Precursor Lesions of the Low-Grade Breast Neoplasia Pathway

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KEYWORDS

• Low-grade breast neoplasia • Flat epithelial atypia • Atypical ductal hyperplasia
• Low-grade ductal carcinoma in situ • Lobular neoplasia • Tubular carcinoma

Key points

- Precursor lesions of the low-grade breast neoplasia pathway often coexist.
- This family of lesions shares morphologic, immunophenotypic, and genetic characteristics.
- Loss of 16q is commonly seen.
- Despite the relationship of these lesions to invasive carcinomas, the risk of progression among the earliest lesions is exceedingly low.

ABSTRACT

The nonobligate precursor lesions columnar cell change/hyperplasia and flat epithelial atypia, atypical ductal hyperplasia and atypical lobular hyperplasia, lobular carcinoma in situ, and low-grade ductal carcinoma in situ share morphologic, immunophenotypic, and molecular features supporting the existence of a low-grade breast neoplasia pathway. The practical implication for pathologists is that the identification of one of these lesions should prompt careful search for others. From a clinical management perspective, however, their designation as "precursor lesions" should not be overemphasized, as the risk of progression among the earliest lesions is exceedingly low. Factors determining which lesions will progress remain unknown.

OVERVIEW

It has been several decades since Azzopardi[1] first described a lesion with low-grade cytologic atypia that had initially been overlooked as an area of fibrocystic change, but that on re-review demonstrated dilated acini lined by 2 to 4 layers of atypical epithelial cells showing enlarged, hyperchromatic nuclei, loss of cell polarity, and occasional mitoses. This index case came to Dr Azzopardi's attention because the patient had developed invasive carcinoma with axillary lymph node metastases 8 years after the original biopsy, and subsequently died of disease. Further study of similar lesions led Azzopardi to speculate that these lesions represented a form of well-differentiated ductal carcinoma in situ (DCIS) for which he proposed the term "clinging carcinoma (of the monomorphic type)," given the lack of intraductal proliferation present. This morphologic observation of the relationship between the lesion we now refer to as flat epithelial atypia (FEA) and invasive carcinoma was remarkably prescient. As is discussed in this review, in addition to the morphologic similarities between FEA and low-grade invasive carcinomas, specifically tubular carcinomas, there is now substantial molecular evidence linking these lesions to one another along the low-grade breast neoplasia pathway.[2–6]

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COLUMNAR CELL LESIONS

DEFINITION AND MORPHOLOGY

Columnar cell change, columnar cell hyperplasia, and FEA are collectively referred to as columnar cell lesions. This family of lesions is characterized by variable dilatation of the acini of the terminal duct lobular unit, with a single to multilayered epithelial lining, cells with apical snouts, and luminal secretions and calcifications. The epithelial cells of columnar cell change are columnar with elongated nuclei arranged perpendicular to the basement membrane (**Fig. 1**). The epithelial cells of columnar cell hyperplasia are also columnar with elongated nuclei arranged perpendicular to the basement membrane, but there is multilayering of the epithelial cells with tufting of the lining of the acini (**Fig. 2**). However, there should be no true

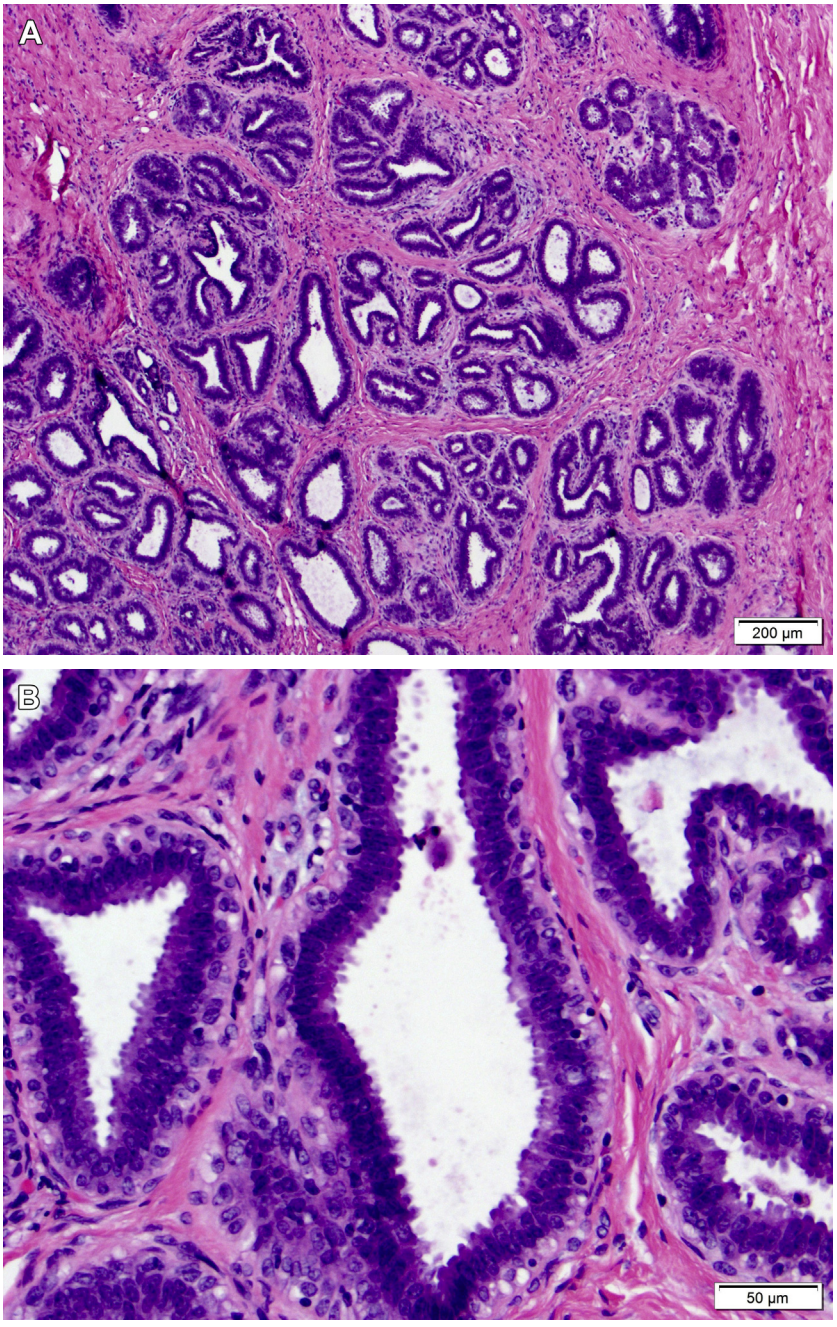

Fig. 1. Columnar cell change. (*A*) Low-power image illustrating the variably dilated acini with irregular contours. (*B*) High-power image demonstrating the regular columnar nuclei arranged perpendicular to the basement membrane.