



Navigating breast health: a comprehensive approach to atypical ductal hyperplasia of the breast management and surveillance

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Abstract

Atypical ductal hyperplasia (ADH) is a benign lesion of the breast that is associated with an increased risk of invasive breast cancer. This review explores the pathophysiology, risk factors for progression to breast cancer, and lifetime management for patients diagnosed with ADH on core needle biopsy (CNB). The management plan for patients diagnosed with ADH includes regular clinical surveillance, diagnostic mammography, along with risk-reduction strategies such as lifestyle modifications or the use of adjuvant endocrine therapies. This review aims to delve into the complexities of ADH from diagnosis to management to aid clinicians in finding the best way to approach this high-risk breast lesion.

Keywords

Atypical ductal hyperplasia, breast cancer, breast magnetic resonance imaging, mammography, breast cancer risk

Introduction

Atypical ductal hyperplasia (ADH) is one of the most common high-risk lesions of the breast and confers an increased lifetime risk of developing invasive breast cancer (IBC). It is an incidental finding that accounts for 10–15% of all high-risk lesions diagnosed by core needle biopsy (CNB) [1, 2]. It is characterized by proliferation of atypical cells involving breast ducts commonly suspected on routine screening mammography (MMO) and diagnosed with CNB [1–3]. It has a wide range of upgrades around 10% to 87% [4–6]. The standard of treatment remains as surgical excision, though the literature reveals extensive debate on the topic, with active surveillance being a possible option for those with a low risk of upgrading to malignancy [1, 7]. This review article aims to summarize the current relevant literature regarding ADH pathophysiology, risk factors, and clinical presentation and to discuss management options.



Methods

The literature search for this project was done in the Ovid MEDLINE database, 2017 to present. A combination of Medical Subject Headings (MeSH) and keywords were used to create the search. Related concepts were combined using the Boolean operator “OR” and then those concepts were combined using the Boolean operator “AND”. The literature review was limited to articles published in the last 6 years and included systematic reviews, meta-analyses, randomized controlled trials, observational studies, and cross-sectional studies. These limitations were applied to the search strategy resulting in 136 references for review. The articles were then reviewed by two independent authors for relevance and quality and some articles were removed. The rest of the articles were all reviewed, and the findings were synthesized as a well-structured comprehensive narrative review.

Pathophysiology

The mean age at ADH diagnosis ranges from around 53–59 years and 67% of those diagnosed with ADH were White, 11% were Asian, 8% were Black, 1% were American Indians or Alaska Natives, and 13% were mixed or other races [2–4, 8, 9]. ADH carries a risk of unsampled malignancy [10]. At the time of excisional biopsy, rates of upgrade to *in situ* or invasive malignancy range from 15% to more than 30% of high-risk breast lesions [11]. Because of these upgrade rates, the current recommendation is an excisional biopsy for ADH identified on CNB. The average latency period for progressing to invasive cancer is around 10 years [6]. ADH is associated with a 3 to 5-fold increased relative risk for breast cancer, approximately 1% absolute risk per year for at least 25 years, and a 10–20% absolute lifetime risk of invasive carcinoma development.

ADH shows similar genetic profiling and immunohistochemistry staining and is considered by some as a direct precursor lesion to low-grade ductal carcinoma *in situ* (DCIS) and low-grade invasive ductal carcinoma. While some regard this as a high-risk lesion and not a precursor lesion, where IBC can develop anywhere in the breast and not only in the area of ADH. Histologically, it affects less than two separate duct spaces or no more than 2 mm area [9, 12–14] whereas DCIS is proliferation of epithelial cells that remain confined to the ductal-lobular unit system without invasion into the surrounding stroma [6]. ADH is initially suspected as abnormalities during routine MMO and can present as a single cluster of calcifications measuring 5 mm and above usually without an associated mass lesion. In addition, it can be seen in lumpectomy, or mastectomy, or any breast tissue sent for pathology.

Risk factors for progression to breast cancer

Several clinicopathologic features help triage patients for excisional biopsy vs. observation. These include the presence of residual calcifications, number of ADH foci on CNB, age of patients at diagnosis, biopsy needle gauge, size of ADH atypia, presence of necrosis or micropapillary features, and lifetime breast cancer risk [2, 4, 8]. Older age may be associated with increased upgrade risk [4, 5, 8]. Genetic markers have also been shown to correlate with the risk of breast cancer development. For example, enhancer of zeste homolog 2 (EZH2) is a tumor marker and its expression had an increased risk of developing breast cancer. Thus, EZH2 expression may serve as a marker in the classification of breast lesions with increased risk of carcinoma and play a role in risk stratification [15].

The factors found to be most likely associated with increased risk for upgrade include multiple duct involvement [8], suspicion for DCIS, ADH found on another high-risk lesion on CNB, and diffuse calcifications on subsequent excision biopsy [1, 3, 11]. The total area of ADH on CNB on upgraded patients ranged from 1–7 mm and 94% of upgraded patients had greater than one duct involved by ADH on CNB, with a range of 1–46 ducts, suggesting patients with only one duct involved with ADH may be at lower risk of upgrade [8].

Several models exist to risk stratify patients, but due to a lack of consensus opinion, the standard of treatment for ADH remains an excisional biopsy (Grade C recommendation).

Lustig et al. [1] designed a risk calculator to stratify patients with ADH diagnosed on CNB into a low-risk cohort using five key risk factors associated with ADH upstaging to cancer. These include ADH coexisting with another high-risk lesion on CNB, incomplete removal of calcifications, suspicion for DCIS, and presence of a lesion greater than 5 mm in size on MMO or ultrasound imaging [1]. Of these risk factors, the two most influential for upgrading were suspicion for DCIS and ADH found alongside another high-risk lesion on CNB [1]. Bong et al. [13] similarly aimed to predict the upgrade risk of ADH on surgical excision but focused primarily on Southeast Asian women who have denser breast parenchyma than White women. They used the three-variable model: mammographic breast density, presence of a mass on ultrasound, and the number of ADH foci with two or fewer ADH foci on biopsy being associated with low upgrade risk [13]. In addition, they eluded that, diffuse calcifications correlated with the increased risk of upgrade on subsequent excision biopsy, and these patients should undergo sufficient and representative core biopsy samples or consider surgical excision to increase accuracy [13].

Several models have been proposed for risk stratification with imaging prior to surgical intervention and assessing the focus span of the ADH and using breast magnetic resonance imaging (MRI) enhancement (seen in DCIS and IBC to predict upgrade risk) [4]. These models recommend active monitoring (AM) for patients with low upgrade risk, such as patients with small imaging size, low foci of ADH, absence of cell necrosis, and no coexisting high-risk lesions with surgical excision if radiographic progression subsequently occurs while under AM [3].

Treatment

There is concern that ADH on CNB under-represents the imaging abnormality and DCIS or IBC could be identified with surgical excision [2, 16]. There is some controversy as to whether surgical excision of ADH is universally warranted, as some studies conclude that active observation is safe for low-risk patients [2–5, 9]. The current standard of care for ADH is surgical excision to avoid missing coexisting IBC. If there is evidence of ADH only on the surgically excised specimen, surgery is complete no additional excision is needed even if the margins are not clear. Vacuum assisted breast biopsy or vacuum assisted excision (VAE) uses larger needles and removes a larger amount of breast tissue and is being used to manage benign breast lesions including ADH. The benefits of this over traditional excisional biopsy can be better cosmetic results with less scarring, less cost, and lower rates of underestimation and overtreatment, without compromising the quality of patient care [17]. ADH can be managed with VAE rather than surgery as a first option as to minimize overtreatment [17]. This involves obtaining a large volume of breast tissue aiming to remove the entire lesion if less than 15 mm [18].

Lifetime management of patients diagnosed with ADH

ADH is considered a high-risk breast lesion and there is an increase in both ipsilateral and bilateral breast cancer risk [11]. The lifetime risk for women diagnosed with ADH, even after surgical excision is higher than average. According to National Comprehensive Cancer Network (NCCN) recommendations, patients diagnosed with ADH should be offered lifetime surveillance. This includes a clinical breast examination every 6–12 months and an annual digital diagnostic MMO with tomosynthesis beginning at the age of diagnosis of ADH but not prior to the age of 30 [19].

Breast MRI has high sensitivity but low specificity which can lead to false positive tests, and in addition, annual MRI scans are shown not to reduce the overall mortality rates associated with breast cancer (sensitivity: 75.2–100%, specificity: 83–98.4%) [20]. MRI is also known to have a high negative predictive value ranging from 90–100%, as well as a low positive predictive value ranging from 33–50% [4]. An annual MRI can be considered in women who have a high lifetime risk of breast cancer (> 20% calculated by risk assessment models), but not before the age of 25 [19]. Breast cancer risk calculators are available to quantify breast cancer risk and include the Breast Cancer Risk Assessment Tool (BCRAT), which is also known as the Gail model, and the International Breast Cancer Intervention Study (IBIS), also known as the Tyrer-Cuzick model. These models provide a population-level estimated 5-year (BCRAT) or 10-year (IBIS)

and lifetime breast cancer risk. However, the BCRAT calculator can underestimate the risk for ADH, whereas the IBIS model can significantly overestimate risk, particularly in patients with a family history of breast cancer [21, 22].

Currently, the United States Preventive Services Task Force recommends discussing risk-reducing recommendations with patients with an estimated BCRAT 5-year risk greater than 3% although discussion regarding these therapies is appropriate for women with a 5-year risk \geq 1.67% [23]. Risk reduction strategies include lifestyle modifications such as healthy diet, regular aerobic exercise, maintaining ideal body weight, and avoidance of smoking and alcohol consumption [17].

The vast majority of ADH is estrogen receptor positive and adjuvant endocrine therapy with selective estrogen receptor modulators (SERMs) such as tamoxifen and raloxifene or aromatase inhibitors (AIs) such as anastrozole and exemestane, is offered to patients who are diagnosed with ADH of the breast [19, 24]. There is significant risk reduction for women with ADH taking SERMs (up to 86%) [24] or AIs (41% to 79%)—an even greater benefit than for women with a calculated high risk (38% relative risk reduction, but there is no reduction in the breast cancer associated mortality [21, 25, 26]. This benefit seems to be greater in younger women. Additional monitoring recommendations can be provided based on the patient's individual risk factors.

Conclusions

In summary, surgical excision is the standard of care for most patients with ADH. But there is ongoing debate that one size does not fit all and adapting active surveillance for lesions deemed to be low risk for upgrade to DCIS or IBC. Accurate risk stratification using key indicators such as coexistence with high-risk lesions, incomplete calcification removal, suspicion for DCIS, and lesion size, particularly in MMO and MRI marks a significant advancement in our ability to identify low-risk cohorts among ADH patients. But due to a lack of consensus with these observations, all patients are offered surgical excision. Additional research and robust data are needed in this area to avoid surgical overtreatment.

Due to the high lifetime risk of breast cancer, all patients diagnosed with ADH should be offered lifelong clinical surveillance with clinical breast examination every 6–12 months, annual diagnostic MMO with tomography, and enhanced surveillance with annual MRI. Risk reduction strategies such as lifestyle modifications and adjuvant endocrine therapies should be discussed for informed decision-making for all patients with ADH.

Abbreviations

ADH: atypical ductal hyperplasia

BCRAT: Breast Cancer Risk Assessment Tool

CNB: core needle biopsy

DCIS: ductal carcinoma *in situ*

IBC: invasive breast cancer

IBIS: International Breast Cancer Intervention Study

MMO: mammography

MRI: magnetic resonance imaging

Declarations

Author contributions

SV: Conceptualization, Supervision, Investigation, Writing—review & editing. NI: Writing—original draft, Conceptualization, Investigation, Writing—review & editing. Both authors read and approved the submitted version.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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