ORIGINAL SCIENTIFIC ARTICLE

Flat Epithelial Atypia: Upgrade Rates and Risk-Stratification Approach to Support Informed Decision Making

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BACKGROUND: Our aim was to determine upgrade rates of pure flat epithelial atypia (FEA) to malignancy and higher-risk lesions and to identify patients with FEA at low risk for upgrade.

STUDY DESIGN: Medical chart review from 2007 to 2016 identified 208 consecutive patients with pure FEA diagnosed by image-guided core needle biopsy who underwent surgical excision (96.2% [200 of 208]) or had at least 2 years of imaging follow-up (3.8% [8 of 208]). Medical records were reviewed for risk factors and surgical outcomes.

RESULTS: Overall upgrade rate of FEA to malignancy was 2.4% (5 of 208). All 5 upgraded cases were ductal carcinoma in situ at operation. The upgrade rate to atypical ductal hyperplasia, lobular carcinoma in situ, or atypical lobular hyperplasia was 29.8% (62 of 208). The FEA lesions in patients with a genetic mutation were more likely to upgrade to malignancy than FEA lesions in patients without a genetic mutation (33.3% [1 of 3] vs 2.0% [4 of 205]; $p < 0.01$). The FEA lesions in patients with a personal history of breast cancer were more likely to upgrade to higher-risk lesions than those without a personal history (47.8% [11 of 23] vs 27.6% [51 of 185]; $p = 0.046$) but were not more likely to be upgraded to malignancy (0% [0 of 23] vs 2.7% [5 of 185]; $p = 0.42$).

CONCLUSIONS: The overall risk of upgrade of FEA to malignancy is low at 2.4%; however, the upgrade rate to a higher-risk lesion is nearly 30%. Surveillance rather than surgical excision of FEA can be a reasonable option for patients without a genetic mutation who opt against chemoprevention. (J Am Coll Surg 2017;■:1−6. © 2017 by the American College of Surgeons. Published by Elsevier Inc. All rights reserved.)

Flat epithelial atypia (FEA) is a high-risk breast lesion that arises from the terminal duct lobular unit and is characterized by low-grade cytologic atypia.[1] Typically, it presents on mammography as grouped amorphous calcifications (Fig. 1) and on sonography as an irregular hypoechoic or complex mass.[2] Historically, surgical excision has been the standard of care for FEA because it has the potential to be upgraded at operation to either ductal carcinoma in situ (DCIS) or invasive malignancy.

Multiple retrospective studies have demonstrated wide variability in FEA upgrade rates, leading to uncertainty about its clinical significance and management. The risk of malignancy associated with FEA has been estimated to be between 0 and 40%.[2-13] Earlier studies have been limited by small sample sizes and selection biases, with selective surgical excision of FEA done in some patients but not in others. In addition, some studies do not differentiate between pure FEA and FEA associated with other high-risk pathologies, such as atypical ductal hyperplasia (ADH). To our knowledge, there are no known reliable clinical predictors of FEA upgrade to malignancy.

At our institution, the standard of care for all patients diagnosed with FEA by image-guided core needle biopsy is surgical excision, allowing for relatively unbiased reporting of upgrade rates. The purpose of this study was to determine upgrade rates of FEA to malignancy and higher-risk lesions and to identify patients who are

Disclosure Information: Nothing to disclose.

Disclosures outside the scope of this work: Dr Lehman has a research grant from GE Healthcare and serves on an advisory board for GE Healthcare.

Presented at the Society of Breast Imaging/American College of Radiology Breast Imaging Symposium, Los Angeles, CA, April 2017.

Received July 1, 2017; Accepted August 24, 2017.

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http://dx.doi.org/10.1016/j.jamcollsurg.2017.08.022
ISSN 1072-7515/17

Abbreviations and Acronyms
ADH = atypical ductal hyperplasia
ALH = atypical lobular hyperplasia
DCIS = ductal carcinoma in situ
FEA = flat epithelial atypia
LCIS = lobular carcinoma in situ

at low risk for upgrade, which could support informed decision making with regard to the reasonable options of surveillance vs surgical excision and chemoprevention.

METHODS

Study subjects

This retrospective study performed at a single large tertiary academic center was approved by the IRB with a waiver for the need to obtain informed consent and was compliant with the Health Insurance Portability and Accountability Act. The Standards for Reporting of Diagnostic Accuracy checklist was used.[14] The study cohort was composed of patients with pure FEA diagnosed by image-guided core needle biopsy from December 1, 2007, to March 31, 2016, who subsequently underwent surgical excision or had at least 2 years of imaging follow-up. We searched our institution's breast imaging information system (MagView) for female patients with image-guided core needle biopsy pathology yielding pure FEA. If a biopsy yielded additional high-risk lesions associated with FEA, such as ADH, lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), radial scar, papilloma, or non-specific atypia, the case was not included in the study. Patients with a known malignancy in the ipsilateral or contralateral breast at the time of FEA diagnosis were also excluded.

Imaging technique and interpretation

Mammograms were performed using full-field digital mammography or digital breast tomosynthesis (Hologic). Mammograms included craniocaudal and mediolateral oblique views of both breasts and additional diagnostic views (such as spot magnification or compression views). Targeted ultrasound with a 12-5-MHz transducer (Philips Healthcare) was performed at the discretion of the radiologist interpreting the diagnostic mammogram.

Magnetic resonance imaging examinations were performed using a 1.5-T or 3-T scanner (GE Healthcare) in the prone position with a dedicated 4-channel (GE Healthcare), 8-channel (GE Healthcare), or 16-channel breast coil (Sentinelle Invivo, Philips Healthcare). Each study included a pre-contrast non-fat-saturated T1-weighted sequence and a pre-contrast fat-saturated T2-weighted sequence. In addition, a pre-contrast fat-saturated gradient-echo T1-weighted sequence was performed, followed by 2 to 4 dynamic post-contrast T1-weighted gradient-echo series images with fat suppression after IV administration of a gadolinium-based contrast agent using a weight-based dosing protocol. Post-processing included sagittal reconstructions, subtracted post-contrast images, and maximum intensity projection images. All images were interpreted by fellowship-trained dedicated breast imaging radiologists using terminology from the *ACR BI-RADS Atlas, Breast Imaging Reporting and Data System.*[15]

Histologic samples for pathologic diagnoses were obtained through core needle biopsies under stereotactic (9-gauge vacuum-assisted biopsy), ultrasound (14-gauge core needle device), or MRI (9-gauge vacuum-assisted biopsy) guidance.

Data collection and statistical analysis

Medical record review was performed in accordance with IRB ethics guidelines. Medical records were reviewed for patient age, risk factors, imaging findings, follow-up imaging examinations, and pathology results from core biopsy and surgical excision. All data were entered into and analyzed with an Excel spreadsheet (2013 version,

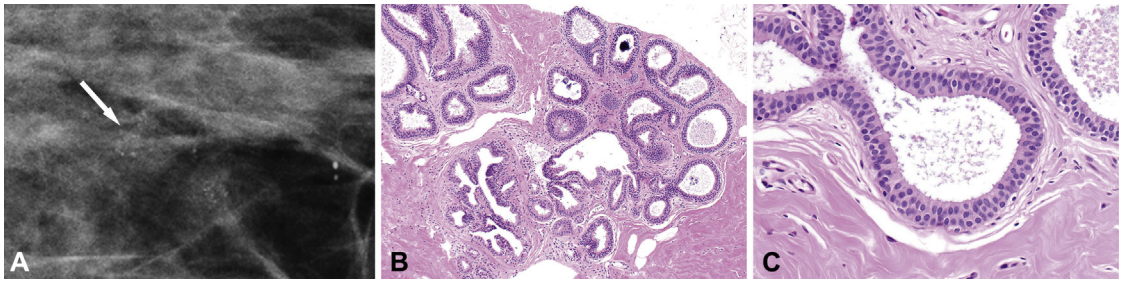

Figure 1. A 47-year-old female with mammographic screen-detected calcifications. Stereotactic core needle biopsy and surgical excision demonstrated flat epithelial atypia (FEA). (A) Craniocaudal magnification view shows grouped amorphous calcifications (arrow). (B, C) Histopathology shows proliferation of monoclonal cells, with low-grade nuclear atypia without complex architecture and calcifications with associated involved ductules, in keeping with FEA.