Flat Epithelial Atypia: A Precursor to Carcinoma

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Purpose

Flat epithelial atypia (FEA) is seen with increasing frequency following biopsy of calcification detected through screening. FEA comprises one to several layers of monomorphic epithelial cells with low-grade cytological atypia lining a dilated terminal duct lobular unit\(^1\). In recent years, FEA has assumed a new significance due to emerging evidence that it may represent the earliest morphological manifestation of ductal carcinoma in situ (DCIS) and a non-obligate precursor of low-grade invasive carcinoma\(^2,3,4\). The biological significance of FEA identified on core biopsy remains unclear and there is limited data to guide management decisions. We aim to review the radiological features of FEA and evaluate the significance of FEA on core biopsy to inform management strategies.
Methods and Materials

We performed a retrospective analysis of all breast needle core biopsies (14G) containing FEA and/or atypical intraductal proliferation (AIDP) as the most significant histopathological finding in the Leeds Teaching Hospitals pathology database from April 2008 to April 2010. Before April 2009, the majority of core biopsies containing FEA and/or AIDP proceeded to diagnostic surgical biopsy. From April 2009 onwards, we introduced a new multidisciplinary team (MDT) agreed patient management pathway incorporating large volume mammotome biopsy to further sample core biopsies containing FEA and/or AIDP, as an alternative to surgical biopsy.

Leeds Patient Management Pathway

The Leeds management pathway is diagrammatically summarised in Figure 1 on page 4. Following a core biopsy diagnosis of FEA and/or AIDP, each case is discussed at the breast diagnostic MDT meeting, to ensure radiological-pathological concordance and assess suitability for mammotome biopsy. Technical factors that would preclude mammotome biopsy include lesions close to skin or areola, and insufficient tissue depth in small breasts. Pathological factors that would favour surgical biopsy include cases with borderline pathology where quantification of the abnormality is crucial in distinguishing atypical ductal hyperplasia (ADH) and carcinoma in situ.

Large volume vacuum-assisted biopsy is performed using the mammotome biopsy system (Ethicon Endo-Surgery, Cincinnati, Ohio, USA). A larger needle (8G or 11G) is used with the intention of obtaining a minimum of 12 cores per lesion. Following further sampling with mammotome biopsy, if the mammotome cores are benign and histologically contain the previous core biopsy site, the patients are returned to routine screening. If the lesion has been adequately sampled and remains as FEA and/or AIDP, annual mammographic surveillance for 5 years is undertaken within the symptomatic service. Diagnostic surgery is prompted if the mammotome cores demonstrate features suspicious for malignancy and patients proceed to therapeutic surgery if upgraded to a malignant lesion.

For each case the following data was recorded: (i) mammographic features (ii) method of further sampling (mammotome biopsy or diagnostic surgical biopsy) (iii) histology from needle core biopsy, mammotome biopsy and surgical biopsy. The cases were then subdivided into the following three categories for analysis: (i) FEA only (ii) FEA with concomitant AIDP (iii) AIDP only.
Fig. 0: Leeds patient management pathway for FEA and AIDP.

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Results

During the study period of April 2008 to April 2010, 90 needle core biopsies contained FEA and/or AIDP as the most significant pathology (Figure 1 on page 8). Of the 90 core biopsies, the following were identified: (i) FEA only in 42% (38/90) (ii) FEA with concomitant AIDP in 21% (19/90) (iii) AIDP only in 37% (33/90). Follow-up data was available for all patients with a mean of 17 months (SD ± 6 months).

Mammographic features

The most common mammographic feature was microcalcifications, present in 92% (82/90) of cases. The calcifications were often indeterminate in nature with a range of appearances from punctate to amorphous calcifications (Figure 2 on page 8). An asymmetrical density was present in 3% (3/90), architectural deformity in 2% (2/90) and a mass in 1% (1/90) of cases. Normal imaging including ultrasonography was demonstrated in 2% (2/90) of cases.

Method of further sampling

Following initial core biopsy, 52% (47/90) of patients had further sampling with mammotome biopsy and 43% (39/90) of patients underwent diagnostic surgical biopsy. Five percent (4/90) of patients had no further intervention; normal imaging with no focal area to localize for subsequent sampling (n=2), patient declined further intervention (n=1) and a patient with multiple comorbidities who died soon after the initial core biopsy (n=1). The patients who had no further sampling following the initial core biopsy diagnosis are under annual mammographic surveillance and have not developed subsequent malignancies to date.

Upgrade to malignancy within each category

Our data demonstrates a stepwise increase in the proportion of cases upgraded to carcinoma from 19% (7/37) in the FEA group through to 29% (5/17) in the concomitant FEA and AIDP group, and 53% (17/32) in the AIDP group (Figure 3 on page 9). All invasive tumours had favorable prognostic factors with a tumour grade of 1 to 2 (Table 1). This trend is supported by Lee et al who retrospectively analyzed 211 breast core biopsies containing FEA and other columnar cell lesions, of which 94 cases had subsequent surgical excisions. Correlation with final excision histology demonstrated DCIS and/or invasive carcinoma present in 14% of excisions with FEA only on core
biopsy, 29% with concomitant FEA and ADH, and 37% with ADH. All invasive tumours were grade 1 or 2, hormone receptor positive and node negative.

**Significance of FEA on core biopsy**

In the FEA only group, there was an upgrade to carcinoma in 19% (7/37) of cases: B5b invasive carcinoma in 1 patient (3%) and B5a DCIS in 6 patients (16%). This is in line with the percentage upgrade to carcinoma on further sampling of FEA of 14-22% reported in the literature\(^6,7\).

The only invasive tumour detected was a grade 1 tubular carcinoma measuring 8mm. This is in keeping with the recognised association between FEA and tubular carcinoma\(^8\). Of note, this case was unique representing the only case in the FEA group demonstrating an architectural deformity on mammography reflecting distortion in the adjacent breast tissue with imaging features suspicious for malignancy. It is likely that the initial core biopsy demonstrating pure FEA was not representative of the lesion in its entirety and this highlights the importance of large volume mammotome biopsy that facilitates more extensive sampling of the lesion and radiological-pathological concordance at MDT review.

In our study, of the 6 cases of DCIS detected, 3 cases were intermediate-grade and 3 cases were high-grade. This is contrary to the existing evidence that FEA is usually seen alongside low-grade DCIS\(^9\). This emphasises that our understanding of the biology of FEA is incomplete and its clinical significance can only be determined with larger studies with long-term follow-up.

**Management options following a core biopsy diagnosis of FEA**

Traditionally, all core biopsies containing atypical epithelial proliferations including FEA proceeded to diagnostic surgical biopsy. Mammotome biopsy is a relatively new technique that permits additional sampling of benign but potentially heterogeneous lesions and procures a larger volume of tissue for detailed histopathological evaluation, reducing the need for surgical biopsy.

Senetta et al\(^10\) demonstrated that FEA as the most advanced lesion on mammotome biopsy (11G), was never associated with malignancy at surgery. This was reinforced by Piubello et al\(^11\) who reported that no further malignancy was found on excision following a diagnosis of pure FEA on mammotome biopsy (11G). These results suggest that surgical
excision is not mandatory in patients with a diagnosis of pure FEA on mammotome biopsy and provides support for our new management pathway.
Fig. 0: Haematoxylin and eosin sections depicting characteristic features of flat epithelial atypia (FEA) and atypical intraductal proliferation (AIDP) on core biopsy. (A) FEA: Dilated terminal duct lobular unit lined by one to several layers of cuboidal cells showing low-grade nuclear atypia. (B) FEA with calcification: Ductules are lined by hyperchromatic columnar epithelium showing apical snouts. Lumina contain secretions and calcifications. (C) FEA with concomitant AIDP: One ductule showing atypical flat epithelial lining with an adjacent duct showing AIDP with cribriform architecture. (D) AIDP: One ductal space shows partial involvement by intraductal proliferation showing both cytological and architectural atypia.

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Fig. 0: Mammograms demonstrating the variable characteristics of calcification associated with flat epithelial atypia. (A) Fine indeterminate calcifications centrally within the breast. (B) Focal cluster of punctate calcifications.

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**Fig. 0:** Flow diagram demonstrating upgrade to malignancy in each category.

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Conclusion

In conclusion, there is a stepwise increase in the proportion of cases upgraded to carcinoma on further sampling of FEA, FEA with concomitant AIDP and AIDP. A core biopsy diagnosis of FEA is associated with malignancy in 19% of cases and hence warrants further tissue sampling. There is increasing evidence that sampling with large volume mammotome biopsy provides sufficient tissue for detailed histopathological evaluation to ensure concomitant malignancy is not missed. The use of mammotome biopsy reduces unnecessary surgical intervention and improves the pre-operative diagnosis rate. It is important that the utilisation of mammotome biopsy is incorporated into a safe patient management pathway with MDT discussion to ensure radiological-pathological concordance.
References


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