ORIGINAL ARTICLE

Spectrum of Flat Epithelial Atypia in Breast Lesions

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ABSTRACT

Objective: To determine the frequency of flat epithelial atypia and its association with breast lesions in trucut biopsies and lumpectomy specimens in the local population.

Study Design: A cross-sectional study.

Place and Duration of Study: The study was conducted in the Department of Pathology at Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center Karachi, Pakistan, from October 2019 to September 2022.

Methods: In total, 286 biopsy specimens of breast tissue diagnosed with various pathologies, including benign and malignant cases, were included in our study. The overall frequency of flat epithelial atypia was noted. Furthermore, the Fischer Exact/Chi-square test of association was applied to observe the association of FEA with other breast lesions. Open Epi software was utilized for sample size calculations, and data was analyzed with SPSS version 22.0.

Results: The most common age range for flat epithelial atypia was 17 to 80 years, and the mean age was 27.05 ± 10.34 SD. Fibroadenoma was the most frequent clinical presentation in 214 (74.8%) cases. Features of flat epithelial atypia were found in a total of 11 (3.84%) cases. However, Ductal Carcinoma in Situ (DCIS) showed 100% positivity for flat epithelial atypia followed by fibrocystic disease (62%), Invasive Ductal Carcinoma(IDC) (15%), and adenosis (12.5%).

Conclusion: The frequency of flat epithelial atypia, was 3.84% in trucut biopsies and lumpectomy specimens of the breast. The Ductal Carcinoma in Situ (DCIS), IDC, fibrocystic disease, and adenosis showed a positive association with flat epithelial atypia .

Keywords: *Breast Cancer, Columnar Cell Change, Ductal Carcinoma in Situ (DCIS), Fibrocystic Disease, Flat Epithelial Atypia, Mammography.*

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Introduction

The advent of mammography as an early screening tool has resulted in the early detection of breast malignancy, its precursor lesions, and other entities closely associated with it.[1] Breast lesions can be accurately sampled by percutaneous breast core-needle biopsy (CNB), which also offers diagnostic histologic data, as demonstrated in various studies. Its great sensitivity for recognizing various image-detected or clinical lesions and identifying cancer was recently proven by a study of more than 4000 core biopsies utilizing multiple core gauge and guidance systems.[2] Flat epithelial atypia (FEA) is a breast tissue lesion detected more frequently in CNB, especially in association with

mammographically detected microcalcifications.[3] The term FEA has been coined by the WHO Working Group on the Pathology and Genetics of Breast Tumors as a type of epithelial atypia frequently encountered by surgical pathologists. FEA is a morphological change observed in various breast lesions, and it is very important to be identified as it may serve as a precursor to cancer. The World Health Organization defines flat epithelial atypia (FEA), as a columnar cell change/ hyperplasia exhibiting mild cytological atypia. It is characterized by the dilated breast ducts lined by 1 or 2 or 3 layers of atypical cuboidal or columnar cells with apical snouts, intraluminal secretions, and calcifications. The nuclei are monomorphic, rounded, hyperchromatic, and mildly elongated with evenly dispersed chromatin, often inconspicuous nucleoli and sparse mitosis. There is an increased cytoplasm compared to normal cells. The myoepithelial cell layer is mostly attenuated.[4-6] In the breast biopsies, isolated FEA have been found in 1 to 2% of cases. Furthermore, several lesions of the breast including atypical ductal hyperplasia (ADH), DCIS, as malignancy have also been reported in association with FEA.[7-9]

Globally 24.5% of females suffer from breast cancer annually.[10] It is also one of the most common cancers among females in Pakistan with a frequency of 30.4%, highest among Asian countries.[11] However, moderate degree of interobserver variability poses a challenge for the diagnostic capabilities of surgical pathologists.[12] It has been now well established that flat epithelial atypia (FEA) is a precursor of breast cancer. With the advent of percutaneous large core needle biopsy and mammographic screening programs, the diagnosis of mammary epithelial atypia has become more common.[5] The detection of FEA can give a diagnostic clue to pathologists as a sign of initiation of cancerous changes; thus, the patient could be advised for regular follow-ups in breast clinics.

The frequency of FEA in breast pathologies among the Pakistani population is not well studied. Regional studies regarding FEA, its association, and co-existence with other lesions are limited. Hence, the present study was designed to determine the frequency of FEA in all the received specimens, including trucut biopsy and lumpectomies. In addition, we also aimed to observe the association of FEA with other breast lesions and the patients' age.

Methods

A cross-sectional study was conducted in the Department of Pathology at Basic Medical Sciences Institute, Jinnah Postgraduate Medical Center Karachi, Pakistan, from October 2019 to September 2022 after IRB approval held on August 08, 2019 vide letter no: IRB no. F.1-2/2019/BMSI-E.COMT/073/JPMC. Open EPI software calculator was utilized for determining the sample size. Using a confidence interval of 95% (z score=1.96) 23%[13] as prevalence from the previous study and 5% allowable error of known prevalence, the sample size was calculated to be 286. The cases of different breast lesions received for histopathology at Basic Medical Sciences Institute (BMSI) Jinnah Postgraduate Medical Center (JPMC), either with benign findings or malignant changes, were included in our study. Those with inadequate tissue material or with improper fixation were excluded. At BMSI, the majority of the breast tissue was received in the form of a lumpectomy specimen. Therefore, in the above-mentioned duration, all cases of small trucut biopsies and lumpectomy samples received at the department were considered in the study. Breast biopsy samples were embedded in paraffin after being preserved in 10% formaldehyde. The sections were cut at different levels and were stained with hematoxylin and eosin. Multiple sections of each slide were reviewed by two histopathologists. The diagnostic criteria of FEA were adopted from the WHO Working Group on Pathology and Genetics of Tumors of the Breast.[3] Data was analyzed using SPSS version 22.0. Descriptive statistics determined the mean and standard deviation for numerical variables. Categorical variables were expressed in frequency and percentages. Fischer Exact/Chi-square test was applied to see the association of FEA with various breast lesions. A *P* value of less than 0.05 was considered significant.

Results

The age range of participants was between 17-80 Years. The mean age was calculated to be 27.05 ± 10.34 SD. Out of 286 cases, about 19 (6.6%) were trucut biopsies, and 267 (93.4%) were lumpectomy specimens. Fibroadenoma (a benign tumor) was the

most frequent clinical presentation in 214 (74.8%) cases, as seen in Table 1. In 286 cases of trucut biopsies and lumpectomy specimens, features of FEA were found in 11/286 (3.84%) cases. DCIS showed 100% positivity for FEA, followed by fibrocystic disease (62%), (Photomicrograph 1) invasive ductal carcinoma (15%) and adenosis (12.5%). The majority of breast lesions presented in the less than 30-year age group, as shown in Table 2. However, in the age range of 50 to 80 years, most (17.6%) of the flat epithelial atypia were recorded. A significant association of flat epithelial atypia was observed with fibrocystic disease, ductal carcinoma in situ (DCIS), and invasive ductal carcinoma (IDC), as shown by their *P* values depicted in Table 1.

Table 1: Distribution of various morphological patterns of breast diseases in association with Flat Epithelial Atypia (n=286)

Morphological patterns of breast lesions	No. of cases n (%)	FEA Positive case n (%)	*P* value*
Fibroadenoma	214 (74.8)	-	-
Phylloides	7 (2.4)	-	-
Mastitis	21 (7.3)	-	-
Fibrocystic disease	8 (2.8)	5 (62.5)	0.000
Adenosis	8 (2.8)	1 (12.5)	0.272
Paget's disease	1 (0.3)	-	-
Ductal carcinoma in situ (DCIS)	2 (0.7)	2 (100)	0.001
Invasive ductal carcinoma	20 (7.0)	3 (15)	0.034
Invasive lobular carcinoma	5 (1.5)	-	-
Total	286 (100)	11 (3.48)	0.000

**Fisher Exact Test*

Table 2: Flat epithelial atypia in association with age groups. (n=286)

Age in years	No of cases n (%)	FEA Positivity n (%)	*P* value*
11-20	43 (15)	0	
21-30	164 (57)	4 (2.4)	
31-40	54 (18)	3 (5.5)	
41-50	16 (6)	3 (18.7)	0.020
51-60	5 (2)	1 (20)	
61-70	2(1)	0	
71-80	2 (1)	0	
Total	286 (100)	11(3.84)	

**Fisher Exact Test*

Discussion

The current study revealed 3.84% FEA positivity among all breast lesion. We considered both trucut biopsies 19 (6.6%) and lumpectomy 267 (93.4%) breast tissue specimens. In Karachi, the public sector hospitals serve many underprivileged populations. Lack of awareness, financial constraints, dearth of availability of facilities such as mammography may cause late presentation of patients, leading to delayed diagnosis. Most cases present at a higher grade of dysplasia or frank carcinoma. Therefore, instead of small biopsies, surgical removal of a lump has to be performed.[14] In the present study, FEA was observed in 3.84% of cases. Biggar et al. and Lavoue et al. also observed a similar 3.7% & 1.5% FEA in their series.[4,15]

The published data has demonstrated the association of FEA with various other lesions of the breast. Ranging from low-grade proliferative lesions to serving as a precursor to malignancy. Columnar call change with mild atypia has now been recognized as an important diagnostic entity. Foci of such changes have been observed in association with proliferative lesions including atypical ductal hyperplasia, ductal carcinoma in situ, and invasive

cancers. However, none of the studies showed presence of FEA in benign breast lesions.[7-9] This finding endorses our results, where we could not find presence of FEA in benign cases of fibroadenoma and mastitis. However, interestingly, the most unique finding in our study was FEA finding in about 62.5% of fibrocystic disease, which is considered an important benign entity. The present study showed that majority of cases presented in third and fourth decade of life. This finding is endorsed by another study from Karachi.[16] It also establishes the fact that breast cancer presentation is a decade earlier in this Asian region in comparison to Western world.[17]

To observe FEA in all breast lesions in the local population, we considered benign, borderline and malignant tumors in our series. Fibroadenoma was the most common 214 (74.8) clinical presentation. Columnar cell atypia was not reported in any of these cases, confirming the complete benign state of the lesion. However, a study showed 20% positivity for FEA in fibroadenoma cases, addressing the significance of careful scanning of benign cases.[18] In association with non-proliferative lesions, a fairly good number of FEA (62.5%) were observed as focal changes with fibrocystic disease (FCD). It is more likely that FEA associated with FCD may progress to in situ lesions or frank malignancy.[3] Thus, there is a need to scan FCD cases for foci of FEA. A study in India reported that 1 out of 20 cases diagnosed with fibrocystic disease showed malignant changes, and therefore, excisional biopsy was recommended as the treatment of choice.[19]

Among pre-malignant lesions, we had a sparse number of cases. The possible reason for this may be that are the region's patients are generally unaware of their diseases, and by the time they present to clinics, it has progressed to the invasive stage. However, in the two DCIS cases, both (100%) had multiple columnar call cell atypia foci. With a *P* value of 0.001, it shows a highly significant association. Srour et al. recorded 47% FEA association with DCIS.[19] Alencherry et al. observed 79% DCIS association in their series.[20]

Invasive ductal carcinoma (IDC) cases showed 15% FEA positivity (p= 0.034). This is supported by an even higher Figure 1 of 23% by Alencherry et al. Another study reported a comparatively less frequent (8.3%) presence of IDC along with FEA and an upgrade of 42.9% of pure FEA cases to Invasive malignancy.[19,20] The frequent association of FEA with malignancy highlights the significance of early detection using mammography and subsequent

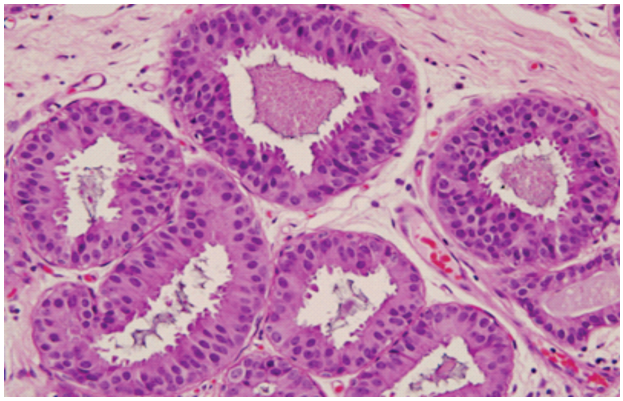

Fig 1: Photomicrograph 1: A focus in fibrocystic disease showing dilated duct lined by 2-3 layers of mildly atypical, flattened, and hyperchromatic cells consistent with FEA (arrowhead). H&E 40X

histopathological evaluation.

Patients with a family history of genetic mutations leading to breast carcinoma are frequently observed to have an upgrade of FEA to high-risk lesions and invasive carcinoma.[21] However, due to the fear of being diagnosed with cancer, patients usually do not consult healthcare workers during the initial stage of the disease, which serves as one of the reasons for mastectomy.[22] Hence, the screening for breast cancer should be started at an early age. The patients at risk, for instance, those who are chronic smokers or suffering from obesity, users of oral contraceptive pills, physical inactivity, or have a strong family history of this malignancy, should be taken into consideration and addressed thoroughly.[18,22]

According to available statistics from various studies, the rate of upgrade of FEA to invasive malignancy varies from 2.4% to 20%. Therefore, surgical excision is recommended. However, due to wide variation in diagnostic criteria, as well as in risk of acquisition of higher lesions associated with FEA, it has been suggested that ,surveillance should be practiced in cases of isolated FEA, lack of family history and genetic mutations, instead of surgical excision.[23-25]

Limitation of Study

Limited data was available on atypical proliferative

lesions of the breast.

Conclusion

Features of FEA were found in a limited number of cases, which were all proliferative breast lesions. Ductal carcinoma in situ cases showed a hundred percent positive association with FEA. In addition, a high frequency of Invasive ductal carcinoma cases revealed the presence of FEA. None of the cases of fibro adenoma showed columnar cell atypia.

Recommendation

In view of the present study we recommend to diligently look for flat epithelial atypia in small tissue biopsies of breast. Further research needs to be conducted for immunophenotypic and molecular correlation of FEA with malignancy. Early breast screening facilities such as mammography should be available at tertiary care public sector hospitals in Pakistan. Patient awareness programs for early screening of breast lesions should be promoted through print and electronic media.

Authors Contribution

NJ: Idea conception, study designing, data analysis, manuscript writing and proof reading

AK: Data collection, manuscript writing and proof reading

RB: Data analysis, results and interpretation

NR: Manuscript writing and proof reading

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