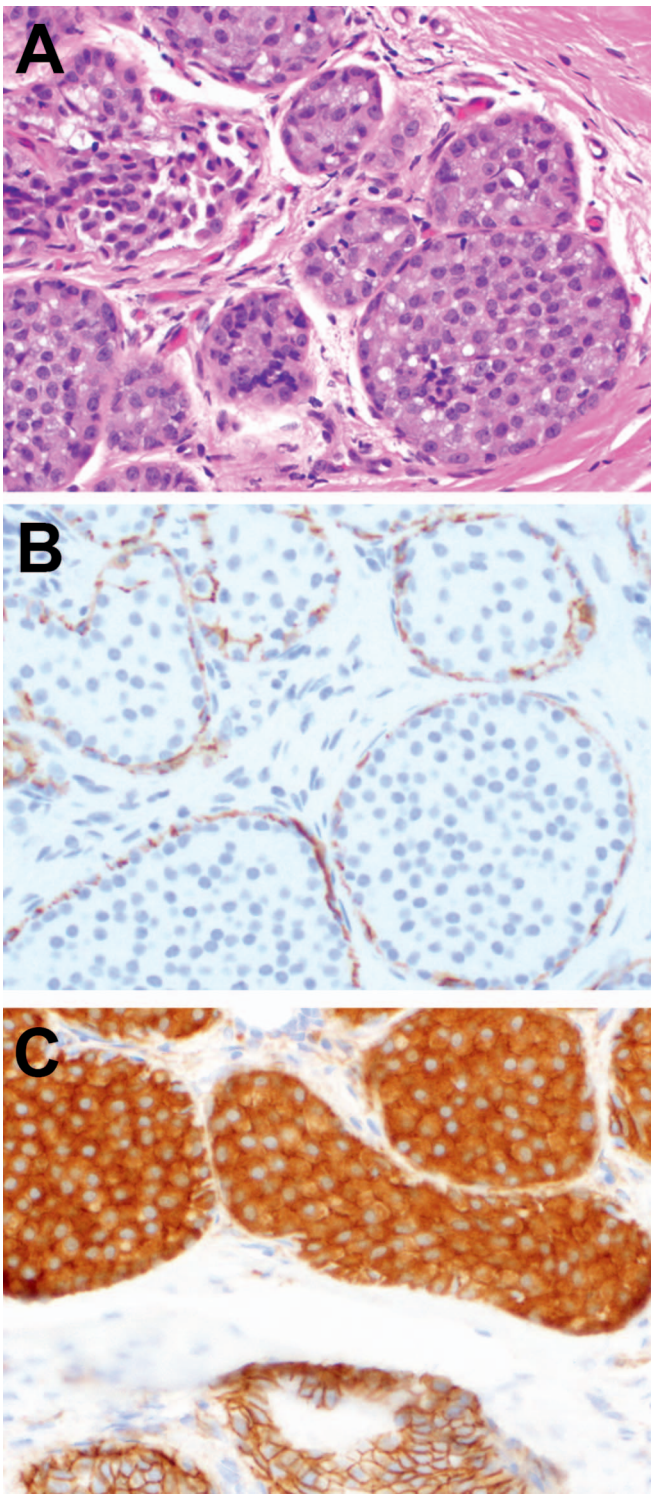

Figure 5. *Lobular carcinoma in situ—E-cadherin and p120 staining. A, Lobular carcinoma in situ (LCIS), classic type. B, An E-cadherin immunostain is completely negative in LCIS, whereas myoepithelial cells show reactivity with E-cadherin at the periphery of the lobule. C, p120 shows cytoplasmic expression in LCIS cells (top of image). For comparison, a benign gland (bottom of image) shows membranous staining with p120 (hematoxylin-eosin, original magnification ×400 [A]; original magnifications ×400 [B] and ×400 [C]).*

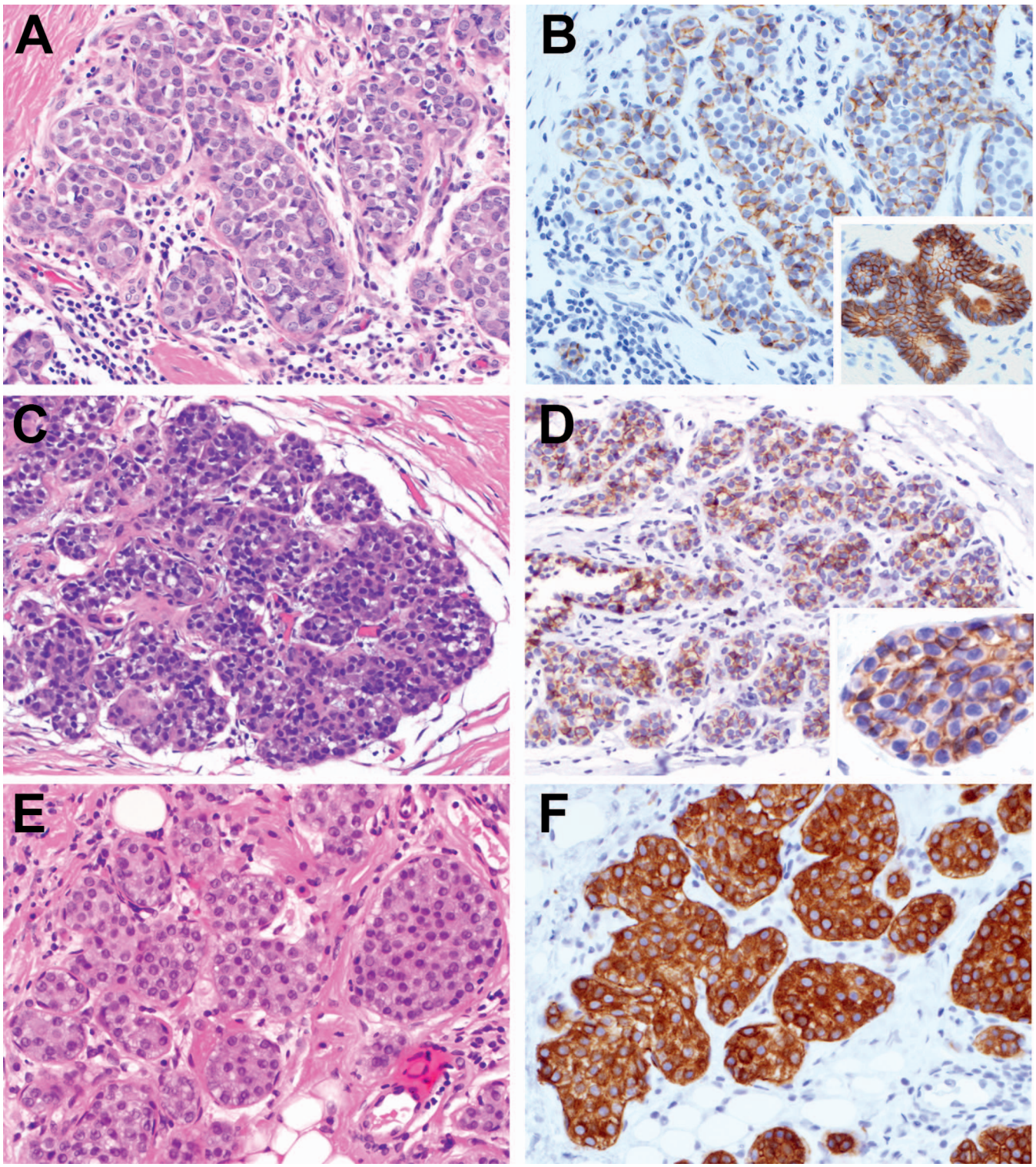

Figure 6. *Lobular carcinoma in situ—aberrant E-cadherin staining. A, Classic lobular carcinoma in situ (LCIS) in a lobule. B, E-cadherin shows weak, fragmented membranous staining in a proportion of the LCIS cell, compared with diffuse, strong, membranous staining seen in an adjacent benign duct (inset). C and D, Case of classic LCIS showing diffuse, aberrant, membranous staining. Higher power field of E-cadherin staining is seen in the inset of D. E and F, Classic LCIS with aberrant cytoplasmic staining (hematoxylin-eosin, original magnification ×400 [A, C, and E]; original magnifications ×400 [B, B inset, D, and F] and ×600 [D inset]).*

lobular carcinoma consistently demonstrate loss of 16q (100%) and gain of 1q (88%) with less-frequent, consistent alterations, including losses of 11q, 8p, and 1p.[41] Furthermore, in these studies, most LCIS and synchronous invasive lobular carcinomas were more genetically similar to each other than they were to other carcinomas,[41] or they shared a similar loss-of-heterozygosity phenotype.[28] More recent molecular data, using next-generation sequencing technol-

ogy, have further supported the clonal relatedness between LCIS and invasive lobular carcinoma. These data show shared somatic mutations between LCIS and invasive lobular carcinoma, most frequently of *CDH1*, *PIK3CA*, and *CBFB* genes.[42,43]

One recent study based on microarray gene-expression profile data suggested that classic LCIS was likely heterogeneous at the molecular level.[44] Unsupervised clustering analysis separated classic LCIS into 2 groups based on the expression of genes involved in proliferation and other cancer canonical pathways, including TGF-β, p53, actin cytoskeleton, apoptosis, and Wnt signaling.[44] In the same study, supervised analysis of matched patient sets from healthy breast tissue, LCIS, and invasive lobular carcinoma identified 169 candidate precursor genes that may have a role in progression from LCIS to invasive lobular carcinoma. Additional studies are needed to determine which LCIS lesions will progress to invasive carcinoma and which molecular alterations are associated with that development.

Pleomorphic and Florid LCIS

Because pleomorphic LCIS and florid LCIS are different from classic LCIS in clinical presentation, morphology, biomarker expression, and clinical outcomes, differences in genetic alterations between them would also be expected. Comparative genomic hybridization data, comparing pleomorphic LCIS to classic LCIS, show that although there are some shared alterations, including loss of 16q, gain of 1q, and loss of 17p, pleomorphic LCIS showed additional recurrent alterations not observed in classic LCIS. These include amplification of the *HER2* gene (17q11.2–17q12), gain of 16p, and loss of 8p.[8] In addition, amplification of *CCND1* gene (11q13.3), which has been seen in classic and invasive, pleomorphic lobular carcinomas,[41,45] was more prevalent in pleomorphic LCIS than it was in classic LCIS in one study.[8] Furthermore, many cancer-related genes are mapped to the chromosomes altered in pleomorphic LCIS [*p53*, 17p13.1; *MEN1*, 11q13; *ATM* , 11q22.3; *CCNF*, 16p13.3; *RB*, 13q14.1–14.2; and *CCND1*, 11q13.3].

Apocrine-type pleomorphic LCIS is more likely to be *HER2* amplified and demonstrates increased genetic instability compared with nonapocrine pleomorphic LCIS.[8] Interestingly, differences in recurrent alterations were also observed between apocrine pleomorphic LCIS and nonapocrine pleomorphic LCIS, which included a gain of 6p (15%) and losses of 3q (22%), 11q (32%), 13q (25%), and 17p (45%).[8] Overall, pleomorphic LCIS, particularly the apocrine subtype, demonstrates greater genetic complexity than does classic LCIS, which may contribute to the more-aggressive clinical behavior of these lesions.[7,8]

Shin et al[7] used array comparative genomic hybridization to compare genomic alterations between florid LCIS, pleomorphic LCIS, and classic LCIS. Losses of 16q and gains of 1q were seen in most lesions, regardless of the morphologic variant. Other recurrent alterations observed in florid LCIS included amplification of 11q13.3 (*CCDN1* gene), loss of 8p, loss of 17p, and loss of 11q. *HER2* was amplified in 10% of florid LCIS cases. Interestingly, florid LCIS showed a more-complex genome, with more aberrations than did pleomorphic LCIS and classic LCIS, and it had greater similarity with the level of genetic complexity in apocrine pleomorphic LCIS than it had with nonapocrine pleomorphic LCIS. Unsupervised hierarchal cluster analysis based on genome copy number profiles segregated the cases of LCIS into 3 groups. Each morphologic variant did not form a separate cluster, and the cluster showing the most genomic alterations, which included amplification of 17q11.2–17q.12 (*HER2*) and 11q (*CNND1*), was enriched in florid LCIS and apocrine type pleomorphic LCIS.[7]

LCIS AS RISK FACTOR FOR THE DEVELOPMENT OF INVASIVE BREAST CARCINOMA

Lobular carcinoma in situ and ALH have been well-established as risk factors for the development of invasive breast carcinoma. Classic LCIS is associated with an 8- to 11-fold increase in the relative risk of developing invasive breast cancer, whereas ALH is associated with a 4- to 5-fold increase in risk.[12,46,47]

In a single-institution study of more than 1000 patients undergoing surveillance for LCIS, the annual rate of developing cancer (invasive carcinoma or DCIS) was 2%, and the cumulative cancer incidence at 15 years was 26%.[3] Cancers occurred in the ipsilateral breast in 63% of cases, in the contralateral breast in 25% of cases, and in bilateral breasts in 12% of cases. For patients who took chemoprevention, the cumulative cancer rate at 10 years was 7% versus 21% for patients who did not receive chemoprevention, and the use of chemoprevention was the only factor associated with decreased incidence of cancer on multivariate analysis.[3] Those results were similar to that found in other studies that showed an overall risk of developing cancer after a diagnosis of LCIS increased by about 1% each year, with an approximate 10% risk at 10 years and 20% risk after 20 years.[48–50] Although morphologic variants of LCIS have more-aggressive histopathologic features (high-grade nuclei, necrosis) and are more often associated with invasive carcinoma at the time of diagnosis, there are insufficient data to show higher rates for the subsequent development of invasive carcinoma in these patients compared with those who have classic LCIS.

LCIS AS A NONOBLIGATE PRECURSOR TO INVASIVE BREAST CARCINOMA

Historically, the role of LCIS as a precursor to invasive breast carcinoma was debatable. Studies showing that patients with LCIS developed ipsilateral and contralateral invasive breast carcinomas in equal frequency[2,46,47,51] and that many of those carcinomas were of ductal differentiation[2,46,47,51,52] lead authors to suggest that LCIS was not a precursor but merely a risk factor for developing invasive carcinoma.[2,46,47,51,52] Additional studies have shown that patients with LCIS develop ipsilateral invasive breast carcinoma 2 to 3 times more often than do patients with contralateral invasive breast carcinomas,[3,11,53–56] and patients with LCIS are 5 times more likely to develop invasive lobular carcinoma than are patients with DCIS.[57] These data, further strengthened by the molecular data discussed above, support LCIS being both a nonobligate precursor and a marker for increased risk of developing invasive carcinoma.

PATHOLOGIC UPGRADE AND SURGICAL MANAGEMENT AFTER DIAGNOSIS OF LCIS IN NEEDLE CORE BIOPSY

Numerous studies have been performed to determine the frequency of finding invasive carcinoma or DCIS, that is, the pathologic upgrade rate, in surgical specimens after a diagnosis of LCIS in a core biopsy sample, as well as to identify certain factors that correlate with pathologic

upgrade. Most of these studies were retrospective analyses of relatively few patients. Other limitations in many of these studies included the lack of detailed correlation with imaging and variable rates of surgical excision, which resulted in a wide range of reported upgrade rates, which varied from 0% to more than 50%.[58–60]

Multiple studies have shown lower upgrade rates when pathologic-radiologic correlation is achieved.[11,61–64] In a single-institution study in which patients diagnosed with lobular neoplasia in a core biopsy sample prospectively underwent excision of the targeted area, Murray et al[63] found a 3% upgrade rate (2 of 72 cases) with imaging-histology concordance versus 38% (3 of 8) with imaging-histology discordant cases. The 2 upgraded lesions found on excision in the concordant cases were a 0.2-cm focus of low-grade DCIS and a 0.2-cm, well-differentiated invasive ductal carcinoma, each of which may have been incidental findings in the excision specimens. Recent results from the first prospective multi-institutional trial (Translational Breast Cancer Research Consortium 020 trial[65]) showed an upgrade rate of 1% (1 of 74 with DCIS) following a diagnosis of lobular neoplasia in a core biopsy. This study included 74 patients with lobular neoplasia diagnosed in a core biopsy for which imaging was concordant and pathology was reviewed centrally. Another recent, large, multicenter study[66] showed an upgrade rate of 3.5% (8 of 228) for cases of lobular neoplasia diagnosed in core biopsy. Upgrades on excision included invasive carcinoma in 3 cases and DCIS in 5 cases. Of note, 1 upgraded case included in that analysis was from a core biopsy in which the targeted calcifications were not adequately sampled in the biopsy. In 2 additional cases upgraded to DCIS, calcifications spanning 3 cm and 6 cm were the target; however, they were deemed concordant.

Pathologic upgrade rates reported for florid and pleomorphic LCIS also vary greatly, with most studies reporting upgrade rates in the range of 25% to 50%.[6,19,41,61,66–69] As expected, many studies include few patients, including some with fewer than 5 patients.[52,64,70,71] A meta-analysis by Pieri et al[68] that included 42 patients with pleomorphic LCIS on core biopsy from 5 studies showed an upgrade rate of 36% (15 of 42; 14 invasive carcinomas, 1 DCIS). Most upgraded lesions in these studies were invasive lobular carcinomas, which were seen in close proximity to the florid or pleomorphic LCIS. The high rates of pathologic upgrade are not surprising because approximately 50% of cases of florid and pleomorphic LCIS cases have been shown to have coexisting invasive lobular carcinoma.[19,20,68,72]

The National Comprehensive Cancer Network[73] (NCCN, Fort Washington, Pennsylvania) states it is reasonable to perform surgical excision of LCIS found in a core biopsy to exclude associated invasive carcinoma or DCIS, but it also adds that classic LCIS involving fewer than 4 terminal duct lobular units in a core biopsy sample for calcifications may be managed by imaging follow-up. This latter criterion is based on data from one retrospective study[74] that has not been reproduced. Data from prospective studies with detailed imaging-pathology concordance indicate that, in the setting of a routine screening, patients diagnosed with lobular neoplasia in a core biopsy can be spared a surgical excision and be followed by imaging. Further, most upgraded lesions seen in these studies are small, low-grade, invasive carcinomas or small foci of DCIS that are not high grade, which themselves may have no effect on survival if left untreated. For florid and/or pleomorphic LCIS diagnosed in a core biopsy, excisional biopsy is necessary, given the frequent association of these variants with invasive carcinoma.

MANAGEMENT OF LCIS

Historically, LCIS was treated aggressively and surgically, either with ipsilateral or bilateral mastectomy.[1,47,75] Numerous studies demonstrating the natural history of LCIS as a risk factor and a nonobligate precursor led to support for long-term follow-up, with or without chemoprevention, in lieu of aggressive surgery.[2] Current NCCN recommendations for surveillance of patients diagnosed with LCIS include interval history and physical exam every 6 to 12 months, with annual mammograms.[73]

Surgical Margins

Obtaining negative surgical margins in excision specimens for classic LCIS is not necessary or recommended. The significance of florid LCIS and pleomorphic LCIS at, or close to, a surgical margin is not as clear, and the benefits of reexcision of close margins and of adjuvant radiation for local control are unknown. Downs-Kelly et al[76] studied a series of 26 patients with pleomorphic LCIS alone or with concurrent, invasive carcinoma diagnosed in excisional biopsies, including a proportion who received adjuvant radiation and/or chemoprevention. One patient (3.8%) developed a local recurrence of pleomorphic LCIS at the lumpectomy site. Pleomorphic LCIS was present at the inked surgical margin in the patient's primary excision, and the patient received chemoprevention after surgery. All other patients were free from disease at a mean of 46 months, including 5 additional patients with pleomorphic LCIS at the inked margin and 11 patients with pleomorphic LCIS within 2 mm of the inked margin in their excisional specimens. In a study by Flanagan et al,[6] none of 21 patients with pleomorphic LCIS in excision specimens (local excision or mastectomy) had recurrences at a mean of 4.1 years, including 7 patients with pleomorphic LCIS present at, or less than, 1 mm from the surgical margin at definitive surgery. Khoury et al[5] reported local recurrences in 6 of 31 patients (19.4%) with pleomorphic LCIS treated with surgery, with or without radiation and chemoprevention for a median of 55.6 months. Recurrences included 4 invasive carcinomas (3 lobular) and 2 cases of pleomorphic LCIS. All 6 patients with recurrences underwent local excision without radiation, and 2 had positive margins at surgery. Based on the lack of sufficient outcome data for pleomorphic LCIS and florid LCIS, the NCCN currently does not make specific recommendations and leaves the decision as to whether to pursue negative margins up to the clinician.[73] In a survey of more than 300 breast surgeons, 53% indicated they would not perform a reexcision for pleomorphic LCIS at the margin, whereas 24% reported they always excise, and 23% said they sometimes excise.[77] This reflects the lack of consensus regarding managing surgical margins for pleomorphic LCIS. There are insufficient data to support the routine use of adjuvant radiation for LCIS of any type.

Chemoprevention

For patients diagnosed with LCIS, the risk of developing invasive breast carcinoma is decreased by approximately 50% with the use of adjuvant endocrine therapy.[3,78,79] The NCCN provides a category 1 recommendation regarding the use of tamoxifen as an option to reduce breast cancer risk in

premenopausal and postmenopausal patients with LCIS. In addition, the NCCN offers aromatase inhibitors or anastrozole as options in postmenopausal patients with LCIS who desire nonsurgical risk reduction.[80]

CONCLUSIONS

Lobular carcinoma in situ can be segregated into 3 morphologically distinct variants (classic, pleomorphic, and florid), which share some morphologic, immunophenotypic, and molecular characteristics, but vary in clinical presentation, biomarker expression, rates of upgrade upon excision, and associated breast malignancies. The role of LCIS as a risk factor and a nonobligate precursor to invasive carcinoma has been well established. Although chemoprevention has been shown to be of great utility in patients with LCIS, the critical piece of information that we now lack is the ability to accurately identify which cases of LCIS will progress. Given the increasing incidence of this disease, further studies evaluating genetic alterations may provide prognostic and predictive information.

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