

SPECIAL ISSUES IN BREAST CANCER  
FLAT EPITHELIAL ATYPIA OF THE BREAST

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Selim M. NASSER

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**ABSTRACT** • “Flat epithelial atypia” is the adopted term by the WHO working group on breast tumor referring to an early neoplastic breast lesion affecting the terminal duct-lobular units. Pathologists have described this lesion under a variety of names including columnar cell lesions and low-grade clinging carcinoma *in situ*. It is usually encountered on breast biopsies performed for mammographically-identified microcalcifications. Because of its relatively frequent association with carcinomas, its recognition in biopsy specimens is important. This review will focus on the histopathologic features, differential diagnosis, biologic potential, clinical significance and management of this lesion.

#### THE EMERGENCE OF FLAT EPITHELIAL ATYPIA

In recent years the interest in lesions composed of columnar cells has become prominent because of their increased occurrence in biopsies performed for mammographically-identified microcalcifications [1-11]. Earlier classifications have focused on the columnar morphology of these lesions. Some authors proposed classifications grouping together lesions with and without atypia based purely on the columnar shape of their cells, therefore uniting unrelated entities [7, 10-12]. Earlier classifications may have fostered the mistaken belief that disparate lesions having in common columnar cells may have also biological relationship. We favored the individualization of a category of columnar cell lesions characterized by low-grade atypicality and proposed the term atypical columnar cell lesion [13]. We emphasized the early neoplastic nature of this lesion and proposed separating it from other columnar lesions. This approach has been favored by the World Health Organization working group on breast tumors that adopted the term “flat epithelial atypia” (FEA) to designate a group of columnar cell lesions with atypia [14].

Interestingly long before eliciting so much interest lead-

Department of Pathology, Clemenceau Medical Center, Beirut; Lebanese American University Medical School.

Correspondence: *Selim M. Nasser, MD. Clemenceau Medical Center. Dept. of Pathology. P.O. Box 11-2555. Beirut. Lebanon.*  
Tel.: +961 1 372888 ext 1952  
e-mail: [selim.nasser@lau.edu.lb](mailto:selim.nasser@lau.edu.lb)



Nasser S. Atypie épithéliale plane du sein. J Med Liban 2009 ; 57 (2) : 105-109.

**RÉSUMÉ** • L’atypie épithéliale plane est le terme adopté par l’OMS pour désigner une lésion mammaire pré maligne affectant les unités ductulo-lobulaires. Les anatomo-pathologistes ont décrit cette lésion, utilisant des dénominations diverses comme métaplasie cylindrique et carcinome *in situ* de bas grade de type *clinging*. Cette lésion est habituellement rencontrée dans le cadre de biopsies mammaires effectuées pour microcalcifications. L’association relativement fréquente de cette lésion avec des carcinomes rend sa reconnaissance importante. Cette mise au point porte sur les caractéristiques histologiques de cette lésion, ainsi que sur son diagnostic différentiel, son potentiel biologique, sa signification clinique et sa prise en charge.

ing to numerous studies and multiple terminologies, this lesion was described at the turn of the 20th century by Warren and Bloodgood as “abnormal involution” [15] and “senile parenchymatous hypertrophy” [16] respectively. Cheatle [17-18], Wellings and Jensen [19] described breast lesions characterized by cystically altered lobules. Azzopardi [20] thoroughly described an under recognized lesion that he called “low-grade clinging carcinoma.” To their merit, the early authors were more attentive to the biological potential of this lesion than to its columnar phenotype.

#### DEFINITION

FEA designates a breast lesion characterized by an alteration of terminal duct-lobular units. These altered units show a proliferation of monomorphic epithelial cells with low-grade cytologic atypia. The atypical cells are frequently but not always columnar. They are arranged in one to several layers but maintain a flat pattern and therefore lack the architectural atypia seen in atypical ductal hyperplasia and in low-grade ductal carcinoma *in situ*. Modern-time pathologists have referred to this lesion with a variety of names: “low-grade clinging carcinoma” [20], “atypical cystic lobule” [4], “atypical cystic duct” [6], “ductal intraepithelial neoplasia of the flat type” [9], “columnar cell change with atypia”, “columnar cell hyperplasia with atypia” [12], “atypical columnar cell lesion” [13], “hyperplastic enlarged lobular units (HELUs)” [21], “ductal intraepithelial neoplasia 1b (DIN1b)” [22], and later as “DIN1a and flat atypia” [14].

## HISTOLOGICAL FEATURES

At low power, FEA usually appear as terminal duct lobular unit(s) with distended or cystically dilated acini. It may contain secretions or microcalcifications, usually of the laminated type. It should be emphasized that recognizing FEA may represent a difficult challenge for those with limited experience. This lesion may be overlooked or disregarded as fibrocystic change if one does not notice that the lumen is lined by mildly atypical epithelial cells arranged in one to up to six layers but conserving a flat pattern, without architectural atypia such as the formation of Roman bridges, micropapillary tufts or secondary lumens (Figure 1). The lack of these features distinguish FEA from atypical ductal hyperplasia and low-grade ductal carcinoma in situ.

High power examination is necessary to make the diagnosis of this lesion. Atypical nuclei are the key diagnostic feature of this lesion but one should be aware that the atypia is subtle. One should not expect to observe markedly atypical nuclei (Figure 2). The latter when present indicate high-grade, clinging, ductal carcinoma in situ. The nuclei in FEA are similar to the one seen in low-grade cribriform DCIS. They are basally located and appear monomorphic, smoothly contoured, slightly to moderately enlarged, round to oval.

In comparison to the nuclei in adjacent normal acini, the chromatin is powdery, evenly dispersed and slightly to moderately hyperchromatic. The nucleoli are usually inconspicuous. Hobnailing occurs in a minority of cases.

The cytoplasm is often columnar but this feature has been overemphasized. The columnar shape may be prominent, but not uncommonly it may be cuboidal. It is more abundant and usually slightly more eosinophilic than normal. It frequently forms apical small blebs or apocrine snouts.

The myoepithelial layer in FEA is usually attenuated and even inconspicuous (Figure 3).

### DIFFERENTIAL DIAGNOSIS OF FLAT EPITHELIAL ATYPIA

FEA must be distinguished from a variety of normal, physiological, and benign conditions.

- Normal large ducts, lobules with physiologic cystic involution, and primitive (type 1) lobules may superficially resemble FEA but they lack cytological atypicity.

- Fibrocystic change may appear similar to FEA but their epithelial lining appears flattened with no cytologic atypia. Apocrine metaplasia in fibrocystic change may resemble FEA; however, apocrine cells have more prominent nucleoli and more abundant and granular cytoplasm. Moreover, the lumen of apocrine cysts often contains foamy histiocytes.

- Blunt duct adenosis is the most common lesion confused with FEA. The distinction between these two lesions may represent a difficult challenge. At low power, these two lesions can appear very similar; however, the



FIGURE 1. FEA with subtle features. *The acini are cystically distended. This lesion may be disregarded as fibrocystic change if the conspicuous lining epithelium, with mildly atypica nuclei, is overlooked.*

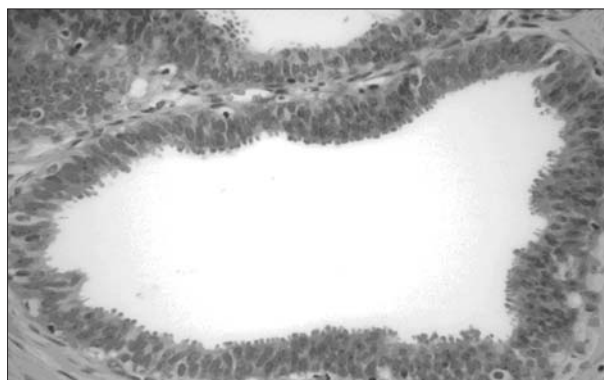


FIGURE 2. FEA with obvious multilayered epithelium with low-grade atypia. *This lesion would hardly go unnoticed.*

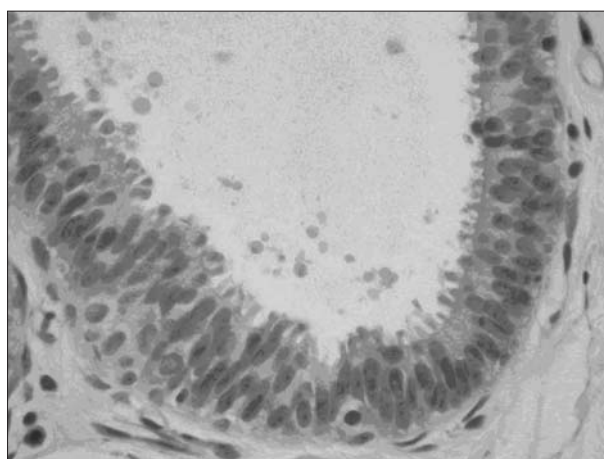


FIGURE 3. Cytological features of FEA: columnar cells with abundant apical cytoplasm and apocrine snouts. *The nuclei are round to oval, enlarged hyperchromatic and arranged perpendicularly to the basement membrane. The myoepithelial cell layer is inconspicuous.*

acini of blunt duct adenosis are more irregular and angulated. In addition, the stroma of blunt duct adenosis appears more cellular. The nuclei of blunt duct adenosis lack atypical features. They are more related to the nuclei of usual ductal hyperplasia with greater variability in size and shape. Moreover, the myoepithelial cell layer in blunt duct adenosis is prominent.

The application of immunohistochemistry may be useful in some cases. The cells of FEA are usually negative for high-molecular-weight cytokeratins, such as cytokeratin 34BE12 and cytokeratin 5/6 which may be helpful to differentiate FEA from lesions with usual ductal hyperplasia that commonly express these types of cytokeratin. However, morphology remains the basis for the definitive diagnosis as expression of these cytokeratins may be absent as well in apocrine cells and some cases of blunt duct adenosis [23].

#### BIOLOGIC SIGNIFICANCE OF FLAT EPITHELIAL ATYPIA

FEA has emerged as an early neoplastic lesion. It constitutes a precursor to some low-grade ductal carcinoma in situ and invasive ductal carcinoma. Data deriving from morphological, immunohistochemical and genetic studies have supported this consideration.

– Morphologically, FEA cells show cytological features comparable, if not identical, to low grade ductal carcinoma in situ, and in some instances to tubular carcinoma. In addition, the frequent coexistence and merging of FEA with low-grade DCIS suggests that the former gives rise to the latter [4-5, 7-8, 20, 24].

– Immunohistochemical studies showed that low-grade DCIS and FEA have identical immunostaining profiles. The cells of both lesions diffusely express estrogen receptors, progesterone receptors and keratin 19. Moreover, 5 to 50% of the cells of both lesions express cyclin D1 [8, 25-26] and the expression of p53 by FEA is similar to that of adjacent DCIS [26-27]. FEA and DCIS both fail to stain for the 14-3-3 $\sigma$  protein [28], cytokeratin 34BE12 and cytokeratin 5/6 [23]. Commonly used receptors in breast cancer show similar expression among FEA, low-grade DCIS and low-grade invasive ductal carcinoma with high expression of estrogen and progesterone receptors and absence of HER2 [21, 27, 29].

– Genetic and molecular studies have brought compelling evidences regarding the neoplastic nature of FEA and its relation to DCIS and invasive carcinoma. These studies, in addition to demonstrating its monoclonal nature [9] showed that FEA, low-grade DCIS and low-nuclear-grade invasive ductal carcinoma have in common similar chromosomal abnormalities such as alterations in chromosomes 16 and 17. Moreover, these studies demonstrated similar gene expression profiles with accumulation of genetic abnormalities accompanying the putative evolution from FEA to low-grade invasive ductal carcinoma [9, 30-33].

#### CLINICAL FINDINGS

FEA does not present with any specific clinical manifestation. It is a nonpalpable lesion that is retrieved in biopsies removed for microcalcifications or as an incidental finding retrieved in specimens removed for other lesions.

#### CLINICAL SIGNIFICANCE

The frequency of FEA, its prognosis and clinical course are not well defined. Current data on the prognosis of FEA are derived from studies that are limited by sample size, retrospective design, or inclusion of FEA within the spectrum of columnar cell lesions which includes unrelated lesions such as blunt duct adenosis. Taken in this context, data from available studies indicate a very low risk of subsequent progression to invasive carcinoma. In a review of 2833 surgical biopsies performed for microcalcifications from 1975 till 2002, de Mascarel et al. [34] found FEA without other associated precursor lesions in 101 (3.5%) cases. Of those, 17 had concomitant cancer but none of the remaining cases developed cancer after a 10-year follow-up. In a series reported by Eusibe et al. [35], none of 25 patients with lesions corresponding to FEA followed for 19 years developed invasive carcinoma. Similarly, none of 59 patients with these lesions progressed to invasive carcinoma as reported by Bijker et al. [36], but the median follow-up period was only 5.4 years in the latter. Boulos et al. [37] reported similar findings in a retrospective study that evaluated the overall cancer risk for 1261 biopsies with columnar cell lesions in 4569 women from the Nashville Breast Cohort. They reported a positive association between columnar cell lesions and atypical ductal hyperplasia, but an elevated breast cancer risk was not supported by their statistical analysis. Moreover, they did not observe significant risk difference among columnar cell lesions with or without atypia.

Conversely, in a study evaluating the type of benign breast lesions occurring in biopsy specimens from 120 patients who subsequently developed breast cancer, Shaaban et al. [38] reported a higher frequency of lesions corresponding to FEA.

These inconclusive data indicate that additional, well designed studies based on standardized nomenclature and uniform histologic and molecular parameters are needed to determine the true risk of progression of these lesions.

Presently, the true risk of FEA appears related with its frequent association with in situ and invasive ductal and lobular carcinomas. Rosen [7] described the association of columnar cell hyperplasia, which include FEA, with both tubular carcinoma and lobular carcinoma in situ. Goldstein and O'Malley [4] noted the frequent association between FEA and tubular carcinoma. Other authors have also noted that FEA is commonly present in cases with ductal carcinoma in situ, lobular carcinoma in situ and invasive carcinomas. As such FEA has been

observed in up to 36% of cases with DCIS [8], in up to 63% of cases with LCIS [39], in up to 84% of cases with tubular carcinomas and in up to 54% of cases with invasive lobular carcinomas [40].

#### MANAGEMENT OF FLAT EPITHELIAL ATYPIA

Currently, management of FEA takes into consideration its potential association with in situ and invasive carcinomas rather than its low risk of progression.

FEA is most commonly observed in specimens removed for microcalcifications. If the specimen is a core biopsy, an excision is indicated to exclude the possibility of associated in situ or invasive carcinoma. This recommendation is supported by preliminary studies reporting the presence of in situ or invasive carcinomas in up to 30% of follow-up surgical biopsy specimens [41-44]. However, some authors [45] recommend surgical excision only when FEA is greater than 10 mm or when it is incompletely removed.

If the specimen is an excisional biopsy, no further treatment is recommended when all microcalcifications are removed, but follow-up of the patient is warranted.

It seems prudent to apply the above recommendations for FEA retrieved as an incidental finding in association with a benign lesion.

The significance and the management of FEA present at the margin of an excisional biopsy for DCIS or invasive carcinoma remain uncertain. Some authors [12] advocate a conservative approach citing the low-risk of progression. Conversely, Moinfar et al. [9] suggested that these lesions which they call atypical columnar cell lesions, might account for recurrences following surgery. In addition, Goldstein et al. [46] noted that atypical ductal hyperplasia, which is related to FEA, was associated with recurrence when present at the margins of excision in breast-conserving surgery. Until additional studies address this issue, it seems prudent to adopt an approach individualized to each patient and based on the extent of disease, the age of the patient and the planned adjuvant therapy.

For the pathologist, the identification of FEA in a biopsy specimen should incite him to perform levels on the paraffin blocks and submit additional tissue blocks, if any, for microscopic examination in order to exclude associated carcinomas.

#### CONCLUSION

FEA has emerged as an early neoplastic lesion. Recent years witnessed increased awareness and recognition of this lesion, but the diagnostic reproducibility of FEA is still limited by the absence of uniform definitions and criteria as well as the lack of standardized nomenclature.

Current data indicates that FEA represents an early stage in the formation of certain carcinomas. Additional studies based on well-defined histological criteria and molecular data should help to further define the clinical significance and management of these lesions. Also,

future studies should evaluate whether FEA constitutes, potentially, the earliest recognizable target in the prevention and prophylaxis of some breast cancers.

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