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Case Report

Angiofibroma of soft tissue: report of two cases and review of literature

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Abstract: Angiofibroma of soft tissue is a recently described tumor, which showed the distinctive histological features. Because of the presence of prominent vascular network, the tumor was easily misdiagnosed as low grade malignant soft tissue lesions. Herein, we present two cases of angiofibroma of soft tissue in a 57-year-old female and a 37-year-old male, respectively. Histologically, both of them were composed of abundant branching vessels and bland spindle cells with variably collagenous to myxoid background. In addition, in case 1, few scattered atypical multinucleated cells could be observed in the tumor, whereas the case 2 demonstrated the obvious capsule invasion. Immunohistochemical staining showed that the two was consistently diffusely positive for vimentin and Bcl-2, focally positive for EMA, and negative for cytokeratin, actin(SM), ALK, S-100, CD31, CD34, MUC4, CD99, CD68 and desmin. Ki-67 proliferation index was less than 1%. Our present cases served to further broaden the morphologic profile of the tumor. It was necessary for being familiar with this neoplasm to avoid overdiagnosis.

Keywords: Angiofibroma, benign, soft tissue, neoplasm

Background

In 2012, Marin˜o-Enrı´quez and Fletcher first described 37 cases of distinctive fibrovascular neoplasm of uncertain cellular origin, namely, angiofibroma of soft tissue [1]. Histologically, the tumor was characterized by abundant thin-walled vessels forming network pattern and bland spindle cells which were haphazardly distributed [1]. Subsequently, approximately 12 cases of angiofibroma of soft tissue were reported in English literature [2-8]. The reported cases showed generally consistent morphologic presentation. Nevertheless, the tumor was easily misdiagnosed as a series of low grade or intermediate malignant tumor such as myxoid liposarcoma, low-grade fibromyxoid sarcoma, low-grade myxofibrosarcoma, solitary fibrous tumor and so on, since the tumor possessed prominent branching or curvilinear thin-walled vessels with variably collagenous or myxoid matrix. Thus, it was indispensable for pathologists to be familiar with the lesion. Herein, we present two cases of angiofibroma of soft tissue, and then reviewed all the described English literatures. Our report tried to expand clinical and pathological presentation of this newly characterized neoplasm.

Case presentation

Case 1

A 57-year-old female was referred to our hospital for complaining of a slow growing mass with slight tenderness of left lower leg detected incidentally for 30 years. Magnetic resonance (MR) imaging revealed a well circumscribed, 3.2×2.6 irregular mass with equal T1signal and long T2 signal located between the subcutaneous and skeletal muscle of left lower leg. The mass showed heterogeneous T2 signal and shadows of strips with equal signal, which was suggestive of the possibility of hemangioma (**Figure 1**). Then, the patient underwent a simple excision in our hospital. The postoperative course was uneventful. There was no evidence of disease after a follow up of 12 months.

Case 2

A 37-year-old male was admitted to our hospital for complaining of a pain of the right knee joint

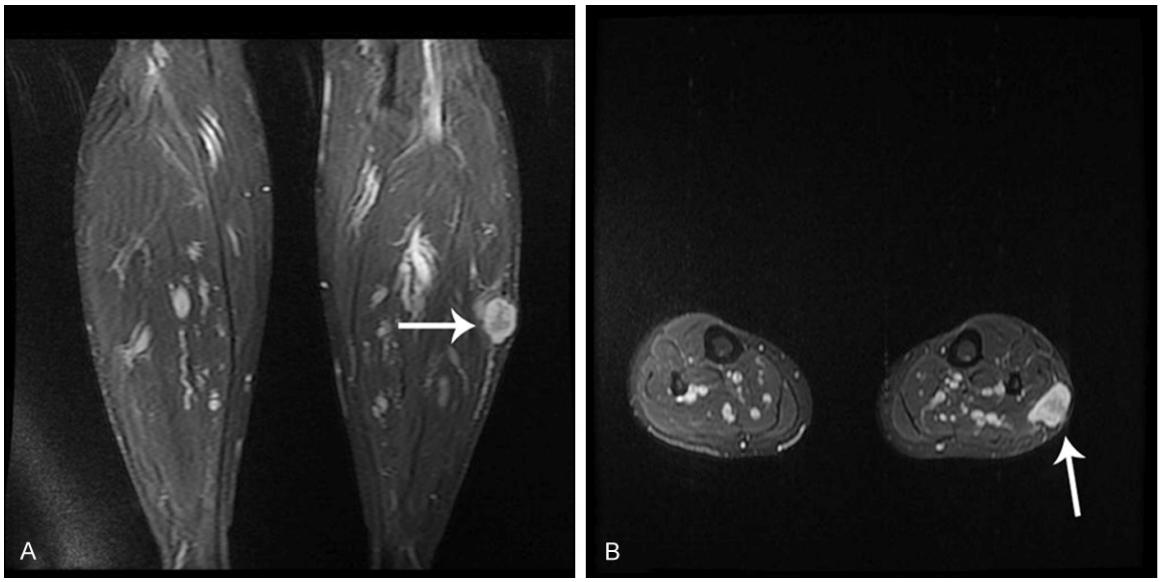

Figure 1. Magnetic resonance imaging manifestation of case 1. A, B. A well circumscribed mass was located between the subcutaneous and skeletal muscle of left lower leg.

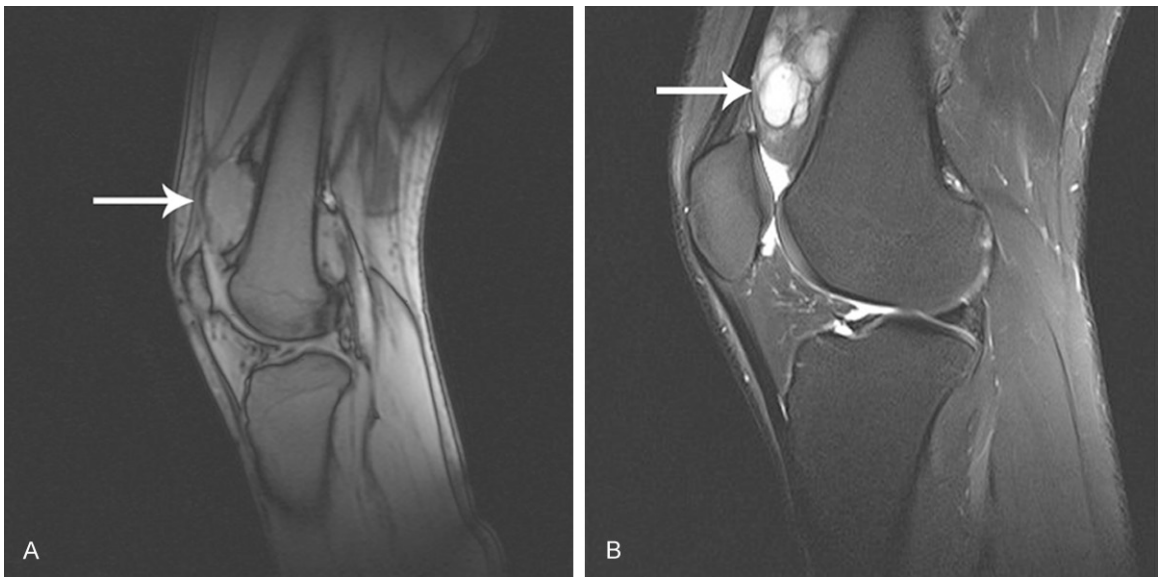

Figure 2. Magnetic resonance imaging manifestation of case 2. A, B. A multilobulated mass located in the subcutaneous tissue of upper patella.

without inducement for 2 months. Physical examination revealed a lobulated, mobile soft tissue mass in the subcutaneous of upper patella. Magnetic resonance (MR) imaging demonstrated a multilobulated mass measuring 4.41 cm in the diameter with long T2 signal located in the subcutaneous tissue of upper patella (**Figure 2**). Then, the patient underwent a wide excision in our hospital, since the tumor was diagnosed as an intermediate malignant tumor because of the capsule invasion during frozen diagnosis. The postoperative course was uneventful. The patient did not undergo adjuvant therapy after excision, and there was no evidence of disease 6 months later.

Materials and methods

The resected specimens were fixed with 10% neutral-buffered formalin and embedded in

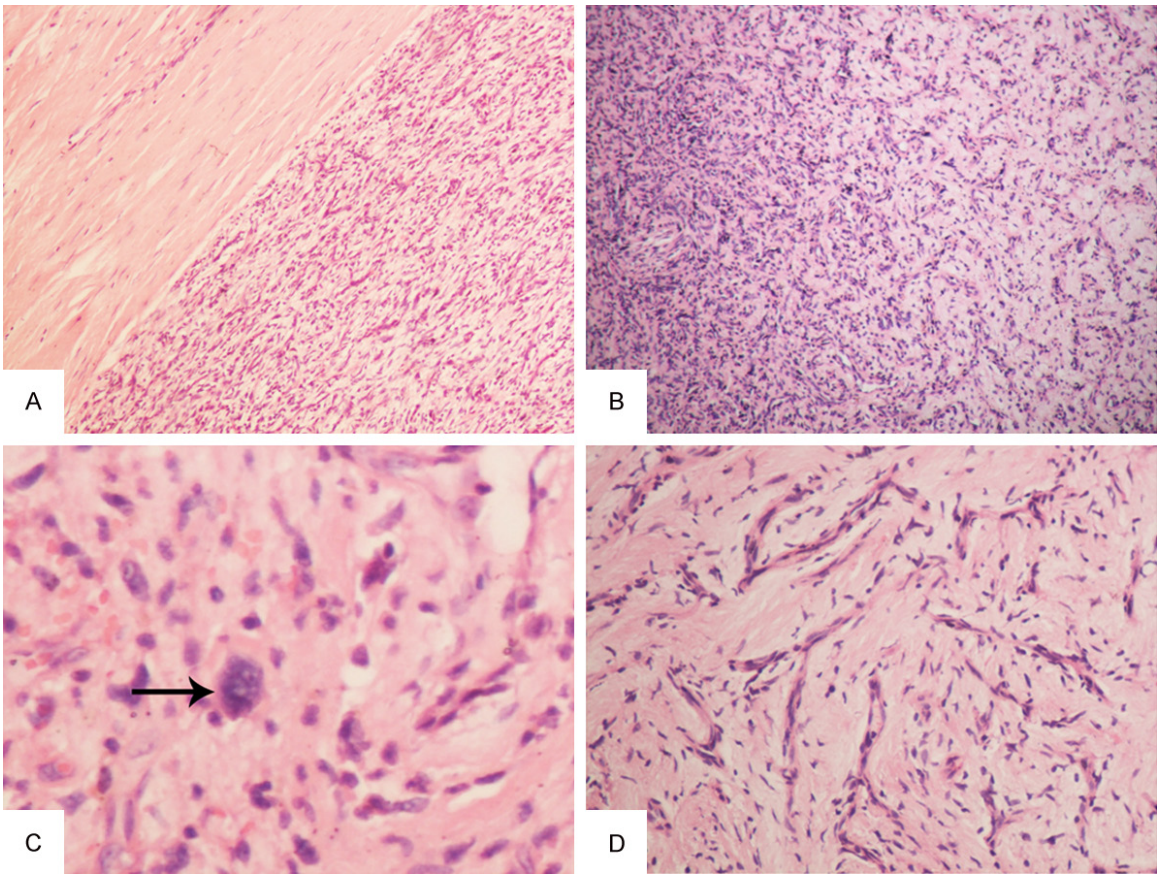

Figure 3. Morphological change of the case 1. A. The tumor was surrounded by a thick fibrous capsule. B. The transition from hypercellular area to hypocellular area with branching vascular network could be observed. C. A degenerative multinucleated cell was present in the tumor. D. The tumor focally showed abundant collagen with few neoplastic cells.

paraffin blocks. Tissue blocks were cut into 4-μm slides, deparaffinized in xylene, rehydrated with graded alcohols, and immunostained with the following antibodies: cytokeratin (CK), Vimentin, epithelial membrane antigen (EMA), Actin(SM), Desmin ALK, S-100, CD31, CD34, CD68, CD99, Bcl-2, MUC4, and Ki-67. Sections were stained with a streptavidin-peroxidase system (KIT-9720, Ultrasensitive TM S-P, Maixin, China). The chromogen used was diaminobenzidine tetrahydrochloride substrate (DAB kit, Maixin, China), slightly counterstained with hematoxylin, dehydrated and mounted. For the negative controls, the primary antibody was replaced with PBS. This study was prospectively performed and approved by the institutional Ethics Committees of China Medical University and conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Results

Gross features

Macroscopically, case 1 showed a well-circumscribed mass measuring 3.1 cm in the diameter. The cut face was firm and gray red in color. Case 2 was multilobulated, and partially encapsulated, measured 4.2×3.8×3.4 cm. The cut face was firm and grayish in color.

Histologic features

Histologically, the two generally shared the similar histologic feature. Both of them were surrounded by a thick fibrous capsule (**Figure 3A**). However, case 2 was divided into multilobulated by the fibrous tissue and focally showed the capsule infiltration (**Figure 4A**). They were mainly composed of two components: prominent vascular network and haphazardly distributed

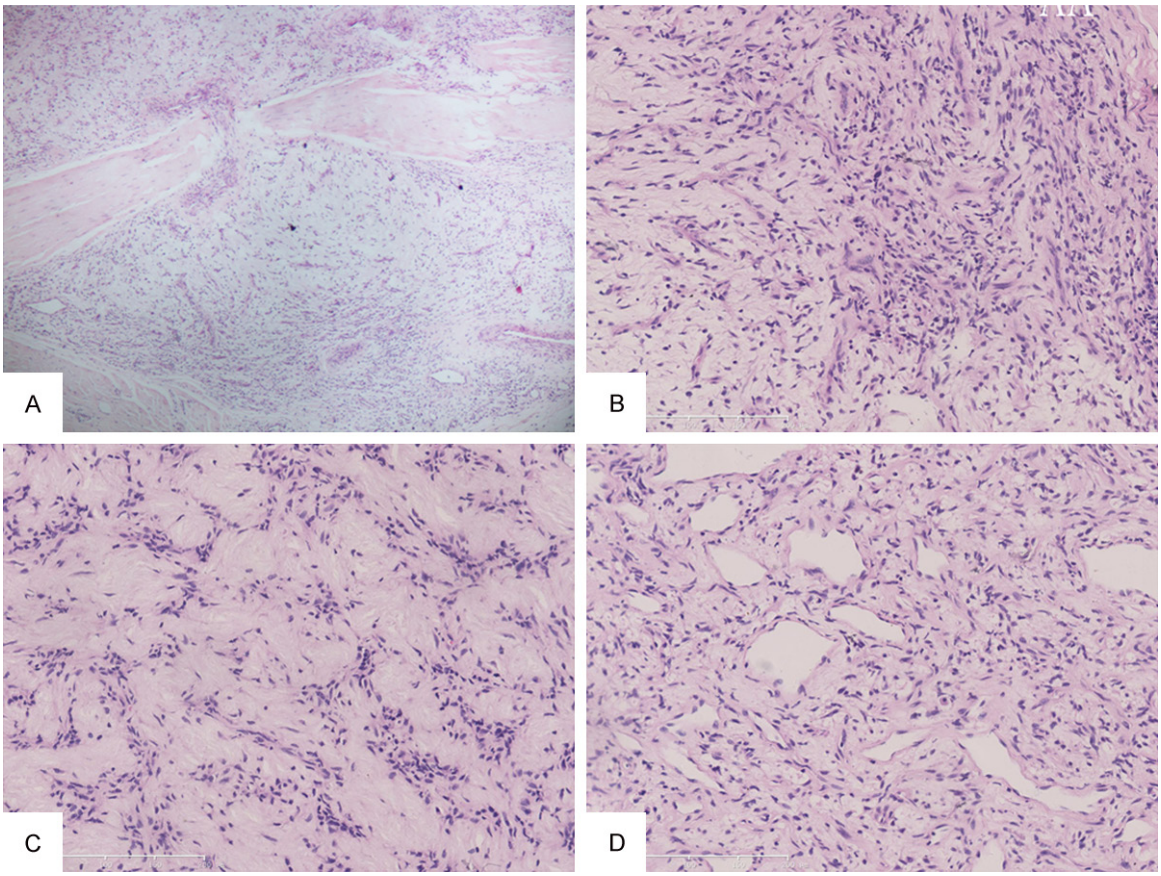

Figure 4. Morphological change of the case 2. A. The tumor penetrated the capsule, and infiltrated into the surrounding tissue. B. The vascular network was distributed in a prominent myxoid matrix. C. The area showing abundant collagen with branching vessels could also be observed. D. Occasionally, dilated thin-walled vessels could be observed.

spindled to ovoid cells (**Figure 3B**). The vascular network was predominantly comprised by branching thin-walled vessels, or curvilinear vessels usually detected in low-grade myxofibrosarcoma (**Figure 4B**). Occasionally, the dilated thin-walled vessels could be observed in case 2 (**Figure 4D**). The spindled to ovoid cells were relatively uniform, showed mild atypia, indistinct boundaries, ovoid nuclei with fine chromatin and small nucleoli. The mitosis of the cells is absent. In contrast, very few atypical multinucleated cells were present in case 1 (**Figure 3C**). The distribution of the neoplastic cells was not uniform. At low power examination, both tumors showed alternating hypercellular areas and hyocellular areas set in variably myxoid to collagenous stroma (**Figures 3D**, **4B**, **4C**). Additionally, scattered lymphocytes could be observed among the neoplastic cells.

Immunohistochemical staining

Immunohistochemical staining showed that the tumor cells of the two were consistently diffusely positive for vimentin and Bcl-2, focally positive for EMA, and negative for cytokeratin, ALK, S-100, CD31, CD34, MUC4, CD99, CD68 and desmin. Ki-67 proliferation index was less than 1%. CD31, CD34 and Actin(SM) staining highlighted the presence of prominent vascular network (**Figures 5**, **6**).

According to the morphological and immunohistochemical findings, the two cases were diagnosed as angiofibroma of soft tissue.

Discussion

Angiofibroma of soft tissue was first described by Marin˜o-Enrı´quez and Fletcher in a series of 37 cases of distinctive fibrovascular neoplasm in 2012 [1]. Subsequently, several cases were successively reported [2-8]. Thus far, approximately 51 cases (including the current two cases) were reported in the English literature. As a recently characterized lesion, its accurate occurrence rate was unclear, since it might not been aware by many pathologists.

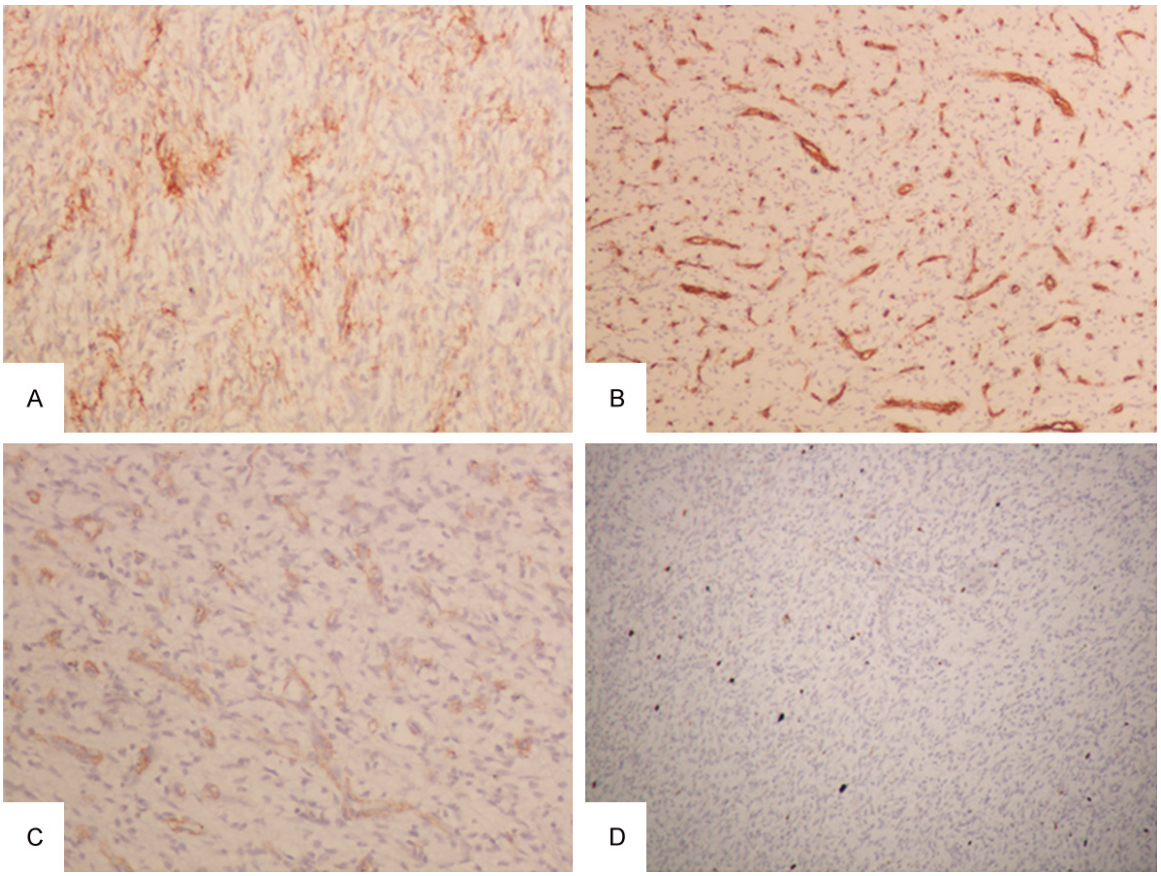

Figure 5. Immunohistochemical staining of case 1. A. The neoplastic cells were focally positive EMA. B. The CD34 staining highlighted the presence of numerous vessels in the tumor. C. Actin(sm) was not expressed in neoplastic cells, but expressed in vessels. D. Ki-67 proliferative index was less than 1%.

Clinically, as listed in **Table 1**, although angiofibroma of soft tissue occurred more commonly in middle-age adults, in fact, it could affect the patients with age from 6 to 86 years [1]. In the first 37 cases described by Marin˜o-Enrı´quez, angiofibroma of soft occurred more commonly in female (25 cases) than male (12 cases). In contrast, the subsequent 14 cases included 9 males and 5 females. Thus, it was necessary for collecting more cases to confirm the gender predominance of the lesion.

The most of reported cases occurred in lower limbs (32/51) and upper limbs (7/51). However, a wide variety of sites including inguinal region [1, 5], chest wall [1, 4], pelvic cavity [1, 5], iliac crest [4], posterior neck [3], breast parenchyma [1] and abdominal wall [1] could also be involved.

Its histological feature has been well documented by Marin˜o-Enrı´quez and Fletcher [1]. The subsequent cases including the current cases showed generally identical morphology. It was characterized by haphazardly distributed spindled to ovoid cells with mild atypia and prominent vascular network. The cells showed inconspicuous boundary, slight eosinophilic cytoplasm, oval or elongated nuclei and small nucleoli. The mitosis was usually rare; occasionally, few cases showed relatively higher mitotic rate [1]. Consistent with the previous studies, the mitotic activities in our cases were completely absent. However, Sugita et al. and Edgar et al. reported few atypical multinucleated cells could be observed in the lesions, respectively [4, 5]. In the case 1, scattered atypical multinucleated cells also presented in focal region. Although this simply meant the degenerative change, it was noted that it might pose a diagnostic pitfall. The most prominent feature of the lesion was the presence of numerous vessels. The majority of them were branching thin-walled vessels. Occasionally,

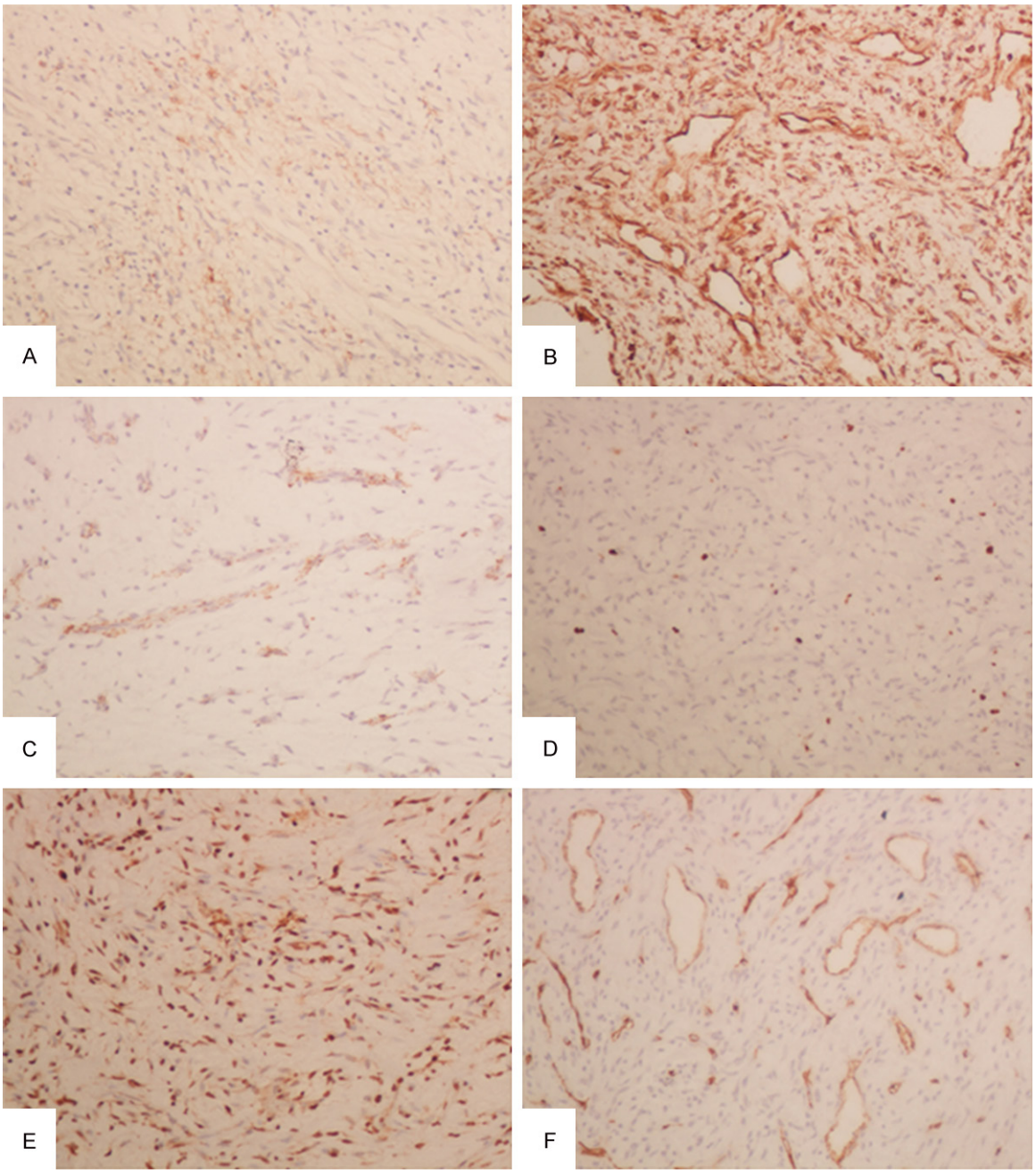

Figure 6. Immunohistochemical staining of case 2. A. The neoplastic cells were also focally positive EMA. B. The neoplastic cells were consistently positively for vimentin. C. Actin(sm) stained the true small vessels rather than the tumor cells. D. Ki-67 proliferative index was less than 1%. E. The tumor also showed strong reactivity for Bcl-2. F. The CD34 staining highlighted the dilated small vessels in the tumor.

they might show staghorn, dilated thin-walled, curvilinear or medium to large-sized vessels. Another morphologic feature was that alternating hypercellular areas and hyocellular area set in variably myxoid to collagenous stroma.

Immunohistochemically, as listed in **Table 2** angiofibroma of soft tissue was consistently positive for vimentin. Moreover, it was variably positive for EMA, S-100, SMA and Desmin [1].

Fukuda et al. then described a case that histiocytoid tumor cells positive for CD68 and CD163 were scattered in the tumor, which was not reported in the other cases [8]. Edgar et al. reported that the tumor cells were focally posi-

Table 1. Review of reported cases of angiofibroma of soft tissue (cases from previous publications and the current case)

Reference	Age/Sex	Location	Size (cm)	Gene fusion	Therapy	Outcome (m)
Sugita [5] 2014	27/F	Upper arm	2	NCOA2 split (32%)	MR	ANED
	38/M	Inguinal region	5.6	NCOA2 split (36%)	MR	ANED
	70/F	Thigh	9.5	NCOA2 split (16%)	MR	ANED
	41/M	Thigh	8	NCOA2 split (36%)	MR	ANED
Fukuda [8] 2014	73/F	Thigh	9.5	NCOA2 gene rearrangement	MR	ANED (6)
Song [7] 2014	51/F	Thigh	2.2	Not done	complete excision	ANED
Lee [6] 2014	37/M	Foot	9.1	t(5;8)(p15;q13)	WE	ANED (27)
Edgar [4] 2013	61/M	iliac crest	7	NCOA2 split (53%)	RE	ANED (9)
	67/M	Chest wall	Not known	Not done	NA	NA
Zhao [3] 2013	57/M	Thigh	2	Not done	SE	ANED (12)
	54/M	Posterior neck	2.6	Not done	SE	NA
Arbajian [2] 2012	41/M	Thigh	Not known	GTF2I/NCOA2 Fusion	MR	NA
Marino-Enriquez [1] 2012	6-86 (median 47)/ F (x25), M (x12)	Lower extremity (x23) Upper extremity (x5) Back (x3) Others§ (x6)	1.2-7.2 (mean 4.3)	t(5;8)(p15;q12) (x4) t(5;8;8)(p15;q13;p11) (x1) gains of 10q24-26, 12q13, and 17p13 (x1)	SE (x29) WE (x6) Amputation (x1) NA (x1)	NED (x23, 6-122) Recurrence (x4, 9, 12, 36 and 120) NA (x9)
Current cases	57/F	Lower leg	3.2	Not done	SE	ANED (6)
	37/M	Knee	4.3	Not done	WE	ANED (12)

F, female; m, months; M, male; NA, not available; NED, no evidence of disease; SE, simple excision; WE, wide excision; MR, marginal resection; RE, radical excision; ANED, alive with no evidence of disease; NA, not available.

Table 2. Review of immunohistochemical staining of angiofibroma of soft tissue (cases from previous publications and the current case)

Reference	EMA	CD34	S100	SMA	Desmin	Others	Ki-67 index
Sugita [5] 2014	+	-	-	-	+(Focal)		NA
	-	-	+(Focal)	-	+(Focal)		NA
	+(Focal)	-	-	+(Focal)	+(Few cells)		NA
	+(Focal)	-	+(Focal)	-	+(Focal)		NA
Fukuda [8] 2014	-	-	-	-	-	CD68+ CD163+	0.4%
Song [7] 2014	+(Partly)	-	-	-	-		<1%
Lee [6] 2014	-	NA	-	-	-		<1%
Edgar [4] 2013	NA	-	-	-	+(Focal)	CD10+(Focal)	NA
	NA	-	-	-	-		NA
Zhao [3] 2013	-	-	-	-	+(Focal)		<1%
	-	-	-	-	+(Focal)		<1%
Arbajian [2] 2012	NA	NA	NA	NA	NA		NA
Marino-Enriquez [1] 2012	44%+ (16/36)	14%+ (5/36)	-	14%+ (5/35)	11%+ (4/35)		NA
Current cases	+(Focal)	-	-	-	-	Bcl-2+(diffuse)	<1%
	+(Focal)	-	-	-	-	Bcl-2+(diffuse)	<1%

NA, not available.

tive for CD10 [4]. The present cases were both diffusely positive for vimentin and focally positive for EMA, negative for cytokeratin, ALK, S-100, CD31, CD34, MUC4, CD99, CD68 and desmin, generally consistent with the previous studies [2-8]. Ki-67 proliferation index was less than 1%, in agreement with the other reports [2-8], indicating the lower proliferative activity of the tumor. Additionally, the two cases also stained for Bcl-2, a marker in fact with widespread positivity in soft tissue tumor, although usually expressed in solitary fibrous tumor and synovial sarcoma [9-11].

It was believed that angiofibroma of soft tissue was generally a benign tumor. In the follow up by Marin˜o-Enrı′quez, local recurrence occurred in 4 cases, among 28 patients. None of the patients developed metastasis, or died of the disease [1]. Also, all the subsequently described patients were free for the disease [2-8]. The current case 1 underwent a simple excision, since the tumor was well encapsulated, whereas case 2 underwent wide excision because of the presence of capsule invasion. The two cases did not undergo any adjuvant therapy, and was alive with no evidence of tumor recurrence or metastasis. Consequently, to the limited data, it appeared that simple excision or wide excision was adequate for treatment.

Cytogenetically, Jin et al. revealed an AHRR-NCOA2 fusion was present in a subset of the tumors [12]. A Novel GTF2I/NCOA2 Fusion was then reported by Arbajian et al. in a new case [2]. Subsequently, rearrangement of the NCOA2 gene was detected by Sugita et al. and others, indicating NCOA2 fusion might be helpful for confirming the diagnosis [4, 5, 8].

The differential diagnosis of the tumor includes a variety of tumors including superficial angiomyxoma, cellular angiofibroma, myxoid liposarcoma, low-grade fibromyxoid sarcoma, low-grade myxofibrosarcoma and solitary fibrous tumor. Superficial angiomyxoma contained abundant delicate thin-walled vessels and myxoid matrix. The presence of inflammatory cells, particularly neutrophils and the expression of CD34 could helpful for confirming the diagnosis [13]. Cellular angiofibroma mainly occurred in the genital region, was characterized by small- to medium-sized vessels with mostly hyalinized walls and usually lacking branching vascular network [14]. Myxoid liposarcoma was characterized by prominent plexiform “chicken wire” capillaries. Compared to myxoid liposarcoma, the vessels in angiofibroma of soft tissue were thicker and more heterogeneous, which was helpful for differential diagnosis [15]. Low-grade fibromyxoid sarcoma could also show

alternating myxoid area and collagenous area, which might pose a great diagnostic challenge. However, low-grade fibromyxoid sarcoma usually lacked the prominent vascular network in angiofibroma. Moreover, immunostaining for MUC4 and molecular detection for FUS-CREB3L1 or FUS-CREBL2 gene fusion could be aid in diagnosis. In our cases, we performed immunohistochemical staining for MUC4, and the negative expression of MUC4 could exclude the diagnosis of low-grade fibromyxoid sarcoma [16]. Although angiofibroma of soft tissue could focally demonstrate the curvilinear vessels presenting in low-grade myxofibrosarcoma, the latter tended to frequently possess more cellular atypia and hyperchomatic nuclei [17]. Solitary fibrous tumor was a distinctive tumor which was characterized by "patternless" pattern, variable morphologic presention, thick collagen bundles and diffue and strong staining for CD34 [11]. In summary, the correct diagnosis should be made based on histological features, immunohistochemical staining and molecular detection.

Conclusion

We present two cases of angiofibroma of soft tissue, which was newly described, and then reviewed all the described English literatures. Although this tumor appeared to show a distinctive morphologic feature, it was easily misdiagnosed as other low-grade or intermediate malignant entities, especially if the one was not familiar with it.

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Disclosure of conflict of interest

None.

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