Annals of Diagnostic Pathology 48 (2020) 151591

Contents lists available at ScienceDirect

Annals of Diagnostic Pathology

journal homepage: www.elsevier.com/locate/anndiagpath

Original Contribution

Clinicopathological and radiological characterization of myofibroblastoma of breast: A single institutional case review

Mingfei Yan[a,c,*], Phillip Bomeisl[a,c], Hannah Gilmore[a,c], Leah Sieck[b,c], Zachariah Kuchta[d], Aparna Harbhajanka[a,c]

[a] Department of Pathology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA
[b] Department of Radiology, University Hospitals Cleveland Medical Center, Cleveland, OH, USA
[c] Case Western Reserve University, Cleveland, OH, USA
[d] Department of Radiology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

ARTICLE INFO

Keywords:
Breast
Myofibroblastoma
Clinicopathology
Radiology
Differential

ABSTRACT

Myofibroblastoma is a rare type of benign myofibroblastic neoplasm in the breast. It is clinically presented as a well-circumscribed mass, usually small in size (usually less than 4.0 cm), and can mostly be cured by local excision. Rare cases of giant myofibroblastoma greater than 10 cm have been reported, but also follow a benign clinical course. Histologically, breast myofibroblastoma is featured by bland fascicles of spindle cells intermixed with thick hyalinized collagen bundles. Mast cells are frequently found within the stroma. However, a wide spectrum of morphological variants can occur in myofibroblatoma, making its diagnosis challenging sometimes. Differential diagnosis of myofibroblastoma with other spindle cell lesions in the breast, either benign or malignant, is also important in practice. In this study, we collected 15 cases of breast myofibroblastoma diagnosed in our institution during a 20 year period. The sizes of these cases range from 0.4 cm to 35.2 cm (mean is 3.7 cm). To our knowledge, the case of giant breast myofibroblastoma we presented here is the largest one reported to date. The histological examination of the cases show great morphological variations. Besides the classical type, features of cellular, collagenized, palisading, epithelioid, myxoid, myoid, solitary fibrous tumor-like are also identified in the case series. Immunohistochemical staining patterns as well as clinical features of the cases are also summarized and compared. All cases in this study show no recurrence on follow-up. In addition, cases that are important differential diagnosis for breast myofibroblastoma are also studied. Their key histological characteristics are compared with myofibroblastoma, and their immunohistochemical and molecular features are discussed.

1. Introduction

Myofibroblastoma (MFB) is a rare type of benign spindle cell neoplasm in the breast. It is derived from myofibroblasts and are usually seen in older patient population. Breast MFB is mostly well-circumscribed and small in size. Most cases are between 1 and 4 cm in greatest dimensions [1]. Histology of classic MFB is featured by fascicles of bland spindle cells and characteristic hyalinized stromal collagen bundles. Besides, a variety of morphologic variants have also been recognized, such as epithelioid, cellular, infiltrative, lipomatous, fibrous, deciduoid, myxoid, palisaded, etc. Lesional cells of breast MFB show immunoreactivities for myofibroblastic markers, such as Desmin, Smooth Muscle Actin (SMA), and Muscle Specific Actin (MSA) [2]. Besides, most MFB is positive for CD34, BCL-2, Vimentin and hormonal receptors like estrogen receptor (ER), progesterone receptor (PR) and androgen receptor (AR) [2-5]. Though MFB of the breast is a benign tumor and local excision is most likely curable [6], its multiple morphologic variants can overlap with other spindle cell lesions in the breast, either benign or malignant. Therefore, understanding the histology of breast MFB and its common differential diagnosis is essential. In this study, we collected 15 cases of breast MFB diagnosed in our institution in a 20-year period. Clinical and histologic features of the cases are summarized. Multiple morphological variants in the case series are demonstrated and compared. In addition, we collected cases of important differential diagnosis to breast MFB, either benign or malignant, and discussed their key differentiating points with MFB.

* Corresponding author at: Department of Pathology, University Hospitals Cleveland Medical Center, Case Western Reserve University, 10900 Euclid Ave., Cleveland, OH 44106-7288, USA.
E-mail address: Mingfei.Yan@UHhospitals.org (M. Yan).

https://doi.org/10.1016/j.anndiagpath.2020.151591

2. Materials and methods

Between 2001 and 2020, 15 cases of breast myofibroblastoma diagnosed in our institution were selected through natural language search. Slides for both biopsy and resection specimens for each case were reviewed by experienced breast pathologists. Immunohistochemical stains were applied to all the cases to conform the diagnosis. Radiological images and clinical information, including patient's age, BMI, past medical history, and biopsy diagnosis were collected from electrical medical record according to institutional review board guidelines. Histological features, including different subtypes of myofibroblastoma and unusual histological findings, were characterized by our pathologists. Besides, the immunohistochemical staining patterns for a panel of markers were summarized and presented in a table. The staining intensity was categorized into 3 classes: strongly and diffusely positive (++), patchy or weakly positive (+), and negative (−). Each patient was followed up to identify any recurrence of the breast lesion. Besides, cases for differential diagnosis of myofibroblastoma were retrieved from our archive. These cases were also reviewed by our pathologists, and their distinguishing histological features were presented. The key differential points for these cases with myofibroblastoma, including histological, immunohistochemical and molecular features, were also discussed and summarized.

3. Clinical and radiological and histological features

We collected 15 cases of breast MFB diagnosed in our institution from 2001 to 2020 (Table 1), in which 20% (3/15) occurred in male and 80% (12/15) in female. Among the 15 cases, 40% (6/15) occur in the left breast, while 60% (9/15) in right breast. The mean patient age at time of diagnosis is 65 year-old (ranging from 32 to 79 year-old). Previous reports have shown rare cases of giant breast MFB, with sizes ranging from 10 to 18 cm [7-10]. Here, we identified one case with unusually big size of 35.2 cm. Overall, the mean size in our series is 3.7 cm (ranging from 0.4 to 35.2 cm). Out of the 15 cases, 2 patients had concurrent invasive ductal carcinoma in the same breast. Concurrent neoplasms seen in other patients include lung solitary fibrous tumor, endometrial carcinoma, papillary thyroid carcinoma, and Warthin's tumor. Four patients have a family history of breast cancer.

The typical imaging appearance of breast MFB is a well-circumscribed, gently lobulated mass with macroscopic fat and variable density on mammography. Breast MFB is usually between 1 and 2 cm in size although it can rarely present as a giant mass (> 10 cm). On mammography, most cases show a round to oval circumscribed mass without associated calcifications (Fig. 1A). The giant breast MFB showed a hyperdense mass with dystrophic calcifications that occupies nearly the entirety of the breast (Fig. 1B). One case has concomitant invasive carcinoma and breast MFB in the same breast (Fig. 1C). Mammographically, the invasive carcinoma is an irregular, hyperdense mass with spiculations. In contrast, the breast MFB is a circumscribed isodense mass.

Breast MFB demonstrates similar benign imaging findings on ultrasound. All of our cases demonstrated a parallel, circumscribed, heterogeneous or hypoechoic mass with variable posterior features, soft elastographic features and mild internal vascularity (Fig. 1D). Posterior features, if present, are generally posterior acoustic shadowing secondary to acoustic impedence caused by the increased internal cellular density of the mass relative to the surrounding normal fat lobules and fibroglandular tissue. The vascularity of breast MFB is reported in the literature as predominantly peripheral vessels, although our case series had multiple MFB that demonstrated mild internal vascularity on color Doppler sonography, which is considered a benign sonographic finding.

Furthermore, the two cases of MFB that were detected by MRI were circumscribed enhancing masses. Both cases of MFB on MRI has macroscopic fat signal within the masses. One demonstrated heterogeneous internal enhancement with washout delayed enhancement kinetics,

Table 1
Clinical features and immunohistochemical staining patterns of breast myofibroblastoma cases.

No.	Age (yr)/sex	Side	Size (cm)	Breast cancer FHx	Concurrent neoplasm	BMI	Biopsy diagnosis	CD34	Desmin	Bcl2	ER	PR	SMA	MSA	Follow-up (yr)	Recurrence
1	68/F	L	1.5	No	None	40.23	Spindle cell neoplasm most consistent with myofibroblastoma	++	++	++	++	++	−		6	No
2	78/M	R	1.6	No	None	26.58	Myofibroblastoma	++	++	++	++	++	+		4	No
3	79/F	L	1.0	No	SFT in right lung	34.23	Spindle cell neoplasm suggestive of myofibroblastoma	++	++					−	13	No
4	70/F	R	1.5	No	Endometrial cancer	32.24	N/A		++					++	11	No
5	48/F	R	1.4	Yes	None	25.96	Spindle cell lesion of breast suggestive of myofibroblastic origin	++	+	++			++	++	12	No
6	71/F	L	1.5	No	IDC in left breast, PTC	36.99	Myofibroblastoma	+	+				−		11	No
7	62/F	R	35.2	No	None	23.37	Spindle cell proliferation suggestive of myofibroblastoma	++	++	++		++	−		5	No
8	32/F	R	2.1	Yes	None	38.74	Benign spindle cell neoplasm with smooth muscle differentiation	++	++				++		2	No
9	67/F	R	0.9	No	IDC in right breast	30.42	Myofibroblastoma			++		++			1	No
10	64/F	R	1.2	Yes	None	47.37	Low grade spindle cell neoplasm consistent with myofibroblastoma	+	++	++	++			+	2	No
11	78/F	L	0.8	No	None	29.52	Benign spindle cell lesion consistent with myofibroblastoma	++					++		11	No
12	50/F	R	0.8	No	None	32.99	Myofibroblastoma		+					+	19	No
13	65/M	R	0.4	Yes	Warthin's tumor	51.1	Spindle cell proliferation consistent with myofibroblastoma			++	++	−			1	No
14	74/M	L	4.1	No	None	23.85	Myofibroblastoma	+	++	++	++	++			1	No
15	69/F	L	1.5	No	None	54.38	Low grade spindle cell lesion favor myofibroblastoma	++	++	++		++		++	0.5	No

Note: F: Female. M: Male. R: Right. L: Left. BMI: Body mass index. FHx: Family history. SFT: Solitary fibrous tumor. IDC: Invasive ductal carcinoma. N/A: Not available. −: Negative. +: Patchy or weakly positive. ++: Strongly or diffusely positive.

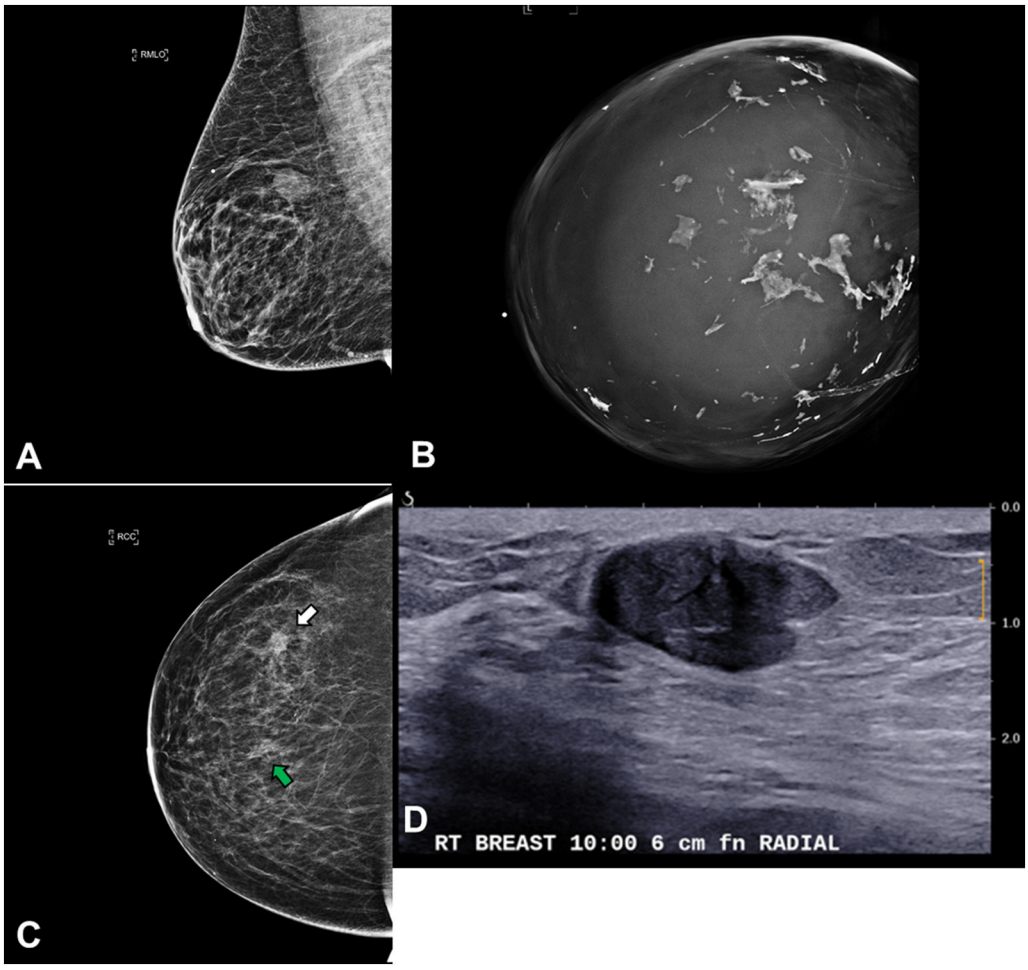

Fig. 1. Imaging features of breast myofibroblastoma. (A) Typical mammography for MFB showing a well circumscribed isodense mass. (B) Mammography for giant breast MFB showing a hyperdense mass with dystrophic calcifications that occupies nearly the entirety of the breast. (C) Mammography revealed concurrent invasive ductal carcinoma (white arrow) and MFB (green arrow). The margins of MFB were less well-circumscribed than (A) and (B), due to overlying fibroglandular tissue and lower density compared to the adjacent carcinoma. (D) Ultrasound of MFB demonstrates a well-circumscribed hypoechoic mass. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

which are suspicious MRI characteristics. The incidentally detected MRI mass had rim enhancement with plateau delayed enhancement kinetics, which are more benign type MRI characteristics.

The gross examination of breast MFB usually show a circumscribed, unencapsulated, round to oval mass. The cut surface is firm, white to tan, and is either smooth or loculated. The giant MFB case in our series shows a well-circumscribed tan-white mass with multiple round nodules on cut surfaces (Fig. 2).

The typical histology of breast MFB is featured by short, intersecting fascicles of bland spindle myofibroblastic cells. Thick, hyalinized collagen bundles between the spindle cells can characteristically separate the spindle cell into groups or clusters (Fig. 3A). Mitotic figure is absent or rare. Mast cells are frequently found in between the spindle cells (Fig. 3B). The borders of breast MFB is circumscribed but not encapsulated (Fig. 3C). MFB usually form an expansile solid mass with pushing borders, and does not entrap breast epithelium. However, one case shows an unusual pattern of breast epithelial entrapment on the periphery of the mass (Fig. 3D), though no entrapment is seen towards the center of the lesion.

Breast MFB has variable cellularities. Compared to the classic type (Fig. 3A), one case shows significantly higher cellularity (Fig. 3E) with more plump and vesicular nuclei. The cells are arranged in long

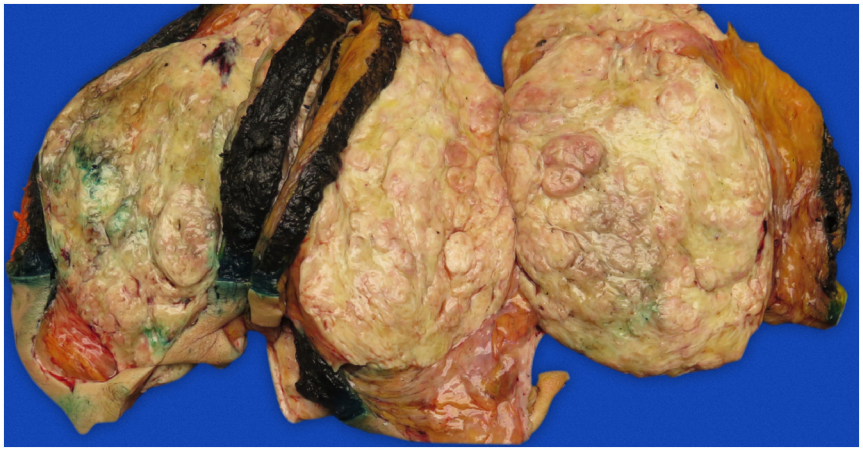

Fig. 2. Gross presentation of a giant breast myofibroblastoma. The gross image for giant MFB. The breast parenchyma is almost entirely replaced by a well-circumscribed mass. The remaining breast tissue is pushed to the periphery. The mass is homogeneously tan, with multiple well-defined nodules within the main mass. No hemorrhage or necrosis is identified grossly in the specimen.

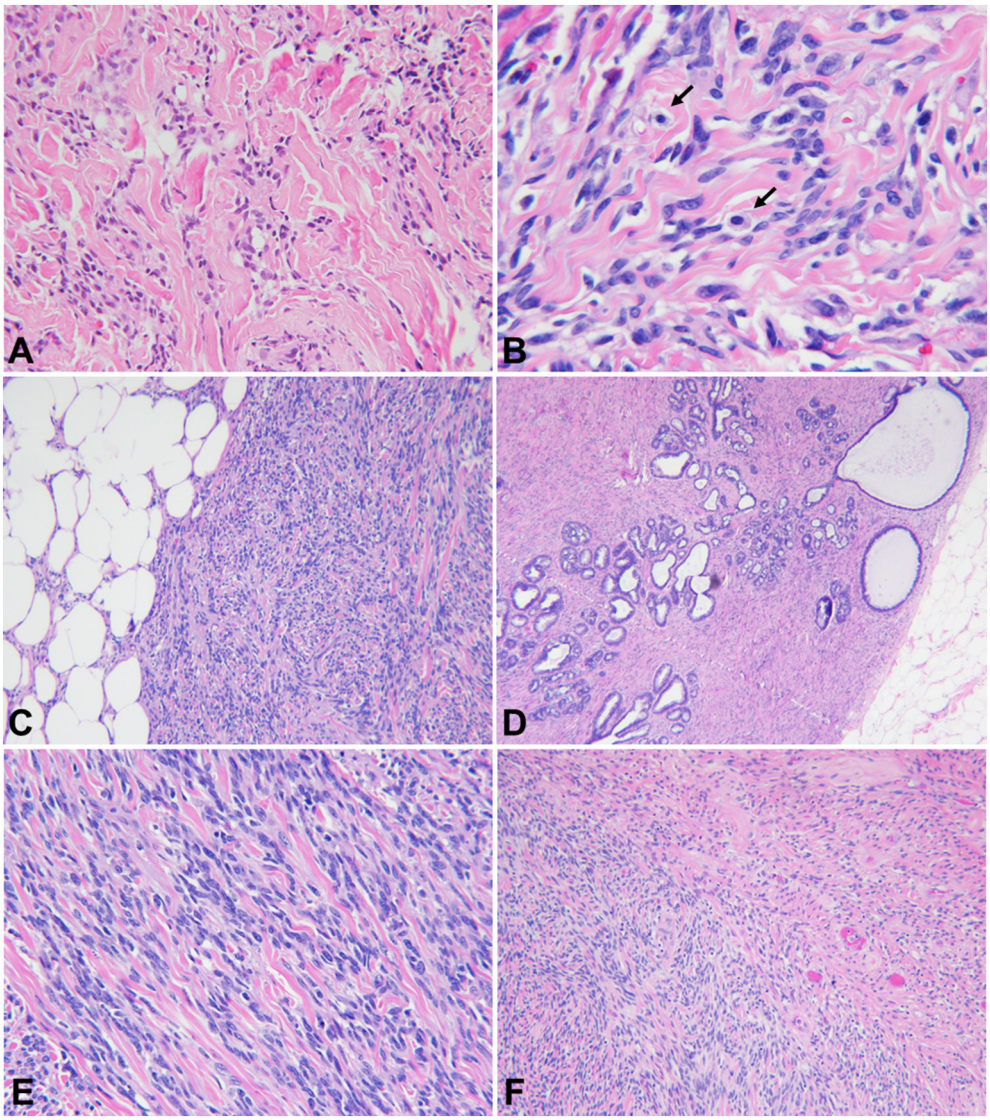

Fig. 3. Histological features of breast myofibroblastoma. (A) Classical morphology of MFB. Short fascicles of spindle cells are intermixed with thick stromal collagen. (B) Stromal mast cells (arrow). (C) Well-circumscribed unencapsulated border of MFB. (D) Peripheral entrapment of breast ducts and lobules. (E) Higher cellularity and plump and vesicular nuclei as compared to classical morphology in (A). (F) Sharp transition between hypercellular area and lower cellular area. (G) Aea of homogenously collagenized stroma and paucicellularity. (H) Focal area showing palisaded pattern of spindle cells, resembling schwannoma. (I) Area with loose collagenized stroma. (J) Focal area of neutrophil aggregates. (K) Perivascular aggregates of lymphocytes. (L) Mature adipose tissue within MFB. (M) Areas with staghorn vessels, resembling solitary fibrous tumor. (N) Myoid cells with abundant eosinophilic cytoplasm and more plump nuclei. (O) Myxoid changes in the stroma with scant myofibroblasts. The thick collagen bundles are characteristic for MFB. (P) Single files of epithelioid cells infiltrating between the collagenized stroma. (Q) Area showing loose cluster of epithelioid cells. (R) Area with small lacunas in a collagenized background, representing the osseous heterologous differentiation of MFB. (Hematoxylin-eosin, original magnification x20 [A, E, G, I, J, K, L, N, O, P, Q, R], original magnification x10 [C, D, F, H, M], original magnification x40 [B]).

fascicles, and the prominent stromal collagen bundles are characteristic. The cellular variant MFB is characterized by densely arranged spindle cells. Herringbone or storiform patterns are not uncommon in this variant, and focal cellular atypia is also allowed [11]. However, no necrosis or hemorrhage should be seen in cellular MFB. One case also demonstrates the sharp transition from hypercellular area to more hypocellular area (Fig. 3F). In comparison to cellular MFB, some cases show significant paucicellularity and highly collagenized stroma. Instead of bundles of hyalinized collagen, the collagenous stroma in one case is more homogenous and wavy (Fig. 3G). This morphologic feature characterizes the collagenized/fibrous variant of MFB can resemble pseudoangiomatous stromal hyperplasia (PASH) [12], which is an important and common differential diagnosis of MFB especially in biopsy specimens.

The case of giant MFB in our series show great variations in histologic morphologies. Besides the classic morphology, areas with hypercellularity (Fig. 3F), palisading cells (palisaded variant) (Fig. 3H), collagenized stroma, and loose stroma (Fig. 3I) are also identified. Interestingly, focal aggregates of neutrophils is seen in this case (Fig. 3J). Since no such finding was reported before, we are not clear if it could be related to the large size and potential necrosis for this case. In another case, perivascular aggregates of lymphocytes is identified (Fig. 3K). Therefore, inflammatory infiltration in breast MFB is not confined to mast cells, but can also comprise neutrophils and lymphocytes at least focally in some cases.

Breast MFB can contain various amount of mature adipose tissue, as seen in one of the cases (Fig. 3L). Those with more than 75% of adipose tissue are named lipomatous MFB [13]. This variant shows intimate mixture of both spindle cells and adipose tissue, which can give an impression of infiltration. Therefore lipomatous MFB can mimic other

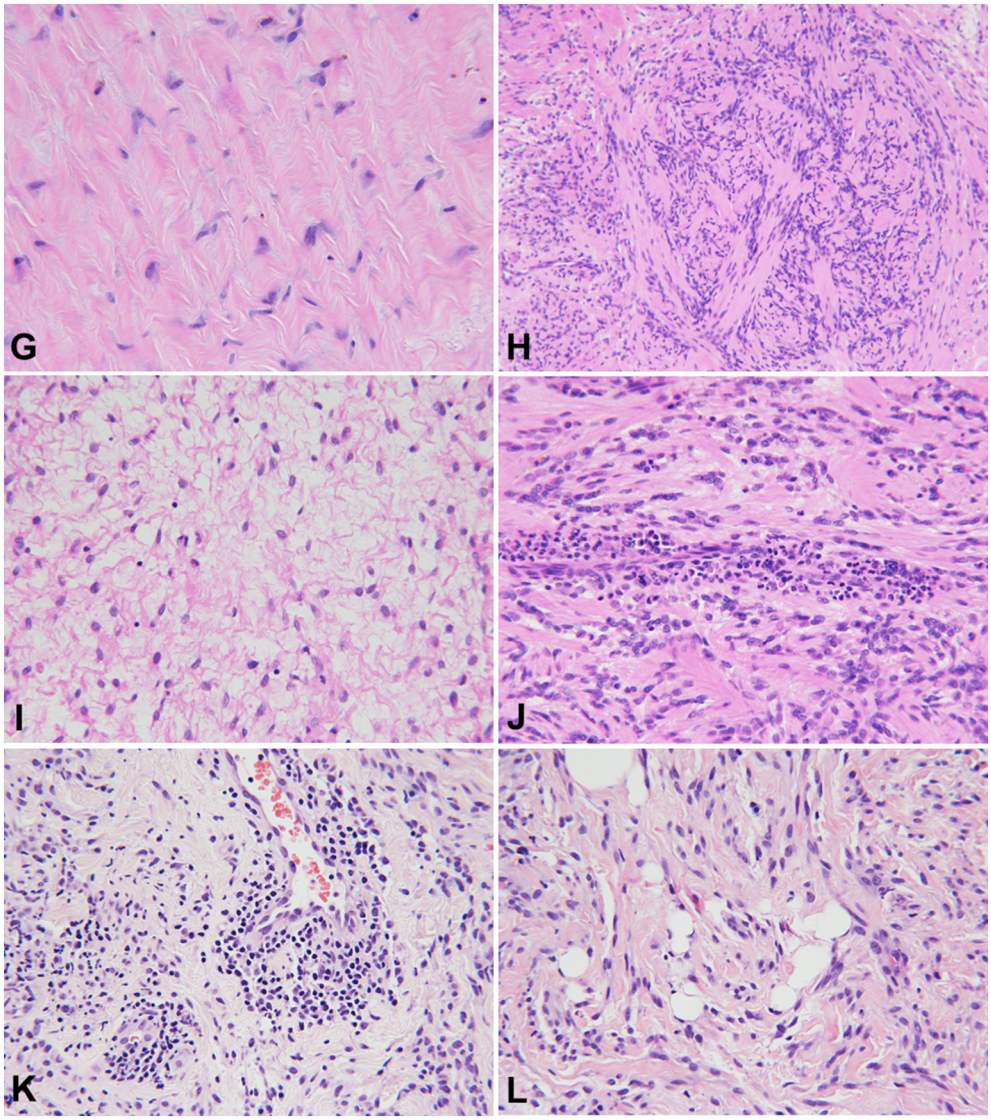

Fig. 3. (*continued*)

more aggressive or infiltrative lesions like metaplastic spindle cell carcinoma, spindle cell liposarcoma, fibromatosis, etc. [13]. Another important differential diagnosis for lipomatous MFB is spindle cell lipoma, which shares same genetic alterations with lipomatous MFB [14]. These two entities may thus represent different variants of a same pathologic process.

One of the cases show prominent staghorn vessels with perivascular hyalinization, resembling solitary fibrous tumor (SFT) (Fig. 3M). Though rare, this morphology was also reported by others [15]. Both MFB and SFT belong to fibroblastic/myofibroblastic mesenchymal neoplasms, and both share similar immunohistochemical reactivities to CD34, SMA and Vimentin [16]. Mixed features of both SFT and MFB can be found in some reported cases of breast spindle lesions [17]. Therefore, though SFT is rarely found in the breast, it can be an important differential diagnosis to MFB morphologically in certain cases. However, the utilization of STAT6 immunostaining can help to differentiate the two in challenging cases [18].

Another morphologic variant we observed in one of the cases is the presence of myoid cells, or cells with smooth muscle cell differentiation. These cells are characterized by plump eosinophilic cytoplasm, and their nuclei also appear to be more plump and oval-shaped (Fig. 3N). This represents the morphologic features of leiomyomatous variant MFB, which is characterized by smooth muscle differentiation of myofibroblasts and cigar-shaped elongated nuclei [19]. This variant shares the same immunohistochemical patterns with classic MFB, with the exception that H-caldesmon can be positive in some cases [20]. Another case shows focal myxoid change with sparse spindle cells (Fig. 3O). If the myxoid change is diffuse across the lesion, the term myxoid variant MFB is used. Myxoid MFB with atypical cells have also been reported [21,22]. Differential diagnosis of this variant include other myxoid neoplasm, like low grade fibromxyoid sarcoma which has been reported in the breast [23].

Epithelioid variant is another important morphologic variant for breast MFB. As seen in one of the cases, the neoplastic cells are rounded rather than spindle, have scant cytoplasm, and form single files infiltrating between the stroma (Fig. 3P) or form loose clusters (Fig. 3Q). Mild variations in nuclear size can be noted. The diagnosis of this variant requires the presence of such epithelioid cells in more than 50% of the area [24]. The epithelioid variant can show nuclear atypia, and closely resembles invasive lobular carcinoma of the breast especially in small biopsy specimens [25,26]. However, the presence of collagen bundles and immunohistochemical negativity for cytokeratin can easily distinguish the two apart.

Finally, one case shows focal area with osseous morphology (Fig. 3R), which is characterized by cells in small lacunas with a collagenized stroma. The osseous or cartilaginous components represent

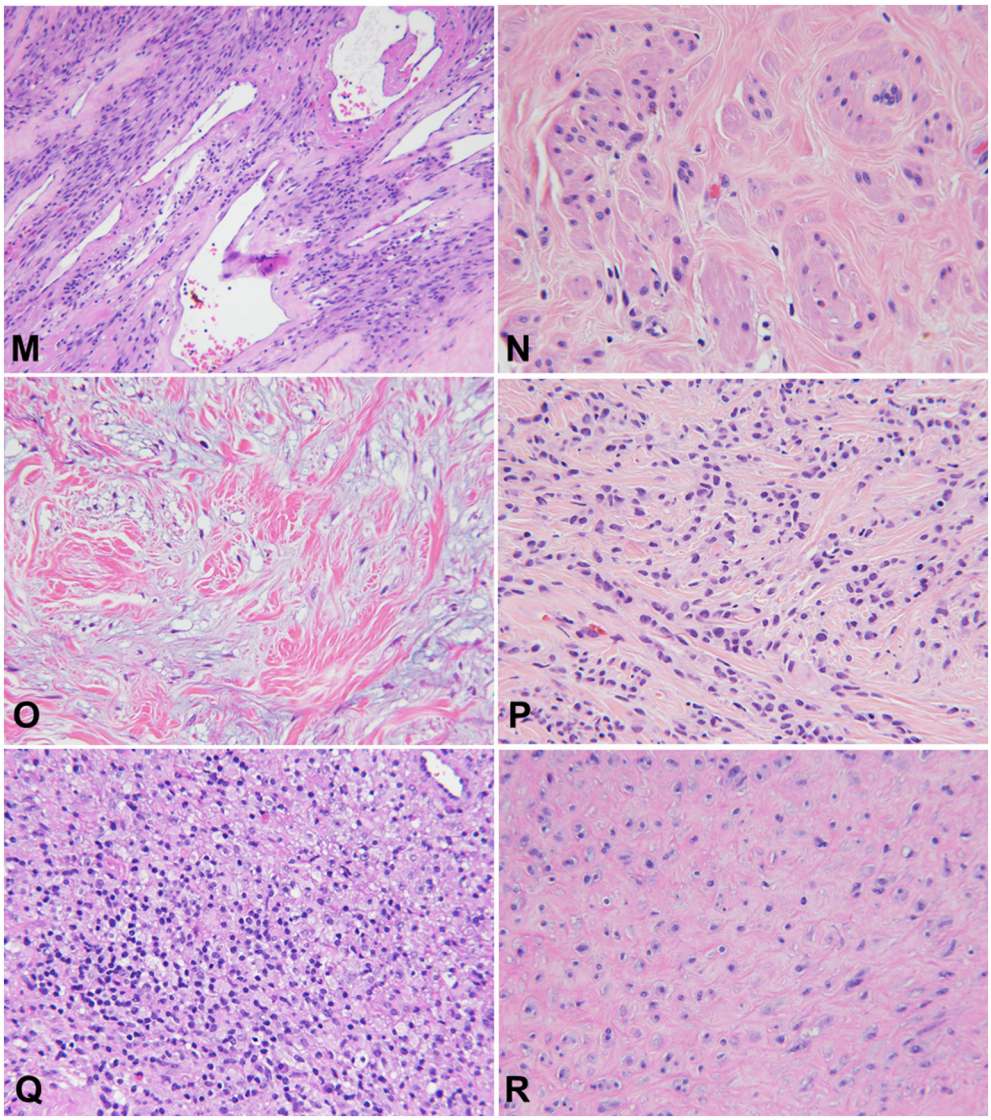

Fig. 3. (*continued*)

the heterologous mesenchymal differentiation. Though not specific, it can be an distinguishing feature for MFB if identified [27]. Similar findings can also be found in metaplastic breast carcinoma, but its differential diagnosis with MFB is usually straightforward by identifying epithelial components, high grade nuclear features and invasive morphology [28].

Though not identified in our cases, other morphologic variants have also been reported for breast MFB. For example, deciduoid-like MFB is a variant with round to oval or polygonal cells, and abundant eosinophilic glassy cytoplasm [29]. The nuclei are large and vesicular with prominent nucleoli. The differential diagnosis for this variant include apocrine carcinoma, rhabdomyosarcoma, epithelioid leiomyoma, melanoma, etc. The infiltrating variant refers to cases with extensive invasive growth pattern into adipose tissue, resembling fibromatosis or carcinoma [30-32]. The lipomatous variant can also produce an pseudo-invasive growth pattern. However, invasion around normal breast epithelium is uncommon in MFB, though it can be observed in rare cases at the periphery of the lesion (Fig. 3D).

Multiple morphological features can co-exist in the same MFB, and the artificial cut-offs for defining the different variants of MFB may not always be satisfied. Therefore, it is not always easy to simply classify a specific case into a certain morphological variant. The histological diversity of MFB may represent its flexibility to differentiate towards different mesenchymal lineages. In difficult cases, immunohistochemical staining as well as genetic tests can be crucial in making the diagnosis. In our case series, all 15 cases are followed up for different length of time, and no recurrence has been found. Therefore, despite the great variations in size or histological presentations, MFB is a benign lesion that can be cured by local excision.

4. Immunohistochemical and molecular features

Breast MFB is a disease with a wide spectrum of histologic morphologies. However, as a mesenchymal myofibroblastic neoplasm, most MFB variants share very similar immunohistochemical reactivities. Most MFB show variable immunoreactivities for myofibroblastic markers, like Desmin, SMA, MSA, and Vimentin [33]. CD34 positivity is also seen in majority of MFB cases, which is also true in SFT [34]. Besides, MFB is mostly positive for one or several hormonal receptors, like ER, PR and AR [2,3,5]. This can be an important differential feature with fibromatosis, SFT, spindle cell lipoma, etc. [35,36]. MFB is also consistently positive for BCL-2, which is potentially regulated by hormonal receptor signaling, especially ER signaling [3,37,38]. It also indicates that hormonal receptor signaling and the activation of downstream BCL-2 may participate in the pathogenesis of MFB. In addition, MFB is variably positive for CD99 and CD10 [39-42].

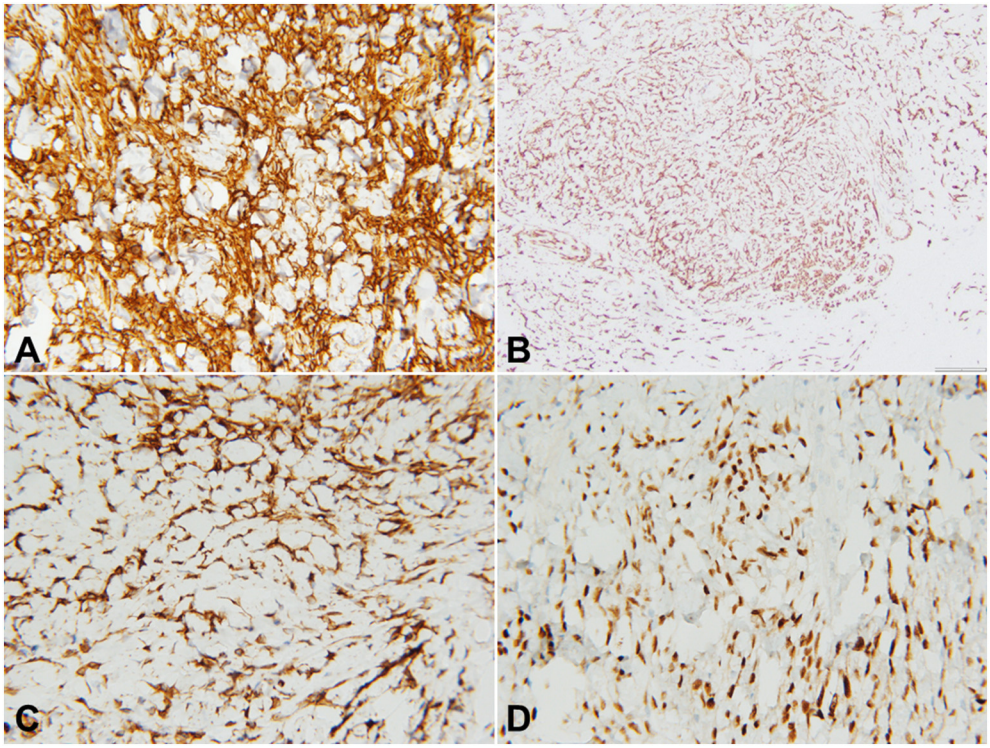

Fig. 4. Immunohistochemical staining of breast myofibroblastoma. (A) CD34 staining with diffusely cytoplasmic positive staining in lesional cells. (B) Desmin staining with cytoplasmic positivity. (C) BCL-2 staining with positive cytoplasmic staining. (D) PR staining with positive nuclear staining. (Hematoxylin-eosin, original magnification x20 [A, C, D], original magnification x10 [B]).

Genetically, MFB is featured by loss of 13q14 and 16q, resulting in partial or complete inactivation of *RB1* and *FOXO1* [14,43]. Similar genetic alterations are also seen in spindle cell lipoma and cellular angiofibroma, and thus indicating the genetic link among these entities [44]. Immunohistochemically, MFB is negative for nuclear staining of Rb in over 90% of the cases [45]. In comparison, differential diagnosis of MFB, like SFT, fibromatosis, nodular fasciitis, are intact for Rb staining.

Immunohistochemical staining of several markers in our case series are summarized and compared (Table 1). Results show that all cases being tested are positive for CD34 (Fig. 4A) and Desmin (Fig. 4B). Specifically, 72.7% (8/11) are strongly positive for CD34, and 27.2% (3/11) are focally or weakly positive. Meanwhile, 75% (9/12) of cases are strongly positive for Desmin, while 25% (3/12) are focally or weakly positive. Staining for BCL-2 is strongly positive in all tested cases (9/9) (Fig. 4C). For hormonal receptors, all tested cases for ER are strongly positive (5/5), while PR is strongly positive in 85.7% (6/7) and negative in 14.3% (1/7) of cases (Fig. 4D). For actins, SMA is positive in 57.1% (4/7) and negative in 42.9% (3/7) of cases; while MSA is positive in 83.3% (5/6) and negative in 16.7% (1/6) of cases. The staining for AE1/3 (0/12), CAM5.2 (0/6), S100 (0/11), P63 (0/5), CK5/6 (0/3) and 34betaE12 (0/3) are negative in all tested cases.

The combination of histological morphology as well as a panel of immunohistochemical staining is usually necessary to make the diagnosis of breast MFB, especially in small biopsy specimens. Here, we also compared the biopsy diagnosis for the 15 cases (Table 1). It appears that, with proper morphologic and immunohistochemical examinations as well as clinical correlations, most cases of breast MFB can be diagnosed correctly on biopsy specimens. Even if it is unsure to make the clear-cut diagnosis of MFB, all cases were able to be recognized as a benign or low-grade spindle lesion with myofibroblastic differentiation, which is important to provide initial diagnostic impression to the treating physicians. Though rarely used, genetic testing can provide additional value for making the correct diagnosis in challenging cases.

5. Differential diagnosis with other spindle cell lesions of breast

Spindle cell lesions of the breast comprise a wide variety of conditions, either benign, locally aggressive or malignant. Due to the multiple morphologic variants of MFB, understanding the differential diagnosis of MFB sometimes appears to be more important than recognizing the features of MFB itself, especially when encountering challenging cases. Therefore, we find it is necessary to elaborate on some of the most common differential diagnosis for breast MFB we encountered on daily practice (Table 2).

Pseudoangiomatous stromal hyperplasia (PASH) is a common spindle cell lesion found in premenopausal women or patients receiving hormonal therapy. Similar to MFB, PASH is due to myofibroblastic proliferation, and is positive for myofibrobastic markers and hormonal receptors [46]. Most cases of PASH are incidental findings, but rare cases can form a nodule or show morphological malignant features [47-49]. Differentiating PASH from MFB is quite common in small biopsy specimens. Histologically, PASH shows prominent anastomosing slit-like spaces in a densely collagenous stroma (Fig. 5A). It involves normal ducts and lobules, and are generally much less cellular than MFB (Fig. 5B). In addition, the formation of PASH is due to hormonal stimulation, and lacks the genetic changes of MFB.

Fibromatosis is another common differential diagnosis for MFB. It is due to fibroblastic/myofibroblastic proliferation, and has long fascicles of spindle cells infiltrating into surrounding structures (Fig. 5C). Desmoid fibromatosis has dense keloid collagen bundles, which is reminiscent of stromal collagen seen in MFB (Fig. 5D). In comparison to MFB, fibromatosis is negative for CD34 and hormonal receptors [50,51]. Genetically, fibromatosis is featured by mutations in either *APC* or *CTNNB1*, which can be reflected by positive nuclear staining of beta-catenin [52,53]. Local invasion and recurrence is common for fibromatosis.

Nodular fasciitis is another type of benign fibroblastic/myofibroblastic proliferation that can rarely occur in the breast. History of previous injury to the breast may be present. The spindle cells do not have a specific growth pattern, and are thus described as tissue culture-like. It does not entrap breast ducts or lobules, but can show peripheral

Table 2
Differential diagnosis of breast spindle cell lesions with breast myofibroblastoma.

Differential diagnosis	Histology	IHC	Molecular
PASH	1. Slit-like clefts resemble vascular spaces. 2. Less cellularity than MFB. 3. Less likely to form a mass as MFB. 4. Entrapping ducts and lobules.	1. Desmin (+), SMA (+), Vimentin (+). 2. ER (+), PR (+). 3. Nuclear Rb (+)	None
Fibromatosis	1. Abundant collagenous matrix. 2. Highly infiltrative. 3. Associated with FAP.	1. Nuclear beta-catenin (+) 2. CD34 (−) 3. Hormonal receptors (−) 4. Nuclear Rb (+)	*APC* or *CTNNB1* mutations
Nodular fasciitis	1. Bland fibroblastic/myofibroblastic cells. 2. Variable cellularity, tissue culture pattern. 3. Myxoid stroma. 4. Extravasated red blood cells. 5. Stromal lymphocytes and giant cells.	1. SMA(+) 2. Focal Desmin (+). 3. CD34(−). 4. Nuclear Rb (+)	*USP6* rearrangement *MYH9* is most common fusion partner
SFT	1. Uniform spindle to oval cells around prominent staghorn vessels. 2. Perivascular hyalinization. 3. Stroma is variably fibrous. 4. Lipomatous SFT contain mature adipose tissue.	1. CD34 (+). 2. STAT6 (+). 3. Focal EMA (+), SMA (+). 4. Desmin (−) 5. Nuclear Rb (+)	*NAB2-STAT6* fusion
Spindle cell lipoma	1. Mixture of mature adipose tissue, bland spindle cells and 'ropey' collagen. 2. Stromal mast cells. 3. Myxoid stroma not uncommon. 4. 'Fat-poor' or 'fat-free' cases are present.	1. CD34 (+). 2. SMA (−), Desmin (−). 3. Nuclear Rb (−).	*RB1* deletion *MDM2* not amplified
Leiomyoma	1. Cells arranged in intersecting fascicles. 2. Abundant eosinophilic cytoplasm. 3. Sparse intervening stroma.	1. H-caldesmon (+) 2. SMA (+), MSA (+) 3. Hormonal receptors (+) 4. CD34 (−)	*HMGA2-RAD51B* t(12;14) *FH* mutation
Invasive lobular carcinoma	1. Single files of low-grade dyscohesive cells. 2. Cytoplasmic vacuoles. 3. ALH/LCIS can be present. 4. Absence of spindle cells. 5. Infiltrative borders.	1. ER (+), PR (+). 2. E-cadherin present in 15%. 3. Positive for cytokeratins. 4. GCDFP-15 (+)	*CDH1* mutations
Metaplastic spindle cell carcinoma	1. Epithelial component or epithelioid cells can be present. 2. High nuclear grade and frequent mitosis for high-grade cases. 3. Infiltrative, encasing normal breast ducts. 4. Stromal lymphocytes common.	1. ER (−), PR (−). 2. Cytrokeratins (+), maybe focal or weak. 3. p63 (+). 4. Desmin (−).	Not specific. Genetic alterations involving *PTEN, TP53, EGFR*, etc.

Note: PASH: Pseudoangiomatous stromal hyperplasia. MFB: Myofibroblastoma. SFT: Solitary fibrous tumor. FAP: familial adenomatous polyposis. ALH: Atypical lobular hyperplasia. LCIS: Lobular carcinoma in situ.

infiltration. Prominent inflammatory cell infiltration, mostly lymphocytes and plasma cells, and extravasated red blood cells are distinguishing features from MFB (Fig. 5E). Same as fibromatosis, nodular fasciitis is also negative for CD34, which can be used to differentiate with MFB [54]. Genetically, nodular fasciitis is characterized by *USP6* translocations [55].

As described above, SFT is an another important differential diagnosis for MFB, both of which belong to fibroblastic/myofibroblastic lesions, and share similar immunoreactivities for CD34, Vimentin and SMA [16]. Fat-forming SFT have also been reported in multiple sites, mimicking either lipomatous MFB or spindle cell lipoma [56-58]. Indeed, some has proposed that SFT, MFB and spindle cell lipoma may represent different lesions that are derived from the same mammary stromal precursor cells [59]. Histologically, SFT is composed of uniform spindle to oval-shaped cells, prominent staghorn vessels, and thick stromal collagens (Fig. 5F). The unique *NAB2-STAT6* translocation and immunoreactivity for STAT6 is most commonly used to confirm the diagnosis [18].

Besides the above mentioned benign lesions, several malignant breast lesions can also raise confusion with MFB. For example, epithelioid MFB can resemble invasive lobular carcinoma as discussed above. Another differential diagnosis is metaplastic spindle cell carcinoma of breast which can present as predominant spindle cell proliferation with or without accompanying epithelial components (Fig. 5G). However, the absence of characteristic thick stromal collagen, prominent cellular atypia and frequent mitosis, infiltrative growth pattern, and positivity for cytokeratin are distinguishing features for metaplastic carcinoma. In addition, breast spindle cell sarcoma also present as predominant spindle cell proliferation (Fig. 5H). The low grade sarcoma may also lack prominent cellular atypia, frequent mitosis or other findings that distinguish it from other benign spindle cell lesions like MFB. However, through careful histologic examination and performing a panel of immunohistochemical markers, it is usually not difficult to make the diagnosis.

6. Summary

Breast MFB is a rare type of breast spindle cell lesion that follows a benign clinical course. Here, we summarized 15 cases of breast MFB diagnosed in our institution during a 20 year period. Most cases are diagnosed in elderly female patients, and their sizes are mostly smaller than 4 cm. However, a case with unusually big size of 35.2 cm is identified in our series, which is by far the biggest case reported. Histological examination of the cases identified a wide spectrum of morphologic features, including cellular, collagenized, palisading, epithelioid, myxoid, osseous, smooth muscle differentiation, etc. Unusual peripheral entrapment of breast ducts and focal aggregates of neutrophils are identified in some of the cases as well. In addition, a combination of heterologous morphological variants can be seen within the same lesion, which is especially true in the giant MFB case we reported. Despite of the morphological variants, immunohistochemical positivity for Desmin, CD34, SMA, MSA, Vimentin, hormonal receptors and BCL-2 can help to confirm the myofibroblastic differentiation of these cases. All cases in this study showed no recurrence on follow up

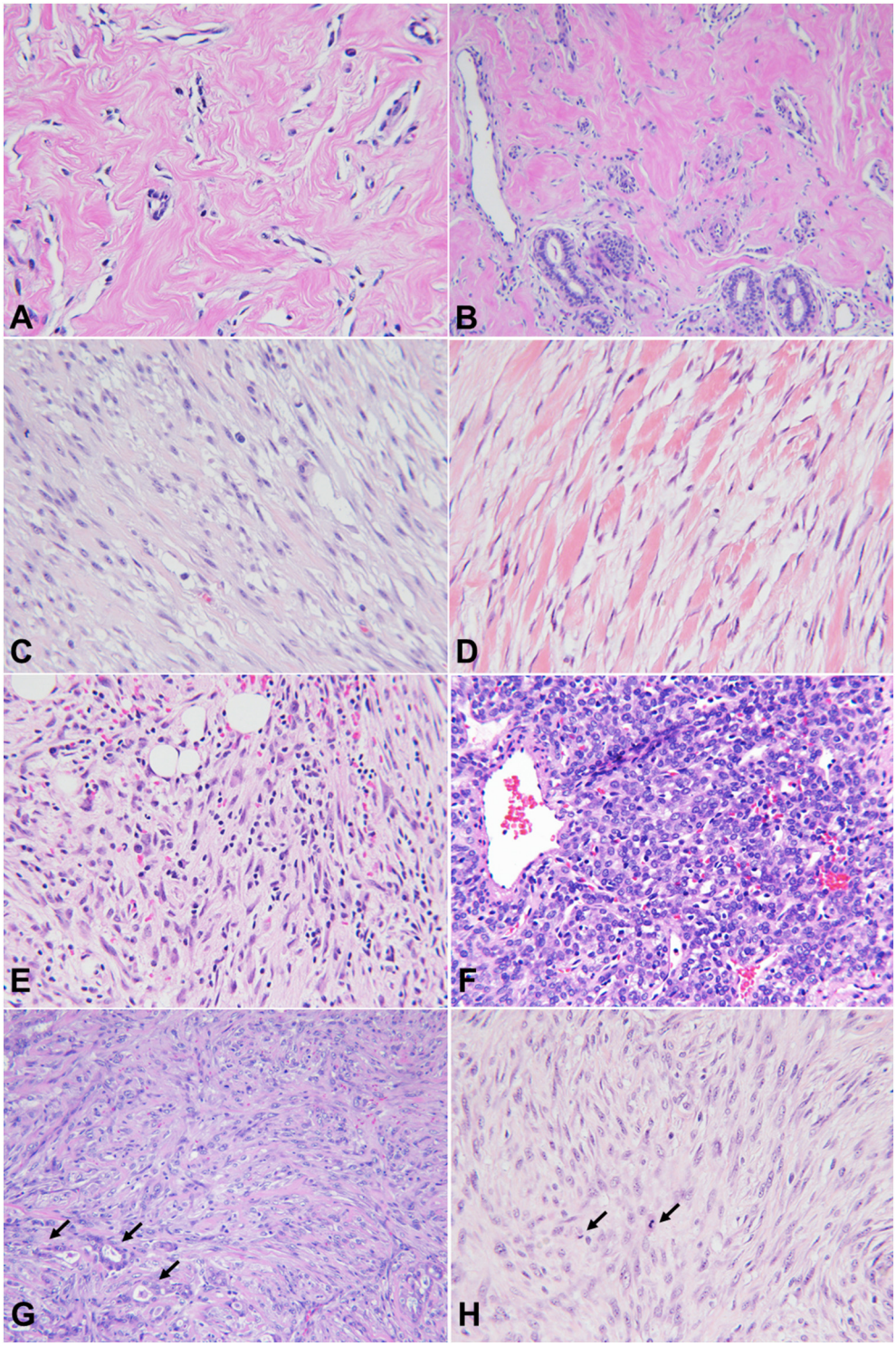

Fig. 5. Common differential diagnosis of breast myofibroblastoma. (A) Nodular pseudoangiomatous stromal hyperplasia (PASH). A 1.1 cm breast mass in a 45 year old female showing bland spindle cells forming slit-like spaces in a highly collagenized stroma. (B) Same case as (A) showing the spindle cell lesion encasing adjacent breast ducts. (C) Fibromatosis. An ill-defined 0.9 cm breast mass in a 58 year old female showing long fascicles of bland spindle cells. The stroma is less collagnized than classic MFB. The lesion is positive for nuclear beta-catenin by immunohistochemistry. (D) Desmoid fibromatosis. A 2.1 cm partially circumscribed mass in a 78 year old female showing fascicles of bland spindle cells intermixed with desmoid-type thick collagen bundles. (E) Nodular fasciitis. Ultrasound identified a 1.0 cm predominantly hyperechoic mass in a 34 year old female with previous breast trauma. Histology shows abundant lymphocytes, plasma cells and extravasated red blood cells are intermixed with a haphazardly arranged spindle cell lesion. (F) Solitary fibrous tumor (SFT). Ultrasound identified a well-circumscribed 2.9 cm hypoechoic mass in 21 year old female. Histology shows predominantly ovoid fibroblastic cells arranged around prominent staghorn vessels. Perivascular hyalinization is identified. The lesion is positive for CD34, BCL-2 and STAT6. (G) Metaplastic breast carcinoma. Mammography identified a 2.4 cm fairly well-defined nodule in a 75 year old female. Histology shows mostly atypical spindle cells streaming between a loosely collagenized stroma. Adjacent atypical ductal structures can be identified, representing the epithelial component of the lesion. (H) Spindle cell sarcoma. Mammography showed a 3.1 cm breast mass with angular margins and thickening of overlying skin in a 76 year old female. Histology shows a predominantly spindle cell lesion with moderate degree of atypia and frequent mitosis (arrows). No prominent thick stromal collagen is identified. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(range from 0.5 to 19 years).

Besides the 15 cases of MFB, we also collected some cases that are common differential diagnosis for MFB in our practice. These cases include both benign and malignant lesions, some of which even share similar immunohistochemical profiles with MFB. Since some of the spindle cell lesions of breast may potentially originate from the same precursor cells, it is not always easy to make the correct diagnosis based solely on histological examination. Staining a panel of immunohistochemical markers appears to be necessary in most cases especially in small biopsy specimens. In addition, molecular tests can be another specific method in challenging cases.

Declaration of competing interest

The research work has no conflict of interest.

References

[1] Magro G. Mammary myofibroblastoma: a tumor with a wide morphologic spectrum. Arch Pathol Lab Med 2008;132:1813–20.
[2] Gocht A, Bosmuller HC, Bassler R, Tavassoli FA, Moinfar F, Katenkamp D, et al. Breast tumors with myofibroblastic differentiation: clinico-pathological observations in myofibroblastoma and myofibrosarcoma. Pathol Res Pract 1999;195:1–10.

[3] Magro G, Bisceglia M, Michal M. Expression of steroid hormone receptors, their regulated proteins, and bcl-2 protein in myofibroblastoma of the breast. Histopathology 2000;36:515–21.
[4] Magro G, Michal M, Bisceglia M. Benign spindle cell tumors of the mammary stroma: diagnostic criteria, classification, and histogenesis. Pathol Res Pract 2001;197:453–66.
[5] Morgan MB, Pitha JV. Myofibroblastoma of the breast revisited: an etiologic association with androgens? Hum Pathol 1998;29:347–51.
[6] Wargotz ES, Weiss SW, Norris HJ. Myofibroblastoma of the breast. Sixteen cases of a distinctive benign mesenchymal tumor. Am J Surg Pathol 1987;11:493–502.
[7] Corradi D, Bosio S, Maestri R, Mormandi F, Curry A, Eyden B. A giant myxoid mammary myofibroblastoma: evidence for a myogenic/synthetic phenotype and an extracellular matrix rich in fibronectin. Histopathology 2008;52:396–9.
[8] Ali S, Teichberg S, DeRisi DC, Urmacher C. Giant myofibroblastoma of the male breast. Am J Surg Pathol 1994;18:1170–6.
[9] Kataria K, Srivastava A, Singh L, Suri V, Yadav R. Giant myofibroblastoma of the male breast: a case report and literature review. Malays J Med Sci 2012;19:74–6.
[10] Abeysekara AM, Siriwardana HP, Abbas KF, Tanner P, Ojo AA. An unusually large myofibroblastoma in a male breast: a case report. J Med Case Reports 2008;2:157.
[11] Schmitt FC, ACM A. Fine needle aspiration cytology presentation of a cellular variant of breast myofibroblastoma. Report of a case with immunohistochemical studies. Acta Cytol 1998;42:721–4.
[12] AbdullGaffar B. Pseudoangiomatous stromal hyperplasia of the breast. Arch Pathol Lab Med 2009;133:1335–8.
[13] Magro G, Michal M, Vasquez E, Bisceglia M. Lipomatous myofibroblastoma: a potential diagnostic pitfall in the spectrum of the spindle cell lesions of the breast. Virchows Arch 2000;437:540–4.
[14] Pauwels P, Sciot R, Croiset F, Rutten H, Van den Berghe H, Dal Cin P. Myofibroblastoma of the breast: genetic link with spindle cell lipoma. J Pathol 2000;191:282–5.
[15] Magro G, Fraggetta F, Torrisi A, Emmanuele C, Lanzafame S. Myofibroblastoma of the breast with hemangiopericytoma-like pattern and pleomorphic lipoma-like areas. Report of a case with diagnostic and histogenetic considerations. Pathol Res Pract 1999;195:257–62.
[16] Damiani S, Miettinen M, Peterse JL, Eusebi V. Solitary fibrous tumour (myofibroblastoma) of the breast. Virchows Arch 1994;425:89–92.
[17] Meguerditchian AN, Malik DA, Hicks DG, Kulkarni S. Solitary fibrous tumor of the breast and mammary myofibroblastoma: the same lesion? Breast J 2008;14:287–92.
[18] Robinson DR, Wu YM, Kalyana-Sundaram S, Cao X, Lonigro RJ, Sung YS, et al. Identification of recurrent NAB2-STAT6 gene fusions in solitary fibrous tumor by integrative sequencing. Nat Genet 2013;45:180–5.
[19] D'Alfonso TM, Subramaniyam S, Ginter PS, Mosquera JM, MacDonald TY, Noorzad Z, et al. Characterization of the leiomyomatous variant of myofibroblastoma: a rare subset distinct from other smooth muscle tumors of the breast. Hum Pathol 2016;58:54–61.
[20] Magro G, Gurrera A, Bisceglia M. H-caldesmon expression in myofibroblastoma of the breast: evidence supporting the distinction from leiomyoma. Histopathology 2003;42:233–8.
[21] Magro G, Amico P, Gurrera A. Myxoid myofibroblastoma of the breast with atypical cells: a potential diagnostic pitfall. Virchows Arch 2007;450:483–5.
[22] Ross JA, Reith J, Asirvatham JR. Myxoid Myofibroblastoma of the breast with atypical cells. Int J Surg Pathol 2019;27:446–9.
[23] Zhang Y, Wan D, Gao F. Primary low-grade fibromyxoid sarcoma of the breast: a rare case report with immunohistochemical and fluorescence in situ hybridization detection. Hum Pathol 2018;79:208–11.
[24] Magro G. Epithelioid-cell myofibroblastoma of the breast: expanding the morphologic spectrum. Am J Surg Pathol 2009;33:1085–92.
[25] Magro G, Vecchio GM, Michal M, Eusebi V. Atypical epithelioid cell myofibroblastoma of the breast with multinodular growth pattern: a potential pitfall of malignancy. Pathol Res Pract 2013;209:463–6.
[26] Arafah MA, Ginter PS, D'Alfonso TM, Hoda SA. Epithelioid mammary myofibroblastoma mimicking invasive lobular carcinoma. Int J Surg Pathol 2015;23:284–8.
[27] Kobayashi N, Oda K, Yokoi S, Kanda H, Hayakawa S, Tang X, et al. Myofibroblastoma of the breast: report of a case. Surg Today 1996;26:727–9.
[28] Wargotz ES, Norris HJ. Metaplastic carcinomas of the breast. I. Matrix-producing carcinoma. Hum Pathol 1989;20:628–35.
[29] Magro G, Gangemi P, Greco P. Deciduoid-like myofibroblastoma of the breast: a potential pitfall of malignancy. Histopathology 2008;52:652–4.
[30] Fukunaga M, Ushigome S. Myofibroblastoma of the breast with diverse differentiations. Arch Pathol Lab Med 1997;121:599–603.
[31] Kazani A, Mastoraki A, Dastamani C, Stafyla V, Kairi E, Psychogios I, et al. Myofibroblastoma of the breast: diagnostic challenges of a rare benign tumor. Indian J Surg 2015;77:501–4.
[32] Yang G, Liang S, Shi X. A novel collision tumour of myofibroblastoma and low-grade adenosquamous carcinoma in breast. Diagn Pathol 2020;15:76.
[33] Deligeorgi-Politi H, Kontozoglou T, Joseph M, Hearn S. Myofibroblastoma of the breast: cytologic, histologic, immunohistochemical, and ultrastructural findings in two cases with differing cellularity. Breast J 1997;3:365–71.
[34] Salomao DR, Crotty TB, Nascimento AG. Myofibroblastoma and solitary fibrous tumour of the breast: histopathologic and immunohistochemical studies. Breast 2001;10:49–54.
[35] Bongiovanni M, Viberti L, Pecchioni C, Papotti M, Thonhofer R, Hans Popper H, et al. Steroid hormone receptor in pleural solitary fibrous tumours and CD34 + progenitor stromal cells. J Pathol 2002;198:252–7.
[36] Devouassoux-Shisheboran M, Schammel MD, Man YG, Tavassoli FA. Fibromatosis of the breast: age-correlated morphofunctional features of 33 cases. Arch Pathol Lab Med 2000;124:276–80.
[37] Bhargava V, Kell DL, van de Rijn M, Warnke RA. Bcl-2 immunoreactivity in breast carcinoma correlates with hormone receptor positivity. Am J Pathol 1994;145:535–40.
[38] Leek RD, Kaklamanis L, Pezzella F, Gatter KC, Harris AL. Bcl-2 in normal human breast and carcinoma, association with oestrogen receptor-positive, epidermal growth factor receptor-negative tumours and in situ cancer. Br J Cancer 1994;69:135–9.
[39] Magro G, Caltabiano R, Kacerovska D, Vecchio GM, Kazakov D, Michal M. Vulvovaginal myofibroblastoma: expanding the morphological and immunohistochemical spectrum. A clinicopathologic study of 10 cases. Hum Pathol 2012;43:243–53.
[40] Magro G, Salvatorelli L, Spadola S, Angelico G. Mammary myofibroblastoma with extensive myxoedematous stromal changes: a potential diagnostic pitfall. Pathol Res Pract 2014;210:1106–11.
[41] Metry M, Shaaban M, Youssef M, Carr M. Myofibroblastoma of the breast: literature review and case report. Case Rep Oncol Med 2016;2016:1714382.
[42] Magro G, Caltabiano R, Di Cataldo A, Puzzo L. CD10 is expressed by mammary myofibroblastoma and spindle cell lipoma of soft tissue: an additional evidence of their histogenetic linking. Virchows Arch 2007;450:727–8.
[43] Magro G, Righi A, Casorzo L, Antonietta T, Salvatorelli L, Kacerovska D, et al. Mammary and vaginal myofibroblastomas are genetically related lesions: fluorescence in situ hybridization analysis shows deletion of 13q14 region. Hum Pathol 2012;43:1887–93.
[44] Maggiani F, Debiec-Rychter M, Vanbockrijck M, Sciot R. Cellular angiofibroma: another mesenchymal tumour with 13q14 involvement, suggesting a link with spindle cell lipoma and (extra)-mammary myofibroblastoma. Histopathology 2007;51:410–2.
[45] Howitt BE, Fletcher CD. Mammary-type myofibroblastoma: clinicopathologic characterization in a series of 143 cases. Am J Surg Pathol 2016;40:361–7.
[46] Powell CM, Cranor ML, Rosen PP. Pseudoangiomatous stromal hyperplasia (PASH). A mammary stromal tumor with myofibroblastic differentiation. Am J Surg Pathol 1995;19:270–7.
[47] Okoshi K, Ogawa H, Suwa H, Saiga T, Kobayashi H. A case of nodular pseudoangiomatous stromal hyperplasia (PASH). Breast Cancer 2006;13:349–53.
[48] Nassar H, Elieff MP, Kronz JD, Argani P. Pseudoangiomatous stromal hyperplasia (PASH) of the breast with foci of morphologic malignancy: a case of PASH with malignant transformation? Int J Surg Pathol 2010;18:564–9.
[49] Lee J, Oh H, Min K. Mammary pseudoangiomatous stromal hyperplasia presenting as an axillary mass. Breast 2005;14:61–4.
[50] Lee AH. Recent developments in the histological diagnosis of spindle cell carcinoma, fibromatosis and phyllodes tumour of the breast. Histopathology 2008;52:45–57.
[51] Ha KY, Deleon P, Hamilton R. Breast fibromatosis mimicking breast carcinoma. Proc (Bayl Univ Med Cent) 2013;26:22–4.
[52] Abraham SC, Reynolds C, Lee JH, Montgomery EA, Baisden BL, Krasinskas AM, et al. Fibromatosis of the breast and mutations involving the APC/beta-catenin pathway. Hum Pathol 2002;33:39–46.
[53] Kim T, Jung EA, Song JY, Roh JH, Choi JS, Kwon JE, et al. Prevalence of the CTNNB1 mutation genotype in surgically resected fibromatosis of the breast. Histopathology 2012;60:347–56.
[54] Donner LR, Silva T, Dobin SM. Clonal rearrangement of 15p11.2, 16p11.2, and 16p13.3 in a case of nodular fasciitis: additional evidence favoring nodular fasciitis as a benign neoplasm and not a reactive tumefaction. Cancer Genet Cytogenet 2002;139:138–40.
[55] Shin C, Low I, Ng D, Oei P, Miles C, Symmans P. USP6 gene rearrangement in nodular fasciitis and histological mimics. Histopathology 2016;69:784–91.
[56] Takeda M, Kojima K, Taniguchi Y, Yoon HE, Matsumura A, Ohbayashi C, et al. Fat-forming variant of solitary fibrous tumor of the pleura, mimicking spindle cell lipoma. Pathol Int 2019;69:309–11.
[57] Liu X, Zhang HY, Bu H, Meng GZ, Zhang Z, Ke Q. Fat-forming variant of solitary fibrous tumor of the mediastinum. Chin Med J (Engl) 2007;120:1029–32.
[58] Cortes LG, Caserta NM, Billis A. Fat-forming solitary fibrous tumor of the kidney: a case report. Anal Quant Cytopathol Histpathol 2014;36:295–8.
[59] Magro G, Bisceglia M, Michal M, Eusebi V. Spindle cell lipoma-like tumor, solitary fibrous tumor and myofibroblastoma of the breast: a clinico-pathological analysis of 13 cases in favor of a unifying histogenetic concept. Virchows Arch 2002;440:249–60.