Assessing intraductal proliferations in breast core needle biopsies

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Abstract

Intraductal proliferations of the breast comprise a heterogeneous group of epithelial proliferations confined to the ductal and lobular system of the breast parenchyma. The correct interpretation and categorization of such lesions can be challenging, especially on core needle biopsy, but are critical for appropriate clinical management as this determines whether surgical excision is or is not required. In this paper we aim to review the histologic criteria and terminology for the spectrum of intraductal proliferative lesions. We will discuss the key morphologic features and diagnostic mimics of usual ductal hyperplasia, atypical ductal hyperplasia, and ductal carcinoma in situ, and provide practical guidelines for interpretation in core needle biopsy specimens.

Keywords Biopsy; breast; breast neoplasms; carcinoma; carcinoma in situ; hyperplasia; intraductal; large-core needle; non-infiltrating

Introduction

Intraductal proliferative lesions of the breast are a diverse group of epithelial proliferations that arise in the acini of the mammary terminal duct lobular unit (TDLU), even though they are referred to as "ductal" proliferations. They have classically been divided into three categories: usual ductal hyperplasia (UDH), atypical ductal hyperplasia (ADH), and ductal carcinoma in situ (DCIS).

Accurate interpretation on core needle biopsy (CNB) can be diagnostically challenging because there is morphologic overlap between these proliferations. Diagnosis requires evaluation of the cytomorphology, architecture, and extent of the proliferation. Because the CNB result will guide the subsequent clinical decisions, including whether or not surgery is required, correct pathologic diagnosis is necessary to prevent inappropriate patient management. Here we provide pragmatic guidelines for handling the diagnosis and reporting of these lesions in CNB specimens.

Usual ductal hyperplasia

UDH, also known as hyperplasia of the usual type, is a benign polyclonal proliferation of ductal epithelium. The normal lining epithelium of ducts and lobules is one cell layer thick. Usual ductal hyperplasia is considered mild when the proliferation is two to four cell layers thick or florid when the lumen is filled and distended by epithelial cells.

Microscopic features

UDH is characterized by a polymorphous population of epithelial cells arranged in a streaming and haphazard, patternless pattern (Figure 1). Cell borders are indistinct and the cells show frequent overlapping. Cytologically the epithelial cells are bland. The nuclei are round to oval in shape and the chromatin texture varies from cell to cell. Intranuclear pseudoinclusions and nuclear grooves, features that are reminiscent of papillary carcinoma of the thyroid, are often present.[1]

UDH has various architectural patterns including solid, fenestrated, and micropapillary.[2] In the solid pattern the epithelial cells fill and distend the acini of TDLU and often appear to be streaming or swirling. In the fenestrated pattern, slit-like spaces, preferentially located at the periphery of the involved space, are present. The epithelial cells are not organized or polarized around these spaces. UDH with micropapillary features is also known as gynecomastoid hyperplasia due to its resemblance to the epithelial proliferation seen in gynecomastia (Figure 2). The micropapillary tufts that project into the lumens of the ducts and lobules have a broad base that taper toward the tip of the micropapillation conferring a "pinched" appearance to the tips. The epithelial cells at the luminal aspect are smaller and more crowded than those at the base. When ducts or lobules are partially involved by UDH, bridges of epithelial cells may be present but the cells maintain their streaming pattern and lack the ridged arcade architecture seen in ADH or DCIS (see below).

Histiocytes and calcifications may be seen in association with UDH. Rarely necrosis or mitoses may be present (Figure 3). UDH is often seen in association with intraductal papillomas and benign sclerosing lesions (radial scar and complex sclerosing lesions).

Immunophenotype and molecular pathology

Immunohistochemical stains for estrogen receptor (ER) and a high-molecular-weight cytokeratin (CK), such as CK5/6, can be utilized to distinguish UDH from ADH or low- or intermediate-grade DCIS in problematic cases. The polymorphous epithelial cells will each stain differently imparting a mosaic staining pattern with CK5/6 and variable staining with ER (i.e. some cells will show strong nuclear staining, others will have weaker staining and still other nuclei will be negative) (Figure 4 and Table 1).[3,4]

The epithelial cells of UDH are polyclonal and do not have consistent genetic alterations. The frequency of loss of heterozygosity (LOH) is low supporting the view that it is not a neoplastic proliferation.[5–8]

Diagnosis, management, and prognosis

Recognition of the cytomorphologic features and architectural patterns of UDH, as well as its association with other entities including papillomas and sclerosing lesions is critical to aid in diagnosis of the entity as benign hyperplasia. When necrosis is present it is helpful to mentally subtract the necrosis and to focus on the epithelial proliferation (Figure 3). The use of immunohistochemical stains in conjunction with the morphology on H&E

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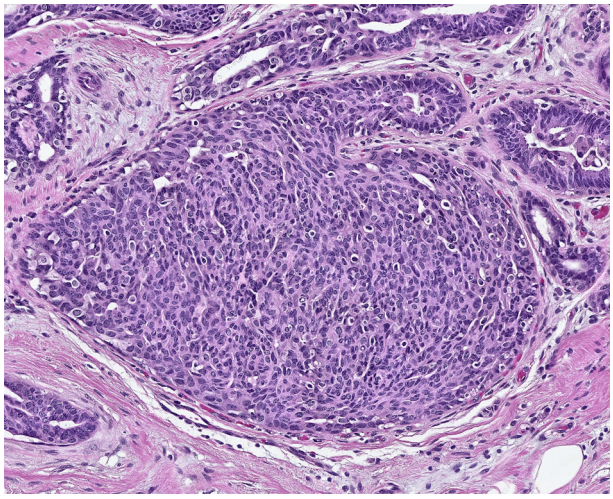

Figure 1 Usual ductal hyperplasia. The polymorphous epithelial cells have a streaming and haphazard arrangement with indistinct cell borders. Some fenestrations and peripheral slit-like spaces are present.

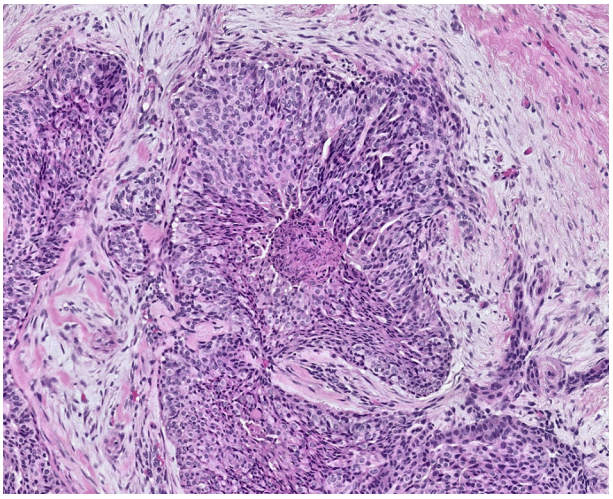

Figure 3 Usual ductal hyperplasia with necrosis. The cytomorphology and the architecture are consistent with a diagnosis of UDH. An immunostain for ER showed a mosaic nuclear staining pattern, supporting the diagnosis of UDH.

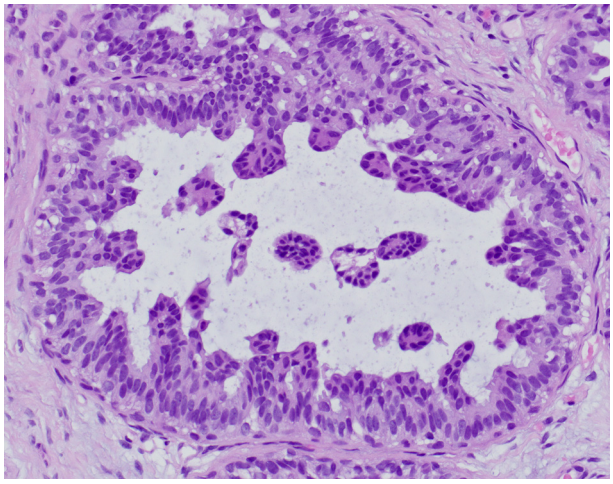

Figure 2 Usual ductal hyperplasia. This pattern has a micropapillary architecture reminiscent of the epithelial proliferation seen in gynecomastia. The epithelial cells at the luminal aspect of the tufts have smaller nuclei than those at the base.

can be very helpful in CNB specimens to prevent overdiagnosis and overtreatment. UDH is not associated with a risk of upgrade to carcinoma (DCIS or invasive carcinoma) when present as the most significant lesion in the CNB; thus excision is not indicated as long as the pathology is concordant with the imaging finding. The subsequent risk of breast cancer following a diagnosis of UDH is 1.5—2 fold, as such there is no indication for increased radiological screening or high risk management in these patients.[9,10]

Atypical ductal hyperplasia

ADH comprises a group of epithelial proliferations that have some features of UDH, flat epithelial atypia, and low-grade DCIS.[2] At least a portion of the proliferation (or the entire proliferation if of very limited extent, see below) has the cytomorphology and architecture of low-grade DCIS. The diagnosis of

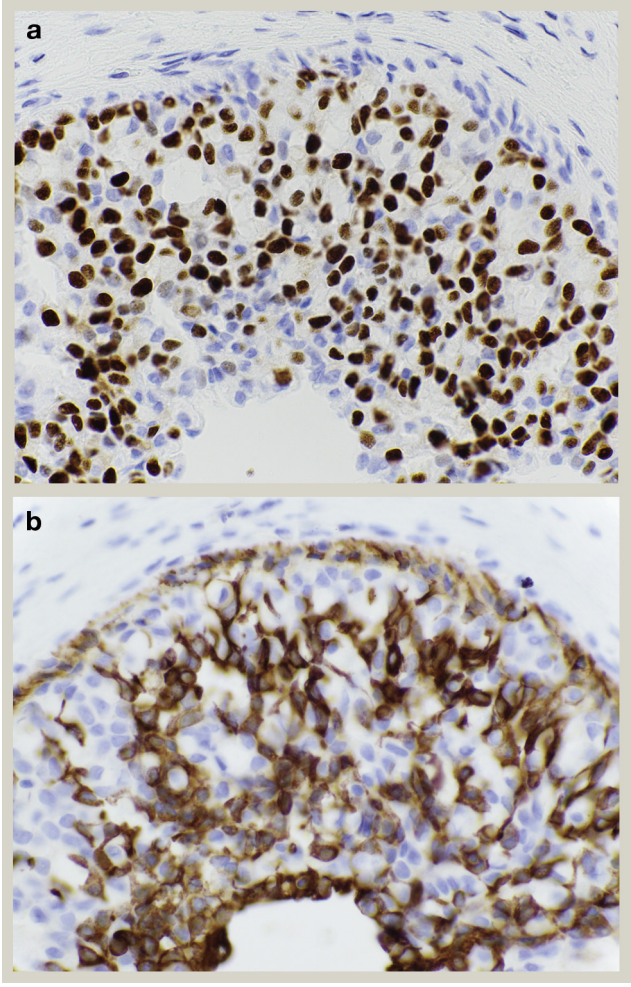

Figure 4 (**a, b**). Usual ductal hyperplasia. ER (**a**) and CK5/6 (**b**) immunostains showing the characteristic mosaic staining pattern of UDH.

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