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Case Report

Clinicopathological characteristics of angiofibroma of soft tissue: report of three cases

Hong-Jun Ma[1], Hai-Ning Huang[2], Lei Li[1], Shuai Chen[1], Ren-Ya Zhang[1]

Departments of [1]Pathology, [2]Pharmacy, Affiliated Hospital of Jining Medical University, Jining, Shandong Province, P. R. China

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Abstract: Angiofibroma of soft tissue (AFST) is a recently-reported, rare, fibrovascular soft tissue neoplasm that commonly develops in the lower extremities of middle-aged women. Here, we report three cases located in the right temporal lobe of a woman, the left popliteal fossa of a female, and the right lower limb of a male patient, respectively, the former of which is first reported in the light of a literature review owing to its anatomical location. Histological and immunohistochemical features were consistent with the diagnosis of AFST. The two female patients have been individually followed up for 20 and 16 months after surgical resection without any local recurrences or any metastases. Meanwhile, we reviewed the clinicopathological characteristics of 81 AFST to further characterize this tumor. In addition, AFST is a benign tumor that should be considered in the differential diagnosis of a solitary fibrous tumor, a low-grade fibromyxoid sarcoma, and low-grade myxofibrosarcoma, to avoid being misdiagnosed as malignant.

Keywords: Angiofibroma of soft tissue, clinicopathological characteristics, differential diagnosis

Introduction

Angiofibroma of soft tissue is a newly described, benign mesenchymal tumor, commonly found in the deep soft tissue of an adult's lower extremities, with painless and slow growth, histologically including hyperplastic spindle cells and dramatically variable vascular networks [1-3]. Here, we present three cases of AFST, one of which occurred in the right temporal lobe and another in the left popliteal fossa, and the explicit diagnosis we made by combining the common pathological features with immunohistochemistry and the imaging examination. To our knowledge, it is extremely rare that AFST is observed in these two regions; therefore, we have discussed its diagnosis and differential diagnosis, and also reviewed earlier studies on 81 AFST, aiming at documenting the clinical and histopathologic features of AFST to facilitate its diagnosis.

Case report

Clinical history

Case 1: A 36-year-old woman presented with a painless mass in the right temporal lobe for 1 year. Physical examination showed the 3×3×2 cm tumor, that was of medium texture, had a clear boundary, and showed good activity. Meanwhile, CT found that it was a subcutaneous and solid nodular mass in the right temporal lobe (**Figure 1A**). There was no evidence of local tumor recurrence or distant metastasis after surgery over a 20-month follow-up period, with good cosmetic and functional outcomes.

Case 2: A 59-year-old woman who found a painless lump in the left popliteal fossa for 10 years had no significant medical history and no abnormalities in the physical examination. Ultrasonography revealed that a mass in the left popliteal fossa with a clear boundary and a low-echo nodule; it measured about 8.0×4.7 cm (**Figure 1B**). Performing a simple resection of the patient, the doctors found no evidence of the tumor adhering to or invading the surrounding tissue. The patient received no additional therapy and was healthy at a 16-month follow-up after surgery.

Case 3: The patient was a 62-year-old man who recently complained of swelling and discomfort in his right lower limb, while the initial abnor-

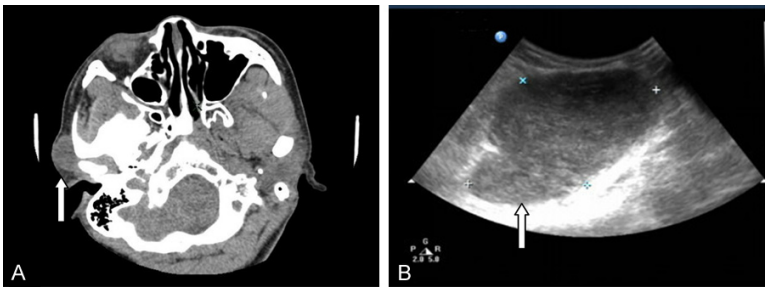

Figure 1. Imaging features of angiofibroma of soft tissue. A. CT scan of case 1 displayed a subcutaneous mass in the right temporal lobe, with clear boundary. B. Ultrasonography of case 2 revealed a well-defined and low-echo nodule mass in the popliteal fossa.

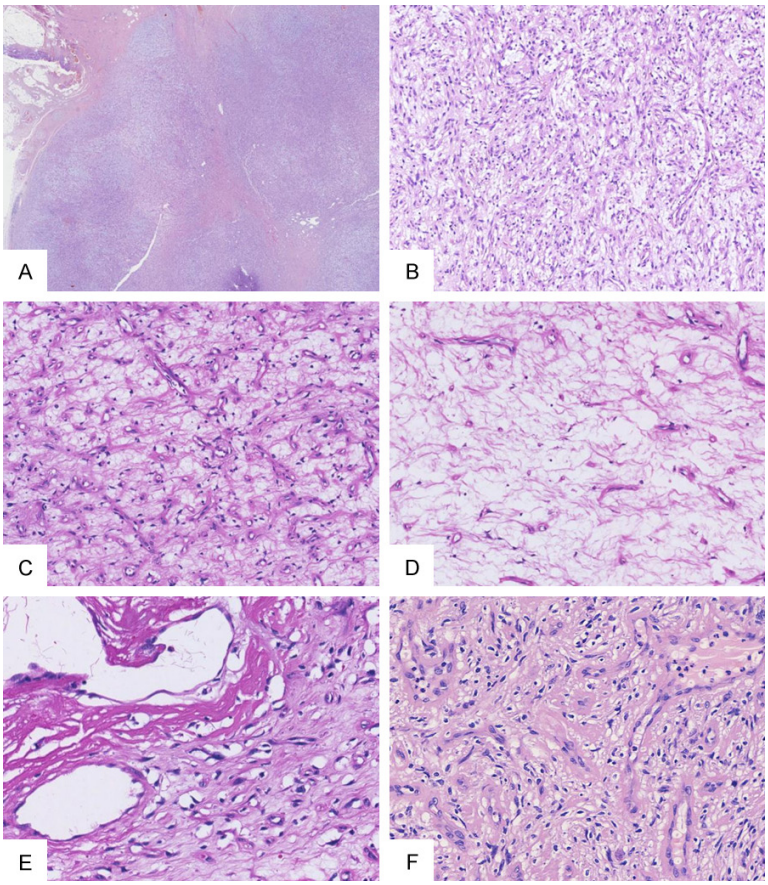

Figure 2. Pathologic findings of angiofibroma of soft tissue. A. The tumor of case 1 was divided into multiple nodules by prominent and large fibrous septa with the clear border (HE, ×10). B. At low magnification, the tumor tissues were characterized by uniform spindle-shaped cells set in a variably collagenous or myxoid stroma with rich vascular networks (HE, ×100). C and D. Case 2 and Case 3 showed alternating zones of hypocellularity and hypercellularity, in which the hypercellular areas showed the relatively abundant spindle cells and collagenous stroma, while the hypocellular areas revealed a glassy and myxoid matrix (HE, ×100). E. Case 2 revealed local fibrinoid necrosis around vessels (HE, ×200). F. At high magnification, case 3 revealed that the vascular wall was accompanied by collagen deposition or transparent degeneration, and obvious inflammatory cell infiltration (HE, ×200).

mality had lasted for 10 years. On physical examination, the right lower limb showed a pro minent and protruding mass, with a clear border. During the operation, the doctors found that it had adhered to the surrounding tissues, and its size was 3×2 cm. No imaging feature or clinical follow-up was available because this was a consultation case from another medical institution.

Materials and methods

Two cases of AFST were retrieved from the consultation files of the Department of Pathology, Affiliated Hospital of Jining Medical University; meanwhile, another case came from the Pathology Reading Conference of Shandong Province. The clinical information was obtained from the medical records or the hospital discharge summary; moreover, all available hematoxylin and eosin (H&E) slides were reviewed by two pathologists with expertise in bone and soft tissue pathology. At the same time, an immunohistochemistry analysis was performed on paraffin-embedded sections using the EnVision two-step method. Primary antibodies used in the study were displayed as follows: EMA (Kit-0011, E29), Actin (Smooth Muscle) (SMA, Kit-0006, 1A4), CD34 (Kit-0004, QBEnd/10), desmin (Kit-0023, D33), and Ki-67 (MAB-0672, MX006), Ready-to-use; Maixin Bio, Fujian, China. Appropriate positive and negative controls were used coincidentally for all the markers tested.

Pathological findings

Grossly, case 1 was a well-circumscribed nodular mass

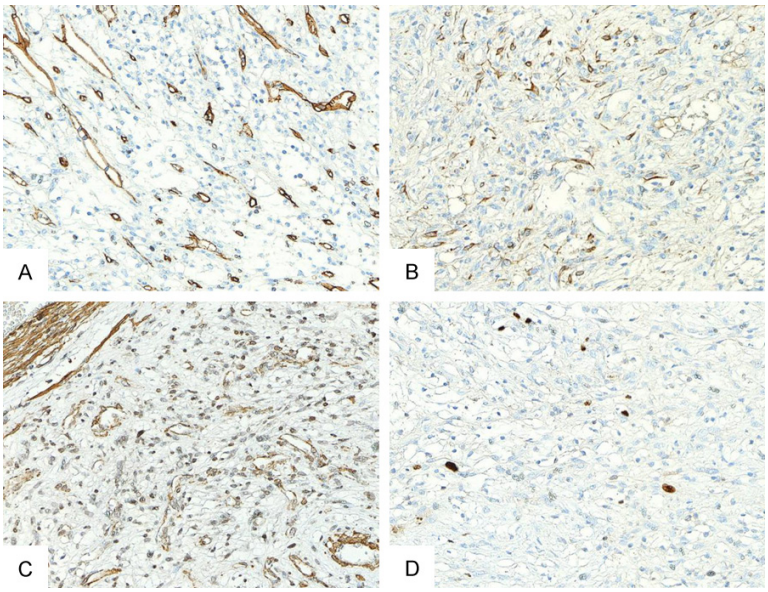

Figure 3. Immunohistochemical stains of angiofibroma of soft tissue. A. Tumor cells were negative for CD34 (×200). As a positive internal control, CD34 was positive in the endothelial cells of the real vessels. B. Tumor cells were locally positive for desmin (×200). C. Tumor cells were locally positive for SMA (×200). D. Ki67 decorated less than 1% tumor cells.

that measured about 3×2.5×2 cm and was attached to the skin, with gray and firm cut surfaces. The cut surface of case 2 also showed an 8.0×4.7×3.5 cm nodular mass, surrounded by fibrous tissue, without obvious bleeding, necrosis, or cystic degeneration. Like the first two cases, case 3 also was a nodular lump that measured about 3.0×2.0×1.8 cm, with a clear boundary, and a gray-red and crisp section. Histologically, the tumors of three cases were all well demarcated and nodular with some fibrous envelope (**Figure 2A**). A microscopic examination revealed the tumor tissues were characterized by uniform spindle-shaped cells set in a variably collagenous or myxoid stroma with rich vascular networks (**Figure 2**). In case 1, the tumor was divided into multiple nodules by prominent and large fibrous septa, followed by the alternating distribution of collagen and mucus (**Figure 2A**, **2B**). The other two cases showed alternating zones of hypocellularity and hypercellularity, in which the hypercellular areas showed the relatively abundant spindle cells and collagenous stroma, while the hypocellular areas revealed a glassy and myxoid matrix, similar to perineurioma (**Figure 2C**, **2D**). Meanwhile, some pathologic regions of case 2 were locally associated with fibrinoid necrosis (**Figure 2E**). At high magnification, the cytoplasm of the spindle cells was rare and pale red, and the nucleus was round or oval, without obvious nucleolus, nuclear fission, or apoptosis. Another characteristic change of the lesion was abundant thin-walled vessels throughout the tumor. It was also easy to find some medium to large blood vessels in the tumor, with varying thickness, resembling antlers. At the same time, case 3 revealed that the vascular wall was accompanied by collagen deposition or transparent degeneration, and obvious inflammatory cell infiltration such as neutrophils (**Figure 2F**).

Immunohistochemistry

EMA and CD34 were consistently negative in the spindle cells of all three cases, while the endothelium of the proliferative vessels in the three cases showed strong expression of the endothelial cell marker (**Figure 3A**). Desmin and SMA were focally expressed in the spindle tumor cells (**Figure 3B**, **3C**), and Ki67 decorated less than 1% lesional cells in all cases (**Figure 3D**).

Discussion

Angiofibroma of soft tissue, a recently defined benign soft tissue tumor entity with fibroblastic cytomorphology and a prominent vascular pattern, was first reported by Mariño-Enríquez et al. in 2012, and subsequently described by Schoolmeester, Arbajian, Edgar, and others, and a total of 81 cases have been reported so far [2-6]. Meanwhile, we referred to these 81 cases and added another 3 cases in our study, and then summarized them (see **Table 1** for details and references). Clinically, as in our cases 2 and 3, AFST most commonly presents as a slowly growing, painless mass located in the deep-seated and subcutaneous soft tissues of the extremities, especially the lower extremity (58/84 cases), accounting for around 69% of the cases we studied [2, 3]. However, the literature also documents the incidence of AFST in other anatomic distributions, including

Table 1. Clinical features of the 84 reported cases of AFST

No.	Information Literatures	Age (year)	Sex	Size (cm)	Site	Clinical Treatment	Follow-up (months)
1	Mariño-Enríquez et al., 2012	6-86 (median 47)	F (×25) and M (×12)	1.2-12.0 (mean 4.3)	Lower extremity (×23)	SE (×29)	NED (×23, 6-122 m)
					Upper extremity (×5)	WE (×6)	Recurrence (×4, 9, 12, 36 and 120 m)
					Trunk (×9)	Amputation (×1)	UA (×9)
						UA (×1)	
2	Schoolmeester et al., 2013	54	F	1.9	Knee	SE	UA
3	Arbajian et al., 2013	41	F	UA	Thigh	UA	UA
4	Edgar et al., 2013	62	F	7.0	Iliac crest	Radical excision	NED (9 m)
		68	M	UA	Chest wall	UA	UA
5	Zhao M et al., 2013	57	M	2.0	Thigh	SE	12
		54	M	3.0	Posterior neck	SE	UA
6	Sugita et al., 2014	27	F	2.0	Upper arm	SE	3
		38	M	5.6	Inguinal region	SE	55
		70	F	9.5	Thigh	SE	24
		41	M	8.0	Thigh	WE	8
7	Song et al., 2014	51	F	2.2	Thigh (R)	SE	NED
8	Fukuda et al., 2014	73	F	9.5	Thigh (L)	SE	6
9	Lee et al. 2014	37	M	9.1	Foot (L)	SE	24
10	Yamada et al., 2016	28-70 (median 50)	F (×6) and M (×7)	2.0-10.0 (mean 5.8)	Lower extremity (×11)	UA	NED (×2, 4, 18 m)
					Trunk (×2)		Recurrence (×1, 96 m, Incomplete resection)
							UA (×10)
11	Panagopoulos et al., 2016	45	M	5.8	Inguinal region	SE	UA
12	Zhao M et al., 2016	31	F	3.1	Lower leg (R)	SE	UA
13	Jeong et al., 2017	50	F	2.5	Cheek (L)	SE	UA
14	Hashino et al., 2017	23	F	3.0	Knee (L)	SE	9
15	Bekers et al., 2017	7-67 (median 50)	F (×6) and M (×8)	1.6-8.7 (mean 3.9)	Lower extremity (×12)	SE (×14)	NED (×10, 3-48 m)
					Upper back (×1)		UA (×4)
					Flank (×1)		
16	Present case*	36	F	3.0	Tempora (R)	SE	20
		59	F	8.0	Popliteal fossa	SE	16
		62	M	3.0	Lower extremity	SE	UA

Lower extremity includes foot, ankle, popliteal fossa, knee, thigh, and lower leg. Upper extremity includes the wrist, arm and forearm. Trunk includes the back, pelvic cavity, breast, inguinal area, iliac crest, pectoralis muscle, and abdominal wall. F, female; M, male; cm, centimeters; m, months; UA, unavailable; NED, no evidence of disease; SE, simple excision; WE, wide excision; NP, no progression; *Current case.

Table 2. Anatomic distribution of 84 cases of AFST

Anatomic Location	Number of Cases
Lower extremity	58
Thigh	24
Knee	12
Popliteal fossa	4
Lower leg	9
Ankle	2
Foot	7
Upper extremity	8
Shoulder	1
Upper arm	3
Forearm	2
Wrist	2
Trunk	15
Back	5
Chest wall	1
Abdominal wall	2
Inguinal region	3
Iliac crest	1
Pelvic cavity	1
Breast	1
Pectoralis muscle	1
Head and neck	3
Temporal lobe	1
Cheek	1
Neck	1
Total	84

the back, inguinal region, chest wall, abdominal wall, pelvic cavity, neck, cheek, and breast (**Table 2**) [1-8]. In the present report we have discussed a case of AFST located in the right temporal lobe with a multinodular structure. To the best of our knowledge, none of the published literature has portrayed the incidence of AFST in the subcutaneous tissue of head. In the meantime, the gender distribution revealed that 49 patients were female and 35 were male, and the age at diagnosis ranged from 6 to 86 years, with a mean of 48 years (**Figure 4**). As reported in the previous literature, we found that AFST tends to occur in middle-aged women (F:M=1.4:1; median 51 years) with a course of several years. Three cases we reported had a long history, including case 2, with a slow-growing mass in the popliteal fossa, and case 3, with a mass in the right lower limb, had both existed for up to 10 years. Nevertheless, because this subtype of soft tumor was only recently documented, more case reports to delineate the exact epidemiologic features are needed.

Macroscopically, the greatest diameter of AFST ranges from 1.2 to 12 cm with a mean size of 4.3 cm, and most of the neoplasms reveal a well-circumscribed nodular lesion and a white to grey cut surface, while case 1 showed a clearly multinodular structure, with which only two cases were reported before [1-3]. Histologically, as is typical of AFST, our three cases were sharply demarcated and surrounded by partial fibrous capsule, and the tumor tissues were characterized by uniform spindle-shaped cells set in a variably collagenous or myxoid stroma with a complex vascular pattern. At low power examination, the lesion of case 1 was divided into multiple nodules by prominent and large fibrous septa, with the alternating distribution of collagen and mucus, and the spindle cells distributed haphazardly throughout the lesion in no particular arrangement, similar to the report of Yamada et al. [3]. Another two cases showed a wide range of hypocellularity and hypercellularity, in which the hypercellular areas showed relatively abundant spindle cells and collagenous stroma, while the hypocellular areas revealed a glassy and myxoid matrix, similar to the perineurioma reported by Ming et al. in 2013 [7]. Meanwhile, some pathologic regions of case 2 revealed fibrinoid necrosis, perhaps due to the large volume of the tumor. At high magnification, neoplasms were composed of bland-looking spindle cells with an inconspicuous cytoplasm, and most cellular nuclei were round, oval or tapering, without any obvious nucleolus, or apoptosis. Another characteristic change of the lesion was the abundant and evenly distributed branching of thin-walled vessels, resembling those seen in myxoid liposarcoma, but the vessels of AFST were bigger and greater in number. Also, on the tumor peripheries of the three cases we observed medium-sized or large-sized blood vessels, with varying thickness, resembling staghorn morphology as Mariño-Enríquez et al. reported. In addition, case 3 revealed collagen deposition or focal hyalinization of the vessel wall, with infiltrates of neutrophils and lymphocytes in the background. The immunohistochemical analysis of EMA and CD34 were completed in our cases, and they were all consistently negative. Meanwhile, positive controls were effective, such as the endothelium of pro-

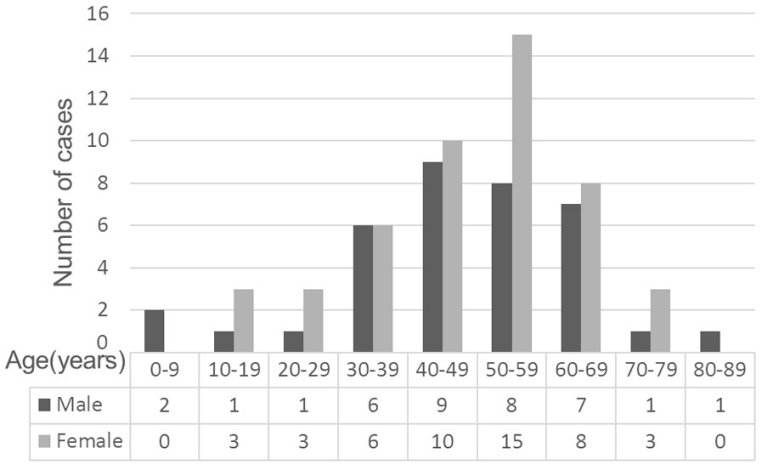

Figure 4. Age and gender distribution in 84 cases of angiofibroma of soft tissue.

liferative vessels in our cases showing a strong expression of CD34, which could rule out our experimental problems. The expression of desmin and SMA observed in a small number of tumor cells coincides with a fibroblastic/myofibroblastic line of differentiation. Similar to previous reports, we found that AFST has no specific immunological markers [9]. The expression of EMA was reported at 44% in the literature, but many soft tissue tumors also express EMA such as perineurioma [10]. However, combined application of estrogen receptor- and CD163-immunostaining could serve as a good guide from the study of Yamada et al.; meanwhile, it was noteworthy to determine whether the histiocytic marker-positive cells were genuine tumor cells [9].

AFST has characteristic genetic features with a frequent and pathogenetically significant chromosomal translocation t(5;8)(p15;q13), resulting in a consistent rearrangement of nuclear receptor coactivator 2 (*AHRR-NCOA2* fusion genes) as documented in earlier case reports [11-15]. According to the report of Jin et al., the *AHRR-NCOA2* chimeric protein can activate the AHR signaling, leading to neoplastic transformation [11]. In addition, the three way t(5;8;8)(p15;q13;p11) translocation has also been described by Mariño-Enríquez et al. and Jin et al., and recently another three way t(7;8;14)(q11;q13;q31) was reported by Arbajian et al., causing a *GTF2I-NCOA2* fusion gene, which indicates that *NCOA2* plays a vital role in AFST's etiology. Although *NCOA2* gene rearrangement was observed in almost all reported cases by FISH (fluorescence in situ hybridization), the rearrangement only occurred in a small population of the tumor cells, which implies that there are limited numbers of true neoplastic cells in AFST. Furthermore, RT-PCR and direct sequencing can also detect the existence of fusion genes, but in only about two-thirds of the cases according to Yamada et al. [3]. Therefore, joint application of the above methods in the diagnosis of AFST would be a useful adjunct.

Although AFST has been proposed as a distinct entity, it also needs to be differentiated from the following neoplasms, including solitary fibrous tumor (SFT), cellular angiofibroma (CAF), low-grade fibromyxoid sarcoma (LGFMS), low-grade myxofibrosarcoma (MFS), myxoid liposarcoma (MLS), and soft tissue perineurioma. It is difficult to distinguish SFT from AFST, because they have the parallel rich fibrovascular stroma and also arise in the deep soft tissue of the extremities. However, SFT lacks the abundant and evenly distributed thin-walled vessels and its tumor cells are diffusely positive for CD34 and Stat6, with specific chimeric fusion gene *NAB2-STAT6* [16]. Cellular angiofibroma (CAF) is another candidate for differential diagnosis because it accompanies uniform, spindle-shaped cells and numerous small- to medium-sized vessels that are similar to the histopathological characteristics of AFST. Nevertheless, the accompanying blood vessels of CAF tend to have thick and hyalinized walls, and its anatomical location commonly emerges in the genitourinary region, which can differ from AFST. Furthermore, both tumors are completely different on *NCOA2* FISH, and CAF reveals the diminished expression of Rb protein due to chromosome 13q14 deletion. Another antidiastole is soft tissue perineurioma that presents uniform bland spindle neoplastic cells arranged in vague fascicular or storiform patterns with myxoid, collagenous or hyalinized stroma, which shares a histologic picture similar to AFST, such as our two cases. However, immunoreactivity for EMA in perineurioma is almost always seen, as well as GLUT1 [17].

Moreover, some malignant tumors such as LGFMS, MFS and MLS, should also be considered due to their relatively moderate cytologic features with fibrovascular and myxoid stroma, easily leading to misdiagnosis. It is a common sense to a pathologist that LGFMS as an important malignant tumor shares a bland spindle cell composition set in abundant fibromyxoid stroma with the angiofibroma. Whereas the strong expression of MUC-4 can be observed in LGFMS, it is negative in AFST. Moreover, LGFMS exhibits significant *FUS-CREB3L2* or *FUS-CREB3L1* fusion gene, while AFST shows obvious *NCOA2* split signals [18]. MFS usually arising in the subcutaneous tissues of the extremities of elderly patients, shows fusiform, or stellate tumor cells with atypical or pleomorphic nuclei against a myxoid background, and possesses infiltrative growth features. Although MFS also reveals elongated, curvilinear, thin-walled blood vessels, it is different from the rich vascular network of AFST [19]. At last, MLS is histologically characterized by a proliferation of short spindle cells with uniform ovoid nuclei, embedded in a myxoid matrix with a plexiform vasculature, which may cause diagnostic confusion with AFST. However, MLS takes on distinctive lipoblasts and more delicate blood vessels, accompanied by a specific translocation t(12;16)(q13-14;p11), which are all helpful to distinguish AFST from MLS [20].

Since the AFST was reported by Mariño-Enríquez et al., it has always shown a benign clinical course. Thus, most patients have been treated with marginal resection without chemotherapy or radiation. According to the literature we have reviewed, data is available for follow-up information of 53 patients with a range of 3 months to 120 months (mean, 23.5 months). Five patients developed local recurrence at 9, 13, 36, 96, and 120 months after the primary tumor diagnosis, in which one case relapsed with incomplete resection, but none developed metastasis. Given the benign clinicopathological features of the AFST as well as our three cases, we should be prudent to avoid excessive treatment.

To sum up, AFST is a benign fibrovascular soft tissue tumor, with rare local recurrences and no biological characteristics of distant metastasis, which often occurs in the extremities of adult females, just as in our results. In addition, we presented a unique case of AFST with a multinodular histological feature, which rarely located in the right temporal lobe of head. Meanwhile, we reviewed nearly all cases of AFST reported previously and discussed their clinical and pathological features, including AFST's differential diagnoses such as some similar malignancies. To avoid overtreatment, it is significant to make an accurate diagnosis of AFST by combining the clinical presentation with radiologic findings and histological features.

Acknowledgements

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Disclosure of conflict of interest

None.

Address correspondence to: Ren-Ya Zhang, Lei Li and Shuai Chen, Department of Pathology, Affiliated Hospital of Jining Medical University, Jining, Shandong Province, P. R. China. Tel: +86-537-2903217; Fax: +86-537-2903281; E-mail: hzzhang_1964@163.com (RYZ); lilei24@163.com (LL); chenshuaiweiyi@126.com (SC)

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