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Columnar Cell Lesions and Flat Epithelial Atypia of the Breast

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Lesions of the breast characterized by enlarged terminal duct lobular units lined by columnar epithelial cells are being encountered increasingly in breast biopsies performed because of mammographic microcalcifications. Some of these lesions feature banal columnar cells in either a single layer (columnar cell change) or showing stratification and tufting but without complex architectural patterns (columnar cell hyperplasia). In other columnar cell lesions, the lining cells exhibit cytologic atypia, most commonly of the low-grade, monomorphic type. Such lesions were included among lesions originally categorized by Azzopardi as "clinging carcinoma" (monomorphic type), and were more recently included among lesions designated "flat epithelial atypia" (FEA) by the World Health Organization Working Group on Tumors of the Breast. The role of columnar cell lesions and, in particular, FEA in breast tumor progression is still emerging. FEA commonly coexists with well-developed examples of atypical ductal hyperplasia, low-grade ductal carcinoma in situ, and tubular carcinoma. These findings, in conjunction with the results of recent genetic studies, suggest that FEA is a neoplastic lesion that may represent either a precursor to or the earliest morphological manifestation of DCIS. However, the few available clinical outcome studies suggest that the risk of progression of FEA to invasive cancer is extremely low, supporting the notion that categorizing such lesions as "clinging carcinoma" and managing them as if they were fully developed DCIS will result in overtreatment of many patients. Additional studies are needed to better understand the biological nature and clinical significance of these lesions.
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Lesions characterized by the presence of columnar epithelial cells lining the terminal duct lobular units (TDLUs) of the breast have long been recognized by pathologists and have been described under a wide variety of names.[1-22] In the premammographic era, columnar cell lesions were identified as incidental microscopic findings in breast tissue removed because of other abnormalities and generally received little attention. Recently, there has been renewed interest in these lesions since they are being encountered with increasing frequency in breast biopsies performed because of the presence of mammographic microcalcifications.[13,14] Some of these lesions feature banal columnar cells that are in a single layer or show stratification and tufting, but without cytologic atypia or complex architectural patterns. In others, the lining cells exhibit cytologic atypia, most commonly of the low-grade, monomorphic type. Such lesions are now included within the category "flat epithelial atypia" (FEA).[23] Finally, some columnar cell lesions feature both cytologic atypia and complex architectural patterns.

The purpose of this article is to review the classification, diagnostic features, differential diagnosis, and clinical significance of columnar cell lesions and flat epithelial atypia of the breast.

Classification and Diagnostic Features

Columnar cell lesions represent a morphologic spectrum that have in common the presence of enlarged TDLUs composed of variably dilated acini that are lined by columnar epithelial cells, ranging from those that show little or no cytologic or

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architectural atypia to those that show sufficient cytologic and architectural features to warrant a diagnosis of atypical ductal hyperplasia (ADH) or ductal carcinoma in situ (DCIS).

The manner in which columnar cell lesions are classified has varied among different authors, and the classification of these lesions continues to evolve. We currently use a modification of the system proposed by Schnitt and Vincent-Salomon.[24] In this modification, columnar cell lesions are classified as either columnar cell change, columnar cell hyperplasia, or flat epithelial atypia.

Columnar cell change represents the simplest of the columnar cell lesions. These lesions are characterized by enlarged TDLUs with variably dilated acini that often have an irregular contour. These acini are lined by one or two layers of columnar epithelial cells with uniform, ovoid to elongated nuclei oriented in a regular fashion perpendicular to the basement membrane, with evenly dispersed chromatin and without conspicuous nucleoli (Fig. 1). Mitotic figures are rarely encountered. Apical cytoplasmic blebs or snouts are often present at the luminal surface of the epithelial cells but are not usually prominent or exaggerated. Flocculent secretions may be present in the lumina of the involved acini. In addition, luminal calcifications may be present.

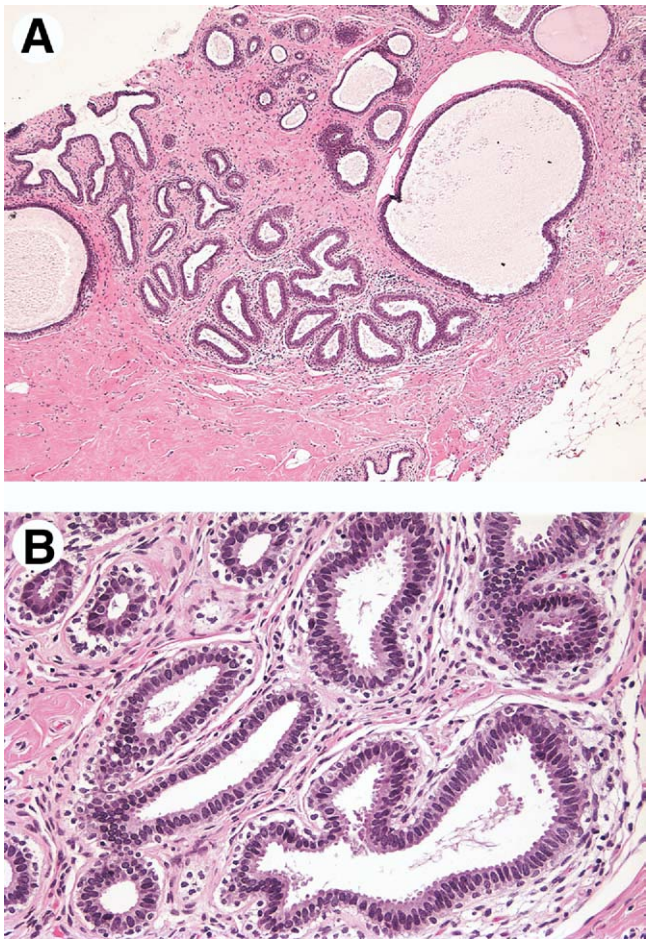

Figure 1 Columnar cell change. (A) Low-power view illustrating a terminal duct lobular unit with variably dilated acini. The acini have irregular contours. (B) Higher power view demonstrates the columnar cell nature of the epithelium. Many of the columnar cells have apical cytoplasmic blebs or snouts. The nuclei are slender, ovoid, and oriented in a regular fashion perpendicular to the basement membrane, imparting a "picket-fence"-like appearance to the epithelium lining these spaces. (Color version of figure is available online.)

Columnar cell hyperplasia is characterized by enlarged TDLUs with variably dilated acini which are often irregular in contour. They are lined by columnar cells that have cytologic features similar to those seen in columnar cell change but which, in addition, show cellular stratification of more than two cell layers. Again, the nuclei are ovoid to elongated and, for the most part, oriented perpendicular to the basement membrane. Crowding or overlapping of the nuclei in these proliferative foci may give the appearance of nuclear hyperchromasia. The proliferating columnar cells may form small mounds, tufts or abortive micropapillations (Fig. 2). Exaggerated apical cytoplasmic snouts and abundant flocculent intraluminal secretions are often present and some of the cells comprising such lesions may have a hobnail appearance. These lesions frequently show intraluminal calcifications which in some instances may have the configuration of psammoma bodies.

Some of the names that have been previously used to describe the lesions we now classify as columnar cell change and/or columnar cell hyperplasia include columnar alteration of lobules,[1] columnar metaplasia,[2] blunt duct adenosis,[4,5] columnar alteration with prominent apical snouts and secretions,[14] enlarged lobular units with columnar alteration (ELUCA),[17,25] hyperplastic unfolded lobules (HUL),[18,19] and hyperplastic enlarged lobular units (HELU),[16] among others.

In the classification previously proposed by Schnitt and Vincent-Salomon,[24] lesions with the architectural features described above for columnar cell change and columnar cell hyperplasia that also exhibited cytologic atypia (usually of the low-grade, monomorphic type) were categorized as columnar cell change with atypia and columnar cell hyperplasia with atypia, respectively. Since the proposal of that classification system, the World Health Organization (WHO) Working Group on the Pathology and Genetics of Tumors of the Breast[23] introduced the term *flat epithelial atypia* (*FEA*) for lesions of the TDLUs in which the native epithelial cells are replaced by one to several layers of cuboidal to columnar epithelial cells that show cytologic atypia, most commonly of the low-grade or monomorphic type. Thus, lesions previously categorized by Schnitt and Vincent-Salomon as columnar cell change with atypia and columnar cell hyperplasia with atypia[24] would be included in the WHO category of FEA. Given that FEA is the term proposed by the WHO Working Group, we believe that for the purpose of standardization it is prudent for pathologists to use this term for these lesions and we have adopted this approach in our clinical practice. It is important to note that lesions currently included within the category of FEA have previously been described by a wide assortment of other names, most notably "clinging carcinoma" of the monomorphic type[5,26] (Table 1).

The cuboidal to columnar epithelial cells comprising FEA most often show low-grade cytologic atypia characterized by the presence of relatively monomorphic, round to ovoid nuclei that resemble those seen in the cells comprising low-