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ORIGINAL ARTICLE

Gary L. Bratthauer · Fattaneh A. Tavassoli

Lobular intraepithelial neoplasia: previously unexplored aspects assessed in 775 cases and their clinical implications

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Abstract Lobular intraepithelial neoplasia (LIN) is currently considered a risk factor for the development of invasive breast cancer of varying morphologies (ductal or lobular) and prognoses in either breast. The reason for the high frequency (50%) of subsequent development of invasive ductal cancers remains unclear and the issue unexplored. A total of 775 LIN cases were retrieved from the Armed Forces Institute of Pathology files and separated into three groups using our three-tiered grading system. The presence or absence of simultaneous invasive cancer (ductal or lobular type) and various grades of ductal intraepithelial neoplasia (DIN) were noted for each case and correlated with the grade of LIN. Of the 775 cases, 80% qualified as LIN 2, with the other 20% being relatively evenly split between LIN 1 and LIN 3. Of the 775 cases, 163 cases were pure LIN, while invasive carcinoma was present in 140 cases. The remaining 472 cases were associated with various grades of DIN. The frequency of associated invasive carcinomas (ductal and lobular) increased from 14% in LIN 1 to 23% in LIN 3. Remarkably, while the frequency of invasive lobular carcinoma increased dramatically from 11% in LIN 1 to 86% in LIN 3, the frequency of invasive ductal carcinoma markedly decreased with advancing grade of LIN from 89% in LIN 1 to 14% in LIN 3. Among the cases of LIN unassociated with invasive carcinoma, DIN was present in 75% of LIN 1, 75% of LIN 2, and 66% of LIN 3 cases. The grade of DIN was directly proportional to the grade of LIN. Based on the higher frequency of invasive lobular carcinoma associated with LIN 3, biopsies with LIN 3 should be evaluated diligently for the presence of an associated invasive lobular carcinoma. Furthermore, an excisional biopsy should be performed when LIN 3 is observed in a core biopsy. The high frequency of DIN associated with LIN might suggest that the subsequent invasive ductal carcinomas originate from the associated DIN and that some of this may represent a different phenotype of the same cells that form the LIN lesion. It is also possible that the neoplastic cells may reflect or retain stem cell characteristics with plasticity and the capacity to attain or progress into either a ductal or lobular invasive phenotype.

Keywords Breast · Lobular intraepithelial neoplasia · Invasive lobular carcinoma · Ductal intraepithelial neoplasia · Intraductal hyperplasia · Ductal carcinoma in situ · Invasive ductal carcinoma

Introduction

Lobular intraepithelial neoplasia (LIN) is currently considered a risk factor for the development of invasive breast cancer of varying morphologies and prognoses, in either breast [9]. The disease is characterized by a proliferation of uniform, generally small, loosely cohesive epithelial cells filling and/or distending the lobules. These cells can also spread in a pagetoid fashion into adjacent terminal ducts. Moreover, this condition is multicentric, existing simultaneously in several lobules in multiple quadrants of the breast, and is often bilateral. Although the cells are neoplastic and the lesion is frequently referred to as "carcinoma in situ", only 20–25% of patients develop invasive breast cancer within 15–20 years of diagnosis [4]. The subsequent invasive carcinoma is observed with nearly equal probability in either breast and may be of either lobular or ductal type, again with equal probability. Therefore, the disease of LIN is indicative of a process that may lead to invasive breast cancer of variable histologic appearances and prognoses.

LIN continues to be subdivided into atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS).

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G.L. Bratthauer (✉) · F.A. Tavassoli
Department of Gynecologic and Breast Pathology,
Armed Forces Institute of Pathology,
14th Street and Alaska Avenue NW,
Washington DC 20306-6000 USA
e-mail: bratthauer@afip.osd.mil
Tel.: +1-202-7822567, Fax: +1-202-7823939

The risk factors for either one of the two are not sufficiently different and the tendency toward invasive cancer development (or the prediction of such) is not necessarily increased with the LCIS designation, though some may argue otherwise. In 1978, Haagensen proposed to replace the terms ALH and LCIS with the designation of LN [1]. Although it is now generally agreed that "LIN" is a risk factor and not an obligate precursor of invasive carcinoma, many continue to use the ALH/LCIS subdivision. At the Armed Forces Institute of Pathology (AFIP), we started using the LN designation following the appearance of Haagensen's study. Subsequently, we started to grade the severity of LN from 1 to 3 to determine whether these grades have any predictive value and to ascertain whether or not they correlate with progression, prognosis, or any other aspect of associated breast alterations. An I for intraepithelial was added to distinguish intraepithelial from invasive lobular neoplasias.

Two concerns prompted this retrospective analysis of 775 cases reviewed over a 3-year period in the recent AFIP files. First, we hoped that a careful assessment of associated changes might provide an explanation for the diversity of subsequent invasive carcinomas. Second, we anticipated that the information concerning the types of associated pathology could help predict the direction of disease progression and assist in management decisions when various grades of LIN are encountered in excisional and core biopsies.

Materials and methods

All LIN cases from 1997 through 1999 (775) were retrieved from the records file at the AFIP. The cases used in the study were all those with a diagnosis of LIN rendered at the AFIP as a second opinion. When information was available, the reasons for biopsy varied from mammographically detected microcalcifications or irregular densities to a clinically palpable mass. In many cases, interpretation of LIN was an incidental finding as would be anticipated from data available in the literature. These cases had all been categorized to reflect grade. The criteria that were used for grading are as follows.

LIN 1. A loosely cohesive cellular proliferation partially or completely filling the acinar (ductular) spaces without acinar distension and often with residual acinar (ductular) lumen (Fig. 1a)

LIN 2. Cellular proliferation completely filling and distending at least some of the ductules in the terminal duct lobular unit but preserving distinct ductular outlines (Fig. 1b)

LIN 3. Cellular proliferation filling and maximally distending the ductules to the point of virtual confluence or, more rarely, proliferation of cells with significant cytologic atypia characterized by nuclear pleomorphism (intraepithelial version of invasive pleomorphic carcinoma), or a pure classic signet ring cell population (Fig. 1c)

When the LIN cells are pleomorphic or of the signet ring cell type, maximum distension of acini is not required. These LIN 3 lesions, in general, and particularly those interpreted as such based on cytologic features (pleomorphism or signet ring cells) are extremely rare, can be quite extensive, and can exhibit necrosis and microcalcifications mimicking a ductal process at first glance. In these cases, the loose cohesiveness of the cells and the presence of intracytoplasmic lumens and pagetoid growth patterns help accurate interpretation of the process. Microcalcification also occurs, albeit very rarely, in LIN 1 and LIN 2. The intent of our three-tiered classification was to provide a framework that would incorporate all variants of lobular disease including rare variants.

LIN 1, LIN 2, and LIN 3 cases were separated and other concomitant disease was noted for each. Cases were separated based on the presence or absence of simultaneous invasive cancer (ductal or lobular type), and the presence or absence of ductal intraepithelial neoplasia (DIN) [10]. Cases were also stratified on the basis of different grades of DIN and the absence of any evidence of ductal disease.

Results

A total of 775 cases of LIN were accessioned from 1997 through 1999. A concurrent invasive cancer was present in 140 (18%) of these cases. Invasive ductal carcinoma accounted for 49% of the 140 cases. The results are summarized in Table 1.

During this time period, there were a total of 65 cases examined with a diagnosis of LIN 1. Of these 65 cases, 14 (22%) also had either an intraductal (of DIN 1c or higher-grade type) or invasive carcinoma. Of the 14 patients with carcinoma, 9 had an invasive phenotype and 8 (89%) of these were of a ductal morphology. Therefore, invasive cancer was seen in 9 of 65 or just 14% of women with LIN 1 diagnosed from 1997 through 1999, and in only 1 of the 9 (11%) patients was the invasive cancer of a lobular phenotype.

There were no intraductal neoplasias of DIN 2 or DIN 3 grade (ductal carcinoma in situ grade 2 or 3) among the cases of LIN 1. Of the remaining 51 LIN 1 patients without carcinoma, 37 (73%) also had a DIN 1a (intraductal hyperplasia), DIN 1b (flat epithelial atypia), or DIN 1c (atypical intraductal hyperplasia). The remaining 14 cases (22%) were pure LIN 1 without any associated ductal abnormality or carcinoma.

There were a total of 618 cases of LIN 2 accessioned from 1997 through 1999. Diagnoses of carcinoma either invasive or intraductal accounted for 33% (n=201) of the total. Invasive carcinoma was only present in 110 (18%) of the LIN 2 cases. In contrast to the predominance of invasive ductal carcinoma among LIN 1 cases, 47% of invasive cancers associated with LIN 2 were purely lobular or displayed prominent lobular features. Of the patients with intraductal carcinoma, 41% were of DIN 2 or DIN 3 grade. As for the 417 women who did not have a simultaneous carcinoma, 290 (70%) had either DIN 1a, 1b, or DIN 1c (extensive atypical intraductal hyperplasia). The remaining 127 (21%) had pure LIN 2 without any evidence of ductal abnormality or carcinoma.

There were 92 cases with a diagnosis of LIN 3 during this time frame. A total of 38 (41%) of them also had either invasive carcinoma or a DIN of grade 1c or higher (conventional DCIS, grades 1–3). Twenty-one of the 92 women with LIN 3 (23%) had an ipsilateral invasive carcinoma, but only 3 (14%) showed a purely ductal morphology. The majority (86%) of these 21 invasive carcinomas were of the lobular type, with 4 of them possessing both lobular and ductal features. Of the 17 patients with intraductal carcinoma, 9 (53%) had either DIN 2 or

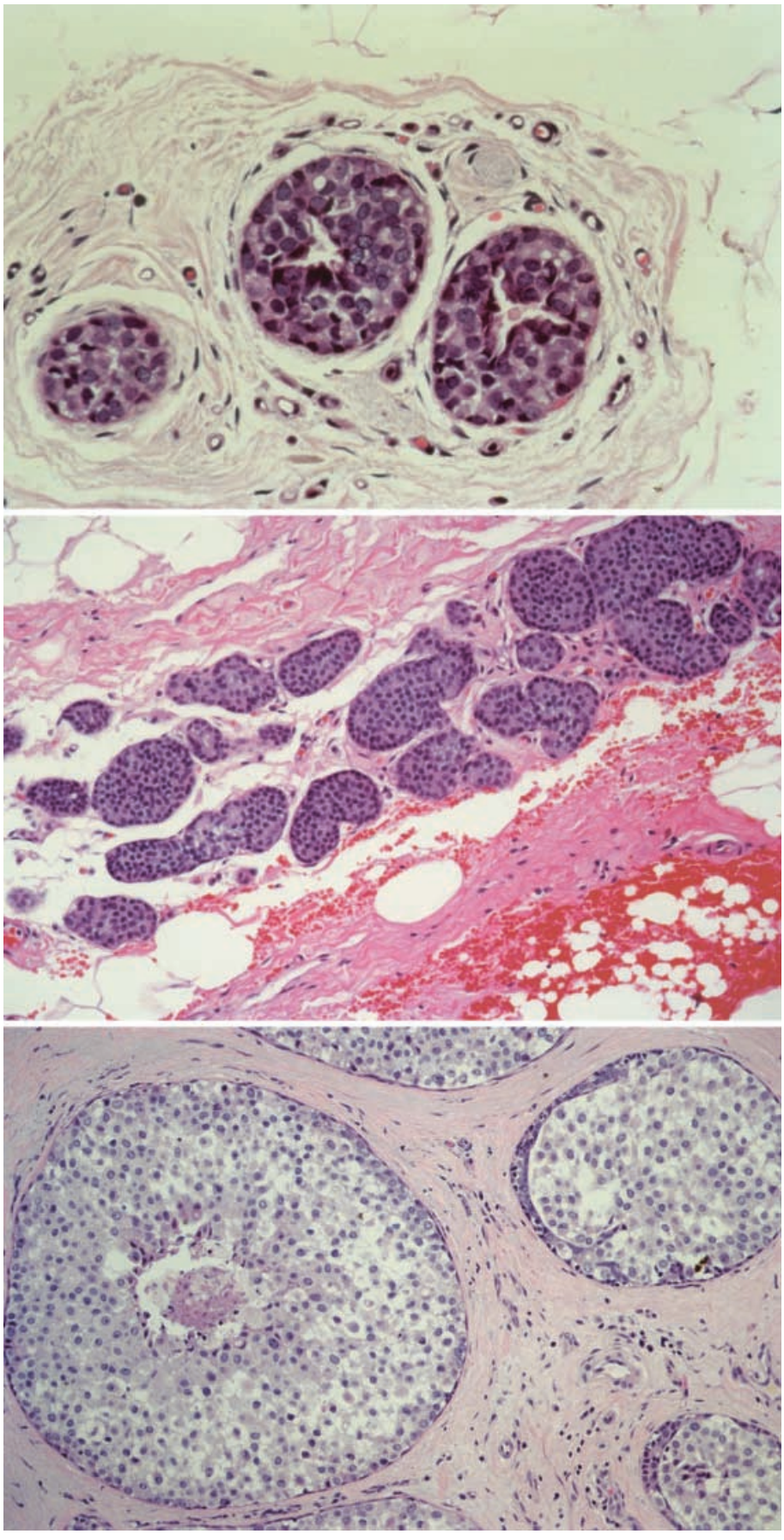

Fig. 1 The typical features of the three grades of lobular intraepithelial neoplasia (LIN). **a** LIN 1: note the increased proliferation without acinar distension or lumen obliteration, crowding the residual ductal epithelium. **b** LIN 2: note the acinar distension with filled lumens but persistence of acinar outlines. **c** LIN 3: note the severe acinar distension by loosely cohesive cells (with residual compressed ductal cells) and overall increased extent of disease with necrosis. Hematoxylin and eosin, **a** ×320, **b**, **c** ×160

Table 1 Concurrent findings in varying grades of lobular intraepithelial neoplasia (LIN). *PLIN* pure lobular intraepithelial neoplasia, *CIVCA* cases with invasive carcinoma, *CIDCA* cases with intraductal carcinoma, *CBIDP* cases with benign intraductal proliferation (intraductal hyperplasia to extensive atypical intraductal hyperplasia), *CNOCA* cases without carcinoma, *DIN* ductal intraepithelial neoplasia, *DCIS* ductal carcinoma in situ

	LIN 1(%)	LIN 2(%)	LIN 3(%)	All (%)
Total number	65	618	92	775
No. PLIN	14 (21)	127 (21)	24 (26)	165 (22)
No. CBIDP	37 (57)	290 (47)	30 (33)	357 (46)
No. CBIDP & PLIN	51 (78)	417 (67)	54 (59)	522 (67)
No. CIVCA	9 (14)	110 (18)	21 (23)	140 (18)
No. CIDCA	5 (8)	91 (15)	17 (18)	113 (15)
No. CIVCA & CIDCA	14 (22)	201 (33)	38 (41)	253 (33)
CIDCA number	5	91	17	113
No. DIN 1c (low-grade DCIS)	1 (20)	43 (47)	8 (47)	52 (46)
No. DIN 2–3 (DCIS grades 2–3)	0	37 (41)	9 (53)	46 (41)
CNOCA number	51	417	54	522
No. DIN 1a-1c (IDH, AIDH, extensive AIDH)	37 (73)	290 (70)	30 (56)	357 (68)

DIN 3. Thirty (56%) of the remaining 54 women without carcinoma also had some DIN 1a, DIN 1b, or DIN 1c (extensive atypical intraductal hyperplasia). There were 24 (26%) cases of pure LIN 3 without any ductal abnormality or carcinoma.

Among a total of 522 LIN unassociated with either in situ or invasive carcinomas, 51 (10%) were LIN 1, 417 (80%) were LIN 2, and 54 (10%) were LIN 3. Of a total of 165 cases of pure LIN, 14 (8%) were LIN 1, 127 (77%) were LIN 2, and 24 (15%) were LIN 3.

Discussion

In analyzing the 775 cases of LIN seen at the AFIP over 3 years, the characteristics of associated invasive cancers almost exactly paralleled data gleaned from over 1100 cases in 18 previously published studies on outcome following a biopsy diagnosis of LCIS/LIN; these data demonstrated roughly a 20% incidence of subsequent invasive cancer that was virtually 50% ductal and 50% lobular in phenotype [9]. This feature, along with the relatively low rate of subsequent invasive cancer development in either breast, has relegated LIN to a marker category portending a higher risk for subsequent development of invasive cancer. On closer scrutiny, assessment of associated pathology in 775 cases of LIN recently reviewed at the AFIP revealed a significant trend toward more prevalent and more aggressive proliferative disease with increasing grade of LIN.

Over the 3-year period of the study, a vast majority of cases (80%) fell into the LIN 2 category. Applying the proposed three-tiered grading criteria, only 8% of the cases qualified as LIN 1. These strict criteria identify a small but uniform group of very early lobular lesions. The LIN 3 cases accounted for 12% of the total and they not only had the most maximally expanded acini or highly atypical, pleomorphic nuclei, but were also among the most extensive of all the LIN lesions. Reflecting 80% of all cases, it makes sense that the features seen in the LIN 2 group were also representative of the entire group of LIN cases as a whole. Given the consultation nature of our practice and the expertise of the pathologists resulting in interpretation of the early lesions (LIN 1), we believe that even a higher proportion of cases in the general practice of pathology fall in the LIN 2 category.

Overall, there was an 18% frequency of associated invasive cancer, and that cancer was within 3% of being split 50:50 between lobular and ductal varieties, whether examining all of the LIN cases or just those designated as LIN 2. However, distinct differences emerged when LIN 2 was compared with the other two groups. The proportion of LIN 1 cases with invasive cancer was 14%, and 89% of these were invasive ductal carcinomas. Among LIN 3 lesions, the frequency of associated invasive carcinoma was 23%, but 86% of these were invasive lobular carcinomas. Advancing from LIN 1 to LIN 3 is associated with a 64% increase in the frequency of invasive carcinoma and more than a 700% increase in the likelihood of these tumors being invasive lobular carcinomas (Table 2). The increasing grade of LIN directly correlates with the frequency of invasive lobular carcinoma; however, there is an almost perfect inverse correlation between the grade of LIN and the frequency of invasive ductal cancer.

At what point then in the progression of lobular disease does the likelihood of developing an invasive lobular cancer exceed the possible occurrence of an invasive ductal cancer? Is the observed increase in the frequency of associated invasive lobular cancer entirely due to increased aggressiveness of the higher-grade LIN? Even

Table 2 Amount of total invasive carcinoma, invasive lobular, and invasive ductal types in different grades of lobular intraepithelial neoplasia (LIN). *IVCA* invasive carcinoma (ductal and lobular), *IVL* invasive lobular carcinoma, *IVD* invasive ductal carcinoma

	% IVCA (*n*)	% IVL(*n*)	% IVD(*n*)
LIN 1	14 (9)	11 (1)	89 (8)
LIN 2	18 (110)	47 (52)	53 (58)
LIN 3	23 (21)	86 (18)	14 (3)

when DIN 1c–DIN 3 are included among the associated cancers, the frequency of associated carcinoma remained directly proportional to lesion grade: 22% in LIN 1, 33% in LIN 2, and 41% in LIN 3. The grade of the DIN lesions also increased with advancing grades of LIN. Higher grade DIN (2 or 3) accounted for 53% of the DIN in the LIN 3 group, 41% of those in the LIN 2 group, and none of those in the LIN 1 group. It is interesting to note that even though the frequency and grade of DIN were highest among LIN 3 patients, invasive ductal carcinoma had the lowest association with LIN 3. This could imply that LIN 3 is far less stable as an intraepithelial process than DIN 2 or DIN 3.

Another interesting finding in comparing these various cases emerged from examination of LIN unassociated with any carcinomas. Fifty-nine percent of LIN 3, 67% of LIN 2, and 78% of LIN 1 cases had no accompanying cancer, invasive or in situ. Among the 54 LIN 3 lesions unassociated with either intraepithelial or invasive cancer, 30(56%) had a low-grade DIN 1a, 1b, or 1c (intraductal hyperplasia to extensive atypical intraductal hyperplasia). Among the 417 LIN 2 and the 51 LIN 1 cases unassociated with in situ or invasive carcinoma, 290 (70%) and 37 (73%) patients had similar lower grade DIN, respectively. There seemed to be a tendency for lower grade DIN to be present in association with lower grade LIN. In a previous study of all types of breast carcinoma, an association with LIN was observed in only a small subset [2].

With the increasing use of needle core biopsy, it is important to have some clues to the nature of lesions that may be present in the remaining breast tissue when LIN is the sole neoplastic proliferation identified in the core biopsy. Therefore, correlation of the type of lesion associated with varying grades of LIN in a large number of cases would be most useful in guiding therapeutic recommendation and could provide valuable information in deciding the optimal management approach. Since a vast majority of core biopsies are due to mammographically detected suspicious microcalcification, and microcalcification is rare in LIN, correlation of the mammographic and pathologic findings is crucial to ascertain accurate sampling of the lesion of mammographic concern if the core biopsy shows only LIN or no calcification. LIN is generally an incidental finding. Therefore, if the core biopsy contains LIN 3, the possibility of an associated invasive lobular carcinoma as well as higher grade DIN must be considered, and, in our opinion, an excisional biopsy is mandatory. A similar conclusion was reached in a recent radiologic study [5]. It should also be noted that microcalcification, detectable mammographically, may occur in LIN 3 [7]. If there is LIN 2, particularly when multiple terminal duct-lobular units are involved, re-excision may be prudent if there is not absolute confirmation that the mammographically detected area of suspicion has been sampled in the core. Core samples with LIN 1 should be examined for the presence of DIN elsewhere. If the basis (most often microcalcification) for the mammographic findings is accounted for in the core sample, further excision is not an absolute necessity.

The reason why a ductal phenotype develops in 50% of the cancers that subsequently occur in LIN patients is unknown and curiously not addressed in the literature. This feature, observed in multiple previous studies that have assessed outcome following a biopsy diagnosis of LIN, was also noted in our study group reflecting concurrent invasive carcinomas, whether assessing the entire group of 775 LIN lesions or the dominant group of 618 LIN 2 cases. Interestingly, not much has been documented regarding reasons or possible mechanisms contributing to this phenomenon. It is conceivable that some of the invasive ductal cancers originate from some of the concurrent DIN. Of the 69 cases with invasive ductal carcinoma, 42 also had a DIN 1c or higher lesion. Another possibility is that, in some cases, an early solid phase of low grade DCIS may be misinterpreted as LIN; assessment of immunoreactive E-cadherin may help to rectify this problem [3, 6, 8]. A more provocative possibility is that one lesion may transform to the other as cellular attributes are gained and lost. Could some of these neoplastic cells manifest a pluripotential stem-cell-like behavior? A further examination of more cases in the LIN 1 and LIN 3 categories as well as investigations at the molecular level may help to better understand this disease.

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