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Myofibroblastic, fibroblastic and myoid lesions of the breast

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A B S T R A C T

Myofibroblastic, fibroblastic and/or myoid lesions are rare in the breast but comprise the majority of mammary mesenchymal spindle cell lesions. Whereas most have similar features to their counterparts at extramammary sites, pseudoangiomatous stromal hyperplasia is considered a breast-specific myofibroblastic proliferation on the same spectrum as myofibroblastoma. Other lesions with myofibroblastic/fibroblastic differentiation include fibromatosis and nodular fasciitis, as well as more aggressive tumors such as the rarely reported myofibrosarcoma, inflammatory myofibroblastic tumor and fibrosarcoma. Lesions with myoid differentiation include benign leiomyoma, myoid hamartoma and leiomyomatous myofibroblastoma, but primary leiomyosarcoma and rhabdomyosarcoma may also rarely arise in the breast. Furthermore, fibroepithelial lesions and metaplastic carcinomas can demonstrate myoid metaplasia. Diagnosis can be challenging, particularly on core biopsy, but benign lesions with or without recurrence potential must be distinguished from more aggressive tumors, especially metaplastic carcinoma and phyllodes tumors. This article will review lesions with myofibroblastic, fibroblastic and myoid differentiation in the breast, with special emphasis on differential diagnosis.

Lesions with fibroblastic, myofibroblastic or myoid differentiation are a rare and heterogeneous group that comprises the majority of mesenchymal spindle cell proliferations in the breast. Among these, pseudoangiomatous stromal hyperplasia (PASH) and mammary myofibroblastoma (MFB) fall along a morphologic spectrum of benign lesions with myofibroblastic differentiation and are likely derived from a CD34+ mammary stromal precursor cell, the presumed multipotency of which may explain the wide histologic spectrum of MFB.[1] Myofibroblastic sarcomas and inflammatory myofibroblastic tumors also arise in the breast but are exceedingly rare.[2–12] The myofibroblastic phenotype of myofibrosarcomas has been confirmed by electron microscopy (EM), but these tumors are unlikely to be directly related to the PASH-MFB myofibroblastic continuum.[4,6–11,13] Other mammary lesions with fibroblastic/myofibroblastic differentiation resemble their counterparts at other sites and include nodular fasciitis and fibromatosis, and primary fibrosarcoma may also rarely be seen.[14–33] Primarily myoid tumors are very rare in the breast and are comprised of leiomyoma and myoid hamartoma, as well as malignant muscle tumors.[34–55] However, fibroepithelial lesions, metaplastic carcinomas and MFBs can also demonstrate myoid metaplasia, which may be related to origin from a multipotent precursor.[56–60]

Many of these lesions are benign, but accurate diagnosis is essential in order to recognize those, such as fibromatosis and fibroepithelial lesions, with recurrence potential, and to distinguish benign proliferations from malignant tumor mimics with more aggressive behavior. In addition to primary sarcomas, the latter group importantly includes metaplastic carcinoma and malignant phyllodes tumor (PT) with stromal overgrowth. Because benign or malignant tumors may be either fundamentally myofibroblastic/fibroblastic/myoid or demonstrate superimposed stromal metaplasia, the differential diagnosis is not infrequently broad, especially on core biopsy, and definitive diagnosis often requires evaluation of the excised specimen. Given the rarity of primary mammary sarcomas, the differential diagnosis in this context also includes metastasis. In most cases, careful attention to morphologic features and ancillary immunohistochemistry will facilitate the correct diagnosis.

Benign myofibroblastic/fibroblastic lesions

Fibromatosis

Fibromatosis is a low grade fibroblastic/myofibroblastic proliferation which may recur locally but lacks metastatic potential.[30,32,61] These lesions may occur in the superficial or deep

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breast or in the axilla but are uncommon, with an incidence of ~0.2% that of mammary carcinomas.[26] In contrast to extra-mammary deep desmoid tumors, fibromatosis of the breast is usually sporadic and not associated with Gardner syndrome.[27,32,62] An association with prior surgery has been described.[28,32] The presentation is often that of a non-tender mass with clinical and radiologic suspicion for carcinoma.[30–32,63] The morphologic features are identical to its counterpart in other sites, being composed of long, sweeping and interlacing fascicles of bland spindle cells with hypochromatic, often tapering nuclei without atypia or mitotic activity.[31] Cellularity and stromal collagenization are variable, with dense keloidal-like collagen bands or loose myxoid stroma. Lymphocytic aggregates are often present at the periphery. The margins are characteristically irregular and stellate, with the spindle cells infiltrating adjacent epithelium and stroma.

It is estimated that approximately one-half of breast fibromatosis cases harbor *CTNNB1* exon 3 mutations, with *APC* mutations identified in one-half of the remainder.[25] Consistent with this, nuclear β-catenin is detected immunohistochemically in the majority of cases.[29,64] However, evaluating true nuclear versus overlapping cytoplasmic staining can be challenging, and nuclear expression may be patchy and not always apparent in core biopsies. Accordingly, lack of nuclear β-catenin does not exclude the diagnosis if features are otherwise compatible.[25] The spindle cells may express SMA and/or focal desmin. Keratins, EMA, CD31, CD34 and S-100 protein are negative.[26]

The differential diagnosis of mammary fibromatosis is broad and includes reactive and bland neoplastic spindle cell proliferations, such as fibromatosis-like spindle cell metaplastic carcinoma (FLSCC), PT with stromal overgrowth, the collagenized variant of MFB, nodular fasciitis, scar and inflammatory myofibroblastic tumor (Table 1). Definitive diagnosis may require evaluation of the excised lesion. The most important differential is with FLSCC, which may mimic fibromatosis clinically, radiologically and histologically.[65,66] Small clusters of epithelioid cells admixed with and blending with the spindle cells may be seen in FLSCC. Other features that favor FLSCC are nuclear atypia (typically mild or moderate in degree) and an elevated mitotic rate (> 2/10 high power fields), which would be unusual in fibromatosis (Fig. 1). The lymphocytic infiltrate of FLSCC is often evenly distributed and lacks the peripheral accentuation of fibromatosis. Immunohistochemistry is useful but should be used with caution in core biopsies. Nuclear β-catenin is neither sensitive nor specific and has been described in up to 23% of metaplastic carcinomas and in PT.[25,29,67] Keratin expression may be focal in FLSCC and therefore negative in small core biopsies. Accordingly, a panel of keratins including high molecular weight keratins is recommended for this differential.[66,68,69] Together, nuclear β-catenin and negative keratin expression can support the diagnosis of fibromatosis when a sufficient sample of the lesion is available for evaluation.

The distinction of fibromatosis from prominent stromal overgrowth of PT can also be problematic on core biopsy when the biphasic nature of PT may not be appreciable. Moderate or severe nuclear atypia, abundant mitotic activity, and necrosis can be found in PT but not fibromatosis. Whereas both may express nuclear β-catenin and actin, CD34 can be positive in some PTs but not fibromatosis and may be useful in this context, with the caveat that CD34 negativity does not exclude PT.[25,26,29,67,68,70,71] High cellularity, nuclear pleomorphism and abundant mitotic activity with a herringbone pattern support a diagnosis of fibrosarcoma.

The distinction of fibromatosis from scar can sometimes be problematic, especially in the context of residual or recurrent fibromatosis versus scar from a prior procedure, and this can affect margin evaluation (Fig. 2). Hemosiderin-laden histiocytes, foam cells, giant cells and a scattered lymphocytic infiltrate favor a reparative process.[72] Reactive myofibroblasts in granulation and scar tissue may express SMA; although nuclear β-catenin staining is usually absent in scar, rare cases may be positive in our experience. In conjunction with the patchy nuclear staining typical of fibromatosis, this marker is therefore not considered reliable to distinguish the two or for margin evaluation in re-excision of residual fibromatosis. Inflammatory myofibroblastic tumors are exceedingly rare in the breast.[2,3,73,74] These tumors morphologically resemble their counterparts arising in other sites and can be distinguished from fibromatosis by a diffuse plasma cell-rich infiltrate, lack of nuclear β-catenin, and often ALK expression, which is due to 2p23 rearrangements.[2,3,64]

Nodular fasciitis

Nodular fasciitis is a self-limited clonal myofibroblastic/fibroblastic proliferation, which is very uncommon in the breast. The clinical and histologic features are similar to lesions arising at other sites.[15–24] Presentation is typically that of a small (< 2 cm) nodule with rapid onset, pain, and tenderness. The lesion may arise in the subcutis or rarely in deeper parenchyma and consists of a mitotically active spindle cell proliferation with so-called tissue culture-like growth pattern in a loose myxoid or microcystic stromal background, although some lesions are collagenized. Nuclear atypia and necrosis are notably absent despite elevated mitotic activity. The center is often less cellular than the periphery. Extravasated red blood cells and a scant lymphocytic infiltrate are often scattered throughout the lesion, which contrasts with the peripheral infiltrates of fibromatosis. The spindle cells consistently express SMA, rarely express desmin and are CD34 negative. Negative keratin and β-catenin expression are helpful in the distinction from FLSCC and fibromatosis, respectively.[64] *USP6* rearrangements have been identified in nodular fasciitis, with *MYH9-USP6* gene fusions found in most but not all lesions; the only documented breast lesion was negative for *USP6* rearrangement.[14,75] The findings support a clonal neoplastic process, but spontaneous regression is characteristic, and recurrence is uncommon.

Pseudoangiomatous stromal hyperplasia

PASH is a benign stromal hyperplasia belonging to a spectrum of myofibroblastic proliferations in the breast, which also includes MFB.[76–78] The lesion is considered an exaggerated response to hormonal stimulation and is associated with premenopausal state, oral contraceptive use and gynecomastia in men.[77–80] PASH is often incidental and has been reported in up to 23% of breast biopsies.[81] Non-tumorous PASH lacks specific imaging findings but may show non-mass enhancement on MRI.[82,83] In contrast, tumorous (nodular) PASH may mimic fibroadenoma and form a mass.[83,85]

The morphologic features of PASH vary depending on cellularity. Conventional PASH consists of a bland spindle cell proliferation forming anastomosing slit-like empty spaces within dense fibrous interlobular and, less often, intralobular, stroma (Fig. 3 **A-B**). Mitotic activity is absent or exceedingly rare. Not infrequently, associated epithelium has columnar cell change or usual ductal hyperplasia associated with looser perilobular stroma, reminiscent of gynecomastia.[84] Fascicular PASH is more cellular, with coalescence of lesional cells into bundles and fascicles and loss of slit-like spaces. (Fig. 3 **D**) In such cases, the morphologic features may merge with MFB.[13,78,85] Conventional and fascicular PASH can arise in fibroepithelial lesions, most commonly benign PTs.[80,86,87] Indeed, if PASH is identified in a fibroepithelial lesion on core biopsy, excision should be considered to exclude PT. Consistent with the myofibroblastic phenotype and derivation from mammary stroma, the spindle cells of PASH express SMA and CD34, as well as hormone receptors (PR more often than ER), but are negative for endothelial markers and keratins.[77–79]

The most important differential diagnosis is with well-differentiated angiosarcoma (AS), in which neoplastic endothelial cells line anastomosing slit-like spaces.[78] The vascular channels of AS