Scholars International Journal of Obstetrics and Gynecology
Abbreviated key title: Sch. Int. J. Obstet. Gynec.
A Publication by "Scholars Middle East Publishers"
Dubai, United Arab Emirates

ISSN: 2616-8235 (Print)
ISSN: 2617-3492 (Online)

Diagnosis and Treatment of Precancerous Breast Lesions: Lobular Carcinoma in Situ

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Review Article

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Article History
Received: 14.07.2018
Accepted: 27.07.2018
Published: 30.07.2018

Abstract: The discovery of precancerous breast lesions has increased considerably with the generalization of screening. There are several classifications, the most used is that of Tavassoli and Al (adopted by WHO) which classifies intra-lobular breast neoplasia into three grades: LIN1, LIN2, LIN3. Lobular neoplasias are considered indicators of risk of invasive cancer. Progress in immunohistochemistry, cytogenetics and molecular biology, made it possible to better understand these lesions separating lesions that can be considered as simple breast cancer risk markers (LIN 1, LIN 2, LIN 3 type I) from those that correspond to true precursors of breast cancer (LIN 3 types II and III). The management varies according to the histological type. The early diagnosis of these lesions thanks to the screening as well as a good management could help reduce the incidence of breast cancer.

Keywords: breast lesions, precancerous, breast cancer, Tavassoli.

INTRODUCTION

The frequency with which pathologists and therefore clinicians are confronted with precancerous lesions of the breast has increased considerably with the generalization of mammographic screening, and probably because of better anatomopathological management of operative specimens.

These precancerous lesions of the breast correspond to epithelial proliferations ducts or lobules divided into several distinct entities:

- Intra-ductal epithelial proliferation, classified in three groups: simple ductal hyperplasia, atypical ductal hyperplasia, ductal carcinoma in situ.
- The flat epithelial atypia, also called metaplasia cylindrical with atypia (MCA).
- Lobular lesions, grouped under the terminology lobular neoplasia. In this term are grouped lesions of very heterogeneous nature, heterogeneity emphasized by the contribution of immunohistochemistry and molecular biology.

Here we will only be dealing with the latter. The point is that they raise many questions, are subject to doubt and controversy [1], leading to a reconsideration of their meaning, their classification and also their management.

Thus, lobular carcinomas in situ have long been regarded as indicators risk of breast cancer, could actually be direct precursors of invasive lobular carcinomas (ILC) [2].

Anatomopathological classification

Lobular neoplasias are characterized by the presence of an epithelial proliferation made of cells identical to each other, of small size, with regular nuclei, abundant cytoplasm sometimes vacuolized, non-cohesive. They develop in the light of acini of lobules that they more or less distend and can also colonize the milk ducts in a pagetoid mode (Figure-1).

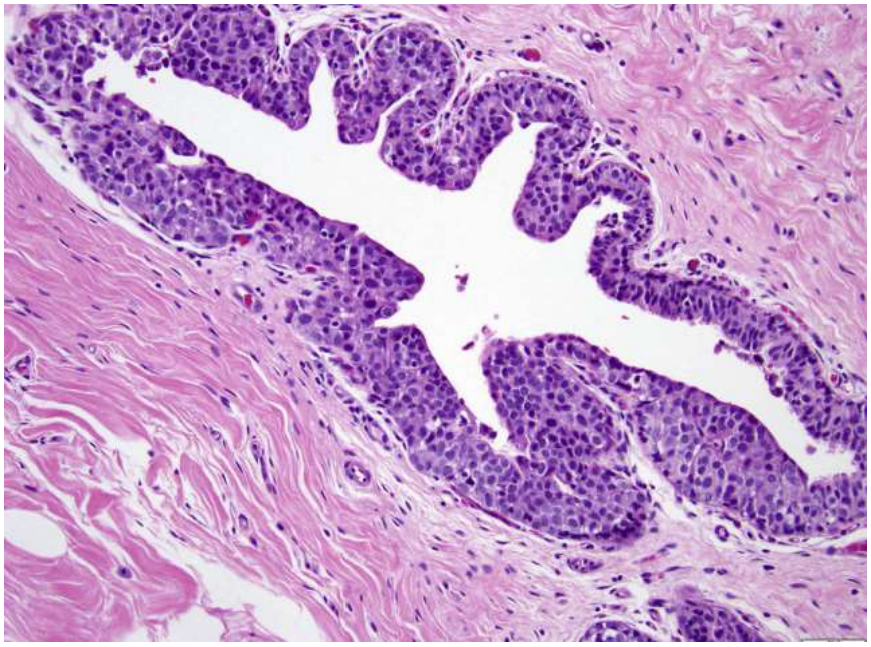

Fig-1: LCIS, classic type, with pagetoid growth in a duct. Magnification x 200 [11]

Their terminology and classification is currently disputed.

A first classification clearly distinguished two types of lesions, atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS), based on the importance of cell proliferation and the morphological consequences it leads to:

- When the acini are partly invaded, not or slightly distended, with a light still visible, or if less than half of the acini of a unit is invaded, we talk about ALH.
- When on the contrary more than half of the acini of a unit is filled and distended by neoplastic cells, the diagnosis of LCIS can be made.

This classification has the merit of separating two entities that have not at all the same prognostic significance, LCIS with a risk of occurrence of invasive cancer twice as high as ALH: ALH is classified as moderate risk (RR x4-5) with a greater risk of developing cancer in the same breast as ALH has been diagnosed, this cancer may be both ductal and lobular, while LCIS is classified as high risk (RR x 8-10), with equivalent risk of developing cancer in one or the other of the two breasts [3].

Tavassoli *et al.*, [4] proposed another classification based on the term of Lobular intraepithelial neoplasia (LIN), which is based on morphological criteria and has three grades: LIN 1, LIN2 and LIN3 [Table 1]. This classification has been adopted by WHO.

LIN1 and LIN 2 represent the majority of LN lesions (approximately 95%)

For Tavassoli [4], the risk of invasive cancer occurring with grade: is the highest for LIN 3, which, at the time of its discovery, is already associated with invasive cancer. LIN 3 lesions are associated with infiltrating lobular carcinoma in 86% of cases, compared with 47% for LIN 2 and only 11% for LIN 1 [5].

This classification is all the more justified if the lobular neoplasias are considered as risk indicators for invasive breast cancer; some studies lead them to consider them more and more as true precursors [6]. 10 to 20% of women with NL develop invasive breast cancer 15 to 25 years later, in the same breast or in the contralateral breast, which may be both ductal and lobular. The cancer occurs preferentially in the same breast and in the territory where the LN had been diagnosed [6], calling into question the concept of equivalent risk for both breasts.

This "filiation" essentially concerns mainly lesions of LIN 3. Molecular biology brings arguments in favor of this filiation: there are indeed molecular alterations common to LN and invasive lobular carcinoma: loss of heterozygosity on chromosomes 17p, 17q, 16q, and a gain in 1q: strong expression of estrogen and progesterone. Similarly, LN, such as invasive lobular carcinoma are negative after immunostaining by the anti-E-cadherin antibody: the loss of expression of E-cadherin is a characteristic of these lesions.

Diagnosis of lobular neoplasia (LN)

Their frequency is low, ranging from 0.5 to 3.8% of biopsies [7]. They particularly affect women between 40 and 50 years, and become less common after menopause. The lesions are multifocal in 50% of cases and bilateral in 30% of cases [6]. They occur on average 10 years earlier than ductal carcinomas in situ.

Classically LN does not have a clinical, radiological or even macroscopic expression. Their diagnosis is usually made "by chance", on a biopsy performed for a focus of microcalcifications or on the examination of an operative specimen. LIN 1 and LIN 2 are very rarely translated by the presence of microcalcifications [7], unlike LIN 3.

Particular importance should be attached to radio-histological confrontation: this confrontation makes it possible to verify that the biopsic samples have indeed covered the lesion, which is a priori the most severe and that they are well representative, but also that the histological result is in agreement with the nature of the radiological images considered as suspicious.

In the literature, rates of underestimation are generally lower in the most recent studies than in the older ones.

Underestimation rates vary according to:

- Radiological characteristics: they are higher in case of mass than in case of microcalcifications
- BIRAD level,
- As well as the sampling technique (use of large caliber needles, coupled with suction systems which allow to obtain a larger tissue quantity) [8]; the risk of underestimation is lower when the radiological image was taken entirely during the biopsy.

Furthermore; lesions of LIN, as for ductal lesions, are not necessarily overlapping with radiological images: these differences in topographic distribution help to explain the rates of underestimation.

Therapeutic management

She ranked on the LIN classification, divided into three categories (LIN 1, LIN 2, LIN 3) [12].

This management was the subject of recommendations published by the Cancer Institute (INCa) in November 2009. It is adapted according to the histological result of the biopsy samples:

LIN1

- Surveillance is only recommended, in the same way as in situ ductal carcinomas treated by conservative surgery.
- In case of risk factors (histological lesions at risk, family or personal antecedents) or radio-histological discordance (non biopsy specimens) representative of the radiological image), a surgical biopsy may be considered.

LIN2

- Biopsy surgery and surveillance.
- For LIN 1 and LIN 2, there is no indication to perform a mastectomy, radiotherapy or hormonotherapy.

LIN3

- The initial treatment is based on a surgical excision with anatomopathological examination of the operative specimen.
- The management is then defined according to the results of this examination.
- The monitoring is identical to that of ductal carcinomas in situ treated with conservative surgery.

Table-2 (from the INCa recommendations) summarizes the action to be taken in the three types of LIN 3.

Table-1: Classification of lobular lesions in LIN (lobular intraepithelial neoplasia) [4]

Grade	Description	Equivalent
LIN1	Partial or complete replacement, or displacement, of normal acini epithelial cells within one or more lobules by the proliferation of generally uniform cells that can fill, but not distend, the affected acinic lumens, compared to unaffected adjacent acini.	ALH without distension of acini
LIN2	More abundant proliferation of identical cells filling and distending some or all acini. The acinar margins remain distinct and persistently separated by stroma in the different acini. Some residual acinic light may persist.	ALH with distension of acini or LCIS
LIN3	-Type 1: Proliferation of identical cells, but sometimes more atypical cells may predominate. An important parameter is the massive degree of distension of acini so that acini can appear confluent. The interacinous stroma is rarely visible (LIN macroacinar) Type 2: proliferating cells of the «ring cell» or pleomorphic type. In this case, a significant acinous distension may not be present (LIN ring cell signet, LIN pleomorphic) -Type 3: acinous distension with central necrosis (necrotic LIN).	LCIS

Table-2: Management the three types of LIN 3

LIN 3 TYPE1 (non-pleomorphic, no necrosis, no kitten ring after examination of the operative specimen)	**LIN 3 TYPE 2 ou 3** (pleomorphic, with necrosis, or kitten ring after examination of the operative specimen)
-Surgical excision and anatomopathological examination of the operative specimen -No recovery if affected banks (idem LIN l and LIN 2) -No radiotherapy -No hormonotherapy -Surveillance (idem DCIS)	-Surgical excision and anatomopathological examination of the operative specimen -Objects of healthy banks for the pleomorphous contingent and / or contingent with necrosis and / or ring cell -Radiotherapy can be discussed -Surveillance (idem DCIS)

The situations in which surgical abstention is retained must have been the subject of a consultation between surgeon, radiologist and anatomopathologist. They assume the absence of [9, 10]:

- Pejorative histological criteria.
- Radiological signal not explained by LN (Mass image or image of architectural disorganization).
- Residual microcalcifications.
- Significant or personal or family history of breast cancer.

Even in these situations, we should be very careful because these criteria have been established retrospectively and have not been validated by prospective studies.

CONCLUSION

Improved knowledge on LN through immunohistochemistry, cytogenetics and molecular biology, has made it possible to better classify these lesions, better know their significance by separating the lesions that can be considered as simple breast cancer risk markers (LIN 1, LIN 2, LIN 3 of type 1) from those that correspond to true precursors of breast cancer (LIN 3 types 2 and 3).

Surgical management consists in:

- Simple surveillance without surgical excision in case of isolated LIN 1 discovered at the biopsy.
- Surgical excision and monitoring in case of LIN 2 to isolated LIN 1 of type 1, identical attitude to that adopted in case of ADH.
- Surgical excision, operative revision in case of a positive margin, discussion of a complementary radiotherapy treatment [13], followed by surveillance; In the other cases, identical attitude (apart from the place of radiotherapy) to that adopted for DCIS.

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