Differential Diagnosis of Benign Spindle Cell Lesions

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KEYWORDS

• Breast • Benign tumors • Spindle cells • Differential diagnosis • Immunohistochemistry

ABSTRACT

Spindle cell lesions of the breast cover a wide spectrum of diseases ranging from reactive tumor-like lesions to high-grade malignant tumors. The recognition of the benign spindle cell tumor-like lesions (nodular fasciitis; reactive spindle cell nodule after biopsy, inflammatory pseudotumor/inflammatory myofibroblastic tumor; fascicular variant of pseudoangiomatous stromal hyperplasia) and tumors (myofibroblastoma, benign fibroblastic spindle cell tumor, leiomyoma, schwannoma, spindle cell lipoma, solitary fibrous tumor, myxoma) is crucial to avoid confusion with morphologically similar but more aggressive bland-appearing spindle cell tumors, such as desmoid-type fibromatosis, low-grade (fibromatosis-like) spindle cell carcinoma, low-grade fibrosarcoma/myofibroblastic sarcoma and dermatofibrosarcoma protuberans.

OVERVIEW

Spindle cell lesions of the breast cover a wide spectrum of diseases ranging from reactive tumor-like lesions to high-grade malignant tumors.[1–6] Although most of the lesions are mesenchymal in nature, there is the possibility that some *carcinomas* may be composed exclusively/predominantly of neoplastic cells that adopt spindled rather than epithelioid morphology. A subset of potentially malignant lesions, consisting of bland-looking spindle cells, are closely reminiscent of several benign entities. In this regard it should be emphasized that benign spindle cells lesions are usually underrecognized and can represent potential pitfalls of malignancy, particularly on a small biopsy. The lack of strict diagnostic criteria and expertise in soft tissue pathology are likely the main reasons that, in the past, have led some investigators to use different names for the same lesion or, conversely, to collect different lesions under the same term.

Benign spindle cell lesions of the breast encompass a wide and heterogeneous spectrum of fibroblastic and myofibroblastic tumor-like or tumor entities.[7,8] By definition, they should be composed exclusively of spindle cells (pure spindle cell lesions), with no mixed epithelial component.[7,8] However, pathologists should be aware of the possibility that normal epithelial mammary structures can be entrapped or displaced within some lesions, particularly in pseudoangiomatous stromal hyperplasia and reactive spindle cell nodule/exuberant scar. Similarly, mature adipose tissue admixed with the proliferating spindle cell component may be part of the lesion (see lipomatous myofibroblastoma and benign fibroblastic spindle cell tumor) and should not be confused with entrapped fat tissue from the adjacent breast parenchyma as seen in desmoid-type fibromatosis, low-grade (fibromatosis-like)

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spindle cell carcinoma and dermatofibrosarcoma protuberans.

To better understand the different morphologies of the lesions, pathologists should keep in mind that myofibroblasts are modified fibroblasts with the capability to contract, and that play a crucial role in both wound healing and tissue remodeling. Myofibroblasts, plumper than fibroblasts, show more abundant pale to slightly eosinophilic cytoplasm, and ovoid nuclei with evident small nucleoli. Although myofibroblasts are usually spindle-shaped cells, their morphology is highly variable, ranging from round, stellate, epithelioid to ganglion-like cells. Immunohistochemically they are variably stained with α-smooth muscle actin, desmin, and calponin. The distinction of each single entity among the benign spindle cell lesions of the breast may be challenging, especially in core needle biopsies. This is mainly because there is overlap among all these mesenchymal proliferations, as they are composed of relatively bland-looking spindle cells with the morphologic features of myofibroblasts, arranged haphazardly, or in short fascicles or with a storiform growth pattern. Similarly, the stroma is usually fibrotic but myxoid changes are not uncommon. Although immunohistochemistry is helpful in revealing the myofibroblastic nature of the cells, it cannot distinguish with certainty the different lesions, as they frequently stain with α-smooth muscle actin and stain variably with desmin. Although there has been progress in cytogenetics and molecular biology, the difficulty in defining, at least in some lesions, the boundaries between a reactive versus a neoplastic process (see inflammatory pseudotumor/inflammatory myofibroblastic tumor) still remains. The differential diagnosis between benign spindle cell lesions and the bland-looking spindle cell tumors with potentially aggressive behavior is crucial to avoid overtreatment of patients. Although immunohistochemistry is mandatory in ruling out low-grade (fibromatosis-like) spindle cell carcinoma (absence of epithelial markers and p63), its role is limited when dealing with desmoid-type fibromatosis and low-grade myofibroblastic sarcoma.

For a practical diagnostic approach, benign spindle cell lesions of the breast parenchyma can be divided into 2 main categories: reactive and neoplastic lesions (**Table 1**). The former is represented by nodular fasciitis, reactive spindle cell nodule/exuberant scar following biopsy/fine-needle aspiration, inflammatory pseudotumor/inflammatory myofibroblastic tumor, and pseudoangiomatous stromal hyperplasia. Among the tumors, the most common is myofibroblastoma, followed by benign fibroblastic spindle cell tumor, leiomyoma, schwannoma/neurofibroma, solitary fibrous tumor, spindle cell lipoma, and myxoma. Both reactive and neoplastic benign lesions need to be distinguished from locally aggressive or potentially metastatic bland-looking spindle cell tumors, including desmoid-type fibromatosis, low-grade (fibromatosis-like) spindle cell carcinoma, low-grade myofibroblastic sarcoma, low-grade fibrosarcoma, and dermatofibrosarcoma protuberans (see **Table 1**).

This review focuses on the key diagnostic features of the most common benign spindle cell lesions of the breast to achieve a nosologically correct classification. The main clinicopathologic features, highlighting the differences between the various entities, are summarized in tables (See **Tables 1–3**). Representative illustrations of the most common lesions are also provided. Awareness by pathologists of the diversity of morphologic and immunohistochemical features exhibited by the most common benign spindle cell lesions of the breast, including their

Table 1
Benign spindle cell lesions of the breast

Classification	Differential Diagnosis
Tumor-like lesions • Nodular fasciitis • Reactive spindle cell nodule/exuberant scar • Inflammatory pseudotumor/inflammatory myofibroblastic tumor • Pseudoangiomatous stromal hyperplasia (fascicular variant)	• Desmoid-type fibromatosis • Low-grade (fibromatosis-like) spindle cell carcinoma • Low-grade myofibroblastic sarcoma • Low-grade fibrosarcoma • Dermatofibrosarcoma protuberans
Tumor lesions Specific to mammary stroma • Myofibroblastoma • Benign fibroblastic spindle cell tumor Not specific to mammary stroma • Leiomyoma • Schwannoma/neurofibroma • Solitary fibrous tumor • Spindle cell lipoma • Myxoma	