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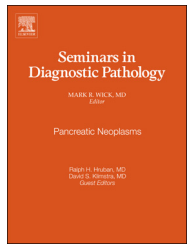

Benign mimickers of malignant breast lesions

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ABSTRACT

Breast pathology is filled with pitfalls, including underdiagnosis of bland-appearing lesions, both invasive and non-invasive, misdiagnosis of malignant lesions as belonging to the wrong subgroup, for example, calling LCIS as DCIS or missing the metaplastic component of an invasive lesion, and overdiagnosis of benign lesions as malignancy. While each is a sin of varying severity, the overdiagnosis of benign lesions can be the most scarring, especially in this age where Angelina Jolie's prophylactic mastectomy is the headline news and patients are pushing for aggressive preventive treatment. In this review, we will consider some of the more common benign lesions and the malignant counterpart that they mimic, with the goal of identifying characteristic features that will lead to the correct diagnosis. Much of the discussions will center around the assessment of core biopsies, as smaller tissue volume is most often contributory to overcalling benign lesions.

Hyperplasia and In Situ Carcinoma

The vast majority of malignant breast lesions arise from the epithelial component, therefore, we will first consider some of the benign epithelial lesions that can be overcalled as malignant and later discuss the mesenchymal lesions that can be concerning for malignancy. Prior to undertaking a discussion of epithelial benign mass lesions that mimic breast cancer, it is prudent to briefly discuss the spectrum of hyperplastic lesions in the breast, which appear in biopsies but are present as bystander lesions or were biopsied for calcifications on mammography. We will briefly cover the features of usual duct hyperplasia, columnar cell hyperplasia, and atypical duct hyperplasia with a brief discussion of the criteria of DCIS, as it is the malignant lesion most similar to the duct hyperplasias. We will also briefly cover atypical lobular hyperplasia in the context of lobular carcinoma in situ.

Usual Duct Hyperplasia

Usual duct hyperplasia (UDH) is infrequently biopsied as a mass lesion or is more commonly present in stereotactic biopsies obtained to assess calcifications.[1] This lesion is defined histologically as hyperplastic or expanded growth within the duct lumen and can simply result from an increased number of cells rimming an intact duct lumen or can be so florid as to nearly obstruct the duct. When the lumens are obstructed, the gaps created by the duct epithelium are slit-like and peripherally located within the lumen, created by crowded cells that are streaming and somewhat haphazardly distributed without respect for adjacent cell borders. Myoepithelial cells are present and associated with the hyperplastic ductal epithelium and can be identified using immunohistochemical stains. Cytologically, UDH consists of cells with round to oval nuclei without nuclear enlargement. Nucleoli are inconspicuous if appreciated. UDH can have an

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element of apocrine metaplasia that can cause the nuclei to appear larger with nucleoli; however, the architectural arrangement of the cells is not changed.

Columnar Cell Lesions

While usual duct hyperplasia is a fairly well-established and well-understood lesion, *columnar cell change* and its corresponding hyperplastic (*columnar cell hyperplasia*) and atypical (*columnar cell hyperplasia with atypia*) forms are lesions that have been described, but with variable terminology including "peritubular hyperplasia" and "flat epithelial atypia," thus making their diagnosis and determination of their diagnostic significance challenging.[2–4] The distinction of these lesions from normal duct epithelium is made by the presence of apical "snouts" or eosinophilic blebs from individual cells into the duct lumen (Fig. 1). Calcifications are often found associated with columnar cell lesions. The cells themselves are more or less columnar with occasionally abundant cytoplasm and small, round, basally located nuclei. Columnar cell change has a single layer of these cells. Columnar cell hyperplasia has pseudostratification of nuclei and the cell layers become more than two cells thick, but remain cytologically bland with minimal change in nuclear to cytoplasmic ratio. Columnar cell hyperplasia with atypia occurs when the hyperplasia develops into a micropapillary-type pattern and the nuclei become atypical with increased size, irregular nuclear membrane, and coarse chromatin. The degree of atypia approaches that seen in micropapillary or clinging DCIS. All of these lesions are technically benign, however, the diagnosis of atypia often results in excisional biopsy, and in one study, up to 18% of women with columnar cell hyperplasia with atypia had associated carcinoma, most frequently low-grade DCIS.[5]

Atypical Duct Hyperplasia and Duct Carcinoma In Situ

The final lesion to be discussed on the spectrum of hyperplasia to DCIS is *atypical duct hyperplasia*, a lesion that is universally accepted to have some features of DCIS, but it does not meet all of the criteria. Recall that *duct carcinoma in situ* (DCIS) has characteristic architectural features that develop as the malignant cells become more separated with less streaming to take on a more regular architecture. There is less crowding, and the cells form round smooth lumens and line up perpendicular to the lumens such that new "mini lumens" are formed with "roman-bridge" development in classic cribriform DCIS. Solid DCIS is discerned from UDH in that individual cells are more respectful of the cell boundaries of their neighbors and the cells themselves appear monotonous. DCIS loses the associated myoepithelial cells present in UDH. Cytologically, DCIS can be of low grade, characterized by small, round nucleoli without prominent nucleoli in cells that take on a classic cribriform pattern. DCIS can also have intermediate-grade nuclei, which are larger with a higher nuclear to cytoplasmic ratio, more course chromatin, and obvious nucleoli. High-grade nuclei are markedly atypical with increased size, nuclear irregularity, course chromatin, and prominent nucleoli. Mitoses may be present. Atypical duct hyperplasia has some but not all of these features (Fig. 2). These shortcomings may be quantitative, in which only a small amount of "DCIS" is present for evaluation or may be qualitative either in architecture or cytologically. The quantitative measurement published by Tavassoli and Norris[6] required for a diagnosis of DCIS is 2 mm or two luminal units, thus making anything less ADH, even with all of the architectural and cytologic features required for the diagnosis. Critics claim that this is not a particularly biologically relevant cut off; however, the distinction between ADH and DCIS on core biopsy is probably not critical given that a diagnosis of ADH on core biopsy nearly always results in an excisional biopsy. Upon re-excision, atypical duct hyperplasia is upgraded to DCIS or invasive carcinoma in 18–47% of cases, depending on the series, and the larger volume of DCIS on excision is the more appropriate lesion on which to obtain biomarkers for hormone treatment and prognostic purposes.[7,8] Regarding quantitative deficits necessitating a diagnosis of ADH rather than DCIS, it should be noted that only lesions with low-grade nuclei can be designated as ADH. Therefore, if a small focus of otherwise classic intermediate-high-grade DCIS is present, a diagnosis of ADH is inappropriate. Qualitative features that may be present to

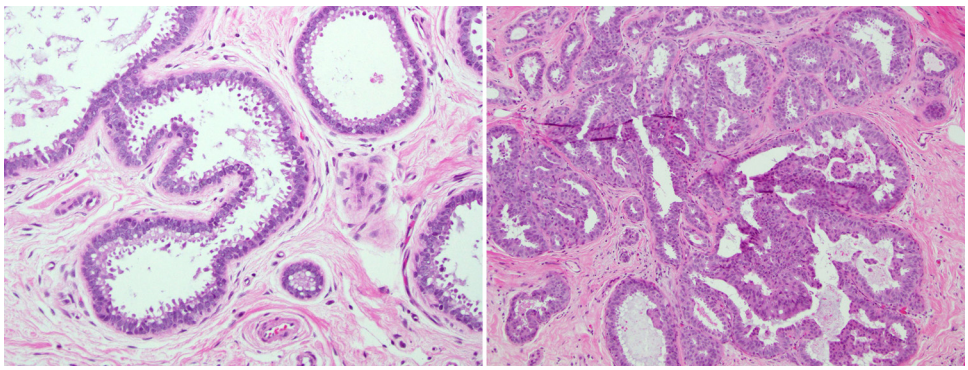

Fig. 1 – Columnar cell lesions. The image on the left demonstrates the characteristic apical "snouts" of *columnar cell change*. The nuclei are generally basally oriented in a single layer and cytoplasmic blebs protrude into the gland lumen. The image on the right demonstrates *columnar cell hyperplasia* with pseudostratification of the cells into more than two cell layers. The nuclei are still roughly basally oriented with cytoplasmic snouts and blebs into the gland lumen and they are not significantly increased in size.