Pure Flat Epithelial Atypia of the Breast on Core Needle Biopsy: No Need for Surgical Excision

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ABSTRACT

Objective: From previous data, pure flat epithelial atypia (FEA) of the breast demonstrated on core needle biopsy (CNB) was related to malignant upgrading. However, FEA itself is not an independent factor for developing breast cancer; therefore, the necessity of subsequent surgical excision is controversial. This study aimed to evaluate the upgrade rate of FEA after surgical excision and to demonstrate the necessity of surgical excision in FEA lesions identified on CNB.

Materials and Methods: This retrospective study involved a review of the clinical features, mammographic and ultrasound findings, and pathological reports of patients with pure FEA found from CNB specimens between January 2010 to January 2019. FEA accompanied with atypical ductal hyperplasia, atypical lobular hyperplasia, ductal carcinoma in situ (DCIS), and invasive cancer (IC) in ipsilateral breast were excluded. FEA upgrade is defined as patients with in situ or invasive cancer presented in surgical excision specimens. The breast imaging results of pure FEA and FEA upgrade subsets were compared.

Results: In total, 45 pure FEA specimens were revealed from CNB; of which, 6 of the pure FEA (13.33%) did not undergo further surgical excision, however, they showed no recurrence during follow-up (median follow-up time: 2.68 years). The majority of FEA cases were detected by mammography in 39 patients (86.67%). Of the 45 patients, 32 were classified into BI-RADS 4B (71.11%), 11 as BI-RADS 4A (24.44%), and 2 as BI-RADS 4C (4.44%). One patient was upgraded to DCIS (2.7%). BI-RADS classification did not differ between upgrade FEA and non-upgrade FEA groups (p=0.49).

Conclusion: Only a 2.7% upgrade rate, omitting the surgical excision of pure FEA from CNB, was possible. Even though our study could not demonstrate a correlation between FEA upgrade and radiological findings, BIRADS 4A was less likely to carry the malignant cells. Furthermore, segmental microcalcification tended to be associated with upgraded lesions, but not significantly.

Keywords: Breast cancer; flat epithelial atypia (FEA); upgrade rate (Siriraj Med J 2021; 73: 727-731)

INTRODUCTION

In recent decades, the diagnosis of flat epithelial atypia (FEA) has been increasing. Previously, FEA was known as intraepithelial neoplasia, albeit with an unclear exact pathological description. In 2003, the World Health Organization (WHO) coined the term "flat epithelial atypia" to describe a lesion where native ductal cells are replaced by atypical columnar or cuboidal cells.[1] The incidence of upgrading to malignancy, in which atypical cells occur concomitantly with malignancy (in

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situ or invasive carcinoma) in larger specimens, after FEA has been diagnosed in core needle biopsy (CNB) specimens as varying from 0 - 42%.[2-4] Therefore, the current standard treatment for FEA after CNB is surgical excision. However, FEA itself is not an independent factor for developing breast cancer. Previous studies found no risk of breast cancer in FEA lesions after 13 years follow-up.[5,6] As a result, the necessity for subsequent surgical excision is controversial. This study aimed to evaluate the upgrading rate of FEA after surgical excision and to evaluate FEA patients identified by CNB who have the potential to avoid surgical excision.

MATERIALS AND METHODS

This study involved a retrospective analysis of medical records and was approved by the Ethics Committee of the Siriraj Institutional Review Board, Faculty of Medicine Siriraj Hospital (Si 482/2019). All pathological reports from CNB specimens diagnosed as FEA from January 2010 to January 2019 were reviewed. Pure FEA from core needle biopsy specimens, defined as only FEA or FEA concomitantly occurring with other non-proliferative or benign proliferative epithelial lesions, were included. All patients had mammography (MMG) and breast ultrasound (US) performed followed by core needle biopsy at Siriraj Hospital. FEA accompanied with atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), ductal carcinoma in situ (DCIS), and invasive cancer (IC) in ipsilateral breast were excluded. However, pure FEA from CNB in one breast with contralateral ADH, ALH, DCIS, and IC were included. All patients underwent excisional biopsy, otherwise in the case of patients for whom surgical excision was not performed, they needed to undergo surveillance at Siriraj Hospital.

Clinical presentation, mammographic and ultrasonographic findings, and pathological reports were collected. For core needle tissue sampling, suspicious microcalcifications were biopsied by stereotactic-guided biopsy using a 14-gauge core-biopsy needle (BARD®MAGNUM®), 14- or 9-gauge vacuum-assisted device (Eviva®, Hologic), and if a mass was targeted, ultrasound guidance with a 14-gauge needle (BARD®, MAGNUM®). The average was obtained from five cores. A radiographic clip was placed in some patients for facilitating follow-up.

Statistical analyses were performed using SPSS software version 21 (IBM SSPS, Chicago, IL). Categorical data was reported as the median with the interquartile range, mean with SD, or as a percentage. The chi-square test was used to examine the association between upgrade to malignancy, the morphology, and the distribution of the microcalcifications. Student's t-test or Mann–Whitney U-test was applied to analyze the continuous data. For the categorical data, the χ^2-test or Fisher-exact test were used to analyze for statistical significance. A p-value less than 0.05 was considered statistically significant throughout this study.

RESULTS

During January 2010 to January 2019, 45 pure FEA lesions diagnosed from CNB were identified. The baseline characteristics of the patients are described in Table 1. Of these 45 lesions, 39 were surgically removed. Six lesions (13.3%) were observed with no following surgery; however, they showed no recurrence during surveillance (median follow-up, 2.7 years; range, 29–2844 days). In this study, only one lesion was found upgraded to DCIS. The median age at diagnosis was 49 years old. Of the 45 patients, 5 (11.1%) had a history of benign breast disease at the index breast, while no-one had a family history of breast or ovarian cancer. The majority of FEA were detected by mammography (39 lesions; 86.7%); whereas, 6 lesions were detected by ultrasonography. When classifying according to BI-RADS classification (Breast Imaging Reporting and Data System, established by the American College of Radiology), 11 lesions were categorized into BI-RADS 4a (24.4%), 32 into BI-RADS 4b (71.1%), and only 2 into BI-RADS 4c (4.4%). All 45 lesions were biopsied; 73.3% stereotactic-guided, 13.3% vacuum assisted, and 13.3% by US-guided (Table 1).

In cases in which surgical excision was done, FEA from CNBs were found as pure FEA in the final surgical specimens in 26 of 39 patients (66.7%) and coexisted with either ADH, IDC, or DCIS in 13 patients (33.3%) (Table 2). Of these latter 13 patients, 1 patient was upgraded to DCIS (2.6% of total pure FEA from CNB), while no-one was associated with invasive cancer, and 1 patient had FEA with ALH (2.6%); meanwhile, 11 patients had FEA accompanied with ADH (28.2%): 8 found with ADH and 3 found with ADH, ALH, or LCIS.

Regarding the radiological findings of the 26 patients whose final surgical specimens had confirmed FEA, 8 of the 26 patients were BIRADS 4a (30.8%), 17 were BIRADS 4b (65.4%), and 1 was BIRADS 4c (3.9%). Four lesions were detected by US and 22 by MMG. The mammographic findings of pure FEA presented with microcalcification (MC) were as described. In terms of the shape, 19 were amorphous, 2 punctate, and 1 round. In terms of the distribution, there were 9 clusters, 8 groups, 4 regional, and 1 linear.

There were 12 lesions for which the final pathological report from the surgical excisional specimen demonstrated

TABLE 1. Baseline characteristics of pure FEA from CNB patients.

Characters	CNB pure FEA (n = 45)
Age (years)	
Range	37–61
Median	49.0
Detected lesions	
Microcalcification	39
Mass	5
Microcalcification with mass	1
BIRADS	
1–3	0
4a	11
4b	32
4c	2
5	0
Target lesion sampling	
Microcalcification	39
Stereotactic	33
Vacuum assisted	6
Mass	
USG-guided	6
Residual calcification	
Yes	16
No	18
Unknown	5
Surgery after FEA identified from CNB	
Yes	39
No	6
Histology of excision specimens	
Pure FEA	26
FEA with AH	12
FEA with cancer	1

Abbreviations: AH: atypical hyperplasia, CNB: core needle biopsy, FEA: flat epithelial atypia

TABLE 2. Radiographic findings according to the final histological results.

Group Factor	Total n = 39, (%)	Pure FEA n = 26, (%)	FEA with AH n = 12, (%)	FEA with DCIS n = 1, (%)	P-value
Detection methods					
MMG	35	22	12	1	
US	4	4	0	0	
BI-RADS					
4A	9	8 (30.8)	1 (8.3)	0	0.49
4B	28	17 (65.4)	10 (83.3)	1 (100)	
4C	2	1 (3.9)	1 (8.3)	0	

FEA combined with high-risk benign breast lesion. Of these 12 lesions, 10 were BIRADS 4b (83.3%), 1 was BIRADS 4a (8.3%), and 1 was BIRADS4c (8.3%). In terms of the shape of the microcalcifications in these 12 lesions, 10 were amorphous, 1 was fine linear, and 1 was punctuate. Interestingly, 1 patient whose final surgical excision specimen showed DCIS was categorized into BIRADS 4b with segmental amorphous microcalcification. When comparing the BIRADS classifications, no difference was observed between the pure and combined FEA subgroups ($p = 0.49$).

DISCUSSION

Overall, 1 lesion in our study was upgraded to DCIS (2.6%) and none of the lesions were invasive carcinoma. In addition, breast cancer did not occur whether omitting the surgical group or following surgery in the group without the upgrading. Despite the risk of subsequent breast cancer of FEA being unclear, just as in previous studies, this could not be proven conclusively[5,7], but FEA itself tended to not increase the risk of subsequent cancer. Said et al. found no increasing long-term breast cancer events when FEA was found concomitantly with either atypical hyperplasia (AH) or proliferative lesions (PL): [AH + FEA 4.74 vs. AH 4.23; $p = 0.59$] and [PL + FEA 2.04 vs. PL 1.90; $p = 0.76$], respectively.[6] In the case of pure FEA after surgical excision, de Mascarel et al. also found that none of the pure FEA patients in their study had breast cancer during 10-year follow-ups.[8] The findings from our study were similar in terms of the rarity of events following upgrading to malignancy in FEA lesions diagnosed on CNB.

In practice, pure FEA from CNB should be followed by surgical removal. This relies on previous evidence, which demonstrated a 10-40% combination of FEA with other malignant lesions (either *in situ* or invasive carcinoma) from CNB specimens.[2-4,9] However, when emphasizing cancer upgrading (DCIS or invasive cancer), the possibility of FEA accompanying these malignant cells is low (7.5%) compared to its co-incidence with other high-risk lesions (18.6%).[2] When vacuum-assisted core needle biopsy (VCNB) was first introduced, the rate of upgrading decreased dramatically. Recent investigations using VCNB reported decreasing histologic upstaging at 0 - 3%.[10,11] However, even our practices did not routinely use VCNB in all microcalcification-detected cases, and our upgrading rate was only 2.6%. The necessity of surgical excision, therefore, is controversial.

Despite the low incidence of malignant upgrading, the rate of combining ADH was high (30.7%). In addition, our study could not demonstrate the correlation between FEA upgrading and radiologic findings. Even though most patients presented with suspicious microcalcifications detected by mammography and were classified into BIRADS 4b, the study population was too small to specify the significance of the imaging classification to discriminate whether the lesion was pure or mixed FEA. In the case of mammographic abnormalities, amorphous microcalcifications were more commonly identified in 30 of 39 specimens (76.9%) than other shapes and the majority were distributed as clusters. In 1 lesion with DCIS upgrading, the patient presented with segmental amorphous microcalcification, which was the only case where the microcalcification was distributed as a segmental shape. Likewise, previous studies failed to identify the specific radiographic characters for FEA upstaging[3,12], which tended to be clustered or segmental amorphous microcalcifications.[3,13] Although, no distinctive breast imaging was noted, FEA diagnosed as BIRADS 4a was less likely to be upgraded, and occurred in only one of 9 patients (11.1%), meanwhile, FEA also occurred with BIRADS 4b (11 of 28; 39.3%) or 4c (1 of 2; 50%); therefore, BIRADS classification was not a good independent predictor for selecting patients to observe instead of performing surgery. Among one of several studies, Alencherry et al. recently reported that one of the independent risk factors to upstaging was a history of cancer in individuals or first-degree relatives[13,14], but no patients in our cohort had a family history of breast cancer.

However, there were some limitations in our study to note. As the pathological definition of FEA has only recently been introduced in the past few decades, there may have been interobserver variabilities of the interpretation among pathologists and it might have been reported as columnar cell change in some cases, thus causing a smaller number to be included in the study population, especially as we could not review all the slide specimens. Another shortcoming, because of the higher cost of vacuum-assisted devices, is that in our hospital, core needle biopsy with a 14-gauge needle rather than VCNB is the most practised technique, which might be less accurate.

CONCLUSION

Flat epithelial atypia is a marker of carrying a high risk lesion rather than for upgrading to breast cancer. Even though the histological finding may show atypical cells, the risk of subsequent breast cancer is very low compared to ADH. Surgical excision may be omitted particularly in cases of pure FEA from core needle biopsy.

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