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Majority of flat epithelial atypia diagnosed on biopsy do not require surgical excision

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ABSTRACT

Background: Borderline risk lesions such as flat epithelial atypia (FEA) are increasingly being diagnosed on biopsy. The need for surgery is being debated. In this study, we determined the frequency of histological upgrade following a diagnosis of FEA on biopsy and evaluated potential predictive factors.
Methods: Retrospective review was done of 194 women who underwent biopsy of indeterminate lesions (total 195 lesions) that were diagnosed as FEA. The review covered a 10-year period. Cases where malignancy was also present together with FEA within the same biopsy cores were excluded.
Results: Lesions diagnosed as FEA on biopsy were mostly asymptomatic and presented as microcalcifications on mammogram. Flat epithelial atypia was the only abnormality detected in one-third of cases, was associated with a benign or another borderline lesion in another third and was associated with atypical ductal hyperplasia (ADH) in another third. Six patients (3.1%) were later found to have ductal carcinoma-in-situ (DCIS) at surgery. The presence of ADH in the biopsy was the only predictor of histological upgrade to malignancy ($P = 0.04$, OR 11.24, 95% CI 1.10 − 115.10), and was present in 5 of the 6 patients. Surgery was advised in the last patient because of radiology-pathology discordance. Thirty-six lesions (18.5%) were not excised and no interval progression or malignancy was found on follow up.
Conclusion: Histological upgrade to malignancy was uncommon in lesions found on biopsy to be FEA. Non-operative management of biopsy-proven FEA can be considered in the absence of ADH and radiology-pathology discordance.

1. Introduction

Asymptomatic indeterminate lesions are increasingly being diagnosed following greater uptake of breast cancer screening and improved mammogram imaging techniques. Classified as BIRADS 4 according to the Breast Imaging-Reporting and Data System (BIRADS), these lesions are further stratified into 3 subcategories, with the likelihood of malignancy ranging from 2% to 10% in BIRADS 4A lesions to more than 50% in BIRADS 4C lesions [1]. Biopsy is discussed and many women will opt for biopsy over close follow up with a repeat scan in another 4–6 months. Many of these indeterminate lesions are diagnosed as borderline risk lesions on biopsy and flat epithelial atypia (FEA) is one of the more common pathologies [2]. The term FEA was introduced in 2003 by the World Health Organization Working Group on the Pathology and Genetics of Tumors of the Breast, and describes neoplastic intraductal alteration characterised by replacement of the native epithelial cells by a single or up to five layers of monotonous atypical cuboidal to columnar cells with apical snouts. Mild cytologic atypia is present but not the architectural atypia typical of atypical ductal hyperplasia (ADH) and ductal carcinoma in situ (DCIS) [3].

The clinical significance of FEA lies in its frequent association with other higher-grade lesions, such as ADH, atypical lobular hyperplasia (ALH) and lobular carcinoma in situ classical type (LCIS) [4–7]. Furthermore, there is some molecular data suggesting that FEA is a precursor lesion in the development of low-grade cancers

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[8,9], and up to 13% of women with biopsy-proven FEA are found with DCIS or invasive cancer at subsequent surgery [4,6,10]. At our unit, FEA is managed as for any lesion with atypia on biopsy, and women found with FEA on biopsy are offered surgical excision. This practice is being reviewed in light of the low frequency of upgrade to malignancy as well as a recent study that reported no increase in long-term breast cancer risk with a diagnosis of FEA [11]. Women with higher risk lesions, such as ADH, ALH and LCIS, are not managed differently from other average risk women at our unit. Neither additional assessments with other imaging modalities such as breast magnetic resonance imaging nor chemoprevention are recommended. Consequently, the identification of such lesions does not change the management of women with FEA. As such, many women with FEA diagnosed on biopsy may not require surgery and can be safely managed non-operatively with serial follow-up scans. We therefore reviewed our management of women diagnosed with FEA on biopsy over a 10-year period. We determined the frequency of histological upgrade to ADH, DCIS and invasive cancer and sought to identify factors predictive of an upgrade to malignancy, in order to guide the decision for surgery.

2. Material and methods

A retrospective review was performed of biopsies performed at our unit from 1st January 2004 to 31st December 2014. This study was approved by the institutional review board (DSRB2014/00211). Cases where FEA was reported in the biopsy specimen were included in the study. Forty-seven cases where FEA was found incidentally at surgery done for an indication other than FEA and 6 cases where FEA was present together with DCIS or invasive cancer in the same biopsy specimen (same lesion) were excluded. Cases where FEA was reported on the biopsy of a lesion separate from a DCIS or invasive cancer, whether in the same or contralateral breast, were included.

All mammograms, breast ultrasonography and image-guided biopsies were reviewed by a dedicated breast radiologist with 7 years of experience in breast imaging. Mammographic and sonographic findings were described according to the BIRADS categories and lexicon [1]. The BIRADS assessment of each lesion was noted. Details of microcalcifications included the size, morphology and distribution of microcalcifications, and complete versus incomplete removal of microcalcifications at biopsy. Details of lesions seen on ultrasonography included the size, shape, margins and echogenicity. Radiology-pathology concordance was checked for all cases. Biopsy was performed by accredited radiologists. Lesions visible on ultrasound (even if also visible on mammogram) were biopsied under ultrasound guidance. This was performed with a 14 gauge BARD needle mounted on a spring-loaded device. An average of 4 cores were taken. Stereotactic biopsies were performed for lesions (mostly microcalcifications) visible only on mammogram, with an 11 gauge vacuum assisted device. An average of 8 cores were obtained and specimen radiography was done at the end of the procedure to document the presence of microcalcifications in the cores. No attempt was made to completely remove the entire lesion in question during the biopsy.

All biopsy and surgical specimens were reviewed by accredited pathologists at our unit. On histology, FEA is characterised by variably distended terminal duct lobular units that are lined by one to several layers of mildly atypical columnar epithelial cells (Fig. 1). These cells typically show relatively uniform, round to ovoid nuclei and pink cytoplasm. Apical snouts are commonly seen, as are flocculent material within the duct spaces that are often associated with calcifications. Mitoses are usually absent. Abnormal architectural bridges, rigid arcades or cribriform structures are not seen in FEA, and the presence of such features should prompt a diagnosis of ADH instead. Atypical ductal hyperplasia has been defined as having some but not all the features of DCIS and a quantitative criterion is often used to distinguish between the two; the lesion being designated as DCIS when cyto-architecturally atypical epithelial proliferation involve at least two complete duct spaces or extend for more than 2 mm. High grade DCIS, on the other hand, is characterised by the presence of high grade malignant epithelial cells involving mammary duct spaces, regardless of the extent of involvement.

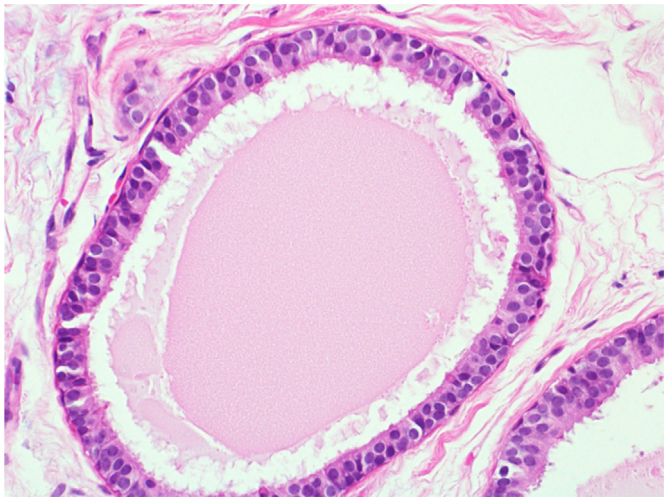

Fig. 1. Flat epithelial atypia characterised by distended duct spaces lined by low grade atypical epithelial cells with nuclear pseudostratification. (H&E, x400).

Demographic, radiological and clinical data were collected from electronic medical records and included the mode of presentation (whether symptomatic or screen-detected), mammographic and sonographic features of the indeterminate lesions, mode of image-guided biopsy, histological analyses of the biopsy as well as surgical specimen. Correlation analyses were performed with Chi-square or Fishers' exact test as appropriate and comparisons between groups were performed with Mann Whitney test; all univariate analyses were performed with GraphPadPrism version 6 (GraphPad software Inc., San Diego CA). Logistic regression to identify independent predictors of histological upgrade to malignancy was performed with Stata package release 11.0 (Stata Corporation, Texas, USA). A 2-tailed P value test was used and a P value of less than 0.05 was considered statistically significant.

3. Results

Over the 10-year period, a total of 195 breast lesions in 194 patients returned with FEA on the biopsy; 2 lesions were present in the same patient. Median patient age was 49 years (ranging from 22 to 79 years). Majority of the lesions (165 of 195, 84.6%) were screen-detected, 4 were detected on surveillance imaging performed for women previously diagnosed with breast cancer and 26 were found on imaging performed to evaluate breast symptoms (a palpable breast lump in 22 patients and breast pain in 4 patients). A positive family history was present in 10 patients. Other than the 4 patients with a personal history of breast cancer, one other patient had previously been diagnosed with lobular neoplasia.

Mammogram was performed in all 194 patients and breast ultrasound was performed in all but 3 patients. Of the lesions biopsied, 151 were classified as microcalcifications, with 107 being of a single cluster. Extent of the microcalcifications ranged from 3 mm to 65 mm and extended over an area larger than 20 mm in 22 cases. The microcalcifications were described as amorphous in 45 patients, as coarse heterogenous in 78 patients and as fine