A Diagnostic Approach to Fibroepithelial Breast Lesions

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KEYWORDS

• Breast • Fibroepithelial lesion • Fibroadenoma • Phyllodes tumor • Periductal stromal tumor

Key points

- Fibroadenomas are common benign neoplasms of the breast. In comparison, phyllodes tumors are relatively rare and possess potential for recurrence.
- Phyllodes tumors are graded as benign, borderline, or malignant based on histologic evaluation of various parameters. A nomogram based on stromal atypia, mitotic activity, stromal overgrowth, and surgical margin status (AMOS criteria) can individualize recurrence risk.
- Distinction of cellular fibroadenoma from phyllodes tumor can be challenging, especially on limited samples such as core needle biopsies.
- The major differential diagnoses of a malignant spindle cell breast tumor are metaplastic spindle cell carcinoma, malignant phyllodes tumor, and (rarely) sarcoma.
- Recent work has generated new insights into the genetic underpinning of this group of neoplasms, including the prevalence of somatic *MED12* exon2 mutations in fibroadenomas and phyllodes tumors, with additional genomic aberrations observed in borderline and malignant phyllodes tumors.

ABSTRACT

Fibroepithelial breast lesions encompass a heterogeneous group of neoplasms that range from benign to malignant, each exhibiting differing degrees of stromal proliferation in relation to the epithelial compartment. Fibroadenomas are common benign neoplasms that may be treated conservatively. Phyllodes tumors are relatively rare lesions, and classified as benign, borderline, or malignant based on histologic evaluation of various parameters. The diagnostic interpretation of "gray-zone" fibroepithelial lesions often imposes formidable demands on a pathologist's skills. This article offers practical recommendations for the diagnostic workup of these lesions, including the appropriate utilization of ancillary investigations and the approach to core needle biopsies.

Fibroepithelial breast lesions encompass a heterogeneous group of biphasic neoplasms that range from benign to malignant, each of which exhibits differing degrees of epithelial and stromal proliferation.

FIBROADENOMA

CLINICAL FEATURES

A fibroadenoma usually presents as a painless, firm, mobile breast lump, often in younger women aged 20 to 35 years. Multiple and bilateral fibroadenomas occur less commonly. Increasingly, nonpalpable fibroadenomas of smaller size are detected by screening mammography. In adolescents, fibroadenomas may attain significant

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dimensions. Patients treated with cyclosporin A immunosuppressive therapy have a propensity for development of fibroadenomas, which may be multiple, bilateral, and of larger size than usual.[1,2] In this patient population, lesional regression and/or stability were observed on substitution of tacrolimus for cyclosporin as an alternative immunosuppressive agent.[3]

GROSS FEATURES

Fibroadenomas are ovoid, circumscribed, white, firm-to-rubbery masses. Although generally 3 cm or smaller, larger fibroadenomas (>4 cm) may occur, especially in younger women. The cut surface, which is typically whitish in color, shows a solid, lobulated appearance that can reveal slender slitlike spaces. Areas of calcification may be present.

MICROSCOPIC FEATURES

A balanced, biphasic proliferation of glandular and stromal elements characterizes fibroadenomas. Although the relative amount of each element may vary, an evenly distributed gland-stroma ratio is usually seen throughout a given lesion. Lesional borders are circumscribed and pushing, without infiltration into surrounding tissue. Of note, fibroadenomas may rarely infarct, especially in gravid patients; the remnant "ghost" architecture of a characteristically balanced biphasic proliferation will suggest the diagnosis.

The stroma of fibroadenomas is typically low in cellularity, shows no significant nuclear atypia, lacks appreciable mitotic activity (except in young or pregnant women), and does not exhibit overgrowth. It frequently has a loose, myxoid quality, especially in younger patients. Myxoid stromal foci may wreathe epithelial elements as prominent cuffs. In older women, the stroma tends to be hypocellular and densely hyalinized. Not infrequently, multinucleated stromal giant cells with nuclear atypia may be found[4–6]; the presence of these cells has not been shown to carry prognostic significance, and should not detract from the correct classification of an otherwise typical lesion. Stromal dystrophic calcifications, often coarse, may be identified. Rarely, ossification may occur, especially in a postmenopausal setting. Pseudoangiomatous stromal hyperplasia (PASH), a benign myofibroblastic proliferation, can on occasion be identified[7] (**Fig. 1**).

The epithelial component of fibroadenomas comprises ductal epithelial cells supported on an intact myoepithelial layer. An intracanalicular pattern of stromal growth compresses associated epithelium into curvilinear, slitlike spaces, whereas a pericanalicular stromal growth pattern circumferentially surrounds epithelial-lined spaces without luminal distortion.[8] Tangential sectioning may impart an appearance of festooning epithelial "beads" describing the underlying glandular arc. Many fibroadenomas demonstrate both intracanalicular and pericanalicular patterns.

A full spectrum of benign and malignant epithelial changes may be seen in fibroadenomas. Benign processes include lactational change, simple cysts, usual ductal hyperplasia, apocrine metaplasia, and sclerosing adenosis. Atypical ductal hyperplasia (ADH) and atypical lobular hyperplasia may be present within fibroadenomas; furthermore, ductal carcinoma-in-situ (DCIS), lobular carcinoma-in-situ, and invasive carcinomas may arise in or secondarily involve fibroadenomas from adjacent breast tissue.

CYTOLOGIC FINDINGS IN FIBROADENOMA

Cytologic preparations of needle-aspirated fibroadenomas typically yield cellular sheets and "staghorn" clusters of epithelial cells, admixed with numerous bare myoepithelial nuclei.[9,10] Background stromal material, including myxoid stroma, also can be seen (**Fig. 2**). Rarely, multinucleated giant cells may be discerned.[11,12] The presence of significant epithelial atypia may suggest the concomitant presence of in situ or invasive epithelial malignancy. It is important to note that aspirates of fibroadenoma represent one of the major pitfalls in overdiagnosis of malignancy on breast cytology due to the accompaniment by occasional nuclear atypia and intact cells.

FIBROADENOMA VARIANTS

Cellular Fibroadenoma

The stroma of a cellular fibroadenoma displays conspicuous cellularity (**Fig. 3**), which may raise the diagnostic possibility of a phyllodes tumor (PT). The distinction of a cellular fibroadenoma from a PT is discussed in detail in a separate section ("Core biopsy of fibroepithelial lesions: challenges and practical recommendations") later in this article.

Complex Fibroadenoma

Defined as a fibroadenoma with at least 1 of the following features: sclerosing adenosis, cysts $\geq$3 mm in size, papillary apocrine metaplasia, and epithelial calcifications, these tumors tend to present at an older age and are of smaller size than conventional fibroadenomas.[13,14] Florid changes may obscure the underlying fibroadenomatous nature of the lesion, especially on limited core biopsy material.