Review

Review of Myofibroblastoma of Breast and Its Most Common Mimickers

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Myofibroblastoma (MFB) is characterized as a benign stromal neoplasm composed of uniform, bland-looking spindle cells that are often arranged in fascicles separated by thick band of collagenous stroma. Variable cellularity is common. Immunohistochemically, the spindle cells are positive for CD34, vimentin, BCL-2, ER, PR, focally positive for smooth muscle actin and negative for cytokeratin, S-100 and CD117. Although classic MFB is typically a bland-looking spindle cell tumor, some unusual morphologic variants may show worrisome malignant-looking cells. Recognition of MFB variants and its wide variety of mimickers is very important for pathologists to arrive at the correct diagnosis, and avoid misdiagnosis of malignancy.

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Key Words*: breast, myofibroblastoma, solitary fibrous tumor, spindle cell lipoma, metaplastic spindle cell carcinoma, myofibroblastic sarcoma, Phyllodes tumor*

INTRODUCTION

Myofibroblastoma of breast (MFB) is a rare benign spindle cell tumor of mammary stroma composed of myofibroblasts. This entity was first described in 1981 by Toker et al. as a benign spindle cell tumor.[1] The term "myofibroblastoma" was established by Wargotz et al in 1987.[2] The original report demonstrated that MFB had a male predominance.[2] However, later studies illustrated that it can occur in both sexes,[3,4] mainly in older men and postmenopausal women.[5] For the past two decades, the incidence of MFB appears to be increasing, most likely due to increased mammographic screening.[6,7] MFB may derive from CD34+/vimentin+ fibroblasts of mammary stroma with variable numbers of MFB cells undergoing smooth muscle, cartilaginous, or osseous differentiation,[3,8,46] which demonstrates its capability of multidirectional mesenchymal differentiation. There is increasing evidence that MFB encompasses a wide variety in morphology,[2,3,4] including cellular,[9] epithelioid,[10] lipomatous,[11] myxoid,[12,13] and infiltrative variants.[9,4,15] In some cases, two or more variants can coexist within the same tumor.[1,4] Due to the broad morphologic spectrum of MFB, this uncommon benign tumor may mimic a wide variety of both benign and malignant breast spindle cell lesions, causing a potential diagnostic pitfall. In this review, MFB variants and its major mimickers will be discussed.

CLASSIC MFB AND ITS MORPHOLOGIC VARIANTS

Clinically, MFB presents as a solitary, painless, firm, freely mobile nodule that usually grows slowly. In most cases, mammography shows well circumscribed and dis-homogeneously solid mass devoid of microcalcifications.[4] Grossly, MFB reveals a well circumscribed nodule or a multiloculated mass, with most measuring less than 4 cm in diameter (2.3 cm on average, ranging from 1 to 4 cm).[16] In rare cases, it can be large (> 10 cm).[17] The cut section reveals a homogeneous, buldging pink to gray whirled surface. Some cases may show lipomatous or mucoid apperance.[12,13] Necrosis and hemorrhage are usually not evident.

Histopathologically, the **classic type** MFB is an unencapsulated tumor, composed of uniform, bland looking spindle cells haphazardly arranged in short fascicles, separated by thick bands of hyalinized collagen bundles and devoid of mammary ducts and lobules. The spindle cells have abundant eosinophilic cytoplasm, round or oval nucleus with 1-2 small nucleoli. Mitotic activity is absent or rare when present (≤2/10 HPF). Prominent mast cells can be seen in tumor stroma, but lymphoplasmacytic infiltration is virtually always absent (**Figure 1**).[1,4,18] The **cellular variant** is characterized by highly cellular, cohesive groups of spindle-shaped neoplastic myofibroblasts with a random arrangement. The nuclei have fine, uniformly distributed chromatin with inconspicuous nucleoli, and mild nuclear atypia may be present.[9] Compared to classic type MFB, the cells have scant cytoplasm and the tumor has ill-defined infiltrative borders, with the typical broad collagen bands being present only focally in the tumor.[9,19] The **epithelioid variant** is defined by tumors composed predominantly (>50%) of epithelioid cells.[20,21] Histologically, the cells are characterized by round to oval neoplastic cells with eccentrically located nuclei and a mild to moderate degree of nuclear atypia, small conspicuous nucleoli, abundant eosinophilic cytoplasm, and rare mitotic figures (≤ 2/ 10

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HPF). Epithelioid cells can be arranged in different growth patterns, including alveolar, single-cell, single-file, solid, and fascicular patterns.[4,14,20,22] This variant can mimic invasive breast carcinoma, especially when the epithelioid cells are arranged in a single file, linear growth pattern.[1,4] The **myxoid variant** is characterized by the spindle cells embedded in the predominantly myxoid stroma.[12,13,14] Some small blood vessels and thin bands of collagen can be present. The cells have oval nuclei with evenly dispersed chromatin, inconspicuous nucleoli, and abundant eosinophilic cytoplasm. Mitotic activity and necrosis are not evident. However, cases of the myxoid variant with prominent nuclear atypia have been reported.[13] The **lipomatous variant** is defined by a tumor with stroma composed of predominantly (> 75% of the entire neoplasm) of adipose tissue.[11,22] This variant is composed almost exclusively of mature adipocytes, uniform in size and shape, with no prominent nuclear pleomorphism. Lipoblasts should not be present. The remaining tumor cells consist of spindly to oval shaped cells with morphological features typical of classic MFB. Some cells may show a mild to moderate nuclear atypia. The two components are admixed to give a fingerlike growth pattern,[11] making it a great mimicker for other benign spindle cell tumors, such as fibromatosis, nodular fasiitis, spindle cell lipoma, and also for low grade malignant spindle cell neoplasms, such as spindle cell liposarcoma and metaplastic spindle cell carcinoma. The **infiltrating variant** is characterized by an invasive growth pattern, with entrapment of fat, mammary ducts and lobules,[9,14,15] mimicking fibromatosis.

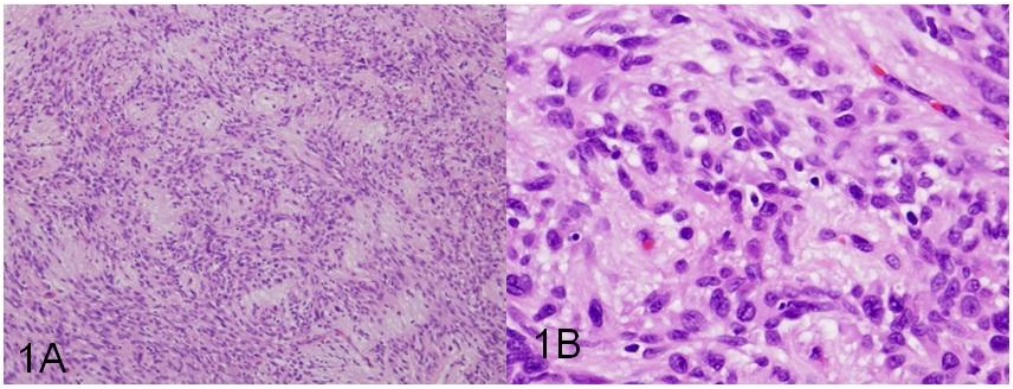

Figure 1. Morphological features of classic MFB.
1A. Haphazardly arranged spindle cells in short fascicles, separated by thick bands of hyalinized collagen bundles (hematoxylin-eosin stain: original magnification × 100).
1B. The spindle cells have abundant eosinophilic cytoplasm, round or oval nucleus with 1-2 small nucleoli. Mitotic activity is absent. Mast cells are present (hematoxylin-eosin stain: original magnification × 400).

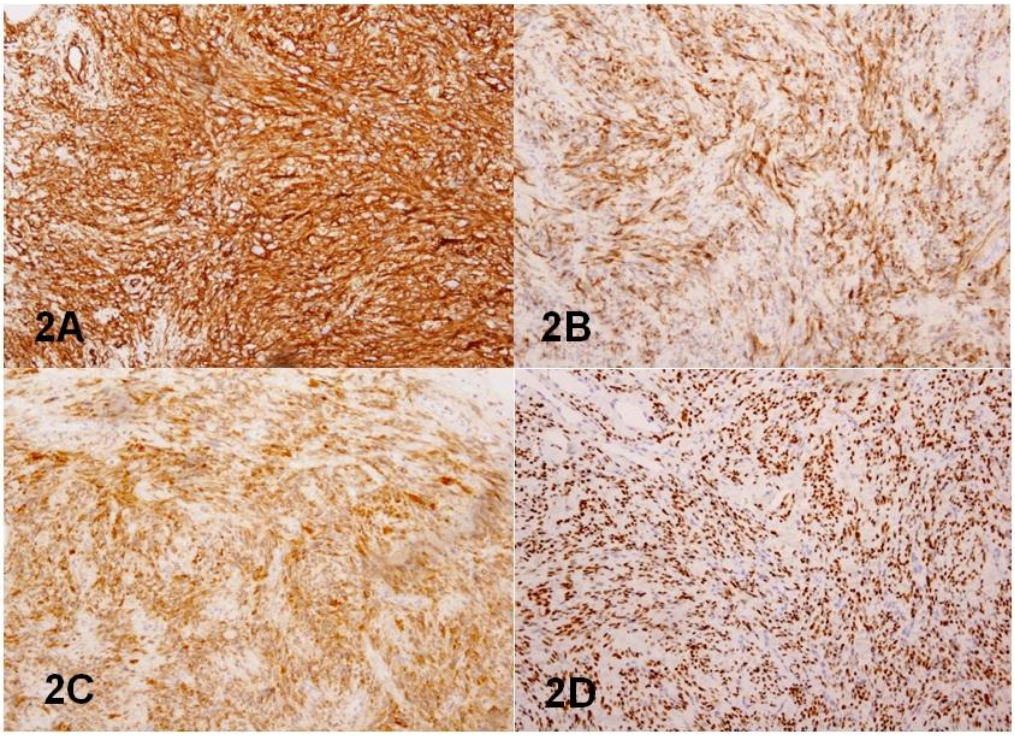

Figure 2. Immunohistochemical features of MFB. The spindle cells show strong positivity for CD34 **(2A)** and vimentin (not shown), variable expression for desmin (**2B**), Bcl-2 (**2C**), and smooth muscle actin (not shown), most cases show ER (**2D**), PR (not shown) and androgen receptor (not shown) reactivity.

Immunohistochemically, the neoplastic cells of MFB are typically positive for vimentin and CD34,[1,4,8,15,19,23] with variable immunoreactivity to SMA, desmin, bcl-2 and CD99. Some cases show focal expression of h-caldesmon in scattered cells, which indicates the mammary fibroblasts are capable of undergoing smooth muscle differentiation. Most MFB are positive for ER, PR and androgen receptors (**Figure 2**).[24,25,26] However, cytokeratins, EMA, S100, HMB-45, and CD117 are consistently negative.

Cytogenetic study by Fluorescence in situ hybridization (FISH) analysis revealed losses of RB/13q14 and FKHR/13q14 loci within tumor cells in several MFB cases,[27] and a partial loss of 16q has also been reported in one MFB case.[28] Interestingly, rearrangements affecting 13q and 16q occur typically in spindle cell lipomas,[27,28,29] providing a strong genetic link between MFB and spindle cell lipoma.

DIFFERENTIAL DIAGNOSIS

The lack of marked cytologic atypia, along with the absence of necrosis and mitotic activity in the classic type of MFB help to verify its benign nature. However, the diverse and complicated morphologic variants of MFB lead to diagnostic challenges for pathologists. A wide variety of benign and malignant breast spindle cell lesions should be considered in the differential diagnoses.

Solitary Fibrous Tumor

Solitary fibrous tumor (SFT) is a benign soft tissue neoplasm that may occur in almost every site in the body. However, only rare such cases were reported in breast.[30] Based on WHO histological typing of soft tissue tumors, SFT consists of spindled fibroblastic cells haphazardly arranged around an elaborate hemangiopericytoma-like vasculature.[31] The cellularity varies within individual tumors, and the hypocellular background stroma can have a myxoid fibrous appearance. Immunohistochemical features are characterized by strong positive staining for CD34 and vimentin, most cases also show bcl-2 positivity.[32] Desmin positivity is infrequent. A subset of tumors has variable immunoreactivity for CD99, SMA, and EMA. Cytogenetic studies of SFT reveal that no consistent abnormality has been detected.[34] There is a great degree of overlap in histologic features and immunohistochemical reactivity between SFT and MFB.[33] Distinguishing features include smooth muscle differentiation, characteristically broad collagen bundles and lack of a prominent hemangiopericytoma-like pattern that are typically seen in MFB and absent in SFT. In addition, cytogenetic abnormalities such as 13q and 16q rearrangements have been demonstrated in MFB[27,28] but not in SFT.

Benign Spindle Cell Lipoma

Benign spindle cell lipoma[35] is characterized by a mixture of mature fat cells and collagen-forming spindle cells with varying degrees of myxoid change. It can greatly mimic MFB, especially the lipomatous variant. Both entities even share some cytogenetic abnormalities.[27,28,29] However, although breast spindle cell lipomas are typically immunoreactive to CD34 and vimentin, they are not reactive to desmin or smooth muscle actin, which can be helpful in differentiating these two entities.

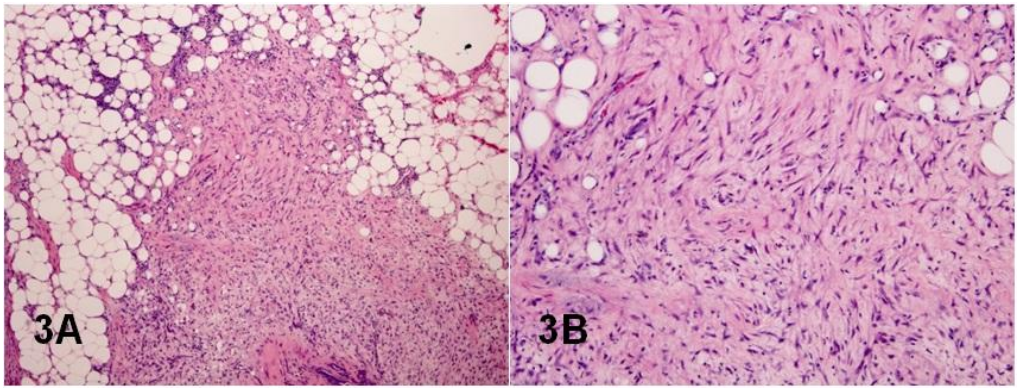

Figure 3. Morphological features of metaplastic spindle cell carcinoma of breast. **3A.** Tumor infiltrates the breast tissue with extension into the adjacent fat (hematoxylin-eosin: original magnification × 40). **3B**. Tumor shows a moderately cellular spindle cell proliferation without appreciable cytological atypia (hematoxylin-eosin stain: original magnification × 100).

Metaplastic Spindle Cell Carcinoma

Metaplastic spindle cell carcinoma is a rare breast tumor. Histologically, its dominant component is sheets of spindle shaped cells and/or sarcomatoid elements. Spindle cell carcinoma can be histologically bland and show minimal cytological atypia (**Figure 3**). Despite the sarcomatous features, the spindle cells are most likely derived from the epithelial cells of mammary glands. Immunohistochemical studies demonstrate the expression of keratin or p63.[36]

Low Grade Myofibroblastic Sarcoma

Low grade myofibroblastic sarcoma is a rare malignant tumor of myofibroblasts. Histologically, the tumor is characterized by fascicles of spindle cells surrounded by dense collagen, with infiltrative margins. The spindle cells have ill defined, pale or eosinophilic cytoplasm. Pleomorphic nuclei and numerous mitotic figures are commonly encountered. Immunohistochemically, at least one myogenic marker (desmin, alpha smooth muscle actin, muscle specific

actin or calponin) is positive. S100, EMA, h-caldesmon, and ALK are consistently negative.[37] Cytogenetic studies reveal multiple chromosomal imbalances in myofibroblastic sarcoma including gains at 1p11→p36.3, 12p12.2 → p13.2, 5p13.2 → p15.3, and chromosome 22 and loss at 15q25 → q26.2.[38]

Phyllodes Tumor

Phyllodes tumors are rare biphasic lesions that account for less than 3% of fibroepithelial lesions of the breast. The tumor is usually a rapidly growing lesion and occurs in middle aged or elderly patients. Phyllodes tumor can be classfied into benign, borderline (**Figure 4**), and malignant based on the degree of stromal cellularity, stromal cell atypia/pleomorphism, the number of stromal cell mitoses, and the nature of the tumor margin.[39] When an atypical spindle cell lesion is identified in a small core-needle biopsy sample without obvious benign epithelial component, phyllodes tumor should be considered in the differential diagnosis of MFB.

Other entities in the list of differential diagnosis include nodular fasciitis,[40,41] leiomyoma,[42] angiomyolipoma,[43] desmoid-type fibromatosis,[44,45,46] and other low grade sarcomas.[47,48] The morphologic and immunohistochemical features are helpful to differentiate these entities.

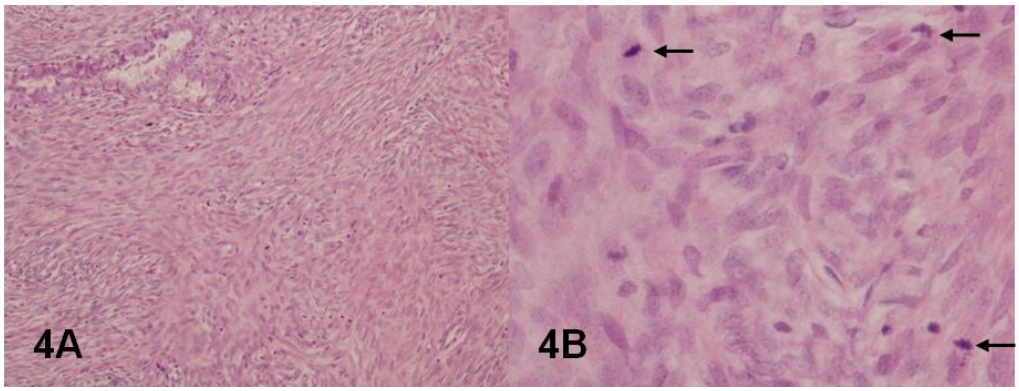

Figure 4. Morphological features of borderline phyllodes tumor of breast.
4A. Tumor shows moderate cellular spindle cell around the glands (hematoxylin-eosin: original magnification × 100).
4B. Tumor shows moderate cellular atypia and intermediate mitotic activity (black arrows) (<10 mitoses/10 HPF) (hematoxylin-eosin stain: original magnification × 400).

CONCLUSION

MFB is a rare benign soft tissue neoplasm. The classic morphologic features show proliferation of bland spindle cells separated by broad collagen bundles. The diagnosis of MFB is generally straightforward in surgical specimens. However, diverse morphologic variants may attribute to an erroneous diagnosis of malignancy or other benign lesions and create a diagnostic dilemma for pathologists. Better recognition of diverse MFB variants and their mimickers is extremely crucial to avoid a misdiagnosis of malignancy. Immunohistochemistry and even cytogenetic analysis may be necessary to arrive at a correct diagnosis in some difficult cases.

CONFLICT OF INTEREST
The authors have no conflict of interest to disclose.

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