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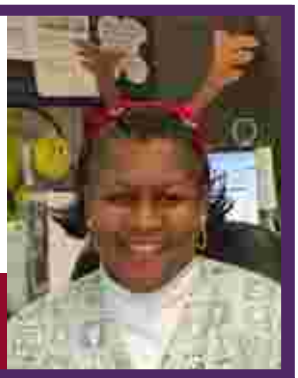

COLUMNAR CELL LESIONS OF THE BREAST

Columnar cell lesions (CCL) are histologic findings characterized by the presence of columnar epithelial cells replacing the normal epithelial lining of the terminal duct lobular units (TDLU) of the breast. These histologic changes have long been recognized by pathologists and described by a variety of different terms (Table 1)[7].

Table 1
Previous Terminology for Columnar Cell Lesions

Blunt duct adenosis
Columnar alteration of lobules
Columnar metaplasia
Hyperplastic terminal groupings
Atypical lobules type A
Columnar alteration with prominent apical snouts and secretions (CAPSS)
Pretubular hyperplasia
Atypical cystic lobules

Renewed interest in defining the clinicopathologic significance in CCL has been sparked by the increased frequency of this observation in breast biopsies performed for microcalcifications identified on screening mammograms (MMG), reported by Lubelsky, *et al.* as an incidence of 21%[8]. Hampering the efforts of those who studied CCL, was a lack of standardized terminology, and a lack of reliable data regarding the clinical significance of CCL, creating difficulties in both the pathologic diagnosis and clinical management of this entity. Recently, however, the World Health Organization (WHO) Working Group of the Pathology and Genetics of Tumours of the Breast (2003) introduced the term "flat epithelial atypia" (FEA) for CCL exhibiting low grade cytologic atypia, but lacking the architectural complexity to qualify as atypical ductal hyperplasia (ADH) or low grade ductal carcinoma in situ (DCIS)[5]. O'Malley, *et al.* then examined the ability of pathologists to reproducibly diagnose FEA and to distinguish it from CCL without atypia[1]. In their study, a study reference pathologist provided seven other study pathologists with a PowerPoint tutorial that included written criteria for, and representative images of, FEA and CCL without atypia. After reviewing the tutorial, the study pathologists examined images in PowerPoint format from 30 CCL and were instructed to categorize as either "FEA" or "not atypical." Overall agreement among the eight pathologists was reported as 91.8% with multi-rater kappa value of 0.83 ("excellent agreement"). O'Malley, *et al.* concluded that the diagnosis of FEA and its distinction from CCL without atypia is highly reproducible with the use of available diagnostic criteria.

Several studies in the recent literature have described the pathologic features of CCL [1-8]. Generally speaking, CCL represent a pathologic process centered on cystic dilation and enlargement of the TDLU. The common finding is that of columnar epithelial cells lining the variably dilated TDLU, demonstrating a morphologic spectrum of changes. The changes range from those that show little or no cytologic or architectural atypia (i.e., columnar cell change/columnar cell hyperplasia **WITHOUT** atypia) to those that have progressive architectural or cytologic atypia (i.e., columnar cell change/columnar cell hyperplasia **WITH** atypia, AKA flat epithelial atypia). If there is sufficient architectural or cytologic atypia to qualify as typical ADH or DCIS, then the appropriate diagnoses should be typical ADH or DCIS. The microscopic features are discussed in more detail below.

Columnar cell lesions WITHOUT atypia (columnar cell change [CCC] and columnar cell hyperplasia [CCH])

Columnar cell change (image 1): From low power, the TDLU contain variably dilated acini, often with flocculent intraluminal secretions and punctate calcifications. The epithelial lining cells are one to two cell layers thick, comprised of thin, flat cuboidal to tall columnar cells which are distributed uniformly and oriented perpendicular to basement membrane. The individual cells may appear crowded and dark but should demonstrate only minimal pleomorphism, with rare to absent nucleoli and mitoses. The cells may have an associated apical cytoplasmic protrusion or "snout" imparting an apocrine appearance to the cell, though not as prominent as can be seen with CCH.

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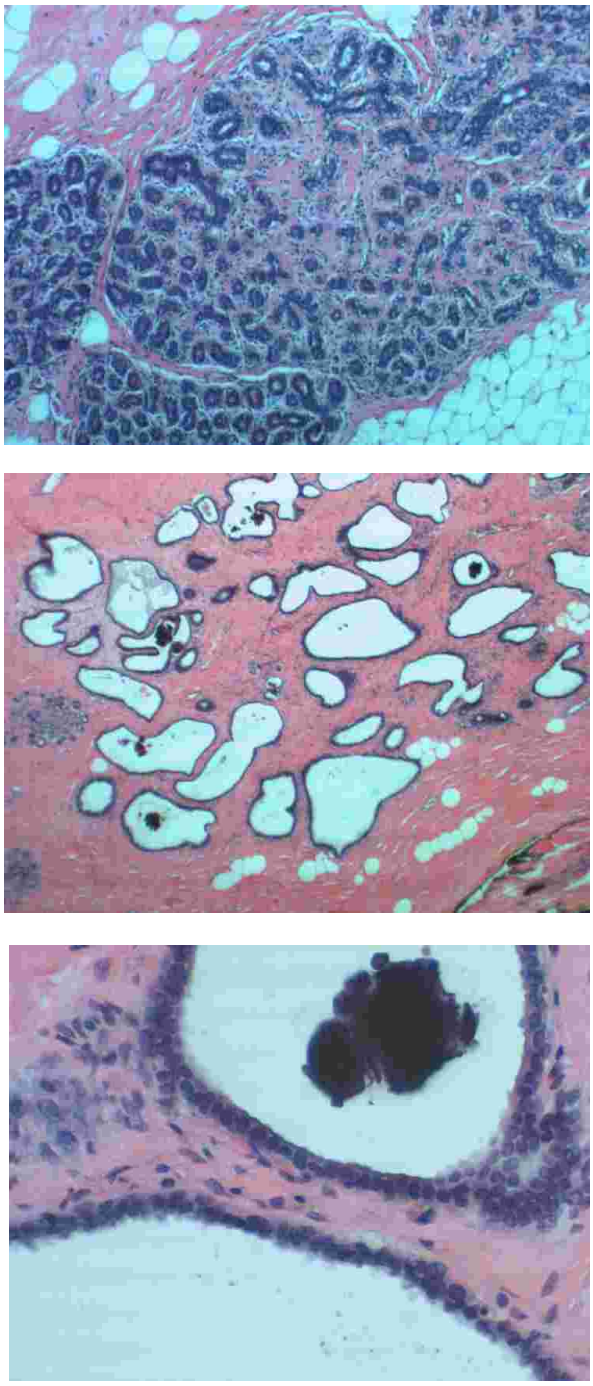

Image 1: Normal breast lobules (top)compared with those demonstrating columnar cell change with dilated TDLU from low power (center). In CCC, the dilated TDLU are lined by a single layer of columnar cells with ovoid nuclei oriented perpendicular to basement membrane(bottom)

Columnar cell hyperplasia (image 2): CCH is similar to CCC in that the lesion is centered on variably dilated TDLU, though there is an accompanying epithelial proliferation more than two cell layers thick, with nuclear stratification, cellular tufting and mounding. Complex architectural patterns such as rigid bars, bridges, or well-formed micropapillae are absent. The epithelial proliferation in CCH is generally similar cytologically to CCC, but with more crowding and nuclear chromasia. Luminal secretions, apical snouts, and calcifications are usually present, and often prominent in CCH.

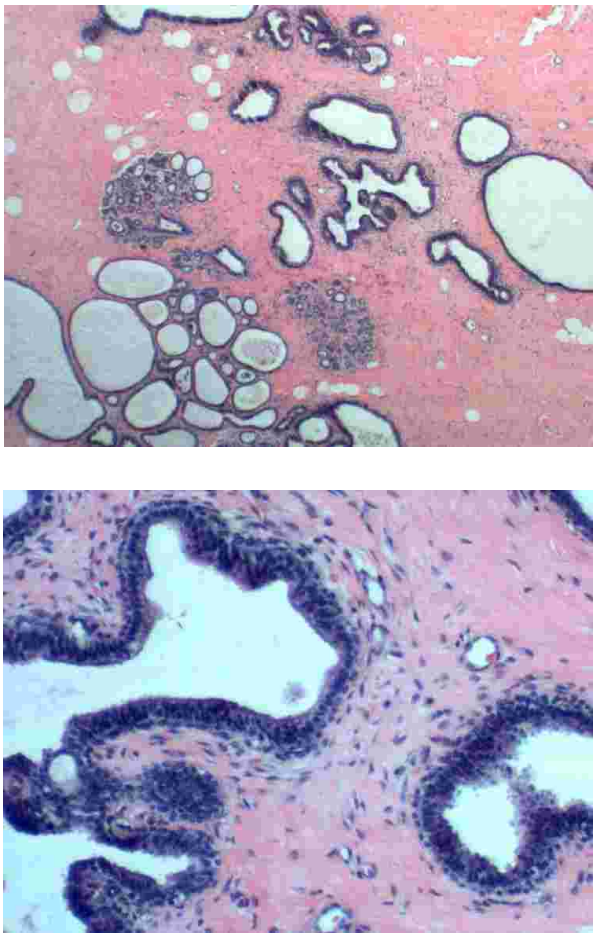

Image 2: Columnar cell hyperplasia with dilated TDLU from low power demonstrating cellular stratification with the formation of small tufts(top). Note the similarity in cytology to CCC where cells are ovoid, with retention of perpendicular orientation to basement membrane (bottom)

Columnar cell lesions WITH atypia

Flat epithelial atypia (i.e., CCC with atypia or CCH with atypia) (image 3): From low power, the TDLU appear "bluer" than normal as the acini are lined by cells which are more typically round, usually lacking polarity and regular orientation to the basement membrane. This cytologic atypia has been described as low-grade or of the monomorphic type, bearing a resemblance to that seen in low-grade DCIS. The acini usually demonstrate a flat growth pattern though architectural atypia in the form of isolated or focal micropapillary growth in a background of otherwise usual CCH can be accepted. Some CCH lesions exhibit progressive cytologic and architectural atypia such as rigid bridging, bars, arcades, cribriform spaces with sieve-like fenestrations or well developed

micropapillae. The most prudent approach to such lesions is to categorize them as either ADH or DCIS depending upon the severity and extent of the cytologic and architectural features present according to classical criteria. In addition, high-grade cytologic atypia is not a feature of CCL with or without atypia, and the presence of such requires a diagnosis of DCIS to be made, even if the cells comprise only a single cell layer.

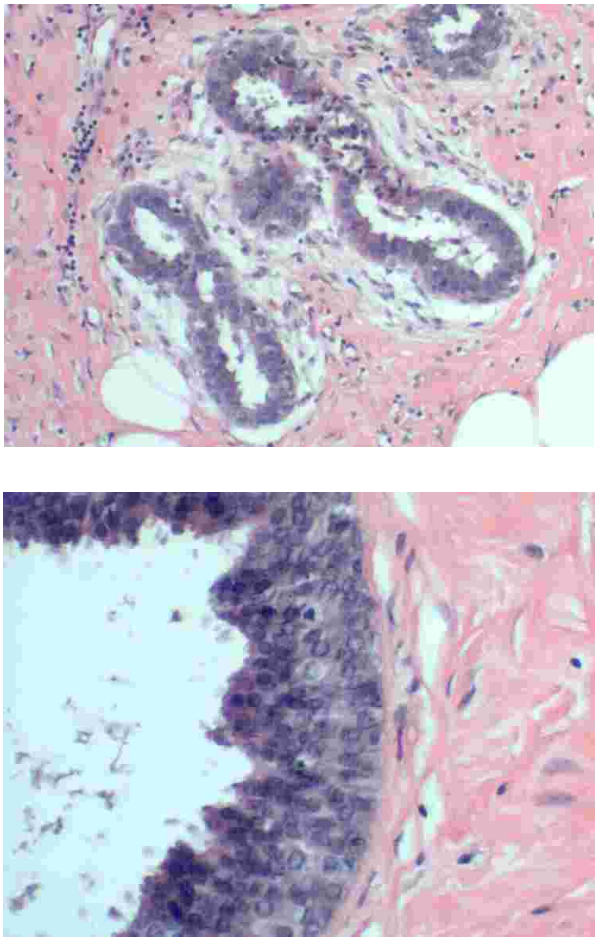

Image 3: Flat epithelial atypia demonstrating dilated acini lined by few cell layers without evidence of architectural complexity, and containing flocculent secretions (top). On high power there is low-grade cytologic atypia of rounded cells with loss of orientation to basement membrane (bottom)

Clinical Implications

It is difficult to assess the clinical significance of FEA due to variations in terminology used in the past and the limited number of cases that have been studied in a systematic fashion. Nonetheless, several small observational studies have clearly shown that the lesion now recognized as FEA commonly coexists with well-developed examples of ADH, low-grade DCIS and tubular carcinoma, and that cells comprising FEA share cytologic and immunophenotypic features with cells comprising these other lesions [2,3]. In a recent study, Collins, *et al.* examined slides from 543 patients with DCIS to evaluate the relationship between various clinicopathologic features of DCIS and the presence of coexistent FEA [4]. In univariate analysis, the presence of FEA was significantly related to DCIS, most commonly with low nuclear grade and micropapillary and cribriform architectural patterns while least commonly with high nuclear grade and comedo pattern. Additionally, FEA was significantly associated with the presence of ADH, lobular neoplasia, and CCL in both univariate and multivariable analyses. They concluded that their observations provide support for a precursor-product relationship between FEA and low grade DCIS lesions that exhibit particular features such as micropapillary and cribriform patterns and absence of comedo necrosis.

Clinical Management

The management recommendations for a patient whose breast biopsy shows CCL are somewhat controversial and evolving as information from additional studies becomes available. Based on the currently available data [1-8], for a core biopsy demonstrating CCL without atypia, no additional pathology work-up or excision is recommended. However, there is recent data indicating that when CCL with atypia/FEA is present in a core biopsy, approximately one-third of follow-up excisional biopsies will demonstrate ADH, DCIS or invasive carcinoma. As such, excision is recommended when CCL with atypia/FEA is present in a core biopsy [7]. Others have additionally recommended excision when CCL with atypia/FEA is present in association with LCIS/ALH, or if residual calcifications are present on follow-up MMG. When CCL without atypia is present in an excision specimen, no additional treatment or further pathologic evaluation is required. As expected, when present in association with diagnostic ADH or DCIS, the recommendation would be to manage the patient as one would manage ADH or DCIS in any other setting. For the pathologist, areas demonstrating CCL with atypia/FEA in an excision specimen should prompt a more thorough search for more significant lesions in the tissue, with most experts recommending obtaining additional levels from the block(s) showing the atypia, and possibly submitting the remaining tissue for histologic examination. Finally, areas demonstrating CCL with atypia should not be included in the microscopic measurement of DCIS size, and should not be considered as a "positive" margin [6,7].

Conclusion

CCL are being encountered with increasing frequency in breast core samples due to widespread use of screening MMG. Additional studies on morphologic, immunophenotypic and genetic features of CCL are needed to better define relationships of various CCL to each other, and to DCIS and invasive breast cancer. Only a few clinical follow-up studies are available for review, which suggest that at least some CCL, especially those with atypia, may represent a precursor lesion of, or risk factor for, low grade DCIS or invasive tubular carcinoma. Additional long term follow-up studies are required for more definitive conclusions.

The pathologists at Rex are aware of the recent studies in the literature and may use the term "CCL with/without atypia" or "flat epithelial atypia" when appropriate. Generally, we recommend a subsequent excision for patients with needle biopsies demonstrating CCL with atypia/FEA, and regard these lesions as a form of early or mild ADH. When present in association with a more significant lesion (i.e., ADH, DCIS, or invasive carcinoma), we may comment on accompanying CCL either in the microscopic description, or in the "Additional Findings" area of the breast cancer microscopic template.

Columnar Cell Lesions - Summarized

Definition

- Columnar cell change (CCC): Presence of columnar epithelial cells lining the TDLU
- Columnar cell hyperplasia (CCH): Presence of columnar epithelial cells more than 2 cells thick lining the TDLU
- CCC/CCH with atypia (flat epithelial atypia): CCC/CCH with the presence of cytologic atypia insufficient for ADH/DCIS by classical criteria
- Columnar cell lesion (CCL): A lesion showing CCC/CCH

Incidence and Location

- Incidence not well established, commonly associated with FCC and microcalcifications
- Bilateral/multifocal

Morbidity and Mortality

- No known morbidity
- Atypia appears to confer an increased risk of malignancy that is not well defined

Gender, Race and Age Distribution

- Premenopausal women 35-50 years old

Clinical Features

- Often identified on mammography with microcalcifications, no symptomatic lesion

Prognosis and Treatment

- Controversial and evolving
- Most authors suggest the CCL with atypia (flat epithelial atypia) on core biopsy be followed by excisional biopsy to allow an intensive search for a more significant lesion (i.e., ADH/DCIS/invasive carcinoma)
- If CCL with atypia (flat epithelial atypia) is found on excisional biopsy, the specimen should probably be sampled thoroughly, with multiple additional levels cut from the original blocks showing CCL with atypia

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