Clinical Imaging 54 (2019) 21–24

Contents lists available at ScienceDirect

Clinical Imaging

journal homepage: www.elsevier.com/locate/clinimag

Breast Imaging

Clinical, imaging, and intervention factors associated with the upgrade of isolated flat epithelial atypia

Erin Alencherry[a,*], Rakhee Goel[a,1], Sarah Gore[a,2], Cheryl Thompson[b], Christina Dubchuk[a,3], Philip Bomeisl[c], Hannah Gilmore[c], Kathryn Dyhdalo[d], Donna M. Plecha[a]

[a] Mather Pavilion B402, 11100 Euclid Avenue, Cleveland, OH, 44106, United States of America
[b] 10900 Euclid Ave., Cleveland, OH, 44106, United States of America
[c] 11100 Euclid Ave., Cleveland, OH, 44106, United States of America
[d] 9500 Euclid Avenue, Cleveland, OH, 44195, United States of America

ARTICLE INFO

Keywords:
Breast atypia
FEA
Clinical management

ABSTRACT

Purpose: This study aims to determine clinical, imaging, and intervention factors associated with the upgrade of flat epithelial atypia (FEA) diagnosed on vacuum-assisted biopsy (VAB) in order to formulate criteria for excision and better assist in management.

Methods: Between 2012 and 2015, 254 patients had a form of atypia diagnosed on ultrasound, MRI or stereotactic VAB and met eligibility for this study. Demographic, imaging, biopsy and pathology characteristics were analyzed for association with upgrade. We compared isolated FEA to all of the atypias grouped together.

Results: Of the 254 atypia lesions, 72 (28%) were isolated FEA, and the upgrade rate was 2.8% (2/72). Statistically significant factors present with upgrade of isolated FEA include personal history of breast cancer and cancer diagnosis on a concurrent separate core biopsy. Other factors associated with upgrade include first degree family history of breast cancer, segmental calcification distribution, extent of calcifications > 2 cm, and < 25% of calcifications removed on biopsy.

Conclusion: In patients with biopsy results of isolated FEA, in the absence of personal or first degree family history of breast cancer, cancer on a concurrent biopsy, segmental calcification distribution, extent of calcifications > 2 cm, and only 0–24% calcifications removed on biopsy, patients may be safely followed with imaging, avoiding unnecessary excision.

1. Introduction

The increased use of percutaneous imaging guided biopsies rather than excisional biopsies for suspicious breast lesions has resulted in higher diagnosis of noncancerous high-risk lesions. Such high-risk lesions include atypical ductal hyperplasia (ADH), atypical lobular hyperplasia (ALH), and flat epithelial atypia (FEA). These atypias have been extensively studied, and management of these lesions is a continued source of discussion due to their potential for upgrade to malignancy. Specifically, patients with ADH and ALH have a 4–5 times higher risk of developing carcinoma as compared to the general population [1]. ADH has been described as a ductal proliferative breast lesion with some, but not all, of the features of a low or intermediate grade ductal carcinoma in situ [2], whereas ALH is considered to be a non-obligate precursor lesion to ILC, as well as a risk indicator of breast cancer in either breast [3]. ADH and ALH are routinely excised due to their higher upgrade rates, although there is discussion as to whether ALH may be able to be monitored without excision in the setting of radiologic-pathologic concordance [4]. Flat epithelial atypia, originally described as a “clinging carcinoma in situ” by Azzopardi et al., remains a controversial high risk lesion, with continued debate in the literature on its clinical significance [5]. The reported malignancy upgrade rate of isolated FEA is generally considerably lower than that of ADH and ALH, with rates in the literature ranging from 0 to 15% [6–9]. FEA can be

* Corresponding author.
E-mail addresses: Erin.Alencherry@uhhospitals.org (E. Alencherry), clw8@case.edu (C. Thompson), Phillip.Bomeisl@uhhospitals.org (P. Bomeisl), Hannah.Gilmore@uhhospitals.org (H. Gilmore), Donna.Plecha@uhhospitals.org (D.M. Plecha).
[1] 110 Kingsley Lane, Norfolk, VA 23505, United States of America.
[2] 1717 North E Street, Suite 300, Pensacola, FL, 32501, United States of America.
[3] 19300 South Park Blvd., Shaker Heights, OH 44122, United States of America.

https://doi.org/10.1016/j.clinimag.2018.11.008
Received 4 May 2018; Received in revised form 23 October 2018; Accepted 19 November 2018
0899-7071/ © 2018 Elsevier Inc. All rights reserved.

found to coexist with a higher risk form of atypia, which may also prompt recommendation for excision [9]. Given these findings, the purpose of this study is to provide further insight on clinical, imaging, and intervention factors associated with atypia upgrade in order to better assist in management of isolated FEA. Our study also looked at factors associated with upgrade rates of other forms of atypia to compare with isolated FEA.

2. Materials and methods

2.1. Study design

We performed an IRB-approved, retrospective review of medical records for all cases of atypia diagnosed at vacuum-assisted breast biopsy (VAB) procedures performed between 2010 and 2015. Patients were referred for either ultrasound, stereotactic, or MRI guided VAB by fellowship-trained breast imagers after a diagnostic workup that received a BI-RADS category 4 (suspicious) or 5 (highly suggestive of malignancy) final assessment.

The various atypias were each classified by breast pathologists according to criteria adopted by the World Health Organization. Under this classification, FEA is characterized as intraductal alteration with replacement of native epithelial cells by a single or 3–5 layers of mildly atypical cells [10]. All patients included in the study had surgical excision performed after biopsy results demonstrated atypia. An upgrade was defined as obtaining ductal carcinoma in situ (DCIS) or invasive cancer at subsequent surgical excision. Patients who did not undergo surgical excision, those in whom the surgical specimen included the biopsy site for a simultaneously diagnosed malignancy on a separate VAB, and those who had a mastectomy performed were excluded from the study. A total of 29 patients did not undergo surgical excision, including 8 with FEA, 16 with ADH, and 5 with ALH. The reasons for lack of surgical excision include: loss to follow up (4 FEA, 12 ADH, 5 ALH), patient preference for observation (4 FEA), physician recommendation for observation due to patient morbidity (2 ADH), and radiation therapy (1 ADH) and hormonal treatment (1 ADH) due to multicentric disease. Between 2010 and 2015, 254 patients met the eligibility for our study. Clinical data and patient demographics for these cases were collected from the electronic medical record. The median age of the 254 patients was 54 years old.

2.2. Image guided vacuum-assisted biopsy

Stereotactic biopsy procedures were carried out on a dedicated digital stereotactic table (Lorad; Hologic, Marlborough, MA) with the patient lying prone. Sampling of the lesions was performed using a vacuum-assisted Hologic ATEC biopsy device (Marlborough, MA) with 9 gauge needles, the majority of which were regular size (170) and some of which were petite size (12). Biopsy specimens from patients with calcifications were routinely examined by specimen mammography. The percentage of retrieved calcifications after biopsy was evaluated retrospectively and quantified as a percentage removed (0–24%, 25–49%, 50–74% and 75–100%). The average number of core samples taken was 9.1 (range 4–18).

Ultrasound guided biopsy procedures were carried out using one of two high resolution ultrasound machines (Phillips Healthcare, Amsterdam, The Netherlands; SuperSonic Imagine, Aix-en-Provence, France). Sampling of the lesions was performed using a vacuum-assisted Hologic ATEC biopsy device with 9 gauge or 12 gauge needles. The average number of core samples taken was 5.1 (range 2–9).

MRI guided biopsy procedures were carried out on a 1.5 or 3 T magnet using a dedicated breast coil with the patient lying prone. Sampling of the lesions was performed using a vacuum-assisted Hologic ATEC biopsy device with 9 gauge needles. The average number of core samples taken was 8.8 (range 5–13).

2.3. Imaging morphology

Breast lesions were categorized into morphologic groups based on imaging results, including mass without calcifications, mass with calcifications, calcifications only, MRI finding, or other. The morphology of calcifications was further classified as amorphous, linear, pleomorphic, coarse, or other. The distribution of calcifications was categorized as grouped, regional segmental, or other. The size of the mass or extent of calcifications was also recorded. Ultrasound characteristics, including shape, margin, echogenicity, presence of posterior features, elastography, and internal vascularity were also recorded for the masses.

3. Statistics

Statistical analysis was based on chi-square and Fisher's exact test for comparison of categorical variables. p values < 0.05 were considered statistically significant.

4. Results

Of the VAB procedures identified, 71.7% (182/254) were stereotactically guided, 20.9% (53/254) were ultrasound guided and 7.5% (19/254) were MRI guided. Of the 254 atypia lesions, 34/254 (13.4%) were upgraded at resection. The 34 upgraded patients included 24 DCIS (70.6%), 1 DCIS/LCIS (2.9%), 8 invasive cancers (23.5%), and 1 mucoepidermoid cancer (2.9%). Of the 150/254 lesions with an isolated atypia, upgrade rates were as follows: FEA 2.8% (2/72); ALH 19.0% (4/21); ADH 31.6% (18/57). The upgrade rates for all isolated atypia and combination atypias are listed in Table 1. Of note, all upgrades had concordant histologic and radiographic findings, although one of the isolated FEA samples was noted to be concordant but thought to be an underestimation of disease.

Among the characteristics tested for potential association with upgrade of isolated FEA, we found some statistically significant intergroup differences (Table 2). There were 14/72 (19.4%) patients with a personal history of breast cancer; these patients had a statistically significant higher rate of upgrade than patients with no personal history ($p = 0.03$). Patients with upgrade of isolated FEA also had a statistically significant higher rate of cancer diagnosis on a separate concurrent core biopsy ($p = 0.0004$). Because of the small numbers statistical significance was not reached in the other categories.

When we evaluated all 254 types of atypia together, including ADH and ALH, there were several statistically significant intergroup differences associated with upgrade to malignancy (Table 3). Patients who presented with a mass with or without calcifications had a statistically

Table 1
Atypia upgrade rates by histology.

	Isolated ADH	Isolated ALH	Isolated FEA	FEA and ADH	FEA and ALH	ALH and ADH	FEA, ALH and ADH	All atypia patients
Upgrade	18	4	2	8	1	0	1	34
No upgrade	39	17	70	66	11	3	14	220
Total	57 (31.6%)	21 (19.0%)	72 (2.8%)	74 (10.8%)	12 (8.3%)	3 (0%)	15 (6.7%)	254 (13.4%)

ADH, atypical ductal hyperplasia; ALH, atypical lobular hyperplasia; FEA, flat epithelial atypia.

Table 2
Analysis of risk factors for upgrade to malignancy in isolated FEA.

	No upgrade	Upgrade	p
Personal history of BC	12/70	2/2	**0.03**
First degree relative with BC	13/70	1/2	0.35
Segmental calcification distribution	4/70	1/2	0.14
Mass	15/70	0/2	1.0
0–24% calcifications removed	4/70	1/2	0.14
Extent of calcifications ≥ 2 cm	4/47	1/2	0.2
Concurrent cancer diagnosis on separate core biopsy	**0/70**	**2/2**	**0.0004**

BC, breast cancer.
Bold values indicate significance at $p < 0.05$.

Table 3
Analysis of risk factors for upgrade to malignancy in all atypias combined.

	No upgrade	Upgrade	p
Personal history of BC	49/220 (22.3%)	14/34 (41.2%)	**p = 0.017**
First degree relative with BC	52/220 (23.6%)	10/34 (29.4%)	p ≥ 0.05
Segmental calcification distribution	10/166 (6.0%)	9/20 (45%)	**p < 0.0001**
Mass	39/220 (17.7%)	13/34 (38.2%)	**p = 0.006**
0–24% calcifications removed	16/164 (9.8%)	8/19 (42.1%)	**p < 0.0001**
Extent of calcifications ≥ 2 cm	19/166 11.4%	9/20 45%	**p < 0.0001**
Papilloma	7/220 (3.2%)	4/34 (11.8%)	**p = 0.045**

BC, breast cancer.
Bold values indicate significance at $p < 0.05$.

higher rate of upgrade than those without a mass ($p = 0.006$). Of the 17 upgraded lesions that presented as calcifications only, 17/17 (100%) were detected by mammography and biopsied using stereotactic guidance. A segmental distribution of calcifications was significantly associated with upgrade ($p < 0.0001$). The extent of calcifications was also found to be of significance, with an area > 2 cm being associated with upgrade ($p < 0.0001$). The mean extent of calcifications for non-upgraded patients was 1.0 cm, while the mean for patients with upgrade was 2.35 cm. Regarding intervention factors, the amount of calcifications removed during biopsy was found to be a statistically significant factor. Patients that had only 0–24% of calcifications removed during biopsy, and thus more calcifications remaining in the tissue, were more likely to have an upgrade ($p < 0.0001$). There was no significant difference in number of core samples between upgraded and non-upgraded patients among any of the three biopsy modalities. There was also no significant difference between regular and petite needles for the stereotactic biopsies ($p = 1.0$).

5. Discussion

In the present study, we assessed the clinical characteristics and imaging features in patients diagnosed with atypia at stereotactic, ultrasound, or MRI guided VAB, with aim to determine a set of criteria for excision of isolated FEA. Because of the low number of upgrades within the isolated FEA group, there were only two factors that were statistically significant, personal history of breast cancer and a concurrent cancer diagnosis on a separate core biopsy. However other factors that were associated with one of the two lesions (50%) upgraded were: a first degree relative with breast cancer, segmental calcifications, < 25% calcifications removed and extent of calcifications ≥ 2 cm. If all of these factors combined were used in the decision process to excise isolated FEA, we would potentially be able to avoid 44/72 (61%) excisions.

These criteria or associations with upgrade of the isolated FEA cases differed slightly compared to the whole group of atypias. There was statistical significance with all of the risk factors evaluated with the whole group of atypias, except for family history of breast cancer. There were no cases of masses associated with upgrade of the isolated FEA cases.

The management of isolated FEA remains a highly discussed topic. At one end of the spectrum, there are studies like Peres et al. that continue to recommend surgical excision for all cases of FEA due to higher upgrade rate [7]. At the opposite end of the spectrum, there are studies like Said et al. that report that FEA does not convey an independent risk for breast cancer beyond those associated with atypical hyperplasia and proliferative disease without atypia [11]. Our findings seem to fall middle of the spectrum and support the use of some clinical criteria to determine which cases of FEA should be excised and which can be followed with imaging surveillance. Several other studies have made similar recommendations for cautious imaging surveillance in certain cases of isolated FEA. Berry et al. recently reported findings that support a period of imaging surveillance for patients with no personal history of breast cancer that have adequate sampling and focal, pure FEA on core needle biopsy pathology [12]. In this study, no upgrades were found in patients without a personal history of breast cancer. Acott et al. also supports the use of personal history of breast cancer as a criteria for surgical excision [13]. A more recent study by Lamb et al. looked at upgrade rates of isolated FEA to higher risk lesions, (ADH, LCIS, ALH, radial scar and non-specific atypia) and found a statistically higher rate of upgrade to higher risk lesions in patients with a personal history of breast cancer. The authors argued that these findings could have implications on risk stratification for chemoprevention [14].

Regarding residual calcification quantities, several studies have also noted the association between residual calcifications and upgrade to malignancy [9,13,15]. Calhoun et al. suggests that it may be feasible to offer surveillance rather than excision for patients with complete removal of targeted calcifications on biopsy; in keeping with this, they recommended that excision should be offered for patients with FEA that had limited sampling of the radiographic findings or discordant radiographic-pathologic findings [9]. Similarly, Dialani et al. reported a 6.9% upgrade to low-grade in situ, with all upgrades having residual microcalcifications. The authors concluded that excision should be performed if there are residual microcalcifications or lesions after biopsy, and imaging follow up may be considered if there are no residuals [15]. These studies support our suggested criteria that samples with only 0–24% of calcifications removed (limited sampling) should undergo excision. Furthermore, Yu et al. found that calcifications in a segmental or linear shape were predictive factors of upgrade [16], which also supports our findings and suggested criteria.

Our study had several limitations, one being that it was retrospective, and it was a single-institution study. Another limitation would be the smaller sample size, because isolated FEA is a relatively rare occurrence. A larger sample of cases would be ideal to increase the power of our established criteria.

6. Conclusion

In summary, from our findings, we created a suggested criteria for excision of isolated FEA found at vacuum-assisted biopsy. This criteria includes personal history of breast cancer, first degree relative with history of breast cancer, extent of calcifications > 2 cm, < 25% calcifications removed on biopsy, segmental calcification distribution, and cancer diagnosis on concurrent separate core biopsy. In the absence of all of these factors, the upgrade rate of FEA is low, which may allow for follow up without excision.

Declaration of interest

None pertaining to this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

[1] Page DL, Dupont WD, Rogers LW, Rados MS. Atypical hyperplastic lesions of the female breast: a long-term follow-up study. Cancer 1985;55:2698–708.
[2] Page DL, Rogers LW. Combined histologic and cytologic criteria for the diagnosis of mammary atypical ductal hyperplasia. Hum Pathol 1992;23:1095–7.
[3] Page DL, Schuyler PA, Dupont WD, Jensen RA, Plummer Jr. WD, Simpson JF. Atypical lobular hyperplasia as a unilateral predictor of breast cancer risk: a retrospective cohort study. Lancet 2003;361(9352):125–9.
[4] Atkins KA, Cohen MA, Nicholson B, Rao S. Atypical lobular hyperplasia and carcinoma in situ at core breast biopsy: use of careful radiologic-pathologic correlation to recommend excision or observation. Radiology 2013;269(2):340–7.
[5] Azzopardi JG, Ahmed A, Millis RR. Problems in breast pathology. Philadelphia: WB Saunders; 1979.
[6] Solorzano S, Mesurolle B, Omeroglu A, et al. Flat epithelial atypia of the breast: pathological-radiological correlation. AJR Am J Roentgenol 2011;197:740–6.
[7] Peres A, Barranger E, Becette V, Boudinet A, Guinebretiere JM, Cherel P. Rates of upgrade to malignancy for 271 cases of flat epithelial atypia (FEA) diagnosed by breast core biopsy. Breast Cancer Res Treat 2012;133:659–66.
[8] Villa A, Chiesa F, Massa T, et al. Flat epithelial atypia: comparison between 9-gauge and 11-gauge devices. Clin Breast Cancer 2013;13(6):450–4.
[9] Calhoun BC, Sobel A, White RL, Gromet M, Flippo T, Sarantou T, et al. Management of flat epithelial atypia on breast core biopsy may be individiualized based on correlation with imaging studies. Mod Pathol 2015;28:670–6.
[10] International Agency for Research on Cancer, Tavassoli FA, Devilee P. Pathology and genetics of tumours of the breast and female genital organs p 65 https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb4/BB4.pdf; 2003, Accessed date: 19 July 2018.
[11] Said SM, Visscher DW, Nassar A, et al. Flat epithelial atypia and risk of breast cancer: a Mayo cohort study. Cancer 2015 May;121:1548–55.
[12] Berry JS, Trappey AF, Vreeland TJ, et al. Analysis of clinical and pathologic factors of pure, flat epithelial atypia on core needle biopsy to aid in the decision of excision or observation. J Cancer 2016;7(1):1–6.
[13] Acott AA, Mancino AT. Flat epithelial atypia on core needle biopsy, must we surgically excise? Am J Surg 2016;212(6):1211–3.
[14] Lamb LR, Bahl M, Gadd MA, et al. Flat epithelial atypia: upgrade rates and risk-stratification approach to support informed decision making. J Am Coll Surg 2017;225:696–701.
[15] Dialani V, Venkataraman S, Frieling G, et al. Does isolated flat epithelial atypia on vacuum-assisted breast core biopsy require surgical excision? Breast J 2014 Nov;20:606–14.
[16] Yu C, Ueng S, Cheung Y, et al. Predictors of underestimation of malignancy after image-guided core needle biopsy diagnosis of flat epithelial atypia or atypical ductal hyperplasia. Breast J 2015;21(3):224–32.