Case Report

Pleomorphic Lobular Carcinoma in Situ: Treatment Options for a New Pathologic Entity

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Clinical Practice Points

- Lobular carcinoma in situ (LCIS) is a dyshesive proliferation of cells that fills the mammary lobules. The cells of classic LCIS are low-grade with small nuclei, dense chromatin, no nucleoli, and a small amount of cytoplasm. Classic LCIS has been found to increase the risk of women developing invasive breast cancer, but LCIS requires no formal treatment except for close observation.
- This pathology also identifies a population of women who may be candidates for chemoprevention. The use of E-cadherin immunostains with these lesions has identified variants of LCIS characterized by acinar expansion, necrosis with calcifications, and nuclear pleomorphism.
- Pleomorphic LCIS is one such variant. These rare lesions are detected mammographically with microcalcifications, and genetic analysis shows that they are from the lobular lineage with more extensive genetic changes than classic LCIS.
- The surgical and adjuvant radiation therapy treatment also is quite different when compared to classic LCIS. This article reviews a case history in which these treatment differences become important and suggests some guidelines for dealing with pleomorphic LCIS.

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Introduction

Not only is breast carcinoma the second leading cause of cancer mortality, it is also the most common form of cancer in women. Accumulation of genetic alterations within a single clone of cells eventually leads to uncontrolled growth. Models of progression of breast carcinoma suggest that the epithelial cell gives rise to carcinoma in situ after first going through phases of hyperplasia and atypical hyperplasia.[1]

In 1941, lobular carcinoma in situ (LCIS) was first described as a preinvasive lesion with inevitable progression to invasive lobular carcinoma (ILC). Total mastectomy was the standard recommendation. Haagensen, while working at Columbia University, was the first to describe LCIS progressing to ILC.[1] In 1978, Rosen stated that total mastectomy with low axillary dissection was the most logical operative procedure for LCIS and that a contralateral biopsy should be performed to rule out bilaterality.[2] By the 1980s, LCIS was accepted as a marker for increased risk rather than a precancerous lesion, and observation became the standard treatment.[3] More recently, LCIS has reverted to being considered a precursor lesion because genetic changes between invasion and in-situ lobular neoplasias are similar. However, the progression to invasive cancer is much slower than its ductal counterparts. For this reason, the standard practice is to not report LCIS in relation to margins on biopsy specimens, no additional surgical excision is performed to obtain clear margins, and radiotherapy is not administered.[4]

The widespread use of immunostains for E-cadherin in the evaluation of in situ lesions with ambiguous morphology has unveiled the existence of noninvasive carcinomas misdiagnosed for years as ductal carcinoma in situ (DCIS). In situ lesions with unquestioned lobular differentiation are now recognized.[5,6] Surgical and radiation therapy treatment for pleomorphic LCIS (P-LCIS) is not well-defined and guidelines are not developed. This report describes a case in which P-LCIS was diagnosed and the subsequent treatment led to controversy and a medical-legal issue.

Case Report

PC is a 47-year-old African-American woman whose past medical history includes hypertension and asthma. The patient had a surgical history of carpal tunnel surgery, cholecystectomy, and hysterectomy, and had no family history of breast cancer. On February 18, 2010, the patient underwent a bilateral diagnostic mammogram that

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showed a cluster of microcalcifications in the left breast in the upper, outer quadrant at 2:00. A stereotactic left-breast biopsy was performed and pathology showed multifocal LCIS with pleomorphic features. No invasion was observed and the tumor was estrogen-receptor (ER)–positive and progesterone-receptor–positive. Moderately pleomorphic, somewhat discohesive cells expanding the lobules were observed with associated microcalcifications. E- cadherin staining was equivocal.

The patient was referred to a surgeon who performed a wire-directed left breast excisional biopsy on March 8, 2010. Pathology showed multifocal LCIS with clear margins. Pleomorphism was not found on the lumpectomy specimen. The patient was subsequently referred to radiation therapy and she received 5876 rads in 33 fractions over 47 days. The patient developed a hematoma during the radiation therapy and had increased pigmentation of her breast. She also experienced dry desquamation and moderate breast edema. On September 24, 2010, the patient was seen in the emergency room with a temperature and erythema of the left breast. A needle aspiration and culture of the lumpectomy site showed gram + cocci in clusters and *Peptostreptococcus* in culture. She was treated with intravenous antibiotics and was taken to the operating room for an incision and drainage (I and D) of the left breast abscess. Six months later the patient continued on oral antibiotics. The lumpectomy and I and D site reconstruction have been delayed until her inflammatory issues are resolved.

A medical-legal issue has been raised concerning the need for lumpectomy to obtain clear margins and the need for adjuvant radiation therapy in women diagnosed with P-LCIS on core biopsy.

Discussion

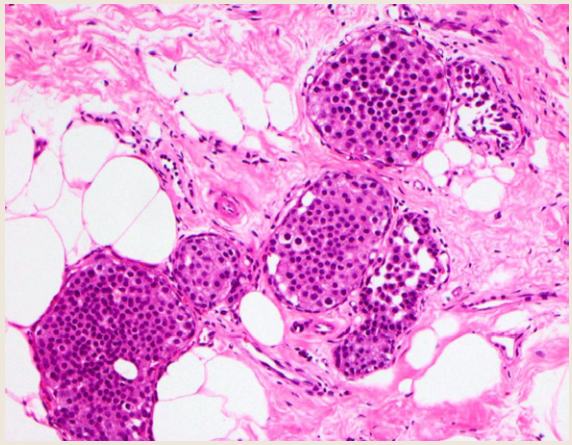
Pathology, Diagnosis, and Treatment of LCIS

In women diagnosed with LCIS, the cells of the lobules proliferate, overgrow, and may become atypical. The cells of classic LCIS are uniform, homogenous, and bland with no mitosis or necrosis. Most cases consist of diploid DNA, low nuclear grade, high ER activity, low proliferation index, and low oncogene expression, all of which indicate benign behavior. LCIS expresses two types of cytomorphology: Haagensen's type A and type B cells. Type A cells display small nuclei with dense and indistinct chromatin as well as no nucleoli (Figure 1). Type B cells are larger cells with larger nuclei, open chromatin with a pale color, and more abundant nucleoli.[7] These cells often co-exist in the same breast or even in the same lobules.

LCIS is found to be homogeneous throughout all breast tissue and should be assumed to be present in both breasts when found on biopsy. LCIS is said to be multifocal in less than 50% of patients and bilateral in 30%. This pathologic entity does not produce calcifications in the breast because of its slow growth.[8] LCIS is present in 1% of all breast biopsy specimens, 7% of all breast cancers, and 20% to 35% of all in situ breast cancers.[9]

Women who are diagnosed with LCIS have a greater chance of developing invasive breast cancer compared to women who do not have LCIS, and the risk is bilateral to the original lesion.[3] More than 50% of the invasive cancers occur 15 years after first being diagnosed with LCIS and 38% occur 20 years after diagnosis.[8] Women who are diagnosed with LCIS develop breast cancer 7.2 times the rate in the general population. Long-term studies have shown that only 15% to

Figure 1 Photomicrograph of Classic LCIS With Cells Filling the Terminal Lobule That are Small, Rounded, and Bland. No Microcalifications are Present



20% of women with LCIS ever develop invasive breast cancer, 50% to 65% of these cases are ductal carcinoma, and 70% of these are in the ipsilateral breast.[10] Recently, evidence has suggested that another subtype of LCIS, the florid subtype, is a true precursor for ILC.[11]

It remains controversial whether LCIS found in a core biopsy must be excised. In the past, patients with LCIS found on core biopsy were treated with a surgical excision, but only if the patient showed no signs of a mammographic abnormality on which the biopsy was based, such as architectural distortion or a mass lesion. Recent studies suggest that further excision may not be necessary for patients after a core biopsy if no more than 3 foci are present.[3] In a recent analysis of LCIS treated with local excision with microscopically negative margins, the ipsilateral breast cancer recurrence was still 14.4% at 12 years.[12] These outcomes are comparable to studies in which patients received local excision without attention to margins.[13] When LCIS is the only pathology found on core biopsy associated with a mammographically detected lesion, sampling error is a concern. LCIS may not accurately represent this radiologic finding and an excisional biopsy is indicated. However, for the most part, re-excision of the original biopsy to obtain clear margins, ipsilateral total mastectomy, sentinel lymph node biopsy, axillary dissection, and adjuvant radiation therapy are not recommended in current guidelines for patients who have classic LCIS.[9] Tamoxifen, selective ER modulators, or aromatase inhibitors may be indicated for chemoprevention efforts. Chemoprevention with tamoxifen taken for 5 years resulted in an initial 86% reduction in the incidence of developing invasive breast cancer compared with placebo in women judged to be high-risk, such as those with LCIS on previous biopsy.[14] Bilateral prophylactic mastectomy for LCIS is a maximal risk-reduction strategy for the future development of invasive breast cancer; however, literature comparisons to chemoprevention are not available, which makes this a personal decision for the patient.

Pathology, Diagnosis, and Treatment of P-LCIS

In all likelihood, P-LCIS was misdiagnosed as DCIS in the past. Pathologists have now learned to recognize in situ carcinomas show-

Figure 2 Photomicrograph of Pleomorphic LCIS With an Expansive Growth of Tumor Cells With Necrosis and Calcifications

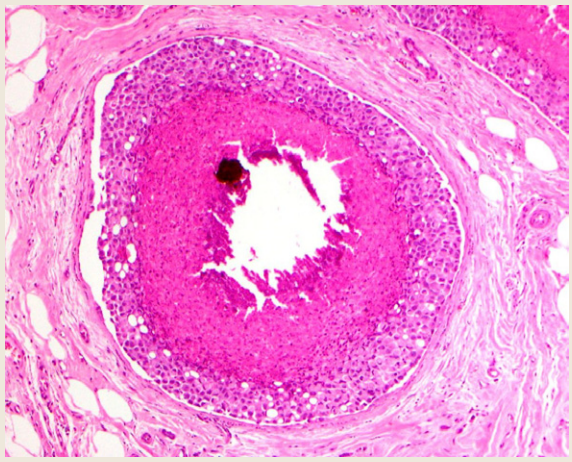
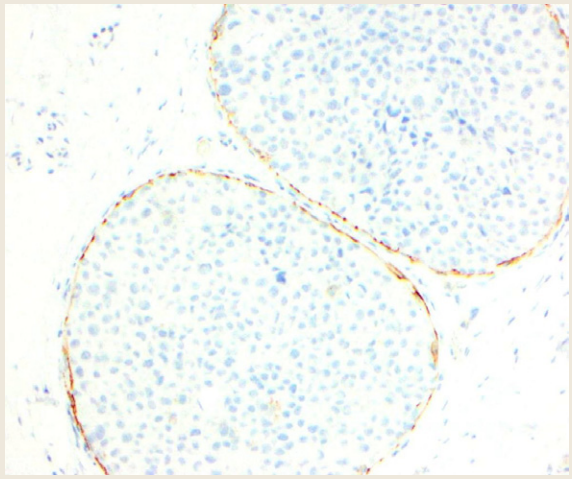


Figure 3 Higher-Power Magnification of P-LCIS Showing Marked Variation in Cell and Nuclear Size

ing unquestionable lobular differentiation, but displaying morphological features typically observed with DCIS. Florid LCIS or LCIS with comedo necrosis is one such lesion characterized by a massive acinar distention.[5] Initially described in 1996, P-LCIS is another such variant consisting of large plasmacytoid and dyshesive cells with abundant cytoplasm.[15] The nuclei of P-LCIS are large and show prominent nucleoli. Massive acinar distention and central necrosis are usually present (Figures 2, 3). P-LCIS can grow in a more deceptive pattern without massive acinar distention. P-LCIS accounts for less than 1% of all epithelial malignancies of the breast, and the natural history of the disease is not well-defined. It can be detected mammographically with calcifications or a mass and is rarely found alone, co-existing in 40% to 67% of patients with an invasive cancer.

Pleomorphic LCIS is a recently described pathologic entity, the diagnosis of which was made possible by the development of new immunostains for E-cadherin and p120.[16] Loss of membrane staining for E-cadherin (cell adhesion molecule; Figure 4) occurs early in the progression of lobular neoplasia and accounts for the cell dyshesion characteristically observed in atypical lobular hyperplasia and LCIS.[17] This genetic and immunophenotypic alteration correlates with lobular differentiation. This stain is commonly used in the evaluation of solid noninvasive neoplasia with indeterminate morphology and is useful in the evaluation of margin status because DCIS and LCIS are treated differently in this regard. A lack of membranous E-cadherin results in mobilization of p120, its intracellular ligand. The redistribution of p120 protein occurs from its usual sub-membranous location to diffuse scattering in the cytoplasm. This shift in the pattern of p120 reactivity on immunostains can also be used to show lobular differentiation.[17]

Figure 4 E-Cadherin Immunostaining of LCIS with tumor cells being negative. Central tumor cells would show positive immunostaining if the in situ lesion was DCIS



Genetic studies suggest that P-LCIS is a more advanced form of LCIS.[6] P-LCIS shares a high proliferation rate and HER2/neu overexpression, similar to more classic LCIS. However, P-LCIS has a higher degree of genomic instability for both amplifications and deletions, lower ER expression, and higher HER2/neu expression than LCIS.

P-LCIS is said to have a worse prognosis than classic LCIS and should be treated more like high-grade DCIS than LCIS; however, the current treatment recommendations are not well defined. If P-LCIS and high-grade DCIS are similar, then complete excision of the lesion with the reporting of margins is a reasonable recommendation. This would be a low-morbidity type of procedure with minimal side effects, although most likely would require use of general anesthesia. After core biopsy, 10% to 15% of DCIS lesions are upgraded to invasive ductal carcinomas when the entire lesion is excised, and studies with P-LCIS on core biopsy show that upwards of 25% of women are upstaged with total excision, making total excision to obtain clear margins a reasonable recommendation.[18]

The literature would also suggest that nodal staging with the lymphatic mapping technique is not as accurate if performed after an excisional biopsy or lumpectomy and is ideally performed after a core biopsy. For this reason, lumpectomy and sentinel lymph node biopsy

have been performed by many clinicians for high-grade DCIS lesions that were diagnosed on core biopsy in anticipation of the 15% upgrade to invasive cancers and the subsequent need for accurate nodal staging in this population. However, because the natural history of P-LCIS is not well defined, making the recommendation for nodal staging after core biopsy in this population of women is a stretch. The recommendation for adjuvant radiation therapy after lumpectomy and the attainment of clear margins is probably also not indicated until the natural history of the entity is better defined. Adjuvant radiation therapy consists of 28 treatments over a 6-week period and is associated with costs and time inconvenience for the patient and a defined morbidity. As shown in the case presented, patients who receive adjuvant radiation therapy have an increased incidence of wound problems (hematoma, infection, poor healing) as well as a delay in adjuvant hormonal or chemotherapy and breast reconstruction. Hormonal chemoprevention should be a strong recommendation because this therapy is well-tolerated and included in the guidelines for classic LCIS.

The role of adjuvant radiation therapy, with its resultant time and cost commitment and added morbidity, must be defined.[18] Because of the rarity of the diagnosis of P-LCIS, prospective studies in the literature to define the natural history and treatment guidelines are limited. These cases should be discussed in a multidisciplinary cancer conference and a consensus for treatment should be reached by the group. With this in mind, a program of total excision of P-LCIS with the reporting of clear margins and hormonal chemoprevention is a reasonable approach for these patients.

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