Lobular Neoplasia

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KEYWORDS

• Lobular carcinoma in situ • Atypical lobular hyperplasia • Lobular neoplasia
• E-cadherin • Breast cancer risk • Chemoprevention

KEY POINTS

- Lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH) are uncommon pathologic findings, representing part of a spectrum of epithelial proliferations referred to as lobular neoplasia (LN). LN can be considered both a nonobligate precursor of invasive breast cancer and a marker of increased risk.
- Loss of E-cadherin expression, caused by mutations, deletions, and methylation, is one of the defining features of LN; however, aberrant E-cadherin expression can be observed in a few lesions.
- A diagnosis of LCIS confers a long-term cumulative risk of a subsequent breast cancer that averages 1% to 2% per year and remains steady over time, resulting in relative risk of breast cancer that is 8-fold to 10-fold greater than the general population risk. ALH is associated with a relative risk of breast cancer 4-fold to 5-fold greater than the general population.
- A diagnosis of LN made by surgical excision does not require further surgical intervention; there is no indication to document margin status in specimens that contain only LN. The presence of LN in a lumpectomy specimen or at the margin is not a contraindication to breast conservation and does not require re-excision.
- Although routine surgical excision after a core biopsy diagnosis of LN is supported by National Comprehensive Cancer Network guidelines, the management of patients with this diagnosis requires a multidisciplinary approach. Excision is routinely recommended when there is radiologic-pathologic discordance and when the diagnosis indicates a less common histologic variant of LN.
- Patients with LN should be informed of their increased risk of breast cancer and counseled regarding both medical and surgical risk-reducing options.

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INTRODUCTION

According to the current World Health Organization classification of breast lesions,[1] lobular neoplasia (LN) is defined as a term that encompasses the entire spectrum of atypical epithelial lesions that originate in the terminal duct-lobular unit (TDLU) of the breast and is characterized by a population of dyshesive cells, which expand the lobules and acini of the TDLUs, and may involve the terminal ducts in a pattern known as pagetoid spread. These lesions were traditionally described under the terms lobular carcinoma in situ (LCIS) and atypical lobular hyperplasia (ALH), which refer to the degree of involvement of the acinar structures of a given TDLU.

The first description of a lesion with features consistent with those currently used to define LCIS dates to 1919, when Ewing described an "atypical proliferation of acinar cells."[2] However, the main characteristics of LCIS were not thoroughly documented until the seminal study by Foote and Stewart in 1941,[3] in which the term LCIS was coined to refer to a spectrum of "noninfiltrative lesions of a definitely cancerous cytology." Based on the frequent identification of LCIS in association with invasive lobular carcinoma (ILC), and following the analogy of ductal carcinoma in situ (DCIS) and invasive ductal carcinoma (IDC), Foote and Stewart[3] hypothesized that the neoplastic cells of LCIS would still be contained within a basement membrane and that this lesion would constitute a precursor of breast cancer development, leading to the recommendation for mastectomy. Emerging data throughout the 1970s from Haagensen and colleagues[4] and others[5] showed that the risk of breast cancer development after a diagnosis of LCIS was lower than that expected for a direct precursor lesion (approximately 1% per year) and was conferred equally to both breasts, generating controversy regarding the significance of these lesions and leading to disparate recommendations for management, ranging from observation only to bilateral mastectomy.

The term ALH was coined in 1978 to refer to a less-prominent in situ proliferation composed of cells cytologically identical to those of LCIS, which were associated with a significantly lower risk of subsequent breast cancer development (approximately one-half of the risk associated with LCIS).[6] However, because the distinction between LCIS and ALH, which is based on quantitative rather than qualitative differences between the lesions (described later), often proves challenging in diagnostic specimens, Haagensen and colleagues[4] put forward the term LN to refer to the entire spectrum of these in situ lesions, including ALH and LCIS.[4]

In current practice, a diagnosis of LN is perceived as a risk factor for the subsequent development of breast cancer. However, observational data suggesting that the risk of breast cancer development after a diagnosis of LN is higher in the ipsilateral than in the contralateral breast, and compelling molecular data that show that ALH and LCIS are clonal neoplastic proliferations that commonly harbor the same genetic aberrations as those found in adjacent invasive cancers,[7–11] have reinstated the notion that ALH and LCIS are both nonobligate precursors and risk indicators of invasive breast cancer. In this article, the clinicopathologic and molecular characteristics of LN are revisited, and the impact of recent developments on the management of these lesions is discussed.

ANATOMIC PATHOLOGY AND CLASSIFICATION

ALH and Classic LCIS

Before introducing the histologic features of LN, it should be emphasized that the terms ALH, LCIS, and LN do not have histogenetic implications and do not imply that these lesions originate in the breast lobules. The term LCIS was chosen by Foote and Stewart to emphasize the histologic similarities between the cells of LCIS and