

# Lobular neoplasia of the breast: review

## *Neoplasia Lobular da mama: revisão*

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### ABSTRACT

Lobular neoplasia of the breast refers to lesions characterized by atypical lobular hyperplasia and by lobular carcinoma in situ. Lobular neoplasia is not only a risk factor but a non-mandatory precursor for the development of invasive carcinoma. Pleomorphic lobular carcinoma in situ is a subtype of lobular neoplasm with an aggressive behavior and high nuclear grade that can mimic high-grade ductal carcinoma in situ. Management and monitoring the patients with lobular neoplasm is controversial, especially when diagnosis is made through core biopsy. Molecular and genomic studies have been able to identify genes that can dispel doubts as to its pathogenesis and allow an approach that may lead to safer and more appropriate therapeutic approaches. This review seeks to describe the most up-to-date approaches to lobular neoplasia of the breast.

**Key words:** Breast Neoplasms; Carcinoma, Lobular; Hyperplasia; Carcinoma Ductal.

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### RESUMO

*A neoplasia lobular da mama refere-se às lesões caracterizadas pela hiperplasia lobular atípica e pelo carcinoma lobular in situ. A neoplasia lobular não é apenas um fator de risco, mas um precursor não obrigatório para o desenvolvimento de carcinoma invasivo. O carcinoma lobular in situ do tipo pleomórfico é subtipo de neoplasia lobular com comportamento agressivo, com alto grau nuclear e pode mimetizar o carcinoma ductal in situ de alto grau. O manejo e o seguimento das pacientes portadoras de neoplasia lobular são controversos, especialmente, quando o diagnóstico é feito por meio da core biopsy. Os estudos moleculares e genômicos têm sido capazes de identificar genes que podem ser dirimir dúvidas quanto à sua patogênese e permitir abordagem que permite abordagens terapêuticas mais seguras e adequadas. Esta revisão procura estabelecer o conceito mais atual sobre a abordagem da neoplasia lobular da mama.*

*Palavras-chave:* Neoplasias da Mama; Carcinoma Lobular; Hiperplasia; Carcinoma Ductal.

### INTRODUCTION

Lobular neoplasia (LN) is a set of lesions characterized by atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS).

LN of the breast was first documented by Ewing,<sup>1</sup> in 1919, when he described a case of “atypical proliferation of acinar cells” and “precancerous changes in a segment of a duct with atypical proliferation”. In 1941, Foote and Stewart<sup>2</sup> characterized LN in situ as a monomorphic population of cells that expanded the terminal ductolobular unit (TDLU) without typical clinical manifestation, of usually multicentric and bilateral presentation. They introduced the term LCIS and recognizing it as

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ductal carcinoma in situ (DCIS), a means of access to invasive cancer, they recommended mastectomy as the standard form of treatment. The term ALH was subsequently adopted to describe morphologically similar, but less developed, lesions.

In 1978, Haagensen et al.<sup>3</sup> suggested the terminology of LN to characterize these changes as it designates a benign proliferation which increases the risk of subsequent cancer in both breasts and which requires strict supervision. The risks seem to exist at relatively the same frequency for both the ipsilateral and the contralateral breasts. Rosen et al.<sup>4</sup>, also in 1978, found 10% of concomitant invasive carcinoma in their sample, besides an increase of 23% in the risk of developing cancer in both breasts after an average 24-year follow-up.

Over the years, ALH and LCIS have proved not to be precursor lesions similar to high-grade ductal comedocarcinoma in situ.<sup>5</sup> Radical surgical treatment is no longer routinely adopted and strict clinical management is considered more suitable.

The arguments that LN is not a mandatory precursor of invasive diseases are based on several important observations:

- the development of an invasive carcinoma after the diagnosis of ALH and LCIS occurs only for some affected patients;
- the incidence of invasive disease is relatively similar in both breasts;
- invasive cancer subsequent to LN is often of the ductal type.

Conversely, Page et al.<sup>6</sup> found that the invasive carcinoma was three times more frequent in the affected breast than in the contralateral one and also that the lobular type was more prevalent than the ductal one. Molecular studies have shown that the genetic characteristics of LCIS and of the subsequent invasive lobular carcinoma are often similar.<sup>7</sup>

This article aims to show the characteristics and the behavior of lesions that fall under the category of lobular neoplasia, as well as implications and management after diagnosis.

## METHOD

A bibliographic study was carried out on Medline, PubMed, Lilacs, and in international scientific articles. Articles were found using keyword search, for example: atypical lobular hyperplasia, breast cancer,

lobular carcinoma in situ lobular and neoplasia, and were selected by title and abstract. Articles were subsequently analyzed by searching the full text.

## DISCUSSION

### Epidemiology of LN

The frequency of LCIS varies from less than 1 to 3.8% of all breast carcinomas. It is generally diagnosed in women aged 40 to 50 years and less than 10% of patients are in post-menopause.<sup>8</sup> There are no specific clinical or mammographic alterations, and the existence of palpable nodules is not frequent. LCIS is rarely seen on a mammography and calcification is uncommon.<sup>9</sup>

The diagnosis of LN is usually based on incidental findings during breast biopsies performed for other reasons. LCIS is characteristically multifocal and bilateral in a large percentage of cases. More than 50% of patients with LN have multiple foci in the ipsilateral breast and about 30% of cases will display a LCIS in the contralateral breast.<sup>10</sup> Such multifocality through clinically undetectable lesions is one of the reasons why the planning of subsequent management is difficult and controversial.

### Histological characteristics of LN

LN displays a spectrum of acinar involvement that can be subdivided into AHL and LCIS. The diagnostic criteria include nuclear, cytological, and architectural characteristics. LCIS and AHL characteristically have a monomorphic population of disjoint cells in the terminal ductolobular unit. LCIS is classified as having small, usually round, disjoint cells with an increase of the nucleus/cytoplasm ratio which distend and fill up the acinar light, affecting more than 50% of acini of the lobular unit. In AHL, less than 50% of acini are affected, with partial or complete filling but with minimal structural strain. The cells are poorly cohesive, yet the architecture of the lobe is usually maintained. Mitoses, calcifications, and necroses are rare. E-cadherin, commonly identified in duct lesions, is usually absent in LN.

It is evident that the distinction between AHL and LCIS has criteria subject to inter- and intra-observer variability. Although adopting the LN terminology to encompass these changes seems preferable, there

is a difference in the risk offered by the two entities; the risk of invasive carcinoma in LCIS is considerably higher than that of AHL<sup>11</sup>.

The additional system for classifying these lesions, proposed by Tavassoli<sup>12</sup>, uses the intraepithelial LN terminology (ILN) and its subdivisions, based on morphological criteria and clinical results. The subdivision is made in three grades, ILN1, ILN 2 and ILN 3. The risk of subsequent carcinoma is related to the increase in ILN grade.

## Pleomorphic LCIS

The pleomorphic subtype of LCIS has recently been more widely recognized and gained notoriety by reason of its differentiated behavior. This form displays larger cells, of disjoint nature typical of LN, but with a typically grade 3 pleomorphic nucleus in the Scarff-Bloom-Richardson system.<sup>13</sup> The cells usually show apocrine differentiation and may show necrosis and microcalcifications, mimicking high grade DCIS. The frequent co-existence of classic and pleomorphic LCIS suggests that a common genetic route may be shared by both, but with different biological aspects and implications.<sup>14</sup>

The pleomorphic type of LCIS has an aggressive behavior, including infiltrative growth and unfavorable clinical course. Moreover, tumors can be positive for Her-2, p53, and Ki-67.<sup>15</sup>

## Differential diagnosis of NL

Besides occasional difficulties in differentiating it from sclerosing adenosis benign lesions to the breast<sup>8</sup> the most important and most difficult differential diagnosis of LCIS is solid low grade nuclear DCIS, which has important morphological similarities, especially when the DCIS involves the acini with minimal or no lobular distortion. Such differentiation is essential since classic LCIS requires strict follow-up and, in some cases, chemoprevention with hormonal therapy, while the DCIS requires surgical eradication and radiotherapy.<sup>16</sup>

## Implications of LN

The subsequent risk of developing breast cancer is different in patients diagnosed with AHL when compared with carriers of LCIS. The risk for patients with AHL is 4 to 5 times higher than for the general

population, while the risk for those with LCIS is 8 to 10 times higher.<sup>17</sup>

## Meaning of LN upon core biopsy

Surgical follow-up is needed when LN is found in core biopsy results. Detection rates of more advanced lesions can vary up to more than 20% when surgical excision is performed upon the diagnosis of LN through biopsy.<sup>19</sup>

## CONCLUSIONS

Histological and immunohistochemical characterization is the first step toward defining and understanding LN pathogenesis. The identification of pleomorphic LCIS as a distinct and aggressive subtype has increased knowledge of the spectrum of LN lesions, causing medical implications and repercussions for patients themselves. Because of its histological and biological heterogeneity, further molecular and genetic studies are of fundamental importance for better management of these lesions in the future.

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