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REVIEW ARTICLE

Is the outcome at surgery different when flat epithelial atypia and lobular neoplasia are found in association at biopsy?

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Objective: To assess the impact on the final outcome at surgery of flat epithelial atypia (FEA) when found concomitantly with lobular neoplasia (LN) in biopsy specimens compared with pure biopsy-proven FEA.
Methods: The approval from the institutional review board of the CHUM (Centre Hospitalier Universitaire de Montréal) was obtained. A retrospective review of our database between 2009 and 2013 identified 81 females (mean age 54 years, range 38–90 years) with 81 FEA biopsy-proven lesions. These were pure or associated with LN only in 59/81 (73%) and 22/81 (27%) cases, respectively. Overall, 57/81 (70%) patients underwent surgery and 24/81 (30%) patients underwent mammographic surveillance with a mean follow-up of 36 months.
Results: FEA presented more often as microcalcifications in 68/81 (84%) patients and were mostly amorphous in 49/68 (72%). After excluding radio pathologically discordant cases, pure FEA proved to be malignant at surgery in 1/41 (2%; 95% confidence interval 0.06–12.9). There was no statistically significant difference in the upgrade to malignancy whether FEA lesions were pure or associated to LN at biopsy ($p = 0.4245$); however, when paired in biopsy specimens, these lesions were more frequently associated with atypical ductal hyperplasia (ADH) at surgery than with pure FEA ($p = 0.012$).
Conclusion: Our results show a 2% upgrade rate to malignancy of pure FEA lesions. When FEA is found in association with LN at biopsy, surgical excision yields more frequently ADH than pure FEA thus warranting close surveillance or even surgical excision.
Advances in knowledge: The association of LN with FEA at biopsy was more frequently associated with ADH at surgery than with pure FEA. If a biopsy-proven FEA lesion is deemed concordant with the imaging finding, when paired with LN at biopsy, careful surveillance or even surgical excision is suggested.

INTRODUCTION

The development of breast cancer is believed to be a multistep process originating in terminal duct lobular units and progressing towards invasive cancer. Many precursor lesions separating normal and malignant epithelium have been known including atypical duct hyperplasia (ADH), lobular neoplasia (LN) encompassing atypical lobular hyperplasia and lobular carcinoma *in situ* (LCIS), ductal carcinoma *in situ* (DCIS) and the more recently described columnar cell lesions.[1] The term flat epithelial atypia (FEA) has been given to columnar cell lesions in which the native epithelium is replaced by one to multiple layers of cells that show low-grade cytologic atypia, whereby the adjective flat denotes the absence of more complex architectural patterns.[1] These lesions are often found in association with microcalcifications.[1–4] They, however, lack specific characteristics but are mostly described as amorphous[5] as well as coarse heterogeneous and rarely fine pleomorphic.[6]

With the widespread use of imaging-guided biopsies as an alternative to surgical biopsy in the diagnosis of subclinical breast anomalies, increased number of high-risk lesions, including FEA, is encountered. Of these high-risk lesions, some harbour a significant risk of demonstrating cancer at excision as ADH and for which the current recommendation remains surgical excision, whereas others, such as LN, may only indicate an increased risk of breast cancer over a female's lifetime, hence close follow-up might be sufficient. In a recent review of the literature,[7] the rate of upgrade of ADH to DCIS or invasive cancer ranges between 10% and 20% in studies submitted to radiological–pathological correlation. The true clinical significance of LN and FEA

remains not clear, and straight guidelines for surgical excision or only surveillance are still lacking for both, especially in cases when the criteria of radiological–pathological concordance are met.

FEA is differentiated from ADH and low-grade ductal carcinoma by the presence of only low-grade cytologic atypia in the absence of architectural atypia. Since these lesions frequently merge into ADH and low-grade DCIS, deeper levels are sometimes necessary to exclude a more serious histological lesion.[3] FEA lesions are also frequently observed in close association with the foci of LN and tubular carcinomas, with which they share cytological features such as prominent apical snouts and low-grade nuclear atypia.[8,9] This suggests that FEA may be a non-obligate precursor in the low-grade breast neoplasia pathway.[1,7,8,10,11]

The reported upgrade rate to malignancy after surgical excision of FEA lesions ranges between 13% and 67% in the studies reported without radiological–pathological correlation hence favouring surgical excision.[6,12] This upgrade rate, however, drops to a range from 0% to 7% in recent studies when all microcalcifications were removed at biopsy and the discordant cases excluded after careful radiological–pathological correlation.[6,7,12] In a review of the literature published in 2012, Verschuur-Maes et al[13] reported an upgrade rate to malignancy at surgery of 9% for surgically excised pure FEA and of 20% when FEA is found in association with ADH at biopsy. Based on this review, we were interested to evaluate the effect of LN on the final outcome at surgery of biopsy-proven FEA lesions found concomitantly with LN on specimens of biopsy.

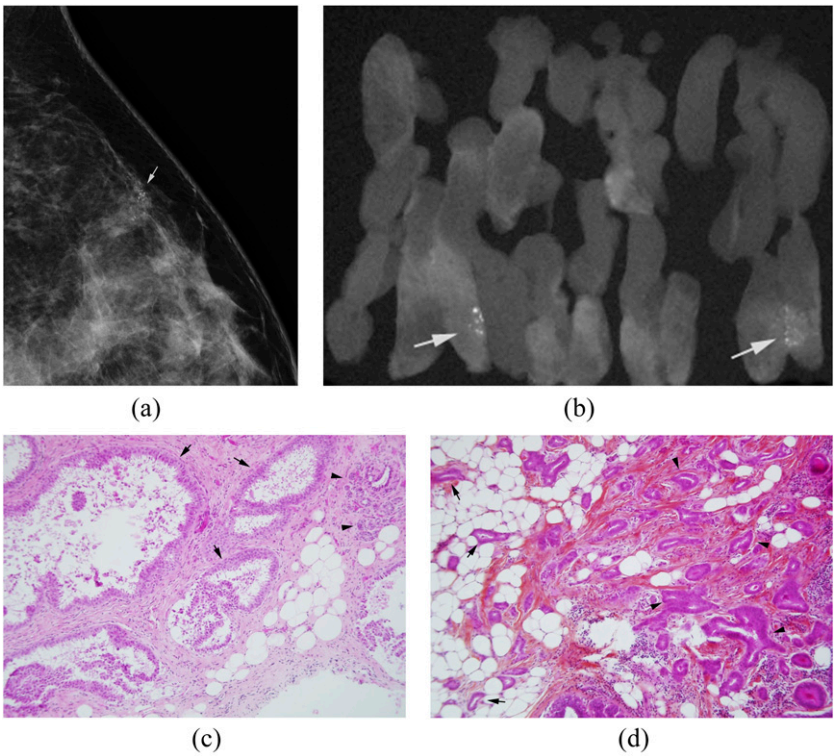
This study aimed:

(1) To assess the impact of LN on the final outcome at surgery of FEA lesions when these are found together in biopsy specimens
(2) To determine the frequency of malignancy at surgical excision of biopsy-proven pure FEA in the breast center of the CHUM.

METHODS AND MATERIALS

Institutional review board approval was obtained, and informed consent from patients was waived. Using our breast centre pathology database, the retrospective review of 8907 imaging-guided core needle biopsies performed between 1 January 2009 and 1 January 2013 identified 110 cases of FEA. Patients were included in the study when the biopsy result yielded pure FEA or FEA with only LN as the most advanced atypical lesion at pathological analysis. Patients with associated atypical ductal hyperplasia (ADH) and ipsilateral breast cancer were excluded, so that 81 patients with 81 FEA lesions constituted our study.

Figure 1. (a–d) 47-year-old female; first screening mammogram. (a) Magnified lateral view demonstrating a cluster of suspicious pleomorphic microcalcifications (arrow) for which stereotactic vacuum-assisted 11-gauge core needle biopsy was recommended and performed. (b) Radiograph of core specimen obtained reveals numerous microcalcifications (arrows). (c) Photomicrograph of core biopsy specimen [haematoxylin phloxine saffron (HPS) stain, magnification ×10] reveals dilated acini lined by stratified columnar cells with low-grade atypia diagnostic of FEA (arrows). Please note the normal-size acini in this terminal ductal lobular unit (arrowheads) contrasting with FEA. (d) Photomicrograph of surgical specimen (HPS stain; magnification ×10) shows atypical tubules invading the fat (arrows) and fibrous stroma (arrowheads) consisting with low-grade tubular invasive carcinoma.



A retrospective review of the imaging features (mammogram, ultrasound and/or MRI) was performed in consensus by two readers with 10 and 25 years' experience in breast imaging using the American College of Radiology, Breast Imaging Reporting and Data System (BI-RADS®) lexicon[14] on dedicated workstations including two high-resolution monitors on the picture archive and communication system (Impax 6; Agfa Healthcare, Belgium).

The lesions sampled were divided into: microcalcifications, masses, distortions and abnormal enhancement on MRI. The histopathological diagnosis was obtained under stereotactic or MR guidance using a vacuum-assisted 10- or 11-gauge device when the radiological anomaly was microcalcifications or distortion on mammogram or abnormal enhancement on MR or sonographic guidance with a 14-gauge spring-loaded needle when presenting as a mass.

Based on its radiological characteristics, the radiological anomaly was categorized according to the BI-RADS lexicon and the degree of suspicion of malignancy into BI-RADS category 4A (low suspicion of malignancy), 4B (moderate suspicion of malignancy), 4C (high suspicion of malignancy) or 5 (highly suggestive of malignancy). The histopathological results at biopsy and at surgery of those lesions that underwent excision were collected from patients' files. The data were analyzed using Pearson's χ^2 tests.

A p-value <0.05 was considered significant throughout this study.

RESULTS

Study population

81 FEA lesions were diagnosed in 81 females (mean age 54 years, range 38–80 years) in our institution between 2009 and 2013. The 81 FEA lesions were pure or associated with LN in, respectively, 59/81(73%) and 22/81 (27%) patients.

Imaging-guided needle biopsies were performed under stereotactic guidance with an 11-gauge vacuum-assisted needle (Mammotome Ethicon Endo-Surgery, Johnson and Johnson, Cincinatti, OH) (70/81; 86%), sonographic guidance with a 14-gauge spring-loaded needle (Bard biopsy system Tempe, AZ) (9/81; 12%) or MR guidance with a 10-gauge vacuum-assisted needle (Suros, Hologic Marlborough, MA) (2/81; 2%).

All patients in our breast centre who underwent a percutaneous imaging-guided biopsy with a pathological result yielding atypia are referred to surgical consult for counselling. Subsequently, surgical excision or follow-up is considered depending on the radiological–pathological correlation, patients' risk factors as assessed by the surgeon and patients' preference.

Overall, 57 patients (57/81; 70%) underwent surgery and 24 (24/81; 30%) mammographic surveillance with a mean follow-up of 36 months (range, 12–84 months). One patient had a repeated ultrasound-guided biopsy 48 months after the initial biopsy despite the fact that the mass was stable, and the histopathological analysis showed only pseudoangiomatous stromal hyperplasia without atypia; six patients were lost to follow-up 1 year after the biopsy and one died from pneumonia the following year. None of the patients followed-up developed a malignancy within the period of surveillance.

Imaging findings

In our study, FEA presented as microcalcifications in 68 patients (68/81; 84%), masses in 9 patients (9/81; 12%), distortions in 2 patients (2/81; 2%) and MR enhancement in 2 patients (2/81; 2%). The radiological anomaly was classified as BI-RADS 4A in 23 patients (23/81; 28%), BI-RADS 4B in 40 patients (40/81; 50%), BI-RADS 4C in 17 patients (17/81; 21%) and BI-RADS 5 in 1 patient (1/81; 1%). When presenting as microcalcifications, they were more frequently grouped in 58/68 (85%) patients or showing a segmental or regional distribution in, respectively, 4/68 (6%) and 6/68 (9%) patients. The microcalcifications were described as fine pleomorphic in 12/68 (18%) patients, as amorphous in 49/68 (72%) patients and as coarse/heterogeneous in 7/68 (10%) patients (Figure 1).

The anomaly was measured with calipers on the picture archive and communication system either on sonographic or, mammographic or MR images. It was 0.5 cm or less in 14//81 (17%) patients, 0.5–1 cm in 43/81 (53%) patients, 1–2 cm in 14/81 (18%) patients and >2 cm in 10/81 (12%) patients. Post-biopsy mammogram showed total removal of the microcalcifications in 41/68 (60%) patients, less or more than half of the cluster of microcalcifications remaining in the breast in, respectively, 15/68 (22%) and 12/68 (18%) of the cases. Sonographic correlates were found in 11 patients (11/81; 14%) presenting as masses that were irregular (4/11; 36%), oval (6/11; 55%) or round (1/11; 9%) with either microlobulated, indistinct or spiculated margins in, respectively, 7/11 (64%), 3/11 (27%) and 1/11 (9%) patients. They were classified as BI-RADS 4A in 4/11 (36%) patients, BI-RADS 4B in 5/11 (46%) patients, BI-RADS 4C in 1/11 (9%) patient and BI-RADS 5 in 1/11 (9%) patient.

Results at biopsy

Pathological analysis of the samples obtained at imaging-guided biopsy showed pure FEA in 59/81 (73%) biopsies and FEA with LN in 22/81(27%) of the biopsies.

Of these 81 FEA lesions, 57 (57/81; 70%), stratified into pure FEA (41/57; 72%) and FEA associated with LN (16/57; 28%), underwent surgical excision.

Table 1. Histopathological results at surgery

Surgical pathology	Number (%)
Benign or FEA ± LN	32 (56)
ADH	17 (30)
DCIS	4 (7)
IDC	4 (7)
Total	57[a] (100)

ADH, atypical ductal hyperplasia; DCIS, ductal carcinoma *in situ*; FEA, flat epithelial atypia; IDC, invasive ductal carcinoma; LN, lobular neoplasia.
[a]57/81 patients underwent surgical excision.

Results at surgical excision

At surgery, benign pathology or FEA with or without LN were found in 32 patients, 32/57 [56%; 95% confidence interval (CI) 42.4–69.3]; ADH in 17 patients, 17/57 (30%; 95% CI 18.4–43.4); DCIS in 4 patients, 4/57 (7%; 95% CI 1.9–17.0); and invasive cancer in 4 patients, 4/57 (7%; 95% CI 1.9–17.0) (Table 1). All cancers found at surgery were of low grade except one case of high-grade DCIS.

No statistically significant difference could be found in the upgrade to malignancy of FEA lesions whether or not these were paired to LN in biopsy specimens; pure FEA and FEA with LN were, respectively, upgraded to cancer in 4/41 (10%) and 4/16 (25%) cases ($p = 0.4245$; $\chi^2 = 0.6378$, degree of freedom = 1) (Table 2).

The total upgrade to cancer after surgical excision of FEA is in our study, 8/57 (14%; 95% CI 6.3–25.8). Of these eight patients in whom surgery showed malignancy, the biopsy result yielding only atypia was considered discordant and surgery was highly recommended in four patients (Table 3). One of them presented with linear microcalcifications, the biopsy of which, revealed FEA associated with LCIS and the three others as a mass and two distortions where the biopsy yielded pure FEA. If we exclude these four cases of which the radiological presentation was deemed discordant with the post-biopsy pathological result of atypia, the total upgrade rate to cancer at surgery in our study would drop from 8/57 (14%; 95% CI 6.3–25.8) to 4/57 (7%; 95% CI 1.9–17.0) and that of pure FEA would be 1/41 (2%; 95% CI 0.06–12.9) instead of 4/41 (10%).

There was a significant association between concomitant presence of LN with FEA at imaging-guided biopsy and final outcome at surgery ($p = 0.012$; $\chi^2 = 8.7836$, degree of freedom = 2) whereby FEA found concomitantly with LN at biopsy proved to be more frequently ADH at surgery than pure FEA.

When the mammographic anomaly was a cluster of microcalcifications, which underwent a stereotactic-guided vacuum-assisted needle core biopsy, there was no association between the presence of post-biopsy residual microcalcifications ($p = 0.4602$) and final malignant outcome. Furthermore, no significant association could be found between the size of the cluster of microcalcifications ($p = 1$), and the BI-RADS classification ($p = 0.4454$) on one hand and upgrade to malignancy at surgery on the other hand.

The final malignant outcome was significantly associated with the radiological presentation whereby FEA lesions presenting initially as masses or distortions were more frequently upgraded to malignancy at surgery than those presenting as microcalcifications ($p = 0.0091$).

DISCUSSION

In our series, pure FEA was found in 59 of 8907 (0.7%) biopsies over 4 years. This is slightly lower to what has been reported, 1.2% and 1.5%.[2,15] Previous studies have observed coexistence of FEA with other forms of atypia and low-grade carcinoma.[1,16] In our study, FEA was associated with LN (atypical lobular hyperplasia and/or LCIS) in 22/81 (27%) cases, which is higher than was previously reported by Peres et al[17] in 8/271 (3%) cases and by Bianchi et al[18] in 90/589 (15.3%) cases.

In agreement with the literature, our results show that most of the FEA lesions (68/81, 84%) present at imaging as microcalcifications which is within the range reported by Peres et al[17] in 95.6% (259/271) cases; Khoumais et al[2] in 75% (78/104) cases; Biggar et al[19] in 69% (35/51) cases; and Solorzano et al[5] in 61% (20/33). These microcalcifications were considered indeterminate, lacking specific features and were often described as amorphous[5] as in our study (49/68, 72%) and fine pleomorphic.[2,20] FEA presenting as masses or asymmetrical densities have been reported by Peres et al[17] in 4.1% (12/271) cases; Khoumais et al[2] in 25% (25/104) cases; Biggar et al[19] in 25% (13/51) cases; and Solorzano et al[5] in 33% (11/33) cases and were found in our study in 11 patients (11/81, 14%) which is within this range. On ultrasound, Solorzano et al[5] described FEA as an irregular mass with microlobulated margins similar to the reported features of DCIS and ADH.[5,21,22] Most of the FEA cases presenting in our study as masses shared these sonographic characteristics and displayed an irregular shape and microlobulated margins in 4/11 (36%) and 7/11 (64%) cases, respectively. Three of them, however, were found associated with a fibroadenoma and one with fibrocystic changes. This could account for some of the benign appearing features encountered at sonography in 6 of our patients [6/11 (55%)], raising the hypothesis that FEA was, in these cases, an incidentaloma at biopsy.

Unlike few studies,[2,17,19] we have found that FEA lesions presenting as masses or distortions were more often upgraded to cancer at surgery than microcalcifications. This could be explained by an undersampling factor considering that these masses were mostly sampled with a 14-gauge needle under

Table 2. Detailed surgical results of biopsy-proven pure flat epithelial atypia (FEA) and FEA associated with lobular neoplasia (LN)

Surgical pathology results				
Biopsy results	Benign or FEA ± LN	ADH	Cancer (*in situ* or invasive)	Total (%)
Pure FEA	28 (68%)	9 (22%)	4 (10%)	41 (72%)
FEA and LN	4 (25%)	8 (50%)	4 (25%)	16 (28%)
Total	32	17	4	57 (100%)

ADH, atypical ductal hyperplasia.

Table 3. Summary of clinicoradiological findings of patients with malignant outcome after surgical excision of a biopsy-proven flat epithelial atypia (FEA) lesion

Patient	Age, years	Radiological presentation	BI-RADS	Biopsy guidance	Needle, gauge	Biopsy result	Concordance	Surgical result
1	52	Amorphous microcalcifications	4B	Stereotactic	11	Pure FEA	Yes	DCIS
2	47	Mass	5	Sonographic	14	Pure FEA	No	IDC grade 1
3	63	Distortion	4B	Stereotactic	11	Pure FEA	No	IDC grade 1
4	55	Distortion	4B	Stereotactic	11	Pure FEA	No	IDC grade 1
5	47	Linear microcalcifications	4C	Stereotactic	11	FEA + LCIS	No	IDC grade 1
6	50	Amorphous microcalcifications	4A	Stereotactic	11	FEA + LCIS	Yes	DCIS
7	67	Non-mass enhancement	4A	MRI	9	FEA + ALH	Yes	DCIS
8	59	Amorphous microcalcifications	4B	Stereotactic	11	FEA + ALH	Yes	DCIS

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; BI-RADS, Breast Imaging Reporting and Data System; DCIS, ductal carcinoma *in situ*; IDC, invasive ductal carcinoma; LCIS, lobular carcinoma *in situ*.

ultrasound guidance. Nonetheless, since FEA is frequently associated with low-grade invasive tubular or lobular carcinoma[9] and since these malignancies are known to often present mammographically as distortions, we assume that FEA result obtained on core needle biopsy of a distortion should be considered discordant and prompt surgical excision.

After careful radiological–pathological correlation and exclusion of the discordant cases, the total upgrade rate to malignancy after surgical excision of pure FEA lesions in our study is 2% (1/41) which is within the range reported in the literature;[6,12] this would be equivalent to a BI-RADS 3 lesion for which follow-up is acceptable; larger studies are, however, needed to confirm this finding.

Our results show that the upgrade rate to cancer at surgery of the lesions, combining FEA and LN, of 25% (4/16) is similar to the results reported by Peres et al[17] of 25% (2/8) but higher than that reported by Bianchi et al[18] of 14.4% (13/90).

In our study, ADH was more often encountered in the excisional biopsies of FEA when these are paired to LN in biopsy specimens than alone. This finding is interesting since many studies have shown that FEA lesions are often linked with atypical hyperplasia, including atypical ductal and lobular hyperplasia, and low-grade carcinoma with which they share many similar molecular alterations suggesting that FEA may be a non-obligate precursor of low-grade carcinoma.[1,4,7,10,11] This may be pertinent to identify, as many authors have suggested that patients with FEA may be at risk of natural sequential progression from FEA to ADH to cancer.[3,7] As suggested by many studies, when columnar cell lesions are found in isolation, the risk of progression to a more advanced lesion is minor.[4,7] Nonetheless, their presence is an excellent indicator for the coexistence of other atypical breast lesions that are associated with elevated cancer risk.[4,16] Since currently there is no clear consensus as to the appropriate management decisions of isolated FEA, especially when deemed concordant with the imaging findings, it might be more prudent for patients with concomitant FEA and LN at biopsy to undergo either close surveillance or even surgical excision in order to exclude more worrisome lesions.

It is known that the amount of tissue obtained on core needle biopsy is determined by the gauge and type of needle used, automated *vs* vacuum-assisted, and may reflect the upgrade rate.[23,24] Although we have found a statistically significant association between the needle type (*i.e.* 14-gauge automated needle *vs* 11-gauge vacuum-assisted needle) and final upgrade rate to malignancy ($p = 0.0015$), this finding could be more likely biased by the fact that different needles sampled different types of lesions. In fact, all FEA lesions presenting as masses were sampled by a 14-gauge needle, whereas vacuum-assisted 11-gauge needles sampled microcalcifications.

Unlike few studies[17,25] that have found a statistically significant association between incomplete removal of the anomaly during sampling and malignant underestimation rate, our results as others'[18,26] show that the final underestimation malignancy rate was not associated with the presence of residual microcalcifications post biopsy.

Our study has some limitations, mainly (1) it is retrospective in design and small in size; (2) it includes few cases of LN associated with FEA; (3) the pathological results were retrieved from

the patients' files and were not retrospectively reviewed by a pathologist. This could account for a major limitation of our study since variability in the diagnosis of challenging cases including FEA was reported in many studies[27,28] and consultation with colleagues regarding these cases can improve diagnostic accuracy;[29] nonetheless, our results highlight the importance of the radiological–pathological correlation that each breast radiologist should undertake after each imaging-guided biopsy. In fact, despite the lack of consensus that persists in the management of FEA and LN, any discordance found between the radiological presentation and pathological result after core needle biopsy should lead to the appropriate management including rebiopsy or surgical excision aimed at detecting any malignancy that could have been otherwise missed.

CONCLUSION

FEA presents most often as microcalcifications, mostly of amorphous type, and less often as a mass displaying features similar to ADH on ultrasound. Our study shows that LN found in association with FEA at core needle biopsy may be an indicator for the presence of other atypical breast lesions that are associated with higher risk of breast cancer, for instance, ADH or even DCIS that can be overlooked by relying only on radiological–pathological concordance as in three of our cases. Hence, in cases where the biopsy-proven FEA result is deemed concordant with the imaging findings, it might be more prudent to recommend close surveillance or even surgical excision of those FEA lesions found concomitantly with LN on biopsy specimens.

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