Clinicopathologic Implications of “Flat Epithelial Atypia” in Core Needle Biopsy Specimens of the Breast

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Abstract

Flat epithelial atypia (FEA) is an emerging entity of uncertain clinical significance, and outcome data are sparse. The aim of this study was to evaluate the clinicopathologic significance of this entity for proper management. All core needle biopsy (CNB) specimens diagnosed as atypical ductal hyperplasia (ADH) from January 2006 to April 2008 were retrieved. H&E-stained slides of 5 levels on each case were reviewed. The differences in upstaging in subsequent excisions in the FEA and ADH group (31/189 [16.4%]) vs the pure FEA group (5/35 [14%]) and pure FEA (5/35 [14%]) vs pure ADH (5/45 [11%]) were not statistically significant. We observed that FEA evolved into ADH at the same site at an average of 3 to 4 levels. Our study concludes that there is an association of FEA with ADH on multiple levels of CNB specimens, and follow-up surgical excision findings for FEA are clinically significant.

Flat epithelial atypia (FEA) is a newly emerging entity of uncertain clinical significance, known in the past to pathologists as columnar cell alterations with apical snouts and secretions with atypia; atypical cystic lobules; ductal intraepithelial neoplasia, flat type; and clinging carcinoma.1 Columnar cell alterations are classified into 2 categories: columnar cell change (CCC) and columnar cell hyperplasia. The vast majority of these lesions are considered benign, and the clinical significance of these entities is under debate. Some of them manifest with cytologic or architectural atypia or both. When architectural atypia is associated, a careful search for atypical ductal hyperplasia (ADH) or for low-grade ductal carcinoma in situ (DCIS) needs to be performed.

FEA is characterized by the dilated ducts lined by 1 or 2 to 3 layers of atypical cuboidal or columnar cells. The cells retain the apical snouts, and the acini contain flocculent secretions and may be associated with calcifications.2–4 FEA differs from CCC by the presence of cytologic atypia and from ADH by the absence of complex architectural atypia. The clinical significance of FEA is beginning to emerge in the literature.

Retrospective studies have shown a high association of these lesions with putative precursor lesions such as lobular neoplasia, low-grade DCIS, and tubular carcinoma, which includes the described Rosen triad.5–9 Based on the results, it was suggested that FEA potentially has a “precursor” role in the development of low-grade DCIS. The role of FEA as a risk lesion needs to be understood, and the question of whether women with FEA should have a follow-up surgical excision remains unanswered.

The outcome data on the incidence of FEA found in core needle biopsy (CNB) specimens are limited, and the reported frequency of upstaging of pure FEA to cancer in the follow-up...
Magnetic resonance imaging–guided biopsies are performed with 9-gauge, vacuum-assisted needles with a 12-mm-long trough; ultrasound-guided and stereotactic-guided biopsies are routinely performed with 14-gauge, non–vacuum-assisted needles and sometimes with 14- and 12-gauge vacuum-assisted needles. Each CNB specimen was evaluated for the presence of microcalcifications and the relationships between FEA and ADH. Because 5 levels were examined for each case, we evaluated and tabulated each level for the presence of FEA and ADH with reference to their respective positions in the tissue levels. As part of our routine histology protocol, we cut 10 blanks—2 before level 1, 2 after level 1, 2 after level 2, 2 after level 3, and 2 after level 4.

The follow-up resection reports were reviewed for presence of a “significant lesion,” which, in our study, included DCIS, invasive carcinoma (IC), or both. ADH (which was pure FEA or ADH and FEA) and the presence of other high-risk lesions were also noted. High-risk lesions were defined in our study as nonmalignant lesions that predispose patients to an increased risk of developing breast cancer.

### Statistical Analysis

The χ² test was used to compare 2 proportions and generate the P values.

### Results

The total number of CNBs performed from 2006 to 2008 was 8,054. More than 99% (8,051/8,054) were stereotactic-guided and fewer than 1% (3/8,054) were ultrasound- or magnetic resonance imaging–guided biopsies. The incidence of ADH (included pure FEA, FEA and ADH, or pure ADH) was 3.7% (301/8,054) and 99% of these cases were biopsied for abnormal calcifications. The mean age of patients in the ADH group was 54 years (range, 29-83 years). The CNB cases associated with DCIS or IC were excluded from the study. For purposes of analysis, we divided the ADH cases into 3 groups: 1, ADH and FEA; 2, pure FEA; and 3, pure ADH.

On review of the 301 cases, 71.1% (214/301) were classified as FEA and ADH (group 1), 13.0% (39/301) as pure FEA (group 2), and 15.9% (48/301) as pure ADH (group 3). The most common high-risk lesions encountered in the 3 groups included lobular neoplasia (LN) 1, intraductal papilloma, and radial scar

Microcalcifications were seen in association with ADH in all 301 cases (100.0%). Besides ADH, microcalcifications were also seen in association with 4 cases of intraductal papilloma (1 case in Group 1 and 3 cases in Group 3) and 1 case of LN in Group 2.

In 17.3% of the cases in group 1 (37/214), we observed that FEA evolved into ADH at the same site at an average of 3 to 4 levels of 5 levels obtained as part of our routine protocol
All surgical excisions for a diagnosis of ADH at our institution are entirely submitted for microscopic examination.

In group 1, follow-up was available for 88.8% of cases (190/214). In the follow-up resections, DCIS/IC was seen in 16.3% (31/190), ADH (included pure FEA, FEA and ADH, or pure ADH) in 35.3% (67/190), and LN in 11.1% (21/190); the lesions were benign in 37.4% of cases (71/190).

In group 2, follow-up was available for 90% of cases (35/39). In the follow-up resections, DCIS/IC was seen in 14% (5/35), ADH (included pure FEA, FEA and ADH, or pure ADH) in 29% (10/35), and LN in 23% (8/35); the lesions were benign in 34% of cases (12/35).

In group 3, follow-up was available for 94% of cases (45/48). In the follow-up resections, DCIS/IC was found in 11% (5/45), ADH (included pure FEA, FEA and ADH, or pure ADH) in 53% (24/45), and LN in 4% (2/45); the lesions were benign in 31% of cases (14/45).

The breakdown of DCIS and IC are shown in detail in Table 2. The most frequently encountered type of DCIS in all groups had low-grade morphologic features. Only 1 case of high-grade DCIS was encountered (in group 1).

Statistical Analysis

The difference in upstaging in group 2 was compared with those in group 1 and group 3. The differences in upstaging in group 1 (31/189 [16.4%]) vs group 2 (5/35 [14%]; \( P = .8728 \)) and group 2 (5/35 [14%]) vs group 3 (5/45 [11%]; \( P = .7742 \)) were not statistically significant.
Discussion

FEA is a constituent of the spectrum of columnar cell lesions (CCLs) that encompasses columnar cell change and columnar cell hyperplasia with atypia but is distinguished from ADH and DCIS by the absence of architectural atypia.\(^3\) As the biologic and molecular silhouette of FEA is unraveling, with the rising association of FEA and low-grade neoplasia,\(^6,11\) it is imperative to be familiar with this lesion in breast specimens.

Our study is one of the largest to highlight the significance of FEA in CNB specimens and also is one of the foremost to evaluate the significance of FEA with reference to the importance of examination of the appropriate number of tissue levels. Our data demonstrate that FEA evolves into ADH at the same site in 3 to 4 tissue levels in a significant number of cases (17.3%), indicative of the interrelationship of ADH and FEA, suggesting that FEA may be the surface depiction of an associated underlying significant architectural lesion. This study, along with the accruing literature on FEA, indicates that the finding of FEA in a CNB breast specimen has the same clinical significance as the finding of ADH in a CNB specimen. It is critically important to be able to properly recognize FEA in CNB levels so that patients will obtain proper surgical follow-up and management. Additional levels of CNB specimens that display FEA commonly demonstrate the criteria for ADH. Our data also show that when comparing the diagnosis of FEA with that of ADH in CNB specimens,
there is no significant difference in the upstaging to carcinoma on the follow-up surgical resections.

Recent molecular studies have shown 2 distinct pathways for the development of breast carcinoma, low-grade and high-grade. Low-grade breast carcinomas strongly express estrogen receptor and have a good prognosis; included in this group are tubular, tubulo-lobular, cribriform, and lobular carcinoma subtypes. CCLs have been shown to be potential precursors in the pathway of development of low-grade carcinoma and are often seen in association with these low-grade malignant entities, in particular, FEA. Furthermore, the similarities that exist in FEA and low-grade DCIS at molecular and genetic levels suggest further that FEA is a nonobligate precursor for the development of low-grade breast carcinomas. A retrospective review of low-grade DCIS showed a significant association with the presence of FEA, particularly with the cribriform and micropapillary subtypes. Low-grade DCIS associated with ADH showed a higher association of FEA, further confirming the association with the low-grade pathway.

In recent literature, LN is integrated as an important component of the family of low-grade neoplasms owing to its high frequency of association with CCLs; in particular, the association of FEA is reported to be up to 26%. LN is also a known risk factor for breast carcinoma and may behave as a premalignant process requiring excisional biopsy. In our study, we observed the most common high-risk lesion encountered in all 3 groups included LN, indicating the close relation of LN and FEA.

The biologic significance of finding FEA in CNB specimens is meager, and the current management remains a dilemma. The clinical concern of whether patients with FEA found by CNB need to have follow-up excision, analogous to the management of patients with ADH diagnosed by CNB, remains to be determined. Data from a few small studies, some reported only in abstract form, indicate that follow-up excisional biopsy of FEA will reveal associated DCIS or IC in up to 30% of cases. This study, although one of the largest, is still limited by the number of pure FEA cases.
cases that have follow-up surgical excision. The data suggest that patients with a CNB diagnosis of FEA will have a 14% incidence of upstaging to DCIS or IC on resection, not statistically different from the incidence of upstaging with ADH. This mathematical observation reinforces the morphologic kinship between FEA and ADH seen on multiple tissue levels. In practice, if there is diagnostic uncertainty about the diagnosis for a CNB specimen, it would be prudent to examine further tissue sections or seek consultation if FEA is in the differential diagnosis.

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**Image 4** A and B, Flat epithelial atypia (FEA) evolving into atypical ductal hyperplasia at the same site in the 3-4 levels in a significant number of cases (demonstrated in 2 cases here); initial 1-2 levels demonstrate FEA characterized by evenly spaced monotonous cells with low-grade cytologic atypia and inconspicuous nucleoli, apical snouts, and intraluminal flocculent secretions (left). Note the development of architectural atypia with formation of bridges and micropapillary projections (A, H&E, ×40) (B, H&E, ×40) demonstrated in 2 cases in 3-4 levels (center and right).

**Table 2** Results of Follow-up Resection Specimens Preceding a Core Needle Biopsy Diagnosis of ADH (FEA, FEA and ADH, or ADH)†

| Follow-up Diagnosis | FEA and ADH (n = 190) | Pure FEA (n = 35) | Pure ADH (n = 45) |
|---------------------|-----------------------|-------------------|-------------------|
| IC                  | 16 (8.4)              | 2 (6)             | 0 (0)             |
| DCIS                | 15 (7.9)              | 3 (9)             | 5 (11)            |
| ADH                 | 67 (35.3)             | 10 (29)           | 24 (53)           |
| Lobular neoplasia†  | 21 (11.1)             | 8 (23)            | 2 (4)             |
| Benign              | 71 (37.4)             | 12 (34)           | 14 (31)           |

† Includes atypical lobular neoplasia and lobular carcinoma in situ.

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma in situ; IC, invasive carcinoma.

* Data are given as number (percentage). For FEA and ADH, follow-up was available for 190 (88.8%) of 214 cases; for pure FEA, follow-up was available for 35 (90%) of 39 cases; for pure ADH, follow-up was available for 45 (94%) of 48 cases.

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