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LOBULAR NEOPLASIA: ATYPICAL HYPERPLASIA AND LOBULAR CARCINOMA IN SITU: LITERATURE REVIEW

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ABSTRACT

Lobular neoplasia pathology is a rare proliferative breast lesion, includes atypical hyperplasia and lobular carcinoma in situ, growing inside ducts and terminal ductolobular units. It represents a marker of increased risk for breast cancer and a non-obligate precursor of malignancy. Evidence available on diagnosis and management is scarce. It is frequently found incidentally associated with other lesions, but can be visible through mammography, ultrasound or magnetic resonance. Due to the risk of underestimation, surgical excision is often performed. The analysis of imaging and histopathological characteristics could help identifying low-risk cases, for which surgery is not necessary. Chemopreventive agents can be used for risk reduction.

KEYWORDS: Lobular neoplasia; atypical lobular hyperplasia; lobular carcinoma in situ; review; chemoprevention.

I- Definition and histological diagnosis

Lobular neoplasia (LN) is asymptomatic and most often incidental diagnoses. In histology, it is a colonization of the ductolobular unit by an atypical proliferation of small non-cohesive cells, which can diffuse in a pagetoid mode to the galactophoric channels with a large caliber. The distinction between atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) depend to the number of invaded acinis and their distension, inside of the degree of lobule infiltration. The last OMS classification 2012.[1] retained a binary separation between them. The distinction between LCIS and ALH is based on the percentage of acini in a lobular unit that are distended and filled by lobular cells. If 50% or more of the acini are expanded or distorted by lobular cells, a diagnosis of LCIS is favored. Lesions that do not meet these criteria are placed in the ALH category.[2]

Recently, more aggressive variants of LCIS, such as pleomorphic LCIS have been identified. Pleomorphic LCIS has higher grade features than classical LCIS.

II- Epidemiology

Lobular neoplasia (LN) was noted in 0.5 to 4% of benign breast biopsies, They occur women of all ages with predominantly in premenopausal women (average age of 49 years) (OMS, 2012).

Lobular neoplasia is a multicentric lesion in almost 85% of patients and bilateral in 30 to 67% of cases.[1]

III- Discovery Circumstances and radiological data

Lobular neoplasia is clinically asymptomatic: no tumor, no skin change, no nipple discharge or nipple eczema, rather incidental discovery, associated with other lesions responsible for a radiological signal. Frequently found in samples of foci of microcalcifications, but these microcalcifications are found in other lesions such as foci of adenosis, cylindrical metaplasia, fibrocystic mastopathy.[2]

IV- Lobular neoplasia risks

1) Risk of invasive cancer

lobular neoplasia is a clonal neoplastic proliferation and a non-obligatory precursor of invasive carcinoma of the ductal or lobular type, with evidence of a genomic profile and chromosomal alterations comparable between lobular neoplasia and synchronous infiltrating lobular carcinoma, with however genomic instability higher in lobular carcinomas in situ pleomorphic.[2]

Currently several studies have shown that the identification of AH and LCIS at image-guided biopsy is associated with an increased risk of developing breast cancer. The entity of this risk seems to be variable, depending on lesion type.

The risk further doubles when the presence of proliferating, high-risk lesions is associated with family history of breast cancer.[4]

2) Risk of underestimating an invasive cancer: The discovery of lobular neoplasia lesions on a radio-guided biopsy therefore poses also the problem of a possible underestimation of an authentic associated carcinoma, not interested in radiological sampling. a few series have reported the rates of underestimation of carcinoma (ductal carcinoma in situ or invasive carcinoma) after additional surgical excision.

In a retrospective series of 78 cases, de Chaudhary et al.[5] The rate of underestimation was 3.4. A retrospective study by Murray et al.[6] the overall rate of underestimation was 2% (2/101), 1.5% (1/81) for atypical lobular hyperplasia and 5% (1 / 20) for lobular carcinoma in situ.

Throughout the literature, very variable rates of underestimation, sometimes relating to very small series, are reported, ranging from 0 to 67% for atypical lobular hyperplasia and from 0 to 60% for the in situ lobular carcinoma.[7] In a recent review.[8] where the authors take only studies with careful radio-histological correlation, the average rate of underestimation was around 2% for ALH and 10% for lobular carcinoma in situ.

The National College of French Gynecologists and Obstetricians (CNGOF) published in 2015.[9] a summary work that goes in the same direction and retains that in the event of a macrobiopsy diagnosis.[9-11] a risk of underestimation of 1.2 to 3.1% for atypical lobular hyperplasia, from 5 to 8.1% for lobular carcinoma in situ classic and close to 50% for lobular carcinoma in situ pleomorphic and / or with necrosis (level of evidence 3 or 4).

V- Management

1) - Criteria for Consideration of Surgical Excision Versus Imaging Surveillance.

In the literature, there is a lack of consensus regarding the need for surgical excision of lobular neoplasia when identified on CNB (core needle biopsy). Prior management recommendations advise the surgical excision for lobular neoplasia. However, new research suggests that under certain circumstances, lobular neoplasia diagnosed on CNB can be managed using imaging surveillance instead of surgical excision, calling to question the necessity of surgery for these high-risk lesions. Undergoing surgery for a diagnosis of lobular neoplasia carries likely financial and psychologic implications, because these women are at an increased life-time risk of developing breast cancer and may require additional surgical intervention in the event of cancer development. Therefore, the ultimate goal and inherent challenge is to identify patients who can be followed safely with imaging surveillance, obviating surgery. A growing body of literature suggests that the likelihood of upgrade is low (less than 5%) with small volume lobular neoplasia on CNB in the setting of radiologic-pathologic concordance.[10,11]

Rendi et al.[10] reported that normal-risk patients who underwent CNB to assess calcifications identified on routine mammographic screening with lobular neoplasia alone did not result in upgrade and therefore may not require excisional biopsy. Patients with any other imaging indication (high-risk screening, determination of extent of disease, follow-up after lumpectomy, evaluation of a clinical finding) or an imaging finding (mass, architectural distortion, MRI enhancement) were found to have a non-zero risk of upgrade at excision.[10]

Middleton et al.[12] evaluated the efficacy of using standard radiologic and histologic criteria to guide the management of patients with LCIS and ALH. Surgical excision was recommended for all cases of radiologic-pathologic discordance and was more likely for cases of LCIS rather than ALH, for targeted rather than incidental lesions, in cases with five or fewer cores taken, and for mass lesions. These same factors were associated with a risk of upgrade at surgical excision.[12] Although no strict guidelines were used to select the cases that would be recommended for surgical excision instead of image surveillance, only five of the cases that were recommended for image surveillance and chemo-prevention were upgraded to malignancy at surgical excision, with three cases developing cancer in a different quadrant from the biopsy site. Despite the study limitations, clinical management of LCIS and ALH with imaging follow-up was shown to be a viable alternative to surgical excision in specific instances.[12] The study recommended clinical management with imaging surveillance for patients with a limited volume (fewer than 3 terminal duct lobular units [TDLUs]) involved by ALH or LCIS and found that for 98% of these patients the lesion was not up-graded on surgical excision.[12]

2) - Chemoprevention and Risk Reduction Strategies

Patients diagnosed with lobular neoplasia, the increased relative risk for breast cancer is a 3.1- to 5.9-fold increase for ALH and a 6.9- to 11.0-fold increase for LCIS.[13,14] Coopey et al.[15] performed a study to evaluate a woman's risk of breast cancer on the basis of atypia type and to determine the effect of chemoprevention in decreasing this risk. Of the 2938 patients with atypical breast lesions, 1658 were documented to have received no chemoprevention, and 11.1% developed breast cancer at a mean follow-up of 68 months.[15] In a subset of patients surgically treated for atypia, those who received no chemoprevention had an estimated 10-year breast cancer risk of 21.3%, whereas those treated with chemoprevention had a 10-year risk of 7.5% ($p < 0.001$).[15] Chemoprevention use was shown to significantly reduce breast cancer risk for all atypia types ($p < 0.05$).[15] In the National Surgical Adjuvant Breast and Bowel Project (NSABP) P-1 trial [74].[16] women at risk due to atypical hyperplasia experienced a 75% reduction in breast cancer development, and those at risk due to LCIS experienced a 46% reduction after tamoxifen treatment. The risk reduction of cancer development was attributable

entirely to a decreased incidence of estrogen-receptor positive breast cancers.[16] An analysis of four randomized trials of tamoxifen chemoprevention found a 38% reduction in breast cancer incidence.[17]

In women with atypical hyperplasia and LCIS, the use of chemoprevention has been shown to reduce breast cancer incidence at 10 years from 21.3% to 7.5% ($p < 0.001$).[15] Despite the benefits of tamoxifen use in high-risk patients, the side effects, particularly endometrial cancer, have limited its use. Raloxifene, a selective estrogen receptor modulator, has been compared with tamoxifen in the NSABP P-2 trial and showed approximately three-fourths of the efficacy of tamoxifen in the prevention of invasive and in situ breast cancer, with somewhat reduced toxicity.[18,19,21] In spite of the adverse effects, current guidelines recommend discussion of tamoxifen chemoprevention with premenopausal women and discussion of tamoxifen and raloxifene with postmenopausal women at high risk of breast cancer.[18,20,21]

VI- CONCLUSION

Lobular neoplasia represents a marker of increased risk for breast cancer and a non-obligate precursor of malignancy. Evidence available on diagnosis and management is scarce. They are frequently found incidentally associated with other lesions, but can be visible through mammography, ultrasound or magnetic resonance. Due to the risk of underestimation, surgical excision is often performed. The analysis of imaging and histopathological characteristics could help identifying low-risk cases, for which surgery is not necessary. Chemopreventive agents can be used for risk reduction.

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