SEMINARS IN BREAST DISEASE

The Changing Paradigm of Lobular Neoplasia of the Breast

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Lobular neoplasia is a spectrum of proliferative lesions that includes atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). When it was first described, LCIS was considered to be a precursor of invasive lobular carcinoma, and was therefore treated with unilateral mastectomy. Gradually, both ALH and LCIS came to be thought of as markers for the development of malignancy in either breast rather than premalignant precursors, and mastectomy for LCIS was abandoned. The most recent data suggest that LCIS may, in selected circumstances, have a behavior more similar to low-grade ductal carcinoma in situ (DCIS). This has led to a reevaluation of the role of surgical treatment for selected atypical cases of LCIS. Definitive data are lacking in this area, particularly with the most histologically aggressive form of lobular neoplasia, pleomorphic LCIS (pLCIS). ALH and LCIS are typically diagnosed incidentally during biopsy for another indication. When seen on core needle sampling, diagnostic surgical biopsy is recommended, because 7% to 10% of patients will be found to have DCIS or invasive cancer at the site of the needle sampling. Because lobular neoplasia is associated with heightened breast cancer risk, careful surveillance is indicated after a complete diagnostic workup. Mastectomy is not indicated for treatment, although bilateral prophylactic mastectomy could be considered in unusual circumstances where other strong risk factors prevail. The lifetime risk of an invasive cancer developing appears to be between 10% and 25% following a diagnosis of lobular neoplasia, which can be decreased by the use of a chemopreventive endocrine agent, such as Tamoxifen.
Semin Breast Dis 8:112-118

KEYWORDS lobular neoplasia, atypical lobular hyperplasia, lobular carcinoma in situ

Breast cancer remains the most common cancer among women in the United States, with estimates that over 200,000 individuals were diagnosed with the disease during 2005.[1] The normal breast is composed of a network of branching ductal segments that intertwine as they extend outward from the nipple into a supportive, vascularized fibrofatty stroma, ending distally as functionally active terminal duct lobular units (TDLUs).[2] Most breast carcinomas begin in the epithelial lining of the TDLU, with nearly 85% arising from the ductal epithelium, and the remaining 15% arising within the lobules. In the epithelium of both ducts and lobules, a spectrum of histological changes can be observed, ranging from hyperplastic changes without atypia, atypical hyperplasia, in situ cancers, and finally invasive carcinoma. This spectrum of proliferative alterations appears to represent a process of malignant degeneration within the ductal and lobular epithelia.[2] However, the frequency and rate at which atypical and in situ lesions progress to invasive cancer is difficult to assess and likely varies with different histological patterns of disease.

Lobular neoplasia is the nomenclature used to describe the spectrum of proliferative changes seen within the lobule units of the breast. Lobular neoplastic lesions include both atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS), both of which are associated with an increased risk of developing a subsequent invasive breast cancer.[3,4] Pathologically, lobular neoplasia is diagnosed when the acini of the terminal duct lobular units are filled and distended by small, uniform, loosely cohesive cells.[2,4] Although somewhat arbitrary, the distinction between ALH and LCIS has historically been based on the degree of histological change observed by the pathologist. Lobular neoplastic lesions have striking similarities to invasive lobular cancers at the cellular level, with most staining positive for estrogen receptors, hav-

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 1092-4450/05/$-see front matter
doi:10.1053/j.sembd.2006.06.008

ing low proliferative index rates, and being ErbB2 (HER-2/neu)-negative.[2]

Although lobular neoplasia has been a recognized clinical entity since the 1940s, its biological behavior remains poorly understood, creating considerable controversy as to its clinical significance and malignant potential. Traditionally, clinicians and pathologists have been reluctant to adopt the global terminology of lobular neoplasia as proposed in the last quarter of the century, and instead have continued to distinguish between ALH and LCIS. Whether lobular neoplasia represents a direct precursor of invasive lobular carcinoma, or if it simply is a marker for the development of invasive cancer somewhere in the breast, remains an area of active debate. Management dilemmas continue to exist as to whether lobular neoplasia warrants surgical excision when it is seen on core needle sampling for diagnostic purposes or if some subset of lobular neoplasia should be removed with negative surgical margins after open surgical biopsy for therapy. Although treatment strategies have evolved from routine mastectomy to surveillance, some continue to question whether more aggressive intervention should occur.

The purpose of this review is to examine the historical background, histopathologic features, clinical presentation, management, and subsequent risk of invasive cancer development to understand the changing paradigm of lobular neoplasia of the breast.

Historical Background

Lobular neoplasia was first described in 1941 when Foote and Stewart published their classic report of LCIS, which is a noninvasive lesion that appeared to arise from the lobules at the terminal microscopic ducts of the breast.[5] At the time of this initial description, LCIS was believed to represent a premalignant lesion due to the fact that it was generally seen in conjunction with invasive lobular breast cancer as illustrated in Godwin's 1952 case report.[6] Together, these early reports were used to bolster the argument that mastectomy was an appropriate therapeutic procedure following a histological diagnosis of LCIS on breast biopsy, which became the standard dogma for the next 40 years.

In the late 1970s, the dominant belief that biopsy proven LCIS required therapeutic mastectomy was challenged when Haagensen argued that LCIS and ALH were fundamentally benign entities. This assertion was based on data from 211 women with pure LCIS who were treated with excision alone, instead of mastectomy, and then followed. Of the 211 individuals, 10% developed an ipsilateral breast cancer, whereas 9% were subsequently diagnosed with a contralateral invasive tumor.[7] Instead of being a premalignant lesion, Haagensen argued that LCIS represented a risk factor for the development of a subsequent cancer of a ductal or lobular variety, and that this subsequent cancer could develop anywhere and in either breast. As a marker for cancer, and not a direct precursor lesion, mastectomy was felt to be overly aggressive and unnecessary in the setting of LCIS.

To dissuade surgeons from considering LCIS to be a malignant lesion inevitably warranting mastectomy, Haagensen recommended the term lobular neoplasia, thereby eliminating the word "carcinoma" from the name and removing any distinction between ALH and LCIS.[7] Somewhat reluctantly, the belief that observation was adequate when lobular neoplasia was diagnosed led to the abandonment of routine mastectomy following a diagnosis of LCIS by the 1990s. The prior dogma that LCIS should be treated with mastectomy was thus replaced by a new dogma that LCIS should never be treated with surgery, because "it isn't really cancer."

As mastectomy was largely being abandoned as treatment for LCIS, a new, potentially more aggressive variant of the lesion was being described. First reported in the 1990s in association with pleomorphic invasive lobular carcinomas, pleomorphic LCIS is generally distinguished from other varieties of LCIS pathologically. Unlike classic LCIS, the pleomorphic variety is characterized by large, pleomorphic cells which can be accompanied by necrosis and may be difficult to distinguish from ductal carcinoma in situ (DCIS) in the absence of special immunohistochemical staining.[8] Although reports are limited and often confounded by the presence of invasive cancer in addition to the pleomorphic LCIS, four studies have suggested that patients with evidence of pleomorphism have poorer outcomes.[9-12] Unfortunately, results from patients with pure pleomorphic LCIS without a concurrent invasive component are lacking, so outcome data specific to pleomorphic LCIS are unknown. Based on results from pleomorphic invasive lobular cancers, it is hypothesized that pleomorphic LCIS may have a more aggressive biology than does classic LCIS.

The concept that lobular neoplasia represents a single pathologic entity of limited malignant potential has been resisted. This reluctance is largely due to differences in the rates of breast cancer development when comparing ALH and LCIS. Several large professional entities, including the National Surgical Adjuvant Breast and Bowel Program (NSABP) and the American Joint Commission on Cancer (AJCC), continue to classify LCIS as a Stage 0, noninvasive lesion distinct from ALH.[13] Although this topic continues to be debated, the prevailing belief is that lobular neoplasia may be both a risk factor for cancer and, in unusual circumstances, a premalignant lesion. Regardless of these arguments, there is agreement that observation rather than mastectomy remains the preferred course of treatment when lobular neoplasia is diagnosed, in the absence of unusual extenuating circumstances.

Histopathology

Foote and Stewart described classic LCIS as a proliferation of small, uniform, loosely cohesive cells that filled and distended the acinar units within a lobule while preserving the overall lobular architecture.[5,14] ALH and LCIS are distinguished histologically by the extent to which acini are distended with lobular epithelial cells. ALH is diagnosed when fewer than 50% of acini are distended (Fig. 1), and LCIS is diagnosed when more than 50% of acini are distended (Fig. 2).

Both ALH and classic LCIS are largely composed of so-called "Type A" cells, which are small and uniform in size,