Frequency and Clinical Significance of Simultaneous Association of Lobular Neoplasia and Columnar Cell Alterations in Breast Tissue Specimens

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Abstract

Lobular neoplasia (LN) and columnar cell alterations (CCAs) may share similar genetic abnormalities, but there is no appreciable literature that addresses the simultaneous occurrence of these lesions in breast core biopsy (CNB) specimens or resection specimens. Three groups of breast tissue were examined: group 1, 68 CNB specimens targeted for “suspicious” microcalcifications (Breast Imaging Reporting and Data System [BI-RADS] 4) and diagnosed with LN; group 2, 2,516 CNB reports for a 1-year period; and group 3, 400 consecutive breast carcinoma resection specimens analyzed for LN and CCAs within the vicinity of carcinoma. In group 1, LN was associated with CCAs in 54% of cases (37/68). In group 2, LN was found in association with CCA in 1.3% of cases (32/2,516). In group 3, 13.0% of cases of CCAs (52/400) were associated with LN. Our study suggests the association of these two lesions in breast tissue is nonrandom and that they may have a common progenitor pathway of neoplastic development.

Lobular neoplasia (LN) is a category that encompasses a broad spectrum of atypical proliferations arising from the terminal duct lobular unit (TDLU), which includes atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS). The reported frequency of LN in benign core needle biopsy (CNB) specimens ranges from 0.5% to 3.8%.1,2 On routine mammographic screening, a high percentage of LN, up to 40%, is associated with microcalcifications and is regarded as a risk factor for the subsequent development of ductal or lobular carcinoma in either breast. Owing to the high frequency of invasive carcinoma identified in the follow-up of up to 20% of resection specimens,4,5 patients with LN in their CNB specimens are considered candidates for surgical excision.

Columnar cell alterations (CCAs) encompass an entire spectrum of morphologic changes, which also arise from the TDLU. The varying entities include a histologic continuum of columnar epithelial cells lining variably dilated TDLU. The simplest of these entities have been termed columnar cell change and columnar cell hyperplasia in the absence of cytologic atypia. With increasing targeted CNB for mammographic calcifications, there has been an increase in the identification of CCAs as a source of calcifications, up to 42%.2 Although CCAs are largely considered benign, their clinical relevance remains obscure.

CCA with atypia, on the other hand, is a newly recognized pathologic entity with an unclear breast cancer risk, although it has been reported adjacent to in situ and invasive carcinomas, with a greater incidence.2 The atypia in the CCAs ranges from “lesions that show mild cytologic atypia” to those that show “significant cytologic and architectural atypical features” to warrant the diagnosis of atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS).2 The World Health
Organization recently introduced the term flat epithelial atypia (FEA). FEA is a descriptive term that encompasses “TDLU lesions lined by one to several layers of columnar cells with low-grade cytologic atypia.” CCAs with cytologic atypia are being identified increasingly by biopsies performed for mammographic microcalcifications. Few studies have suggested that at least some of these lesions may represent a precursor of DCIS or the earliest morphologic manifestation of DCIS.

CCAs and LN are known to be multifocal processes. Recently, molecular studies evaluating loss of heterozygosity have shown a molecular kinship within the morphologic spectrum of CCAs and low-grade carcinomas. In addition, molecular studies of LN have shown alterations in 17p similar to those observed in CCAs. Although few studies have examined the association of LN and CCAs, it has been our experience in daily practice that we have observed frequent association of LN and CCAs. The goal of this study was to determine the frequency and significance of simultaneous association of LN and CCAs in various breast tissue sources.

Materials and Methods

The archives of the Department of Pathology, Magee Women’s Hospital of UPMC, Pittsburgh, PA, were searched for the 1998-2006 period for the diagnoses of ALH and LCIS. LCIS was histologically defined as complete involvement of lobules by neoplastic cells with more than 50% of a lobule distended by neoplastic, monomorphic cells. ALH was defined as lobules distended by neoplastic cells, falling short of the criteria for LCIS. In our study, we adhered to the use of the term LN to encompass ALH, LCIS, or both for the purpose of convenience.

CCAs were histologically defined as columnar cells with apical snouts and cigar-shaped nuclei with or without hyperplasia. CCAs included the entire morphologic spectrum of lesions involving the TDLU—columnar cell change and columnar cell hyperplasia. CCAs with atypia were defined as columnar cell hyperplasia with cells showing low-grade atypia, characterized by relatively round monotonous nuclei. We included the cases of FEA under the category of CCAs.

ADH was defined as architectural atypia in association with cytologic atypia. No cases of ADH or “clinging” or “flat” DCIS were considered as within the spectrum of CCA in this study. Cases with a pleomorphic variant of LCIS (grade 3 nuclei, extreme nuclear pleomorphism, or comedo-type necrosis) were excluded from the study.

Three sources of breast tissues were examined for evaluation of LN coexistent with CCAs (LN and CCAs): Group 1 included 68 CNB specimens targeted for “suspicious” microcalcifications with a radiologic impression of Breast Imaging Reporting and Data System (BI-RADS) 4 and with diagnoses of LN. The follow-up resection specimens were reviewed and evaluated for the presence or absence of LN and for their close association with CCAs. Group 2 included 2,516 cases of consecutive breast core biopsies during a 1-year period (January 1, 2005, to January 1, 2006). Cases in which LN and CCAs appeared in the diagnosis were reviewed. Proximity of the two lesions and associated microcalcifications were also noted. Group 3 included slides from 400 consecutive breast resection specimens in which patients had a history of carcinoma that were analyzed for LN and CCAs in the vicinity of the carcinoma (DCIS, infiltrating ductal carcinoma [IDC], and infiltrating lobular carcinoma [ILC]). Specimens were from needle-localized segmental, simple, and radical mastectomies.

Statistical Analysis

Statistical analysis was performed. P values were calculated for the 3 groups using GraphPad Software (GraphPad, La Jolla, CA).

Results

The 3 specimen tissue types were separately analyzed. The frequency of coexistent CCAs and LN is shown in **Figure 1**, and representative cases are shown in **Image 1**. Analyses of the 3 groups were as follows:

**Group 1**

Calcifications were identified in all 68 cases (100%). Of the 68 cases, 31 (46%) exhibited LN only, and 37 cases (54%)
exhibited LN and CCAs, of which 8 cases (22%) showed both entities within the same TDLU and 29 cases (78%) within the same core specimen but not in the same TDLU. None of the cases of CCAs showed atypia. Calcifications were localized to CCAs in 9 (13%) of 68 cases and to LN in 12 (18%). In the follow-up resection specimens, 5 cases of carcinoma were found (1 tubular carcinoma and 3 DCIS) in association with the group of LN and CCAs. The described triad of tubular carcinoma, LN, and CCAs was seen in 1 case.\cite{11,13} Three cases of carcinoma (1 each of IDC, ILC, and DCIS) were found in association with the group of LN only cases. The upstaging of carcinoma in patients with LN and CCAs was 14% (5/37) in comparison with 10% (3/31) for the LN only group.

Group 2

Of the 2,516 pathology reports from CNBs reviewed retrospectively, 32 reports (1.3%) identified LN and CCAs in the final diagnosis.

Group 3

Slides from 400 consecutive breast resection specimens in which patients had a history of carcinoma were reviewed. Of the 400 cases, 52 (13.0%) were found to have LN and CCAs. Of the 52 cases, 40 (77%) were seen in the vicinity of carcinoma (9 cases of DCIS, 19 cases of IDC with or without DCIS, and 12 cases of ILC with or without DCIS). No residual carcinoma was seen in the other 12 cases (23%). Of the 40 cases, CCAs with atypia were associated with carcinoma (in situ and

\[\text{Image 11} \text{ A and B, Columnar cell alterations (CCAs) in association with lobular neoplasia (LN) and calcifications. C, LN with associated calcifications. D, CCAs with associated calcifications (LN).}\]
invasive) in 16 (40%) (2 cases of DCIS, 11 cases of IDC, and 3 cases of ILC) vs 24 (60%) (7 cases of DCIS, 8 cases of IDC, and 9 cases of ILC) of CCAs without atypia Table 1.

Figure 2 shows an algorithm for significance of the association of LN and CCAs in the 3 groups of breast tissue specimens.

**Discussion**

LCIS was described initially by Foote and Stewart in 1941 as “a disease of small lobular ducts and lobules” and described as a “lesion composed of loosely cohesive small cells with small, uniform nuclei that involve the lobules in a solid growth pattern.” This lesion occurs in multiple lobules and is always a disease of multiple foci. The distinction between ALH and LCIS is thought to be arbitrary and semiquantitative, and the term “lobular neoplasia” suggested by Haagensen is thought to be a better-defined entity and more reproducible.

The relative risk of developing an invasive cancer with LCIS is 9 times higher than in the general population and 4 to 5 times for ALH. The time for the development of invasive cancer in an individual patient after a diagnosis of LCIS is difficult to predict. Page et al found that 67% of patients developed cancer 15 years after the initial biopsy. Rosen found similar results in a study in which more than 50% of patients developed invasive cancer between 15 and 30 years after, with an average of 20.4 years. In summary, clinical follow-up studies have shown that women with LN have an increased risk of invasive cancer that is distributed equally for both breasts, and subsequent invasive cancer might be ductal or lobular. Such studies led to the view that LCIS represents a risk indicator for subsequent invasive breast cancer rather than a precursor lesion.

The true incidence of LCIS remains vague, with a reported frequency up to 8% in breast biopsies with benign results. Calculifications have been found in up to 40% of LCIS, and a lesser association has been found with higher-risk lesions like radial scar or ADH.

The current management guidelines for LCIS are not adopted uniformly; a follow-up surgical excision is performed when there are overlapping features with DCIS, an association of LN with high-risk lesions, and when there is an imaging-pathology discordance. The appropriate management of finding LN only on CNB specimens has been addressed by some studies and remains controversial. The overall incidence of finding carcinoma on a follow-up excision for LN on CNB specimens is reported to be up to 20%. The risk of upstaging of CNB specimens with LN is increased further when the LN is associated with calcifications. Our study revealed a 13% incidence of upstaging to carcinoma in CNB specimens with LN and CCA cases but only a 9.6% incidence of upstaging in cases with LN alone.

CCAs include a spectrum of lesions that arise from the columnar cell lining of the TDLU, usually present as nonpalpable, clustered, indeterminate or suspicious microcalcifications on mammography. They are indistinguishable from other causes of suspicious microcalcifications such as ADH and DCIS and require CNB or excisional biopsy for diagnosis. They are classified into 2 categories: columnar cell change and columnar cell hyperplasia. The majority of these lesions are considered benign, and their clinical significance is under debate. Some of them manifest with cytologic or architectural atypia or both. When architectural atypia is associated, a careful search for ADH or for low-grade DCIS needs to be performed.

In mammographic lesions targeted for calcifications, the frequency of LN in CNB specimens is up to 40%. In

**Table 1**

<table>
<thead>
<tr>
<th>Carcinoma Type</th>
<th>LN + CCAs With Atypia Cases</th>
<th>LN + CCAs Without Atypia Cases</th>
<th>Total</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCIS</td>
<td>2 (5)</td>
<td>7 (18)</td>
<td>9 (23)</td>
<td>.06</td>
</tr>
<tr>
<td>IDC</td>
<td>11 (28)</td>
<td>8 (20)</td>
<td>19 (48)</td>
<td>.5</td>
</tr>
<tr>
<td>ILC</td>
<td>3 (8)</td>
<td>9 (23)</td>
<td>12 (30)</td>
<td>.04</td>
</tr>
<tr>
<td>Total</td>
<td>16 (40)</td>
<td>24 (60)</td>
<td>40 (100)</td>
<td>.1</td>
</tr>
</tbody>
</table>

CCAs, columnar cell alteration; DCIS, ductal carcinoma in situ; IDC, infiltrating ductal carcinoma; ILC, infiltrating lobular carcinoma; LN, lobular neoplasia.

* Data are given as number (percentage). Percentages may not add due to rounding.

The presence of CCAs with or without atypia was compared.

**Figure 2** Algorithm of the significance of lobular neoplasia in association with columnar cell alterations in 3 breast tissue specimens.
comparison, CCAs are reported in the CNB specimens in up to 12.0%.10,16 We have observed in our practice an association of LN coexistent with CCAs in various breast tissues. In our study, in which the simultaneous occurrence of the 2 entities was carefully examined, we found a significantly higher association of coexisting LN and CCAs in targeted CNB specimens of up to 54%. The upstaging of CNB specimens containing these two pathologic entities in the follow-up excisions is 3 times higher in cases of LN and CCAs than in LN alone. We also observed that in larger resection specimens with carcinoma, the frequency of finding LN and CCAs is up to 13%. However, the finding of CCAs with atypia vs without atypia in the vicinity of carcinoma was not a significant finding (P = .1).

Our study results suggest the association of LN and CCAs is a frequent occurrence, especially in CNB specimens targeted for calcifications. In our CNB specimens, we observed the presence of these 2 lesions within the same TDLU in up to 30%, which further supports their nonrandom occurrence and probable molecular kinship. Columnar cell lesions provide a background for the development of a variety of low-grade carcinomas.7,17 Our results document the overall low incidence of LN in breast tissue and demonstrate the focused finding of LN and CCAs in breast imaging with suspicious calcifications. Similar to other reports,7,17 our clinical follow-up data suggest that it would be clinically prudent for patients with a core biopsy diagnosis of LN and CCAs to undergo excisional biopsy owing to significant upstaging in the follow-up excision specimens. Molecular studies are warranted to further examine the significance of the relationship of these entities.

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