Flat Epithelial Atypia of the Breast

Melinda F. Lerwill, MD

Flat epithelial atypia is a presumably neoplastic alteration of terminal duct-lobular units that is characterized by the replacement of the native luminal epithelium by ductal cells demonstrating low-grade cytologic atypia. The atypical cells maintain a “flat” pattern of growth without evidence of architectural atypicality. Morphologic, immunohistochemical, and molecular investigations suggest that flat epithelial atypia represents an early step in the evolution of low-grade ductal carcinomas. It is frequently seen in association with atypical ductal hyperplasia, low-grade ductal carcinoma in situ, invasive tubular carcinoma, and lobular neoplasia. The risk for subsequent breast carcinoma remains to be defined, but flat epithelial atypia likely represents a nonobligate precursor with an extended time course to progression. Certain benign alterations may superficially mimic its appearance; careful attention to cytologic and architectural characteristics can help one distinguish these unrelated entities from flat epithelial atypia.

(Arch Pathol Lab Med. 2008;132:615–621)

Flat epithelial atypia is a modern name for an alteration of terminal duct-lobular units that was first recognized more than a century ago1,2 and appears to represent an early stage in the development of low-grade ductal carcinoma.3 Flat epithelial atypia is characterized by the replacement of native luminal cells by one to several layers of monomorphic epithelial cells with low-grade cytologic atypia. The atypical cells are frequently columnar but are occasionally cuboidal. As the cells increase in number, they pseudostratify but maintain a “flat” pattern of growth along the ductal or acinar wall; that is, they do not form architecturally atypical structures such as micropapillae, trabecular bars, or cribriform spaces. In essence, flat epithelial atypia can be defined as a ductal epithelial proliferation demonstrating low-grade cytologic atypia in the absence of architectural atypia.

The frequent association of flat epithelial atypia with biopsy-targeted microcalcifications has spurred much of the recent interest in these lesions. An unintended consequence of this interest, however, has been a quagmire of terminology that has made appraisal of the literature difficult and has obscured, to some degree, the key diagnostic features of this early form of ductal neoplasia. The multitude of contemporary names used for lesions equivalent to flat epithelial atypia have included “columnar cell change or hyperplasia with atypia,” “columnar alteration with prominent apical snouts and secretions with atypia,” “ductal intraepithelial neoplasia 1-flat type,” “atypical cystic lobule,” “atypical cystic duct,” “small ectatic ducts lined by atypical ductal cells with apocrine snouts,” and “clinging in situ duct carcinoma flat type,” among others.4-10 Prior to the recent adoption of the term flat epithelial atypia by the World Health Organization working group on breast tumors,3 designations using the word “columnar” gained notable popularity. The cells of flat epithelial atypia are indeed often columnar, but it should be remembered that it is the low-grade cytologic atypia and not the shape of the cell that is the key diagnostic hallmark. Furthermore, many diverse entities in the breast contain columnar cells; most are nonatypical and biologically unrelated to flat epithelial atypia and should not be confused with such.

HISTOLOGIC FEATURES

A diagnosis of flat epithelial atypia is primarily a cytologic one, requiring medium-power to high-power microscopic evaluation to recognize the presence of low-grade cytologic atypia. Architectural features do not play as large a role in the diagnosis of flat epithelial atypia as they do in other mammary epithelial proliferations, although certain architectural alterations are helpful for identifying involved terminal duct-lobular units on scanning magnification. In particular, the involved lobules are enlarged when compared to adjacent normal lobules (Figure 1, A and B). This enlargement is due to dilatation of the terminal ductules and acini, the degree of which is variable. In some examples, the distended glands can span a millimeter or more. The terminal ductules often show the earliest evidence and greatest degree of alteration, with the changes then progressively affecting the acini. In well-developed examples of flat epithelial atypia, the dilated acini appear cystic and rounded. Somewhat branching configurations may be seen in earlier, less well-developed lesions. The intralobular stroma frequently become diminished as the glandular spaces become increasingly dilated.

Although flat, the lesion demonstrates distinguishing features on scanning magnification. Most notably, one sees a uniform increase in epithelial thickness along the entire
Figure 1. Histologic features of flat epithelial atypia. A, Variably dilated terminal duct-lobular units containing intraluminal secretions and associated calcifications (hematoxylin-eosin, original magnification ×62.5). B, Enlarged terminal duct-lobular unit with prominently thickened epithelial layer (hematoxylin-eosin, original magnification ×125). C, Classic low-grade ductal atypia (hematoxylin-eosin, original magnification ×800). D, Variant nuclear morphology with more open chromatin and small nucleoli (hematoxylin-eosin, original magnification ×800). E, Characteristic pseudostratification of the atypical cells; myoepithelial cells are inconspicuous (hematoxylin-eosin, original magnification ×800). F, Even nuclear spacing imparts an orderly appearance (hematoxylin-eosin, original magnification ×250).
perimeter of involved glands (Figure 1, B). This is largely caused by the pseudostratification of the atypical cells as they increase in number. The atypical cells also are usually larger and taller than normal luminal cells, and this too contributes to the increased epithelial height. The evenly thick, bandlike epithelium of flat epithelial atypia is rather distinctive when seen lining dilated cysts, as it contrasts with both the thin, flattened epithelium usually encountered in nonapocrine cysts and the papillary hyperplasia of proliferative apocrine cysts.

The key to a diagnosis of flat epithelial atypia is the identification of low-grade cytologic atypia. The atypical nuclei are monomorphic, hyperchromatic, and mildly enlarged (Figure 1, C). They are round to oval and have smooth nuclear contours without grooves or notches. The nuclei classically have fine, powdery chromatin that is evenly dispersed (Figure 1, C), although slightly more open chromatin is sometimes seen (Figure 1, D). Nucleoli are often inconspicuous, but 1 or 2 small nucleoli may be encountered. Mitotic activity is sparse. Certain cytoplasmic alterations tend to accompany the low-grade nuclear atypia. The cytoplasm is usually increased in amount compared with normal luminal cells (Figure 1, C). It tends to be pale eosinophilic or amphophilic in color and fine and nongranular in quality. The atypical ductal cells often accumulate cytoplasm at their apical poles, resulting in tall apical compartments and frequent cytoplasmic snouts or blebs that protrude into the lumen. Cell borders tend to be more conspicuous than in benign epithelial proliferations. Although the atypical cells are most frequently columnar, they can be cuboidal in some instances.

When flat epithelial atypia is composed of a single layer of atypical cells, the nuclei remain basal. As the cells increase in number, they pseudostratify, and the nuclei come to occupy variable positions within the cell (Figure 1, E). In either setting, the atypical nuclei remain evenly spaced, lending an orderly appearance to the proliferation (Figure 1, F). If the nuclei are oval, one can appreciate that they are regularly oriented, with their long axes perpendicular to the basement membrane. The even distribution of the nuclei in flat epithelial atypia differs from the more jumbled and somewhat disorderly arrangement of nuclei commonly seen in nonatypical epithelial proliferations.

Intraluminal secretions are frequently present. They are often flocculent and basophilic, but are occasionally dense and eosinophilic (Figure 1, A). The secretions have a proliferative apocrine cysts, blunt duct adenosis, and early usual ductal hyperplasia. The lack of cytologic atypia is the key criterion that distinguishes these lesions from flat epithelial atypia. Architectural features can provide secondary, supportive information that may be useful in problematic cases.

Microcysts that occur in fibrocystic changes may resemble the dilated glandular spaces of flat epithelial atypia. In nonapocrine microcysts, the lining cells are flat or low cuboidal and do not demonstrate evidence of low-grade cytologic atypia. They contrast with the tall, often pseudostratified layer of atypical epithelium seen in flat epithelial atypia (Figure 2, A). Apocrine microcysts may also resemble flat epithelial atypia, as they are frequently lined by columnar-shaped cells with apical blebs. Apocrine cells, however, contain characteristic round nuclei with open chromatin and prominent nucleoli. The nuclei differ from those of flat epithelial atypia, which are hyperchromatic, contain powdery chromatin, and have inconspicuous nucleoli. The cytoplasm in apocrine cells is more voluminous and granular than that of flat epithelial atypia. Additionally, proliferative apocrine changes are usually papillary rather than pseudostratified.

Perhaps an even greater challenge is to distinguish flat epithelial atypia from the alteration known as blunt duct adenosis. Most pathologists use the term blunt duct adenosis to refer to a form of lobular hypertrophy in which the glands become dilated, and this lesion can closely resemble flat epithelial atypia. In the early, proliferative phase of blunt duct adenosis, the luminal cells are columnar, with prominent apical cytoplasm and slightly enlarged nuclei. These features overlap with those of the atypical ductal cells that characterize flat epithelial atypia. Several observations, however, can help differentiate between the two. Although the glands of blunt duct adenosis are dilated, they have tubular or branching shapes (Figure 2, B) that differ from the more globoid, cystically dilated glands seen in flat epithelial atypia. The intralobular stroma in blunt duct adenosis is typically expanded and mildly cellular (Figure 2, B), contrasting in appearance with the inconspicuous and diminished intralobular stroma seen in flat epithelial atypia. The myoepithelial cells in blunt duct adenosis are especially prominent, often being larger than those in unaltered lobules and forming a continuous ring around the gland (Figure 2, C). Their prominence markedly differs from the myoepithelial cell attenuation characteristic of flat epithelial atypia.

Although the nuclei in blunt duct adenosis are frequently enlarged and may appear seemingly “atypical,” careful observation will reveal that they are more similar to the nuclei of usual ductal hyperplasia than to those of flat epithelial atypia. They are ovoid, with small grooves or notches, slightly granular chromatin, and small nucleoli (Figure 2, C). These characteristics differ from those of low-grade ductal atypia, in which the nuclei are smoothly contoured, have fine, powdery chromatin, and often lack nucleoli. The nuclei in blunt duct adenosis also tend to tilt and overlap slightly, unlike the upright, evenly distributed, and more widely spaced nuclei of flat epithelial atypia.
Figure 2.  A, Cystic flat epithelial atypia with distinctive thickened and cellular epithelium evident even at low power (hematoxylin-eosin, original magnification ×62.5).  B, Blunt duct adenosis (hematoxylin-eosin, original magnification ×62.5).  C, Cytologic features of blunt duct adenosis; note prominent myoepithelial cells (hematoxylin-eosin, original magnification ×800).  D, Early usual ductal hyperplasia with small tufts of mature hyperplastic cells (hematoxylin-eosin, original magnification ×500).  E, Very early lobule involvement by flat epithelial atypia. Changes first occur and are most pronounced in the terminal ductule (top right); the atypical cells, which are larger and paler, then replace the native epithelium in a structurally normal lobule (hematoxylin-eosin, original magnification ×250).  F, Continued accumulation of the atypical cells then leads to progressive dilatation and expansion of involved terminal duct-lobular units (hematoxylin-eosin, original magnification ×125).
Early usual ductal hyperplasia may also superficially resemble flat epithelial atypia. In usual ductal hyperplasia, the cells closest to the basement membrane are columnar and contain nuclei that are larger than those seen centrally. In early examples, these peripheral columnar cells may constitute the sole or dominant cell population, with only a few smaller, more mature hyperplastic cells present along the luminal border. The columnar hyperplastic cells have enlarged nuclei with open chromatin that may at first glance cause concern for atypia, but they do not demonstrate the hyperchromasia or monomorphism that typifies flat epithelial atypia. Instead, the nuclei appear similar to those seen in blunt duct adenosis, both in their cytologic characteristics and their spatial arrangement. Attention to any areas where the cells begin to pile up into the lumen is also helpful. The presence of typical hyperplastic features in those proliferative foci is a very reassuring sign that the associated columnar cells are not atypical (Figure 2, D).

Admittedly, the cytologic differences between flat epithelial atypia and these nonneoplastic alterations may be subtle. Attention to both the architecture and cytology will usually enable one to resolve problematic cases. Lobules with the classic appearance of blunt duct adenosis—branching and tubular glands, expanded stroma, and prominent myoepithelial cells—usually do not harbor atypical ductal cells. It has been suggested that unfolded lobules, such as those in blunt duct adenosis, are the background in which flat epithelial atypia arises. Careful morphologic observations, however, indicate that flat epithelial atypia typically arises in structurally normal terminal duct-lobular units. Replacement of the native epithelium by the atypical cells occurs first, with glandular dilatation and lobular unfolding representing secondary phenomena (Figure 2, E and F).

At the other end of the spectrum, flat epithelial atypia must be differentiated from conventionally defined atypical ductal hyperplasia and low-grade ductal carcinoma in situ. The latter entities are characterized by the presence of both cytologic and architectural atypia, whereas flat epithelial atypia is characterized by the presence of low-grade cytologic atypia in the absence of architectural atypia. Therefore, the occurrence of micropapillae, trabecular bars, Roman arches, cribiform spaces, or solid growth in what might otherwise be regarded as flat epithelial atypia warrants a diagnosis of atypical ductal hyperplasia or ductal carcinoma in situ, depending on the degree of architectural atypicality. Since flat epithelial atypia often merges into atypical ductal hyperplasia or ductal carcinoma in situ (Figure 3, A), deeper levels should be considered in particularly extensive or proliferative examples in order to exclude a more serious lesion.

Rarely, lesions that are flat and demonstrate low-grade cytologic atypia represent ductal carcinoma in situ. In these cases, the flat layer of atypical cells is greater than five or six cell layers thick. This type of flat, low-grade ductal carcinoma in situ is uncommon and almost always occurs in conjunction with more typical patterns, aiding in its recognition. Flat epithelial atypia should also be distinguished from high-grade clinging carcinoma, in which the nuclei show marked pleomorphism. High-grade nuclear atypia is not part of the spectrum of flat epithelial atypia, and its presence warrants a diagnosis of high-grade ductal carcinoma in situ, regardless of the degree of stratification. Rare columnar cell lesions demonstrate nuclei that are higher grade than those of typical flat epithelial atypia but not pleomorphic enough to warrant a diagnosis of high-grade carcinoma. Pathologists currently differ in their opinion on these lesions; some prefer to classify them as either flat epithelia atypia or atypical ductal...
expression of the possible tumor suppressor protein 14-3-3
thelial atypia.

should be noted that immunostains for high-molecu-
lar-weight cytokeratins, such as cytokeratin 34βE12 and
cytokeratin 5/6, are of limited value in the distinction of
flat epithelial atypia from the above differential diagnoses.
The cells of flat epithelial atypia are usually negative for
high-molecular-weight cytokeratins, but so too are apo-
crine cells, the luminal cells of blunt duct adenosis, the
peripheral columnar cells of usual ductal hyperplasia, and
the neoplastic cells of atypical ductal hyperplasia and duc-
tal carcinoma in situ.13 Morphology, therefore, remains the
mainstay for distinguishing these entities from flat epithe-
lial atypia.

BIOLGIC SIGNIFICANCE

Evidence that flat epithelial atypia represents an early
stage in the development of low-grade ductal carcinoma
comes from morphologic, immunohistochemical, and mo-
lecular investigations.

Flat epithelial atypia frequently merges with low-grade
ductal carcinoma in situ when both are present in the
same biopsy (Figure 3, A).5,7 The 2 lesions are character-
ized by the same type of low-grade cytologic atypia, and
the only morphologic difference between them is that the
latter is no longer flat but demonstrates architectural atyp-
ia. The anatomic mingling and cytologic similarity of flat
epithelial atypia and low-grade ductal carcinoma in situ
strongly suggest that the former represents a stage in the
evolution of the latter.7 Flat epithelial atypia also is fre-
quently seen in association with invasive tubular carci-
noma (Figure 3, B),9,14-16 and the 2 lesions share similar
cytologic characteristics. The spatial relationship and
shared cytologic features once again suggest a biologic
relationship.

The immunohistochemical profile of flat epithelial atyp-
ia mirrors that of low-grade ductal carcinoma. The major-
ity of epithelial cells in flat epithelial atypia stain for ker-
atin 19, estrogen receptor, and progesterone receptor.7 The
cells show variable but increased expression of cyclin D1,
and they are uniformly negative for Her-2/neu.17,18 Ex-
pression of p53 has been found to parallel that of adjacent
carcinoma.7 Flat epithelial atypia also shows decreased
expression of the possible tumor suppressor protein 14-3-
3 sigma, similar to in situ and invasive ductal carci-

Comparative genomic hybridization, loss of heterozy-
gosity, and gene expression studies also support that flat
epithelial atypia represents a step in the evolution of low-
grade ductal carcinoma. Recurrent loss of 16q, a genetic
hallmark of low-grade lesions, is seen in flat epithelial
atypia.20-22 Identical loss of heterozygosity patterns has
been found in flat epithelial atypia and associated carci-
nomas.20 Nonrandom X chromosome inactivation has been
identified in cases of flat epithelial atypia and associated
invasive tubular carcinoma, indicating that the two lesions
arose from the same neoplastic clone.20 Flat epithelial atyp-
ia has a gene expression profile that clusters with that seen
in low-grade ductal carcinomas, both invasive and in
situ.23 Additionally, some studies demonstrate a progres-
sive accumulation of genetic abnormalities that correlates
with an increasing degree of pathologic severity.21,24 Over-
all, these molecular studies support a role for flat epithe-
lial atypia as a precursor to low-grade ductal carcinoma.

Some authors have found evidence of related molecular
abnormalities in columnar cell lesions they have classified
as lacking cytologic atypia and have suggested that non-
antypical columnar cell proliferations represent precursors
to atypical ones.21,24 It is difficult to evaluate these data
because of the high degree of interobserver variability in
diagnosing minimal ductal atypia. The illustrated exam-
pies, however, appear generally distinct from typical blunt
duct adenosis and early usual ductal hyperplasias, lesions
which, when carefully defined, are unlikely to be related
to flat epithelial atypia.

CLINICAL SIGNIFICANCE

Many important clinical parameters of flat epithelial
atypia remain to be elucidated. We do not know the fre-
quency of the lesion in the general population or the de-
mographic characteristics of women with flat epithelial
atypia. Even the distribution of flat epithelial atypia in the
breasts is not well studied. We do know that flat epithelial
atypia frequently coexists with several types of low-grade
neoplasia: low-grade ductal carcinoma in situ, lobular neo-
plasia (atypical lobular hyperplasia and lobular carcinoma
in situ), and invasive tubular carcinoma (Figure 3, A
through C).7,9,14-16,27,28

Oyama et al27 found that 36% of low-grade ductal carci-
nomas in situ in their study were associated with flat
epithelial atypia. Brogi et al25 discovered that up to 63%
of women with lobular neoplasia have or will develop flat
epithelial atypia. Abdel-Fatah et al16 reported that up to
84% of pure invasive tubular carcinomas have flat epite-
hal atypia in the background, as do 70%, 86%, and 54%
of mixed tubular, tubulolobular, and lobular carcinomas,
respectively. These studies do not address the converse
question, namely, the frequency with which these lesions
are found in association with flat epithelial atypia. Brat-
thauer and Tavassoli26 provide some data from this angle:
in a review of 1000 cases in which flat epithelial atypia
was the most significant ductal intraepithelial lesion, they
found that 7% had concurrent invasive carcinoma and 26%
had coexistent lobular neoplasia.

Little is known about the prognostic significance of flat
epithelial atypia. The risk for development of breast car-
cinoma and its expected time course have not yet been
defined. The literature contains only a few studies that
address this issue. Eusebi et al20 evaluated the clinical out-
comes of 25 women with lesions equivalent to flat epithe-
lial atypia after an average interval of about 19 years.
None of the women developed invasive breast cancer, and
only 1 (4%) suffered a recurrence of flat epithelial atypia.
Bijker et al27 found that 59 women with well-differentiated
clinging carcinoma, which is comparable to flat epithelial
atypia, remained free of progression or recurrence after a
median interval of 5.4 years. Shaaban et al26 calculated a
relative risk of 2.32 for carcinoma for a group of analogous
lesions they termed blunt duct adenosis with atypical colum-
nar cell metaplasia; the number of cases was small, however,
and the results did not achieve statistical significance. Al-
though the available data are based on a limited number
of patients and sometimes short follow-up intervals, they
suggest that women with flat epithelial atypia have a low
risk for subsequent breast carcinoma. It is likely that flat
epithelial atypia represents a relatively indolent, nonobli-
gate precursor to ductal carcinoma. Larger clinical studies
with extended follow-up, however, are needed to more
fully understand the long-term breast cancer risk in these
patients.
A more immediate clinical concern is whether patients with flat epithelial atypia on core biopsy need to have follow-up excision, akin to the management of patients with atypical ductal hyperplasia diagnosed on core biopsy. Data from a few small studies, some only reported in abstract form, indicate that follow-up excisional biopsy will reveal associated ductal carcinoma in situ or invasive carcinoma in 13% to 30% of cases. Larger studies are needed to more fully address this issue, but until such information is available, these data support a recommendation for follow-up excision after a core biopsy diagnosis of flat epithelial atypia.

Additional surgery is not considered necessary when flat epithelial atypia is the most significant finding in an excisional biopsy, since the risk for direct progression to carcinoma appears limited. Similarly, the presence of flat epithelial atypia at the surgical margin in cases of carcinoma is not an indication for reexcision. Currently, no data exist regarding the role of tamoxifen for risk reduction in patients with flat epithelial atypia. Some investigators feel that close clinical follow-up after excision may be the most appropriate course of management, as the risk for subsequent carcinoma appears low. The management of high-risk patients diagnosed with flat epithelial atypia or those with particularly extensive disease remains to be addressed.

CONCLUSION

Flat epithelial atypia encompasses a wide spectrum of changes, ranging from minimal examples that many would not recognize as atypical to ones that border on ductal carcinoma in situ. Increasing evidence supports that flat epithelial atypia represents an early step in the evolution of certain low-grade in situ and invasive ductal carcinomas. Its presence in a biopsy should prompt one to look for associated ductal carcinoma, atypical ductal hyperplasia, and lobular neoplasia. If identified in a core biopsy, flat epithelial atypia warrants follow-up excision. Our understanding of the biologic behavior of flat epithelial atypia remains incomplete, but it likely represents a relatively indolent, nonobligate precursor to low-grade ductal carcinoma. Additional studies that better define its clinicopathologic characteristics, the risk for subsequent breast cancer, and the time course to progression are needed in order to determine optimal clinical management.

References
32. Kunju LP, Kleer CG. Significance of flat epithelial atypia on mammotome core needle biopsy: should it be excised? Hum Pathol. 2007;38:35–41.