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Review

Flat epithelial atypia of the breast: characteristics and behaviors

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Abstract

BACKGROUND: Flat epithelial atypia (FEA) increasingly is being recognized as a pathologic entity on core needle biopsies. However, definitive management of this columnar cell lesion remains debatable because its malignant potential is unknown.

METHODS: A PubMed search for "flat epithelial atypia" and "columnar cell lesions" was performed.

RESULTS: FEA commonly was encountered in the background of higher-grade lesions such as atypical ductal hyperplasia, ductal carcinoma in situ, and tubular and lobular carcinomas. Its molecular and cytogenetic profile revealed some alterations similar to precancerous lesions. Pure FEA on core needle biopsies was upgraded to higher-grade lesions on subsequent surgical excision.

CONCLUSIONS: Current management of FEA is best achieved through a multidisciplinary review considering various factors to determine if surgical excision is warranted. Further studies are required to elucidate the malignant potential of this columnar cell lesion.

The initiation of breast cancer screening programs and the consequent increase in the number of biopsies performed for mammographically detected abnormalities have given rise to a previously uncommon pathologic entity: the columnar cell lesion (CCL). CCLs showing atypia initially were described as "monomorphic clinging carcinoma in situ" by Azzopardi[1] in 1979, who inferred an uncertain risk of invasive carcinoma associated with the lesion based on his experience with a few cases.[2] Although described 3 decades ago, the clinical relevance and management of this lesion remains unclear. In addition, the lack of a unified nomenclature and clear pathologic definition has resulted in difficulty in comparing various studies. In an attempt to standardize the definition and description of CCLs, the World Health Organization recently introduced the term *flat epithelial atypia* (FEA), defining it as a "presumably neoplastic intraductal alteration characterized by the replacement of native epithelial cells by a single layer or three to five layers of mildly atypical cells."[3]

This article reviews the current literature on the clinical relevance and management of FEA found on core needle biopsies (CNBs) in asymptomatic patients with nonpalpable breast abnormalities detected primarily by mammography.

Methods

Data for this review were collected through a PubMed search for "flat epithelial atypia" and "columnar cell le-

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Table 1 Pathologic comparison of FEA

	CCC	CCH	FEA	ADH	DCIS
Cell layers lining acini	<2	>2	1–5	Irregular	Irregular
Architectural atypia	None	None or noncomplex*	None or noncomplex	Complex	± Complex
Cytonuclear atypia	None	None	Low grade	Low grade	High grade

*Complex pattern was shown by micropapillations, cribiform pattern, arcades, and cellular bridges.

sions." Articles were restricted to English and French with no other exclusion criteria. Relevant articles were selected and reference lists were further cross-examined.

Pathology: Terms and Definitions

Benign columnar cell lesions (lacking cytonuclear atypia) are categorized into columnar cell change (CCC) or columnar cell hyperplasia (CCH) depending on the number of cell layers within the acini. Surgical excision is not required for these lesions given the absence of atypia.[4] In the literature, FEA can be referred to by several other terminologies including CCC with atypia,[4] CCH with atypia, atypical cystic duct and lobules,[5] clinging carcinoma (monomorphic type), columnar alternation with prominent apical snouts,[6] ductal intraepithelial neoplasia 1–flat type,[7] small ectatic ducts lined by atypical ductal cells with apocrine snouts,[8] and pretubular hyperplasia.[9] Unlike atypical ductal hyperplasia (ADH), which is characterized by its cytonuclear atypia as well as an abnormal architecture, FEA is defined as a low-grade cytonuclear atypia lacking complex structural patterns such as arcades, micropapillae, cribriform spaces, and fronds[10–12] (Table 1).

However, given the subtlety in differentiation, interpathologist reliability in the diagnosis of FEA has been questioned with difficulty cited particularly for establishment of cytologic atypia.[13] O'Malley et al[14] showed a 91.8% (95% confidence interval [CI], 84.0%–96.9%) agreement among 8 breast pathologists who were instructed to classify CCLs without atypia and FEA with a κ value of .83 (95% CI, .67–.94).

Presence of FEA With Higher-Grade Breast Lesions

The management of FEA remains controversial because its clinical significance is unclear; ductal carcinoma in situ (DCIS) and ADH have been well established with a 4 to 5-fold increased risk for invasive cancer,[15] however, the risk associated with FEA remains unknown. Given its high prevalence in CNBs (3.7%–10%),[16–18] systematic excisional biopsy would lead to a sharp increase in surgical procedures requiring increased resources and perhaps overtreatment of a slow progressing indolent lesion. However, its prominent presence in the background of higher-grade lesions is worrisome and perhaps a possible indicator of its potential as a precursor to in situ or invasive carcinoma (Table 2).

Coexistence: DCIS and FEA. Oyama et al[19] initially noted the coexistence of FEA with DCIS on surgical specimens as well as the proximity between the lesions. After analyzing 21 cases, FEA was found in 36% of samples with DCIS versus in only 3% without DCIS. A larger study with 543 women diagnosed with DCIS found a concurrent presence of FEA in 19% of cases.[20] FEA was found more frequently in low-grade DCIS showing features such as micropapillary/cribiform pattern, lack of comedo necrosis, and only low-grade nuclear atypia. A possible evolutionary pattern was suggested because FEA was found 3 times more often in DCIS samples that also housed ADH, and twice as often in samples with lobular neoplasia.

Table 2 Results of surgical excisions for pure FEA on CNBs

	n	Benign	FEA	ADH	TC	LN	DCIS	IDC
de Mascarel et al[43]	101		84 (83%)		4 (4%)	1 (1%)	12 (12%)	0
Piubello et al[16]	20	4 (20%)	10 (50%)	1 (5%)	0	5 (25%)	0	0
Senetta et al[17]	36	14 (38%)	22 (62%)				0	0
David et al[47]	40	9 (22.5%)	19 (47.5%)	5 (12.5%)	0	0	3 (7.5%)	4 (10%)
Kunju and Kleer[50]	12	3 (25%)		5 (41%)		1 (8%)	1 (8%)	2 (16%)
Lim et al[37]	5	1 (20%)		3 (60%)			1 (20%)	0
Bonnett et al[36]	9	4 (44%)		3 (33%)			2 (22%)	

LN = lobular neoplasia; IDC = infiltrating ductal carcinoma.