Int J Clin Exp Pathol 2013;6(10):2208-2215
www.ijcep.com /ISSN:1936-2625/IJCEP1308009

*Case Report*

# Angiofibroma of soft tissue: clinicopathologic study of 2 cases of a recently characterized benign soft tissue tumor

Ming Zhao[1], Ke Sun[2], Changshui Li[1], Jiangjiang Zheng[1], Jingjing Yu[1], Jie Jin[1], Wenping Xia[3]

*[1]Department of Pathology, [3]Department of Radiology, Ningbo Yinzhou Second Hospital, Ningbo, Zhejiang 315100, China; [2]Department of Pathology, The First Affiliated Hospital, College of Medicine, Zhejiang University, Hangzhou, Zhejiang 310003, China*

Received August 4, 2013; Accepted August 27, 2013; Epub September 15, 2013; Published October 1, 2013

**Abstract:** Angiofibroma of soft tissue is a very recently characterized, histologically distinctive benign mesenchymal neoplasm of unknown cellular origin composed of 2 principal components, the spindle cell component and very prominent stromal vasculatures. It usually occurs in middle-aged adults, with a female predominance. Herein, we describe the clinical and pathologic details of 2 other examples of this benign tumor. Both patients were middle-aged male and presented with a slow-growing, painless mass located in the deep-seated soft tissue of thigh and left posterior neck region, respectively. Grossly, both tumors were well-demarcated, partial encapsulated of a grayish-white color with firm consistence. Histologically, one case showed morphology otherwise identical to those have been described before, whereas the other case showed in areas being more cellular than most examples of this subtype tumor had, with the lesional cells frequently exhibiting short fascicular, vaguely storiform and occasionally swirling arrangements, which posed a challenging differential diagnosis. Immunostains performed on both tumors did not confirm any specific cell differentiation with lesional cells only reactive for vimentin and focally desmin and negative for all the other markers tested. This report serves to broaden the morphologic spectrum of angiofibroma of soft tumor. Awareness of this tumor is important to prevent misdiagnosis as other more aggressive soft tissue tumor.

**Keywords:** Soft tissue tumor, benign, angiofibroma, fibrovasular tumor, differential diagnosis

## Introduction

Aside from vascular tumors, soft tissue tumors featuring of a spindly cellmorphology and a prominent vascular pattern encompass a growing array of benign and low-grade malignant entities of different cell differentiation, such as fibroblastic/myofibroblastic (cellular angiofibroma [1], solitary fibrous tumor (SFT) [2], low-grade fibromyxoid sarcoma (LGFMS) [3], and low-grade myxofibrosarcoma [4]), and lipomatous (myxoid liposarcoma [5]). Distinguishing these morphologically confusing neoplasms is of considerable clinical significance because of different therapeutic selections.

Angiofibroma of soft tissue is a most recently characterized benign fibrovascular neoplasm [6-8]. Clinically it usually occurs in middle-aged adults with a female predominance and presents as a slowly growing, painless, well-defined mass located in the soft tissues of the extremities, often in relationship to joints or fibrotendinous structures [6]. Histologically, soft tissue angiofibroma is characterized by the presence of a proliferation of relatively uniform, bland spindle cells set in a variably myxoid-to-collagenous stroma with a prominent and complex vascular network [6-8]. Immunohistochemically, the neoplastic cells are focally positive for epithelial membrane antigen; occasional cases may show scattered cells that stain CD34, smooth muscle actin and desmin [6]. Depending on the clinicopathologic context, soft tissue angiofibroma can be mistaken for all the above mentioned neoplasms with similar histologic appearance. In this paper, we present our experience with 2 examples of this benign tumor, one of which exhibits a more cellular proliferation of the lesional cells than most examples of

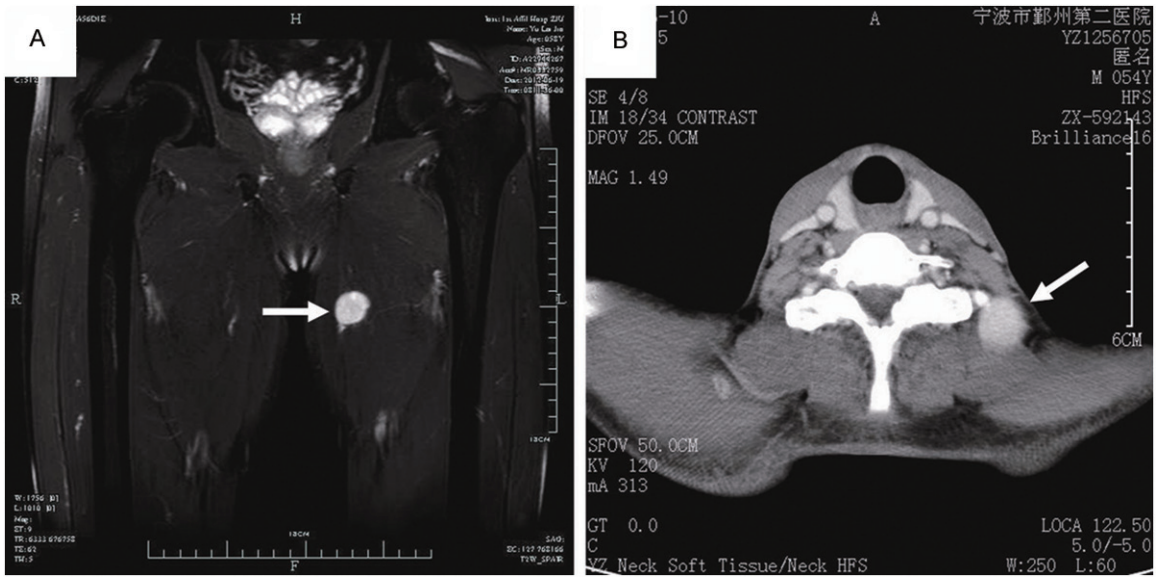


**Figure 1.** Imaging features of angiofibroma of soft tissue. A. Contrast-enhanced magnetic resonance imaging scan of case 1 showed a well-defined ovoid soft tissue, hyperintense to muscle, located deep to the musculus gracilis of the left thigh. B. Contrast-enhanced computed tomography scan of case 2 revealed a homogeneously enhancing, well-defined, firm soft tissue mass located in the left posterior neck region between the first and second intercostal space.

this tumor type have being, posing a challenging differential diagnosis.

## Case presentation

*Case 1*

A previous healthy 57-year-old man was incidentally identified to have a painless mass in his right thigh. Imaging studies including a magnetic resonance imaging scan demonstrated a well-demarcated, obviously enhancing round mass measuring 2-cm in maximum diameter located in the spatium intermusculare of the femoribus internus (**Figure 1A**). No extensive into the surrounding soft tissue or bone was noted, evidence of tumor association with a peripheral nerve was also unidentified. Given a suspicious for a benign neurogenic tumor, the patient underwent simple tumor excision. His recovery was uneventful and there was no evidence of tumor local recurrence or distant metastasis 12 months after surgery.

*Case 2*

This was a 54-year-old man presented as an incidentally identified, painless mass in his left posterior neck region of 3-year duration. His past medical history was unremarkable. Contrast enhanced computed tomography scan revealed a homogeneously enhancing, well-defined, firm soft tissue mass located in the left posterior neck region between the first and second intercostal space (**Figure 1B**). The patient proceeded to simple surgical excision. Intraoperative examinations showed that the tumor was well-demarcated, measuring 2.8 × 2.6 cm, located at the cervical paravertebrae and the possibility of a benign neurogenic tumor was indicated by the surgeons. The patient was discharged a week after the surgery with an uneventful postoperative recovery. No further clinical follow-up is available as this was a very most recently case.

## Methods

Representative sections of both tumors were fixed overnight in 10% neutral buffered formalin, embedded in paraffin and 4-μm sections were stained with hematoxylin and eosin. Immunohistochemical analysis was performed using the avidin-biotin complex immunoperoxidase technique and a panel of commercially available primary antibodies was used including: cytokeratin AE1/AE3 (AE1/3; DAKO, Glostrump, Denmark), epithelial membrane antigen (EMA; E29, DAKO), vimentin (V9, DAKO), smooth muscle actin (SMA; 1A4, DAKO), desmin (D33, DAKO), CD31 (JC/70A, DAKO), CD34 (QBEnd/10, DAKO), S100 protein (polyclonal,

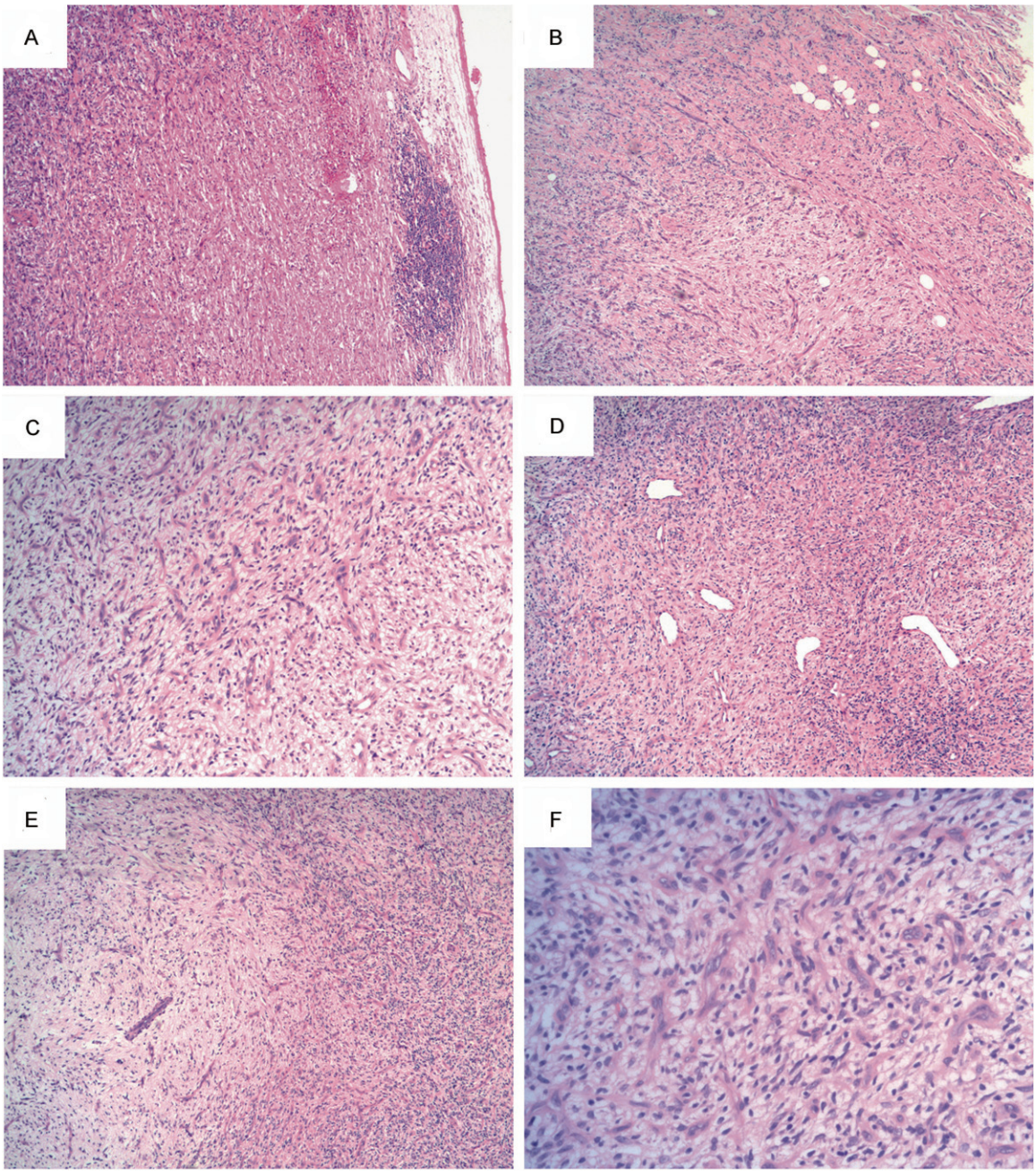


**Figure 2.** Microscopic features of case 1. At low power, the tumor was partially surrounded by a thin fibrous capsule which contained a tiny aggregate of small mature lymphocytes (A), however, uneccapsulated areas of the tumor showed tumor cells focally infiltrated into adipose tissue (B). The tumor cells were haphazardly arranged and set in a variably collageous or myxoid background with very prominent, thin-walled branching vascular network (C), and occasionally ectatic hemangiopericytoma-like vessels were presented (D). E showed the smooth transition of myxoid and relatively hypocellular areas to collagenous and more cellular areas. High power examination showed that the spindle neoplastic cells were generally uniform, bland and contained small amount pale cytoplasm and tapering nuclei (F).

DAKO), CD21 (2G9, DAKO), CD35 (Ber-MAC-DRC, DAKO), and Ki67 (MIB-1, DAKO). Appropriate positive and negative controls were run concurrently for all the markers tested.

### Pathologic findings

Cut surface of case 1 showed a well-circumscribed firm mass measuring 2.5 × 2.3 × 2.2

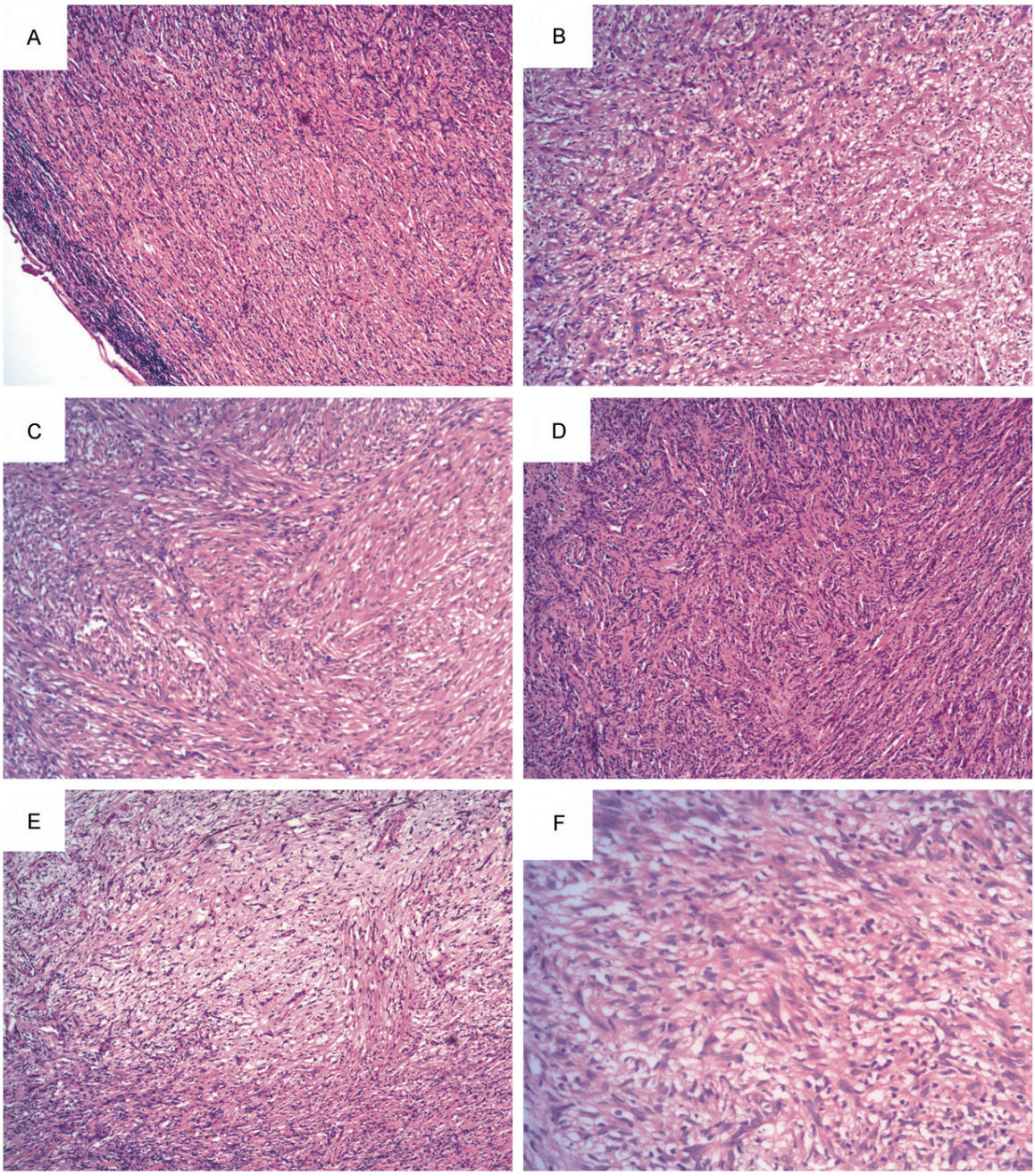


**Figure 3.** Microscopic features of case 2. As to case 1, this tumor was also partially encapsulated with a tiny of lymphoid aggregates located at the periphery of the lesion (A). Except small areas demonstrating the typical histologic appearances of soft tissue angiofibroma (B), other areas were much more cellular with lesional cells frequently showing short fascicular (C), storiform (D) and occasionally swirling (not shown) arrangements. The extracellular matrix was mainly collagenous and occasionally myxoid or edematous (E). On high magnification, the tumor cells were quite nondistinctive with inconspicuous, palely eosinophilic cytoplasm and bland nuclei (F).

cm surrounded by adipose tissue, of a grayish-with color and consistent texture. Case 2 was a partial encapsulated tumor measuring 3 cm in maximum diameter with homogeneous tan-white, firm cut surfaces.

Microscopic examination showed that both tumors demonstrated strikingly similar histological appearance and consisted of a proliferation of cytologically uniform spindle cells and a very prominent thin-walled branching vascular

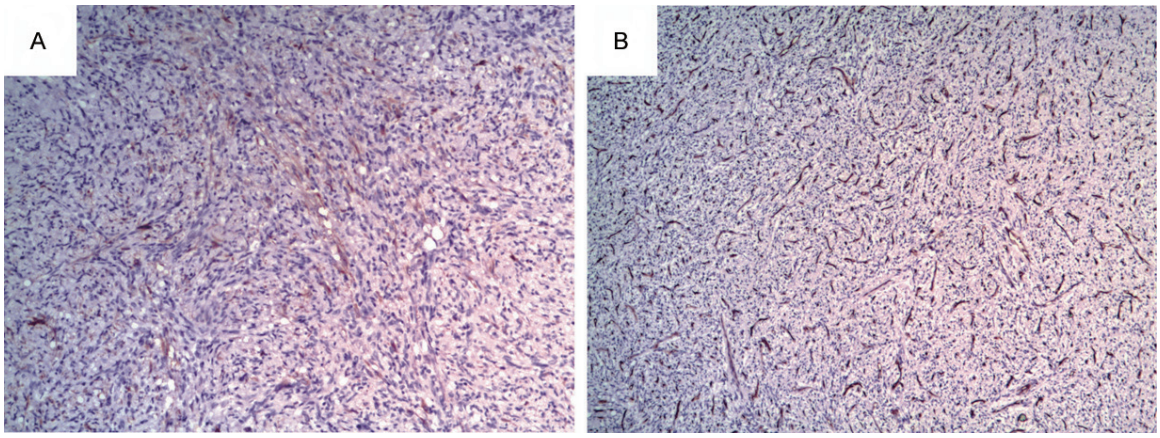


**Figure 4.** Immunohistochemistry analysis of both tumors did not confirm any specific cell differentiation with lesional cells only reactive for vimentin and focally desmin (A) and negative for all the other markers tested. CD34 staining highlighted the endothelial cells lining the rich vascular network but did not label the tumor cells (B).

network (**Figures 2**, **3**). At low-power examination, both tumors were well demarcated and partially surrounded by a fibrous capsule of variable thickness (**Figures 2A**, **3A**). However, evidence of tumor cells extension into the resection margins was noted in both tumors. In addition, foci of tumor cells infiltration into adjacent adipose tissue were also observed in case 1 (**Figure 2B**). Case 1 showed mild regional variation in cellularity with the spindly neoplastic cells being distributed haphazardly throughout the tumor without a particular growth pattern (**Figure 2C**). Whereas case 2 was a much more hypercellular tumor with the lesional cells frequently exhibiting short fascicular, storiform and occasionally swirling arrangements, having a resemblance to perineurioma, benign fibrous histiocytoma, or follicular dendritic cell sarcoma (**Figure 3B-D**). On high magnification, the spindle-shaped tumor cells in both cases were generally bland and uniform with small amount pale-to-eosinophilic cytoplasm and tapering nuclei with fine chromatin and inconspicuous nucleoli (**Figures 2F**, **3F**). No nuclear hyperchromasia and pleomorphism were identified, mitotic and apoptotic activities were not evident. Another distinctive histologic feature noted in both tumors was the prominent vascular pattern which consisted of innumerable small thin-walled, branching vessels evenly distributing throughout the lesion (**Figures 2**, **3**). In addition, ectatic larger-sized, hemangiopericytoma-like vessels, and vessels with thicker wall showing perivascular hyalinization were also occasionally presented in these tumors (**Figure 2D**). The extracellular matrix was mainly collagenous and occasionally myxoid or edematous in both cases and the transition of collagenous areas to myxoid zones was usually smooth and gradual (**Figures 2E**, **3E**). Inflammatory cells mainly mature small lymphocytes and occasional plasma cells were admixed with the spindle cells throughout the tumor and a multiple tiny lymphoid aggregate located at the periphery of the lesion was observed in both cases (**Figures 2A**, **3A**). Immunostains performed on both cases showed spindle cells diffusely labeling for vimentin and focal labeling for desmin (**Figure 4A**) and no expression of AE1/3, EMA, SMA, c-kit, CD21, CD35, or S100 protein. CD31 and CD34 staining highlighted the endothelial cells lining both the numerous thin-walled and the hemangiopericytoma-like vessels but not labeled the tumor cells (**Figure 4B**). Ki67 decorated less than 1% lesional cells in both cases.

## Discussion

Angiofibroma of soft tissue is a distinctive fibrovascular neoplasm most recently described by Marino-Enriques and Fletcher [6] in a series of 37 cases in 2012, with additional cases reported by Schoolmeester [7] and Edgar [8] and colleagues subsequently. Clinically, as in our case 1, angiofibroma of soft tissue most commonly presents as a slowly growing painless mass located in the deep-seated as well as subcutaneous soft tissues of the extremities, predominantly the lower extremity, often in relationship to joints or fibrotendinous structures [6]. However, it can display a broad anatomic distribution including back, chest wall, abdominal

wall, pelvic cavity and even parenchymal organ [6, 7]. Case 2 in the current study was located in the deep-seated soft tissue of left posterior neck region between the first and second intercostal space, which is the first report of soft tissue angiofibroma occurring in the head and neck region. Both patients in our study were male patients, which is in contrast to the previous description that angiofibroma of soft tissue seemed to have a female predominance affecting the male population twice as frequently as the male population [6]. However, because this subtype of soft tumor is a very recently characterized lesion, the exact epidemiologic features are waiting for accumulation of more cases to delineate.

The microscopic features and immunohistochemical findings of both our cases were essentially identical to those have been previously characterized for angiofibroma of soft tissue [6-8]. The only difference was that our case 2 which was a much more hypercellular lesion than most examples of this tumor have being. The arrangements of leisonal cells in short fascicles, vague storiformity and swirl in areas of this case were remarkably different from the typically haphazard and patternless distribution of tumor cells noted in ordinary soft tissue angiofibroma [6] and posed a challenging differential diagnosis with both benign and malignant spindle cell tumors of different cell differentiation. In addition, lack of specific immunohistochemical markers for soft tissue angiofibroma to date further complicates this diagnostic confusion, although EMA has been reported to be expressed in approximate 50% soft tissue angiofibroma cases [6], this marker is very unspecific and can be expressed by many other soft tissue tumors of a variety of cell differentiation [6]. Cytogenetic analysis of angiofibroma of soft tissue have revealed a balanced t(5;8)(p15;q13) chromosomal translocation resulting in the gene fusion of the aryl hydrocarbon receptor repressor (*AHHR*) and nuclear receptor coactivator 2 (*NCOA2*) genes in a subset of cases [6, 7, 9]. In addition, a threeway t(5;8;8)(p15;q13;p11) translocation has also been described in one case [6, 9], and recently a case was reported to carry a t(7;8;14)(q11;q13;q31) causing a *GTF21-NCOA2* fusion gene [10]. Because these novel gene rearrangements have not been detected in the histological mimickers of angiofibroma of soft tissue to date, thus fluorescent in situ hybridization (FISH) assay for *AHRR* or *NCOA2* rearrangements has been suggested to serve as a reliable laboratory test for the diagnosis of soft tissue angiofibroma [10], however, this detecting technique has not been widely available currently [8] and it has also been noted that a substantial subset of analyzed soft tissue angiofibromas were negative for the fusion gene [10].

The differential diagnosis of angiofibroma of soft tissue is centered on other highly vascular, spindle cell neoplasms such as solitary fibrous tumor (SFT), low-grade fibromyxoid sarcoma (LGFMS), and myxoid liposarcoma. SFT can occur in a variety of locations outside the pleura, similar to that of angiofibroma, the spindle neoplastic cells in SFT are cytologically bland and often take on patternless growth architecture. In addition, regional variation in cellularity, thick collagenous fiber deposits, foci of stroma myxoid degeneration, and large-sized branching hemangiopericytoma-like vessels can also be noted in both the two tumors, however, SFT lacks the innumerable, evenly distributed, arborizing thin-walled vessels characteristic of angiofibroma. Furthermore, the tumor cells in SFT typically show strong and diffuse expression of CD34 [2]. LGFMS typically affects young adults and presents as a larger and more deeply localized mass, it shares a bland spindle cell composition and alternating collagenous and myxoid areas with soft tissue angiofibroma [3]. In addition, LGFMS commonly shows spindled cells arranging in a whorling pattern, which have a somewhat resemblance to that of our case 2. However, in contrast to our case, LGFMS usually has a much lower cellularity and less prominent ramified vasculatures with an arcade-like appearance. Genetically, LGFMS shows t (7; 16) *FUS-CREB3L2* or t (11; 16) *FUS-CREB3L1* [11], unlike angiofibroma of soft tissue. Myxoid liposarcoma also features a bland spindle cell population and a prominent plexiform of thin-walled capillaries, hence the possible diagnostic confusion with angiofibroma of soft tissue. However, it shows scattered univacuolar and multivacuolar lipoblasts throughout the lesion as well as stromal mucin pools not seen in angiofibroma of soft tissue [5]. Furthermore, the vascular network of angiofibroma of soft tumor have thicker wall and are more curvilinear and numerous than the deli-

cate “chicken wire” vessels of liposarcoma. At the genetic level, myxoid liposarcoma shows most often t (12; 16) *FUS-DDIT3* and less commonly t (12; 22) *EWS-DDIT3* [12]. Soft tissue perineurioma, which is characterized by bland spindle cells with delicate bipolar processes arranged in a storiform, whorled or fascicular pattern with various amounts of collagenous deposits, may also enter into the differential diagnosis of angiofibroma such as our case 2 [13]. However, by immunohistochemistry, perineurioma nearly always expresses EMA, largely expresses CD34 and less commonly SMA. It is generally believed that the prominent vascularization is not a typical feature of soft tissue perineurioma. However, Zamecnik et al [14] most recently have reported a case of soft tissue tumor showed typical perineurial cellmorphology and immunophenotype but contained very prominent thin-walled vasculatures throughout the lesion similar to the vascular pattern in angiofibroma of soft tissue. In their original paper, Marino-Enriques and Fletcher [6] presumed the fibroblastic differentiation of angiofibroma of soft tumor largely based on the morphologic features and on the lack of specific immunoprofile of the tumor cells. Although 44% cases of angiofibroma in their series expressed of EMA, Marino-Enriques and Fletcher commented that EMA positivity in angiofibroma of soft tissue seemed not to reflect perineural cell differentiation because the tumor cells typically lacked the characteristic cellmorphology and growth patterns of perineurioma. However, immunostains for other perineural cell markers, such as claudin-1 and GLUT-1, were not performed in their study [6]. Thus, as Zamecnik et al [14] have indicated, the line of cell differentiation in soft tissue angiofibroma remained unclear, perineural differentiation in soft tissue angiofibroma could not be excluded with certainty for the present time, and that additional studies were needed.

Other diagnoses that may be considered in the more cellular case 2 are benign fibrous histiocytoma, inflammatory myofibroblastic tumor, and follicular dendritic cell sarcoma. Attention to the characteristic morphologic characteristics of both the spindle cell component and the distinctive vascular network of angiofibroma and with the aid of immunohistochemistry stain to demonstrate no specific differentiation of the lesional cells will help to easily distinguish this distinctive tumor from these above mentioned mimickers.

In summary, we present 2 examples of the recently characterized benign fibrovascular neoplasm, termed angiofibroma of soft tissue, with one case located at an unusual site and displaying a much more hypercellular lesion with various growth patterns than most examples of this tumor type have being. Awareness of the unique histopathologic features of these lesions should allow for their ready distinction from other more aggressive soft tissue tumors.

## Acknowledgements

The authors thank Dr Christopher D. M. Fletcher of Brigham and Women’s Hospital, Boston, MA, USA for his expert opinion in case 2.

## Disclosure of conflict of interest

None.

**Address correspondence to:** Dr. Ming Zhao, Department of Pathology, Ningbo Yinzhou Second Hospital, No.1 North Qianhe Road, Yinzhou District, Ningbo, Zhejiang 315100, China. Tel: +86-574-83039018; Fax: +86-574-83038515; E-mail: zhaomingpathol@163.com

## References

[1] Iwasa Y, Fletcher CD. Cellular angiofibroma: clinicopathologic and immunohistochemical analysis of 51 cases. Am J Surg Pathol 2004; 28: 1426-35.

[2] Fletcher CDM, Bridge JA, Lee JC. Extrapleural solitary fibrous tumour. In: Fletcher CDM, Bridge JA, Hogendoom PCW, Mertens F, editors. World Health Organization classification of tumours of soft tissue and bone. Lyon, France: IARC Press; 2013. pp: 80-2.

[3] Evans HL. Low-grade fibromyxoid sarcoma. A report of 12 cases. Am J Surg Pathol 1993; 17: 595-600.

[4] Mentzel T, Calonje E, Wadden C, Camplejohn RS, Beham A, Smith MA, Fletcher CD. Myxofibrosarcoma. Clinicopathologic analysis of 75 cases with emphasis on the low-grade variant. Am J Surg Pathol 1996; 20: 391-405.

[5] Fletcher CDM. Tumors of Soft Tissue. In: Fletcher CDM, editor. Diagnostic Histopathology of Tumors. 4rd ed. Philadelphia: Churchill Livingstone Elsevier; 2013. pp: 1796-870.

[6] Mariño-Enríquez A, Fletcher CD. Angiofibroma of soft tissue: clinicopathologic characterization of a distinctive benign fibrovascular neo-

plasm in a series of 37 cases. Am J Surg Pathol 2012; 36: 500-8.
[7] Schoolmeester JK, Sukov WR, Aubry MC, Folpe AL. Angiofibroma of soft tissue: core needle biopsy diagnosis, with cytogenetic confirmation. Am J Surg Pathol 2012; 36: 1421-3.
[8] Edgar MA, Lauer SR, Bridge JA, Rizzo M. Soft tissue angiofibroma: report of 2 cases of a recently described tumor. Hum Pathol 2013; 44: 438-41.
[9] Jin Y, Möller E, Nord KH, Mandahl N, Von Steyern FV, Domanski HA, Mariño-Enríquez A, Magnusson L, Nilsson J, Sciot R, Fletcher CD, Debiec-Rychter M, Mertens F. Fusion of the AHRR and NCOA2 genes through a recurrent translocation t(5;8)(p15;q13) in soft tissue angiofibroma results in upregulation of aryl hydrocarbon receptor target genes. Genes Chromosomes Cancer 2012; 51: 510-20.
[10] Arbajian E, Magnusson L, Mertens F, Domanski HA, Vult von Steyern F, Nord KH. A novel GTF2I/NCOA2 fusion gene emphasizes the role of NCOA2 in soft tissue angiofibroma development. Genes Chromosomes Cancer 2013; 52: 330-1.
[11] Guillou L, Benhattar J, Gengler C, Gallaqher G, Ranchere-Vince D, Collin F, Terrier T, Terrier-Lacombe MJ, Leroux A, Marques B, Aubain Somerhausen Ned S, Keslair F, Pedeutour F, Coindre JM. Translocation-positive low-grade fibromyxoid sarcoma: clinicopathologic and molecular analysis of a series expanding the morphologic spectrum and suggesting potential relationship to sclerosing epithelioid fibrosarcoma: a study from the French Sarcoma Group. Am J Surg Pathol 2007; 31: 1387-402.
[12] Dal Cin P, Sciot R, Panagopoulos I, Aman P, Samson I, Mandahl N, Mitelman F, Van der Berqhe F, Fletcher CD. Additional evidence of a variant translocation t (12; 22) with EWS/CHOP fusion in myxoid liposarcoma: clinicopathological features. J Pathol 1997; 182: 437-41.
[13] Hornick JL, Fletcher CD. Soft tissue perineurioma: clinicopathologic analysis of 81 cases including those with atypical histologic features. Am J Surg Pathol 2005; 29: 845-58.
[14] Zámečník M, Mukenšnabl P, Chlumská A. Angiofibroma-like perineurioma. Report of a case. Cesk Patol 2013; 49: 86-8.