Flat Epithelial Atypia: A Review of Current Concepts

Amy L. Adams*

Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA

Abstract: Columnar cell change in breast epithelium is frequently encountered in biopsies performed for evaluation of radiographically detected microcalcifications. While columnar cell change by itself is typically of no clinical consequence, on occasion cytologic atypia may be present, a finding now termed "flat epithelial atypia (FEA)". Morphologic, immunophenotypic, and genetic associations between FEA and low grade *in situ* and invasive breast carcinomas provide compelling evidence that FEA represents a precursor lesion in the spectrum of low grade breast neoplasia. Despite this information, the ultimate clinical impact of FEA and, thus, the best management strategy for it remains unknown. Herein, current concepts regarding FEA are reviewed, including pathologic definition, evidence supporting its role as a neoplastic precursor, and suggested management strategies.

Keywords: Columnar cell change, biopsy, FEA, DCIS, CGH.

INTRODUCTION

With the advent of screening mammography in the early 1980's, the incidence of ductal carcinoma *in situ* (DCIS) of the breast increased dramatically [1]. The association of DCIS with characteristic, radiographically identifiable microcalcifications has allowed for more frequent detection of breast carcinoma in its pre-invasive state. As these microcalcifications have proven to be amenable to evaluation by core needle biopsy, interpretation of such specimens is now commonplace in routine pathology practice.

Not surprisingly, introduction of the practice of breast core biopsy has called attention to a histologic finding, atypical columnar cell change, whose place in the spectrum of breast neoplasia has not been entirely well defined. Columnar cell lesions are now commonly encountered in breast core biopsies performed due to detection of radiographic microcalcifications [2]. While columnar cell change by itself is not worrisome, some columnar cell lesions do exhibit varying degrees of cytologic atypia. For the last 30 years similar atypical columnar proliferations have been described in the medical literature under a variety of monikers, including atypical lobules type A [3], clinging carcinoma [4], columnar alteration with prominent apical snouts and secretions with atypia [5], columnar cell change/hyperplasia with atypia [6], and ductal intraepithelial neoplasia of the flat monomorphic type [7]. Most recently these alterations have been termed "flat epithelial atypia" by the World Health Organization Working Group on the Pathology and Genetics of Tumours of the Breast [8].

PATHOLOGIC FEATURES

The term "columnar cell change" refers to terminal duct-lobular units with dilated acini lined by one or two layers of columnar epithelial cells of regular size and shape, oriented perpendicular to the basement membrane. The nuclei of these columnar cells are bland and uniform, ovoid in shape with finely dispersed chromatin without conspicuous nucleoli. Mitoses are not typically observed. Apical snouts are commonly present along the luminal surfaces of the cells, and the dilated acini often contain microcalcifications and secretions [2, 6] (Fig. **1a-c**).

In columnar cell hyperplasia, the cells exhibit the same nuclear and cytoplasmic features described above, but they demonstrate stratification of more than two cell layers. The cells may appear hyperchromatic due to nuclear crowding or overlapping. Occasional small mounds, tufts, or short micropapillations of cells may be observed, but true micropapillae, stiff bridges or arcades, and cribriform spaces should not be present [2, 6].

"Flat epithelial atypia" (FEA) is now the commonly used term for columnar cell change/hyperplasia exhibiting mild cytologic atypia. In its most usual form, the atypia manifests as cuboidal cells with features similar to those seen in low grade DCIS. The nuclei are round, small, uniform, and evenly spaced, with finely dispersed to slightly marginated chromatin. Nucleoli are inconspicuous, and mitoses are rare. The histologic picture may be subtle, requiring high power microscopic examination to confirm the presence of atypia [2, 9] (Fig. **2a-c**).

Less commonly, FEA presents as columnar cells exhibiting more traditional features of cytologic atypia. Nuclei display a greater degree of pleomorphism, with clumped chromatin and conspicuous nucleoli. The nuclear-to-cytoplasmic ratio is slightly increased. Mitoses, while rare, may be seen [2, 9]. In this form of FEA, the nuclear features have been described as being similar to those of tubular carcinoma [2].

It is important to keep in mind that FEA is not always "flat", as the lesions may contain mounds, tufts, or short micropapillations as seen in columnar cell hyperplasia. Architectural atypia in the form of cribriform spaces,

*Address correspondence to this author at the Department of Pathology and Laboratory Medicine, Emory University School of Medicine, Atlanta, GA, USA; Tel: 404 712-8804; E-mail: aladam2@emory.edu

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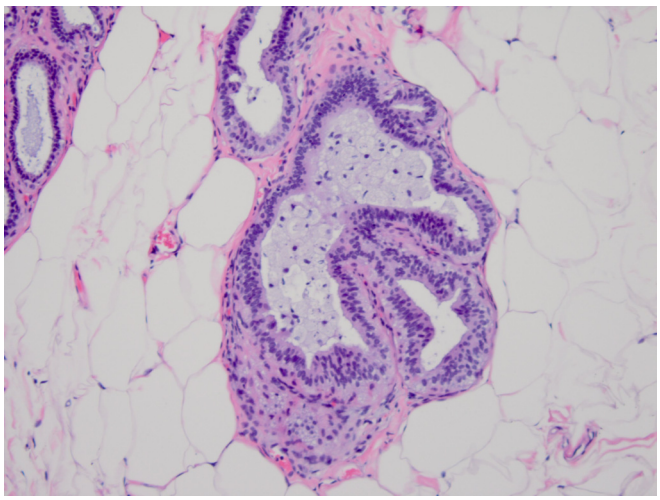

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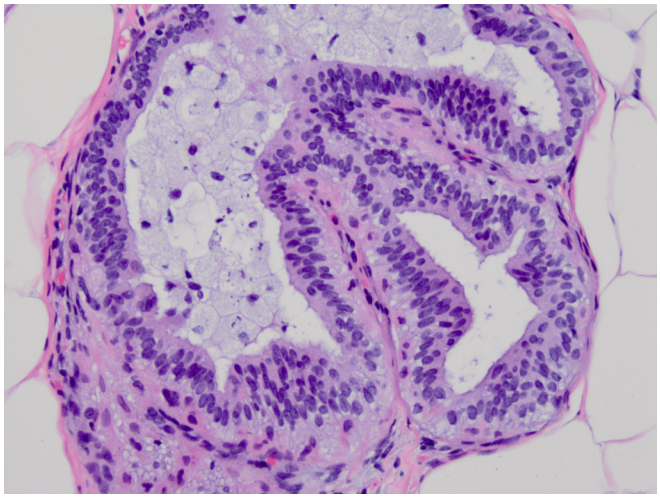

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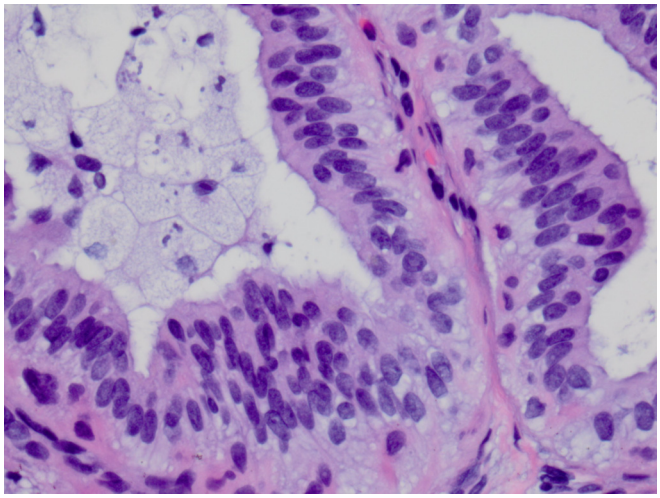

Fig. (1). Columnar cell change. (**a**, **b**) Dilated duct space lined by 1-2 layers of bland columnar cells, 10x and 20x. (**c**) Individual cells contain elongated, ovoid nuclei with finely dispersed chromatin and inconspicuous nucleoli, 40x.

"Roman bridges", or well-formed micropapillae, however, should not be present. Rather, proliferations containing such should be designated as atypical ductal hyperplasia or DCIS as appropriate based on the degree of cytologic and architectural atypia present [2].

RELATIONSHIP TO BREAST NEOPLASIA

The significance of FEA in the spectrum of breast neoplasia has long been debated, but the evidence, both observational and molecular, that FEA represents a neoplastic precursor is mounting. A convincing association between FEA and atypical ductal hyperplasia, low grade DCIS, invasive tubular carcinoma, and/or lobular neoplasia has been illustrated by a number of studies [5, 10-14]. Indeed, awareness of the so-called "Rosen Triad" of columnar cell lesions (including FEA), tubular carcinoma, and lobular carcinoma *in situ* has prompted close attention to biopsy specimens containing any one of these lesions in order to exclude the presence of the other two [13, 15].

Citing molecular evidence that columnar cell lesions (of which FEA is a subset) have chromosomal abnormalities similar to low grade *in situ* and invasive breast carcinoma, Abdel-Fatah and colleagues reviewed 147 low grade breast carcinomas, including pure tubular carcinoma, tubular carcinoma of the mixed type, classic infiltrating lobular carcinoma, and tubulolobular carcinoma [16]. They found a high prevalence (91%) of columnar cell lesions with tubular carcinoma, the majority of these exhibiting cytologic atypia consistent with FEA [16]. These results led to the conclusion that columnar cell lesions, including FEA, are part of a family of low grade precursor, *in situ*, and invasive neoplastic breast lesions [16].

In another large series, Collins *et al*. reviewed 543 cases of DCIS to assess the association between FEA and various clinicopathologic features, including specific features of DCIS [17]. The presence of FEA was found to be associated with DCIS exhibiting low nuclear grade, micropapillary and cribriform patterns, and the absence of necrosis in a univariate analysis [17]. In a multivariate analysis, features of DCIS independently associated with FEA included micropapillary and cribriform patterns and absence of necrosis.[17] The authors concluded that the findings support the idea of FEA as a precursor to certain forms of DCIS [17].

Columnar cell lesions, including those which could be classified as FEA, have been shown to express estrogen and progesterone receptors, as well as luminal cytokeratins such as CK19/18/8, but they are typically negative for basal cytokeratins (CK5/6 and CK14) and Her-2/neu [6, 10, 18-20]. This immunophenotype differs from that of usual ductal hyperplasia, which generally expresses CK5/6 and CK14 in a large number of cells, and more closely resembles that of atypical ductal hyperplasia and low grade DCIS [18]. Indeed, in a recent large series, FEA, along with atypical ductal hyperplasia, lobular neoplasia, DCIS, and concomitant low nuclear grade invasive breast carcinomas, was shown to be positive for CK19/18/8, ER-α, Bcl-2, and cyclin D1 [19]. This immunophenotype differs from that observed in high nuclear grade invasive carcinoma, leading the authors to conclude that FEA, together with atypical ductal hyperplasia, low grade DCIS, lobular neoplasia, and low nuclear grade breast carcinoma, constitute a family of low grade precursor, *in situ*, and invasive neoplastic lesions [19].

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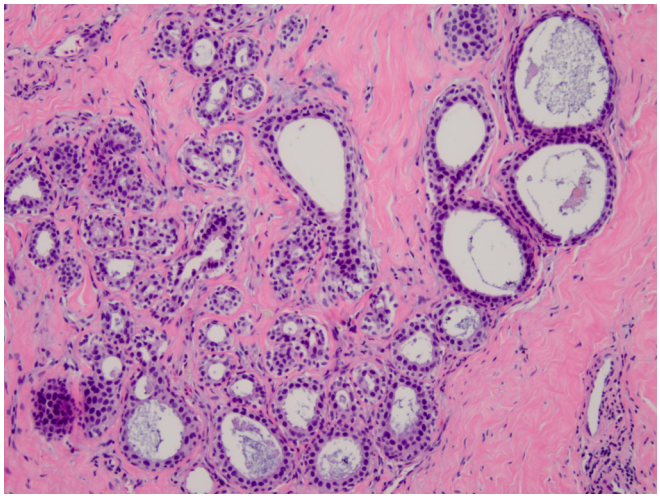

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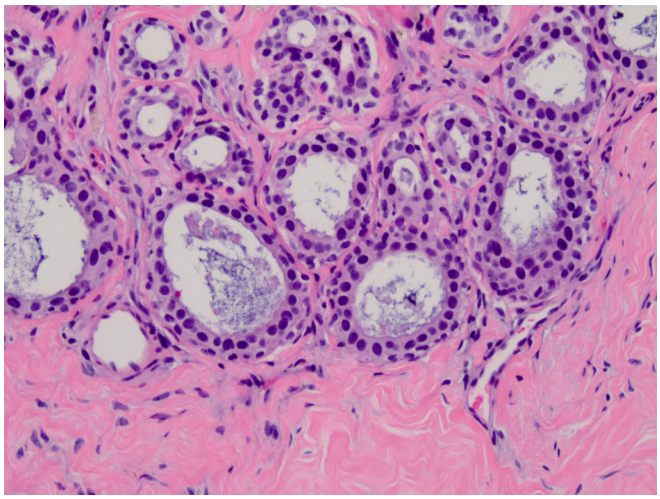

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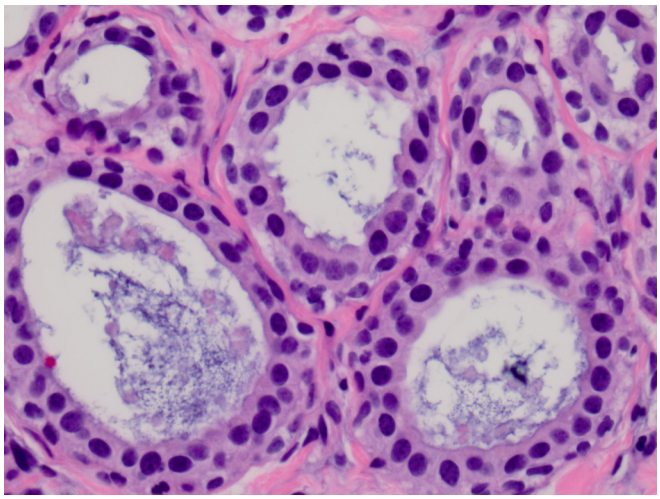

Fig. (2). Flat epithelial atypia. (**a**, **b**) Dilated ducts and acini lined by cuboidal cells with occasional apical snouts, 10x and 20X. (**c**) Nuclei are small, round, uniform, and evenly spaced, with finely dispersed chromatin and inconspicuous nucleoli. Note the similarity to cells observed in low grade DCIS, 40x.

Aside from these morphologic and immunophenotypic associations, there is molecular evidence to suggest FEA may be a neoplastic precursor. In one of the earliest studies which examined genetic abnormalities in such lesions, Moinfar *et al*. used PCR to examine loss of heterozygosity (LOH) in lesions termed "ductal intraepithelial neoplasia-flat type" [7]. Using eight probes for loci known to harbor high rates of LOH in DCIS, they demonstrated LOH in 77% of cases, most commonly involving chromosomes 11q and 16q [7]. These abnormalities were similar to those present in the adjacent *in situ* and invasive carcinoma. In contrast the adjacent normal epithelium showed LOH infrequently in only 6% of cases [7]. A similar study has shown increasing genetic damage as the morphologic continuum progresses from FEA to DCIS to invasive carcinoma [21].

By means of comparative genomic hybridization (CGH), Simpson and colleagues demonstrated that columnar cell lesions, including those which could be classified as FEA, contain a range of chromosomal gains and losses which showed similarities to genetic characteristics observed in low grade DCIS and low grade invasive carcinoma, including low numbers of chromosomal alterations in general, more frequent genomic losses as compared to gains, and recurrent loss of 16q [18]. They also noted that the degree of morphologic atypia observed in the columnar cell lesions closely paralleled the level of genetic instability demonstrated by CGH [18].

CLINICAL SIGNIFICANCE

Taken together, the morphologic, immunophenotypic, and genetic associations between FEA and low grade *in situ* and invasive breast carcinomas provide compelling evidence that FEA represents a precursor lesion in the spectrum of low grade breast neoplasia. Despite this fact, determining the natural history and thus the best management of patients with FEA as the most advanced lesion on a core needle biopsy has proven difficult, in part due to the varying terminology reported in the literature.

In one of the earliest studies on the subject, Eusebi *et al*. in their long-term follow-up study of *in situ* carcinoma identified 41 cases of what was then termed "clinging carcinoma" [22]. Of note, 13 of these patients were described as having micropapillary architecture which likely would be classified as atypical ductal hyperplasia today, rather than FEA. Nine patients had high grade nuclear features, which would also take them out of the category of FEA by current standards. Two of these 41 patients developed recurrent DCIS over a 9 year period after the initial biopsy. However, for one patient both the initial lesion and the recurrent "DCIS" were described as "clinging carcinoma, flat type, with monomorphic nuclei", consistent with FEA by today's definition. The other patient had clinging carcinoma micropapillary type with monomorphic nuclei, perhaps better classified as atypical ductal hyperplasia using current standards. Though three patients developed subsequent infiltrating carcinomas, all occurred in cases of high nuclear grade, or pleomorphic, "clinging carcinoma". No patients with monomorphic "clinging carcinoma" developed infiltrating cancer [22]. Similarly, Bijker *et al*. found no recurrences in 59 patients with "well differentiated DCIS with clinging architecture" in their review of data from the

European Organization for Research and Treatment of Cancer trial 10853 [23]. In a more recent study which included 84 cases of FEA as the most advanced lesion on surgical biopsy, no subsequent carcinomas were diagnosed over a 10 year follow-up period [24].

In their study of 63 patients, Martel and colleagues reported subsequent infiltrating carcinoma in 9 patients (14.3%) with an initial core biopsy diagnosis of pure FEA over a 9 year period [25]. Seven of these were in the ipsilateral breast, while two were in the contralateral. The timeframe in which these invasive carcinomas developed ranged from 2 to 9 years. Of note, none of the five patients who underwent repeat biopsy within 3 months of the index specimen were found to have *in situ* or invasive carcinoma [25]. Based on their findings, Martel's group concluded FEA represents a marker of slightly increased risk for the subsequent development of invasive breast carcinoma [25].

In contrast to Martel's findings, other authors have reported that pure FEA on core needle biopsy may be upstaged to *in situ* or invasive carcinoma on a corresponding follow-up excision in 13% to 30% of cases [26-29]. Such observations have led to the recommendation that pure FEA, as the most advanced lesion on core biopsy, warrants a follow-up excision [6, 9, 27]. Until more is known about the biologic potential of these lesions, however, recommendations have fallen short of requiring re-excision when FEA is present at the margin of an excisional biopsy specimen [6, 9]. Martel and colleagues suggest a different approach, however [25]. Their recommendations include examination of 3 additional levels when FEA is encountered on core biopsy. If a more advanced lesion is not identified in the deeper levels, Martel concludes follow-up excision is not mandatory, as long as there are no other concerning clinical or radiographic features; they do, however, recommend close clinical follow-up with biannual mammograms in the ensuing 2-3 years [25].

As we gain more knowledge about the clinical significance of FEA, a reasonable approach to its management on core biopsy seems to be examination of additional tissue levels to exclude the presence of a more advanced lesion such as atypical ductal hyperplasia or DCIS. In cases where pure FEA remains the most advanced lesion in the core biopsy specimen, excisional biopsy is still warranted, given its close association with low grade *in situ* and invasive neoplasms. In certain select situations, close clinical and radiographic follow-up may be an acceptable alternative, in lieu of excision, if no worrisome clinical or mammographic features are present.

In summary, FEA has become a commonly encountered entity in breast core biopsy specimens performed for identification of microcalcifications on mammography. Observational, immunohistochemical, and molecular evidence suggests it represents a precursor to low grade *in situ* and invasive breast carcinomas. While some studies indicate FEA may be a marker for subsequent development of breast carcinoma, others have shown that, in a significant number of cases, FEA as the most advanced lesion on core biopsy may be upstaged to *in situ* or invasive carcinoma on follow-up sampling, suggesting excision of these lesions is warranted. Additional studies are required to provide better understanding of the clinical significance of FEA and to best determine its management.

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