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Atypical epithelial hyperplasia of the breast: state of the art

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Abstract

Introduction: Atypical epithelial hyperplasia (AEH) of the breast is considered benign histological lesions with breast cancer risk. This review focuses on clinical signification and management of AEH that remains controversial.

Areas covered: A review of published studies was performed using medline database. In this review, we fully describe the current evidence available. In particular, we describe 1) data from immunohistochemistry and molecular studies that suggest AEH is a precursor of breast cancer; 2) epidemiological studies demonstrate low rate of breast cancer in women with AEH; 3) surgical excision is necessary after diagnosis of AEH, such as lobular carcinoma in situ or atypical ductal hyperplasia, on core needle biopsy; 4) although current recommendations are evolving to fewer (if not no) excisions for flat epithelial with atypia and classic lobular neoplasia found on percutaneous biopsy (without radiologic indications for excision).

Expert commentary: HEA management steel need prospective evidences, but recent retrospective data give some clue for less invasive management for some of HEA.

Key words: atypical ductal hyperplasia; columnar cell lesions with atypia; lobular neoplasia; atypical lobular hyperplasia; lobular carcinoma in situ; core needle biopsy; surgical excision; breast cancer.

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1- Introduction

The increase in the relative frequency of atypical hyperplasia (AH) lesions of the breast coincided with the generalisation of organised breast cancer screening in France: the frequency of pure AH lesions in a series of surgical breast biopsies was 3.6% in 1985 [1] and 23% in 2007 [2]. Atypical hyperplasia of the breast, considered benign histological lesions with breast cancer risk, come under the broader category of fibrocystic breast disease: the common findings are epithelial hyperplasia (i.e. proliferation of cells beyond the 2-layer architecture of the epithelium lining the lactiferous ducts and lobules) and abnormal appearance and arrangement of cells. Currently, AH is divided into atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA) and lobular neoplasia (LN), which itself is further divided into atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) [3]. AH lesions do not included ductal carcinoma in situ (high grade or low grade), which were true precursor of invasive breast carcinoma. The clinical significance of these lesions is still subject to controversy. At the least, all are markers of breast cancer risk: women with one of these lesions have a higher risk than the general population of developing cancer in the ipsilateral and contralateral breast [4]. Some types of AH are not just risk markers but probably veritable precursors of invasive malignant lesions, constituting a necessary but insufficient step in the natural history of the cancer [5-8]. For these reasons, clinicians have to confront several issues: (a) discovery of such lesions on a breast specimen obtained under image guidance (and hence fragmentary in nature) raises the issue of whether the radiological signal is representative of the histology, making positive and differential diagnosis problematic for the pathologist and presenting the dilemma of whether to proceed to surgical biopsy for analysis of the whole signal; (b) uncertainty surrounding the natural history of the lesions translates into: closer surveillance if they are considered only markers of cancer risk, or surgical excision if they are considered precursor lesions; and extreme caution with regard

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to combined oestrogen–progestogen hormone treatments or even chemoprevention [9, 10]); (c) surgery of these lesions, which are usually non-palpable, is associated with particularities with respect to their localisation, the orientation of the excised tissue following as closely as possible the histological diagnosis, and positive or negative margins depending on whether or not they are considered precursor lesions.

The present article begins with nosology of AH of the breast, then management of the lesion is described in detail for the different histological groups (ADH, LN, FEA), whether they are discovered in a percutaneous breast specimen or surgical specimen and are associated or not with an invasive lesion. The specificities of breast surgery subsequent to the discovery of pure AH on percutaneous biopsy are given. Finally, the role of menopausal hormone replacement therapy (HRT) and chemoprevention in patients with AH is discussed, using the international literature.

2- Materials and methods. A review of published studies was performed. Medline baseline searches were performed using the following key words: atypical ductal hyperplasia, columnar cell lesions with atypia, flat epithelial atypia, lobular neoplasia, atypical lobular hyperplasia, lobular carcinoma in situ, core needle biopsy, breast cancer, precursor lesion, hormonal replacement therapy. For each breast lesion, identified publications were assessed for clinical practice in epidemiology, diagnosis and patient management.

3- Results

3.1- Nosology of atypical hyperplasia

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AH can be divided into three broad groups: atypical ductal hyperplasia, lobular neoplasia and flat epithelial atypia.

3.1.1 - Flat Epithelial Atypia (FEA). This pathological entity has only recently been designated as such [3, 11, 12]. Its histology corresponds to that described under other names (clinging carcinoma of the monomorphic type [13], ductal intraepithelial neoplasia of the flat monomorphic type [7], columnar cell change with atypia [11, 12], flat epithelial with atypia [3], clinging DCIS, etc.). Columnar metaplasia is a ductal neoplastic alteration in which normal luminal cells are replaced by 1 to 3-5 layers of columnar cells (cells with apical "snouts" and luminal secretions) and the terminal duct lobular unit (TDLU) shows low grade atypia (variability in cell height, higher nucleus-to-cytoplasm ratio, round nuclei with nucleoli, loss of polarity in relation to the basement membrane, etc.) [3]. Two forms of columnar metaplasia are distinguished: columnar cell change, in which acini are lined by one or two layers of modified epithelial cells; and columnar cell hyperplasia, in which acini are lined by more than two layers of epithelial cells. They may be associated with mammographically detectable microcalcifications. FEA can be distinguished from columnar cell change by the presence of cellular atypia and from ADH and ductal carcinoma in situ (DCIS) by the absence of architectural atypia [11, 12, 14, 15]. The incidence of pure FEA was approximately 3.5% of surgical breast biopsies in 2007 [16]: it is frequently discovered secondary to BIRADS (ACR) 4 microcalcifications, which are present in 50 to 75% of cases. The biological and clinical significance of FEA is still not known with certainty. Sometimes the three forms of AH (FEA, ADH, LN) co-exist in a single breast surgical specimen and sometimes in the same TDLU [2, 17-21]. These 3 lesions, co-existing in a single breast surgical specimen, have similar immunophenotypical and cytogenetic profiles, such that FEA may be considered a precursor or as the first (non-obligate) morphological expression of LN and ADH [21]. In breast surgical specimens, FEA is also frequently associated with more

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serious lesions such as low-grade DCIS and invasive carcinomas (especially the tubular subtype). For some authors, this is sufficient to consider FEA as a precursor to invasive disease [17, 18, 20, 22]. In addition, immunophenotyping studies have shown a similar expression profile between, on the one hand, FEA and, on the other hand, DCIS and invasive carcinoma lesions [8, 20, 23, 24] (high expression of oestrogen and progesterone receptors, BCL-2, low Ki-67 and well-differentiated immunohistochemical cytokeratin profile (CK5- and CK18+)). Similarly, cytogenetic studies of FEA lesions associated with DCIS and invasive carcinoma lesions showed the same changes in the genetic molecular profile [7, 8, 25]. For these authors, the continuum of phenotypical and cytogenetic lesions constitutes the basis for considering FEA to be a (non-obligate) precursor of low-grade DCIS and invasive carcinoma [7, 8, 20, 21, 25] in which FEA represents the first step on the carcinogenesis pathway [8, 21]. However, in the few series with long-term follow-up — involving 25, 101 and 59 patients followed up for 19, 10 and 5 years, respectively — the diagnosis of FEA did not lead to invasive carcinoma [13, 16, 26-30]. FEA therefore has a very low risk of becoming invasive and in light of the data from these series, it cannot be considered a precursor of breast cancer. More data are required to determine the clinical and biological significance of FEA.

3.1.2. - Atypical ductal hyperplasia (ADH). ADH is an intraductal monomorphic cellular proliferation with some but not all of the cytological and architectural characteristics of low grade DCIS (a round nucleus and/or a stable nucleus-to-cytoplasm ratio and/or regular cellular architecture without particular organisation) [2]. There are 2 quantitative criteria that distinguish ADH from low-grade DCIS: the presence of homogeneous involvement of not more than 2 membrane-bound spaces; or a size of less than 3 mm. [3, 31].

The mean age at diagnosis is 46 years. The incidence of pure ADH was approximately 2.1% of surgical breast biopsies in 1985 [1] and 12% in 2007 [16]. This lesion is classified in the

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moderate-risk group (relative risk of 4 to 5) for breast cancer [4, 32, 33] with higher risk in those with a first-degree family history [1]. ADH has no clinical manifestations, but is associated with radiological microcalcifications; it is usually discovered fortuitously in breast tissue. The clinical and biological significance of ADH remains subject to controversy. Cytogenetic studies of ADH have revealed the development of heterozygosity (especially 16q-) and allelic rearrangements similar to those of DCIS and invasive carcinoma, rendering ADH a non-obligate step in the carcinogenesis pathway [21, 34, 35]. However, epidemiological studies have shown that the natural history of this lesion does not necessarily culminate in invasion [16, 32, 33]: 2 cases of DCIS and 5 cases of invasive carcinoma were observed after a median follow-up of 160 months in 220 patients with pure ADH on an excision specimen [16]. Therefore, this lesion is currently considered a risk marker for breast cancer for management purposes.

3.1.3 - Lobular neoplasia (LN). LN is the proliferation of small, discohesive (due to lack of E-Cadherin expression), monomorphic cells causing distension of the terminal duct lobular unit and possible pagetoid spread into lactiferous ducts [3]. This lesion is usually multifocal and bilateral [36, 37]. Lobular neoplasia is characterised by the absence of E-Cadherin (a transmembrane protein) staining on immunohistochemistry [3]. Lobular neoplasia refers to a spectrum of lesions formerly called atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) [36]. In ALH (3a), less than half of the lobules of a lobular unit have been invaded. In LCIS (3b), cellular proliferation affects more than half of the acini of the lobular unit [36]. Another LN dichotomy, currently enjoying widespread use, divides it into classic and pleomorphic forms. Pleomorphic lobular neoplasia is distinguished from the classic form by its pleomorphic cytological appearance (discohesive cells with large cytoplasm, eccentric nucleolus), frequent necrosis, microcalcifications [3, 38, 39]. Most pleomorphic LN lesions are type 3 LN. Lobular neoplasia has no radiological or clinical manifestations; it is usually

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discovered fortuitously in breast tissue readily biopsied for microcalcifications. ALH is classified as a moderate-risk lesion (relative risk of 4 to 5) [4] with a higher risk of developing breast cancer, of ductal or lobular histology, in the breast in which ALH was diagnosed [40]. LCIS is classified as a high-risk lesion (relative risk of 8 to 10) [4] with an identical risk in both breasts [41]. The mean age at diagnosis is 46 years [42]. The incidence of pure LN was approximately 1.6% of surgical breast biopsies in 1985 [1] and approximately 7.8% in 2007 [16]. The clinical and biological significance of LN remains subject to controversy. Immunophenotyping and cytogenetic studies demonstrate the lesional similarities with concomitant invasive carcinoma (high expression of oestrogen and progesterone receptors, low Ki-67 and well-differentiated cytokeratin profile (CK5- and CK18+)), and these findings lead some to consider LN as a precursor of invasion [43]. However, epidemiological cohort follow-up studies show that the natural history of the lesion does not necessarily lead to invasion [16, 44, 45]: 7 cases of IC were observed following median follow-up of 160 months of 139 patients with pure LN on an excision specimen [16]. Therefore, the current consensus is to consider classic LN a risk marker [3] for breast cancer rather than a precursor of invasion. As regards the pleomorphic form of LN, epidemiological studies are lacking, but in view of the strong association with invasive lobular carcinoma, this lesion is classified as a precursor of invasion [3, 38, 39].

To summarise, the immunohistochemistry profiles of these three lesions are similar and one could be inclined to classify them as precursors of invasion; however epidemiological follow-up studies have shown that the natural history of these lesions does not lead to invasion, so the current consensus is to classify them as only risk markers for breast cancer for management purposes (with the exception of pleomorphic LN) (Table 1).

3.2 - Diagnosis of atypical hyperplasia after percutaneous sampling

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The clinical and biological significance of AH remains subject to debate: it is variously considered a risk marker for breast cancer or a precursor of invasion. This distinction comes to the fore when AH is discovered on percutaneous breast biopsy. If AH is a risk marker, follow-up surgical excision does not present any therapeutic benefits and one must develop a primary prevention strategy in this population at risk of breast cancer. On the other hand, if AH is a precursor of invasion, follow-up surgical excision is mandated for secondary prevention of breast cancer, with resection *in sano*. Moreover, radiological techniques for breast biopsies yield a certain number of false negatives, hence a risk of missing malignant lesions. So even if AH is a risk marker for cancer, its identification on percutaneous biopsy may require follow-up diagnostic surgery. Techniques for radiologically guided breast sampling are continually evolving: the quantity of tissue ranges from 17 mg with an automated gun with 14 G needle to 110g for an aspiration system with a 10 G probe (Vacora® system) [46, 47]. The increase in the breast volume obtained under radiological guidance is associated with a concomitant increase in the specificity of the sample and reduces the number of false negatives. In the long term, improvement in the diagnostic sensitivity of radiological techniques will reduce the indications for follow-up surgical excision. However, the size of the needles used, the use or not of an aspiration system and the number of samples taken remain at the discretion of the radiologist (6 to 27 cores in the literature [46]). The sampling technique for a given radiological signal is not standardised. All these difficulties prevent a consensus from being reached for secondary lumpectomy after diagnosis of pure AH on percutaneous biopsy.

3.2.1 - Pure FEA on percutaneous breast biopsy. Villa *et al.* analysed 121 cases of FEA diagnosed on macrobiopsy (9 G for 57 cases and 11 G for 64 cases) who then underwent excision surgery. The underestimation rate of malignancy was 5.8% (7/121) without a significant difference between the two types of macrobiopsy. However, the underestimation

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rates were 0 (0/85) in the absence of residual microcalcifications post-macrobiopsy versus 19.4% (7/36) when microcalcifications persisted [48].

Ceugnart *et al.* reported an underestimation rate of 6% (3/52) from a retrospective series of 52 cases of FEA diagnosed on macrobiopsy (11-8 G) who then underwent excision surgery [49]. The underestimation rates reported for FEA diagnosed on macrobiopsy (≤11G) varied from 0 to 20%: 0 (0/33 and 0/24) for Piubello *et al.* [50] and de Mascarel *et al.* [2]; 3.2% (3/95) for Uzoaru *et al.* [51]; 8.4% (2/24) for Sohn *et al.* [52]; 14% (4/28) for Solorzano *et al.* [53]; 20% (3/15) for Ingegnoli *et al.* [54]. In cases of FEA diagnosed on microbiopsy, Khoumais *et al.* found an underestimation rate of 10% (10/94) and Kunju *et al.* found a rate of 21% (3/14) [19, 55].

As current recommendations are evolving to fewer (if not no) excisions for FEA found on percutaneous biopsy (in the absence of radiologic indications for excision).

3.2.2. - Pure ADH on percutaneous breast biopsy. With regard to pure ADH identified on percutaneous biopsy, there have been many series evaluating the underestimation rate, which varied according to the technique (size of needles, aspiration system). Colombo *et al.* conducted a literature review: in 16 studies with 1929 cases of ADH [56], the underestimation rate varied from 13 to 21% in studies that exclusively or mostly included macrobiopsies (9-11 G) and 34 to 65% in studies with microbiopsy only (14 G) [56-71].

In the literature, the most common predictors of underestimation of malignant lesions (in situ or invasive) after identification of ADH are [56-59, 61-72]:

- Microbiopsy (14 G) versus macrobiopsy (9-11 G)
- Mammography ACR 4/5 versus 3, architectural distortion
- Lesion with clinical symptoms, mass, visible on ultrasound
- Initial radiological size > 15mm

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- Persistence of radiological signal post-biopsy (residual calcifications)
- Multiple foci ≥ 3
- Marked cytonuclear atypia
- Less well trained pathologist

In the series of Travade *et al.*, half of the ADH patients (31/62) were not operated upon but monitored mammographically (1 patient lost to follow-up). In the group of women who did not undergo surgery and in whom macrobiopsy led to disappearance of the microcalcification focus (mean size of microcalcification foci: 6 mm (2-10mm)), no cancer was found during a median follow-up of 35.5 months (range: 22-62 months) [73].

Forgeard *et al.* [74] proposed a decision-making algorithm based on recursive partitioning, with no surgery if:

- the microcalcification focus measures less than 6 mm and macrobiopsy leads to complete disappearance of the microcalcification focus
- the microcalcification focus measures less than 6 mm but with persistence of microcalcifications or if the focus measures between 6 and 21 mm (with or without residual microcalcifications) and there is a maximum of 2 foci of ADH.

Uzan *et al.* developed a continuous predictor based on a logistic regression model (i.e. a nomogram) based on 3 factors: age, disappearance of radiological lesions after macrobiopsy and size of microcalcification focus (< or > 16 mm) [75].

3.2.3. - Pure LN (ALH and LCIS) on percutaneous breast biopsy. In a cohort study involving 184 cases of ALH or LCIS diagnosed on radioguided breast biopsy, Shah-Khan *et al.* reported underestimation rates of malignancy (in situ or invasive) as determined by surgical excision [76]. Among the 184 cases, 147 (79.9%) were ALH and 37 (20.1%) were LCIS. Follow-up surgical excision was performed in 101 cases (54.9%): 81/147 ALH and 20/37 LCIS (surgery group). The surveillance group contained the remaining 83 cases (66/147 ALH and 17/37

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LCIS) for which 65 cases with follow-up data enabled an analysis of data with median follow-up of 53 months (6-135 months). The breast biopsy was a macrobiopsy (9-11 G) in 143 cases (74/101 (73%) from the surgery group and 69/83 (83%) from the surveillance group) and a microbiopsy (14 G to 18 G) in 41 cases. The underestimation rates were 1.2% (1/81) for ALH and 5% (1/20) for LCIS (p=0.36). In the surveillance group (n=65), an ipsilateral cancer was observed in 1/51 (2%) cases of ALH and 3/14 (21%) cases of LCIS (p=0.04). In the surgery group, an ipsilateral cancer was observed during follow-up (median follow-up of 47.9 months (6-212 months)) in 1/61 (1.6%) cases of ALH and in no cases of LCIS (p=0.6). A contralateral cancer was diagnosed in 3/112 (2.7%) cases of ALH and in 1/26 (3.8%) cases of LCIS (p=0.6) [76]. Muray *et al.* reported similar findings [77]. Shah-Khan *et al.* and Muray *et al.* concluded that surgery not be systematically performed in cases with histology-radiology concordance.

In the series by Zhao *et al.* involving 237 cases (163 ALH and 74 LCIS), the underestimation rate, determined by presence of a malignant lesion (in situ or invasive) on follow-up surgical excision, was 3.1% (5/163) for ALH cases and 8.1% (6/74) for LCIS cases. A macrobiopsy (9 G) had been performed in 98% of cases [78].

In cases of ALH or classic LCIS, the risk is higher in the presence of a limited biopsy (microbiopsy 14 G versus macrobiopsy 11-8 G) or lesions greater than 20mm or classified BIRADS (ACR) 4/5 on initial imaging and a high number of foci (>4) — although the last parameter is difficult to analyse histologically. The underestimation risk seems low (<3-5%) in the recent series with cases of ALH or classic LCIS found on macrobiopsy with verification of good histology-radiology concordance [76, 77, 79-82]. If these different criteria are met, particularly histology-radiology concordance, close surveillance without surgery may be sufficient [30-35].

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As current recommendations are evolving to fewer (if not no) excisions for classic LN found on percutaneous biopsy (in the absence of radiologic indications for excision). Conversely, non-classic LCIS (i.e. pleomorphic LCIS, LCIS with necrosis and, for some authors, florid LCIS) carries a high risk of malignant lesion and represents a formal indication for surgical excision [56, 83, 84].

3.3. - Specificity of breast excision surgery: surgical excision for non-palpable lesions

There are no specific recommendations concerning the excision technique for non-palpable AH lesions found on percutaneous biopsy. This surgery requires preoperative localisation. There are several localisation methods, the classic one being placement of a metal marker under radiological guidance before the procedure. Given that the majority of patients are young women (mean age at diagnosis of 46 years) undergoing surgery for benign lesions, cosmetic considerations are important and indirect incisions are preferred. Furthermore, given the non-negligible rate of DCIS and invasive carcinoma on definitive histology (0% to 46% depending on AH), the surgical excision must remove the part of the breast from the pectoral muscle to the cutaneous plane centred on the marker. In cases of invasive carcinoma or DCIS, histological analysis of the excision specimen will render the margin status interpretable. For the same reason, the specimen must be orientated by the surgeon and radiologist in order to ascertain that the radiological signal is completely removed and at a distance from the edges of the specimen. Intraoperative frozen section analysis of the surgical specimen is not recommended (no target nodule for the pathologist, difficult histological analysis with borderline lesions, risk of not leaving any tissue for the permanent section). As a result of these constraints, in cases of invasive carcinoma or ductal carcinoma in situ, the diagnosis is known post-operatively. The patient must therefore be informed of the possibility of a second procedure for excision margins and if necessary for lymph node analysis. The axillary lymph node analysis presents the problem of performing sentinel lymph node biopsy on a previously

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operated breast. This is not recommended but feasibility studies are currently underway in France after studies demonstrated that there was no increase in the rate of false negatives with sentinel lymph node biopsy performed on a recently operated breast [85].

3.4. Management of surgical margins in presence of pure atypical hyperplasia

3.4.1. - Pure flat epithelial atypia in a surgical specimen. FEA has only been designated recently and there are no data on the effect of margins positive for FEA in a breast surgical specimen. In view of the low malignant potential of this lesion in the 3 cohort follow-up studies [2, 13, 26], the authors do not recommend re-excision [11].

3.4.2. - Pure atypical ductal hyperplasia in a surgical specimen. There are few studies evaluating the effect of positive margins in a surgical specimen with pure ADH. One study indicated that margins positive for ADH had no effect on the development of invasion [86]: this series had a small number of patients and short follow-up. Arora *et al.* consider that ADH at margins is a marker of an adjacent malignant lesion justifying further surgery [87]: in this study, underestimation could be interpreted as a false negative of the surgery, which did not remove the target radiological lesion. Given the expected low malignant potential of ADH following surgical excision (3% after a follow-up of 160 months [16]), further surgery for margins positive for ADH in a surgical specimen is not recommended [3].

3.4.3. - Pure lobular neoplasia in a surgical specimen. LN lesions are often multifocal and bilateral [42] and negative margins vis-à-vis this lesion do not guarantee that all LN lesions have been removed from the ipsilateral (and also contralateral) breast. Classic LCIS is considered a risk marker for breast cancer and it is recommended to not perform further surgery for margins positive for classic LCIS in a surgical specimen [3]. Pleomorphic LCIS must be approached distinctly, specifically as a precursor lesion of breast cancer for which excision with negative margins is recommended [3, 38, 45]. Some teams even treat it as DCIS

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with radiotherapy in case of conservative treatment [38, 45]. However, the benefits of such radiotherapy have never been studied for pleomorphic LCIS.

In conclusion, in cases of pure AH identified on surgical breast biopsy, the consensus is to not perform further surgery in cases of positive margins for the lesion considered (with the exception of pleomorphic LCIS).

3.5. - Management of surgical margins in presence of atypical hyperplasia and invasive cancer

3.5.1 - Flat epithelial atypia with DCIS or IC in a surgical specimen. There are no series evaluating the margin status vis-à-vis this lesion in association with DCIS or IC, but given that flat epithelial atypia has low potential for recurrence or progression to invasion, the margins for this lesion may be disregarded [12].

3.5.2 - Atypical ductal hyperplasia with DCIS or IC in a surgical specimen. There are few studies evaluating the effect of margins positive for ADH in surgical specimens with ADH in association with DCIS or IC. Arora *et al.* consider that the presence of ADH at or less than 1 mm from margins is a marker of an adjacent malignant lesion justifying re-excision [87]; but in this study, rather than fear of missing a malignant lesion, attention must be drawn to the incomplete surgery that did not excise the totality of the signal. In view of the low expected potential for development of ADH after surgical excision (3% for follow-up of 160 months [16]), re-excision for margins positive for ADH on a surgical specimen is not recommended [3].

3.5.3 - Lobular neoplasia with DCIS or IC in a surgical specimen. Studies involving invasive carcinomas in association with lobular neoplasia lesions show that margin status vis-à-vis lobular neoplasia does not affect recurrence-free survival or the rate of cancer recurrence [88-90]. Re-excision for margins positive for classic LN in a surgical specimen is not

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recommended [3]. As regards pleomorphic LCIS, margins negative for the pleomorphic LCIS component are essential for achieving local control of the disease [38], because this lesion is considered a precursor, a hypothesis verified for the specific case of invasive lesions surrounded by pleomorphic LCIS.

In conclusion, in cases of identification of AH in association with LCIS or IC on a surgical specimen, the consensus is to not perform further surgery in cases of positive margins for the AH lesion (with the exception of pleomorphic LCIS).

3.6. - Role of hormone replacement therapy in patients with atypical hyperplasia of the breast

AH is at the least a risk marker for breast cancer: its presence places the patient at a higher risk of breast cancer than the general population [4]. Hormone replacement therapy (HRT) increases the relative risk of breast cancer in non-selected populations, as has been shown in an American intervention study [91] and British [92] and French [93] observational studies.

The effect of HRT or oestrogen-only therapy in a normal breast is to increase the risk of development of a benign proliferative lesion without [94-97] or with atypia [97] (Table 5). The effect of HRT in a population of patients with proliferative lesions of the breast without atypia is also to increase the risk of development of AH [98] (Table 5). It is difficult to evaluate the extent to which taking HRT induces a potential additional risk of developing breast cancer in the population with AH, owing to the low incidence of AH lesions and the paucity of studies addressing this issue.

The results of published studies are contradictory, but they all have confounding factors [99-104]: the studies were published over a period spanning 20 years during which terminology as well as pathological evaluation of breast lesions evolved considerably; even the nature of the hormonal treatment, in terms of the molecules used and the duration of treatment and the

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daily dosage, are not homogeneous between series or within the same series, thereby affecting the development or not of an increased risk of breast cancer; the follow-up period of these studies is variable and possibly insufficient for detecting a late effect of the prescribed therapy on AH if one considers the developmental sequence with hyperplastic lesions becoming atypical hyperplastic lesions. The classic biases of retrospective studies are also apparent, particularly the "healthy patient" bias in which the treatments are offered to patients with the fewest breast risk factors and better able to tolerate the treatments. All the publications agree that HRT induces the development of benign proliferative pathologies of the breast with or without atypia but they disagree over whether HRT increases the risk of progression to the next stage in the carcinogenesis model, namely that of atypical hyperplasia. All in all, the majority of authors remain reticent about the use of HRT in this population that is already at higher risk of breast cancer: Gayet *et al.* notably conclude that discovery of AH in a patient on HRT should prompt consideration of whether to continue HRT [98].

Two major prevention trials (NSABP-P1 and IBIS-I) have included women with atypical hyperplasia as a specific entry riterion making them eligible to join these placebo controlled trials of tamoxifen for breast cancer prevention [9, 105]. Both trials have reported on the effect of tamoxifen in women with AH or LCIS. In the P1 trial, a larger effect of tamoxifen was seen for women with AH (86% reduction) compared to those in the trial overall (49% reduction) [9]. In the same way, two other trials have evaluated aromatase inhibitors for breast cancer prevention [106, 107], and both have explicitly reported on their effect among women with AH. A reduction in breast cancer incidence of 39% was found with exemestane when compared to placebo. Thus, the role of chemoprevention for reducing the risk of breast cancer in patients with AH was evidenced. Nevertheless, a meta-analysis of five studies found generally lower acceptance rates of chemoprevention (14,8% on average) [108]. A more recent study of high-risk women also found modest acceptance of chemoprevention (10,6%)

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[109]. Thus, even though the benefit/risk ratios for chemopreventive agents are favourable for many women, studies show that these agents are infrequently prescribed and used [110]. Further research is needed to better understand the barriers preventing wider use of chemoprevention.

4. - Conclusion

Atypical hyperplasia of the breast is a field in constant flux, in terms of nosology and its role in carcinogenesis pathways. Immunohistochemical and cytogenetic studies hold that AH lesions are precursors of invasive breast cancers, but epidemiological cohort studies have demonstrated a relatively low rate of invasion [16] such that these lesions (with the exception of pleomorphic LN) should rather be considered a risk marker for breast cancer for management purposes. Discovery of an AH lesion on percutaneous breast biopsy is an almost systematic indication for surgical excision, regardless of the size of the needle used and the number of samples obtained. This follow-up surgical excision requires surgical rigour and close cooperation with the radiologist. In a breast surgical specimen, margins positive for an AH lesion do not mandate a further surgical procedure (with the exception of pleomorphic LN) because local control of the disease does not seem to be impaired. Finally, hormone replacement therapy in patients with AH must be limited to those who absolutely need it and who have received necessary information. The role of chemoprevention for patients with AH is still under debate.

5. Expert commentary: For atypical ductal hyperplasia and lobular carcinoma in situ, surgical excision is commonly recommended, but for atypical lobular hyperplasia and flat epithelial with atypia, close follow-up without surgery could be recommended. Expectant management is feasible after multidisciplinary consensus.

6. Five-year view: Prospective studies are required to determine which women with breast

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atypical epithelial hyperplasia on radiological sampling could be spared surgery. Nevertheless, current recommendations are evolving to fewer (if not no) excisions for flat epithelial with atypia and classic lobular neoplasia found on percutaneous biopsy (in the absence of radiologic indications for excision). Although the benefit/risk ratio of chemopreventive agents is favourable for many women, studies show that these agents are infrequently prescribed and used. The role of chemoprevention needs to be determined for women with AEH.

7. Key issues:

- Atypical ductal hyperplasia (ADH), flat epithelial atypia (FEA), atypical lobular hyperplasia (ALH) and lobular carcinoma in situ (LCIS) are proliferations of monomorphic epithelial cells in the terminal ductal lobular unit as defined by the histological criteria of the 2012 WHO classification.

- For ADH diagnosed on percutaneous biopsy, the rate of underestimation (i.e. missing invasive breast carcinoma or ductal carcinoma in situ) varies from 13 to 21% (LE3). Predictors of underestimation are 14 G instead of 9-11 G biopsy, BI-RADS category 4-5 versus 3, architectural distortion, clinically symptomatic lesion, mass, ultrasound signal, radiological size > 15mm, persistence of post-biopsy radiological signal (residual calcifications), multiple foci ≥ 3, marked cytonuclear atypia and less experienced pathologist.

- For FEA diagnosis on percutaneous biopsy, the underestimation rate (i.e. missing invasive breast carcinoma or ductal carcinoma in situ) is between 0 and 20% (LE4). In cases of ALH or LCIS diagnosis on vacuum-assisted core needle biopsy, the underestimation rate of malignancy varies between 3% and 17%, mainly depending on histology-radiology concordance. In cases of non-classic LCIS, the underestimation rate is around 50%.

- For ADH, ALH, LCIS, FEA: surgical excision is recommended, but expectant management is feasible following multidisciplinary discussion.

- For LCIS: the relative risk of cancer is 8 and specific follow-up is recommended.

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- For ADH and ALH: the relative risk of cancer is 4 and specific follow-up is recommended.
- For FEA: the relative risk of cancer is less than 2.

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Declaration of interest

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Table 1. Description of the 3 types of atypical hyperplasia of the breast: atypical ductal hyperplasia, lobular neoplasia (ALH/LCIS) and flat epithelial atypia.

	ADH	LN (ALH/ LCIS)	FEA
Description	Intraductal monomorphic cellular proliferation with some of the cytological and architectural characteristics of ductal carcinoma in situ (round nucleus and/or stable nucleus-to-cytoplasm ratio and/or regular cellular architecture without particular organisation). A lesion displaying all the histological characteristics of low grade DCIS but measuring less than 2 mm is also classified as ADH.	Proliferation of small, monomorphic, discohesive (due to lack of E-Cadherin expression) cells causing distension of the terminal duct lobular unit and possible pagetoid spread into lactiferous ducts.	Replacement of normal luminal cells of the terminal duct lobular unit by 1 to 3-5 layers of: - columnar cells (cells with apical "snouts" and luminal secretions) - with low grade atypia (variability in cell height, higher nucleus-to-cytoplasm ratio, round nuclei with nucleoli, loss of polarity in relation to the basement membrane, etc.) - absence of architectural atypia (i.e. absence of absence of bridging, cribriforming or micropapillations)

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Immuno histochemistry	E-cadherin + 34BE12 +/- ER+ and PR+ CK 5- and CK18+	E-cadherin - 34BE12+ ER+ and PR+ low Ki 67 CK5- and CK18+	E-cadherin + 34BE12 - ER+ and PR+ low Ki 67 CK 5- and CK18+
Incidence (/surgical biopsies)	12%	7.8%	3.5%
Mean age	46 years	46 years	?
Relative risk of breast cancer	4	4.2	?
Management	Surgical biopsy Clear margins not necessary Surveillance	Surgical biopsy for LCIS Surgical biopsy could be avoided for HLA Clear margins not necessary (except for pleomorphic LN) Surveillance	Surgical biopsy could be avoided Clear margins not necessary Surveillance

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Table 2. Pure flat epithelial atypia on percutaneous breast biopsy.

	Number of cases with pure FEA on percutaneous biopsy	Number of follow-up lumpectomies (%)	Number of DCIS and/or IC discovered on lumpectomy	% underestimation
Kunju *et al.* (2007) [19]	14	14 (100%)	3 DCIS/IDC	21%
David *et al.* (2006) [111]	56	40 (71%)	7 DCIS/IC	17.5%
Guerra-Wallace *et al.* (2004) [112]	39	31 (79%)	4 DCIS/IC	13%
Bonnett *et al.* (2003) [113]	---	9 (--)	2 DCIS/IDC	22%
Nasser *et al.* (2003) [114]	---	27 (--)	6 DCIS/IC	22%
Brogi *et al.* (2002) [115]	---	23 (--)	7 DCIS/IC	30%

FEA: Flat epithelial atypia; DCIS: ductal carcinoma in situ; IC: invasive carcinoma; IDC: invasive ductal carcinoma

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Table 3. Pure atypical ductal hyperplasia on percutaneous breast biopsy.

	Number of cases with pure ADH on percutaneous biopsy	Number of follow-up lumpectomies (%)	Number of DCIS and/or IC discovered on lumpectomy	% underestimation
Doren *et al.* (2008) [116]	---	51 (--)	17	33%
Sohn *et al.* (2007) [117]	88	78 (89%)	14	17%
Liberman *et al.* (2007) [118]		13 (87%)	5 DCIS	38%
Winchester *et al.* (2003) [119]	77	65 (84%)	11	17%
Rao *et al.* (2002) [120]	31	31 (100%)	11	35%
Darling *et al.* (2000) [121]	86	86 (100%)	16	19%
Brem *et al.* (1999) [122]	20	16 (80%)	4	25%

ADH: atypical ductal hyperplasia; DCIS: ductal carcinoma in situ; IC: invasive carcinoma

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Table 4. Pure lobular neoplasia on percutaneous breast biopsy.

	Number of cases with pure LN on percutaneous biopsy	Number of follow-up lumpectomies (%)	Number of DCIS and/or IC discovered on lumpectomy	% underestimation
Cangiarella *et al.* (2008) [123]	---	38 (--)	3	8%
Hwang *et al.* (2008) [79]	---	87 (--)	10	11%
Londero *et al.* (2008) [124]	35	28 (80%)	13	46%
Lavoué *et al.* (2007) [125]	70	52 (74%)	10	19%
Renshaw *et al.* (2006) [126]	---	92 (42%)	8	8.6%
Mahoney *et al.* (2006) [127]	27	20 (74%)	5	25%

LN: lobular neoplasia; DCIS: ductal carcinoma in situ; IC: invasive carcinoma

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Table 5. Risk of benign proliferative lesions of the breast with or without atypia and use of hormone replacement therapy.

Authors	Type of study	Type of hormone therapy	RR of benign epithelial proliferation without atypia in patients receiving vs patients not receiving hormone treatment	RR of atypical hyperplasia in patients receiving vs patients not receiving hormone treatment	RR of breast cancer in patients with a BPP receiving vs not receiving hormone treatment	Medi an follo w-up
Hofseth *et al.* [94]	Observational study	E + P	increased	NC	NC	-
Rohan *et al.* [95]	Randomised prospective study	E	RR = 2.1	NS	NC	7 yrs
Rohan *et al.* [96]	Randomised prospective study	E + P	RR = 1.74	NS	NC	5.5 yrs
Gayet *et al.* [98]	Retrospective study	HRT	NC	2.5 In the benign breast pathology population	NC	-
Cui *et al.* [97]	Randomised prospective study	HRT	2.03	2.03	NC	7.8 yrs
Byrne et	Case-control	HRT	-	-	1	-

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al. [104]	study				NS	
Dupont *et*	Retrospective	HRT	NC	NC	1	20 yrs
al. [103]	cohort study				NS	
Dupont *et*	Retrospective	HRT	NC	NC	1	10 yrs
al. [102]	cohort study				NS	
Ross *et al.*	Case-control	E	NC	NC	increased	-
[100]	study					
Thomas *et*	Prospective	E	NC	NC	1.8	12.9
al. [99]	cohort study					yrs
Hoover *et*	Case-control	E	-	-	1.1	-
al. [128]	study				NS	
Brinton *et*	Case-control	E < 10 years	-	-	1.1	-
al. [101]	study				NS	

E: Oestrogen; P: Progesterone; NS: Not significant; NC: Not communicated; HRT: Hormone replacement therapy (E or E+P not distinguished in the studied group); AH: atypical hyperplasia of the breast; BPP: benign proliferative pathology of the breast.

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