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Angiofibroma of soft tissue: Current status of pathology and genetics

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Summary. Angiofibroma of soft tissue (AFST) is a new soft tissue tumor entity described in the 2020 World Health Organization Classification of Soft Tissue and Bone Tumors. It most often arises in the lower extremities of middle-aged adults and pursues a benign clinical course with a low rate of non-destructive local recurrence. Histologically, the lesion consists of uniform bland spindle cells in a fibromyxoid stroma with a prominent vascular network. The vascular component forms a complex arrangement of small, thin-walled branching blood vessels. By immunohistochemistry, AFST is variably positive for epithelial membrane antigen, desmin, smooth muscle actin, CD34, CD68, CD163 and estrogen receptor. The exact etiology of AFST remains unknown, but it appears genetically distinct, with a balanced t(5;8)(p15;q13) translocation resulting in a fusion of aryl hydrocarbon receptor repressor (AHRR) and nuclear receptor coactivator 2 (NCOA2). Knowledge of this recently described entity is important because it can mimic a variety of intermediate and malignant soft tissue tumors, including solitary fibrous tumor, low-grade fibromyxoid sarcoma, myxoid liposarcoma and low-grade myxofibrosarcoma. We review AFST, with an emphasis on the diagnostic spectrum, recent molecular genetic features and the differential diagnosis.

Key words: Angiofibroma, Soft tissue, Fusion gene, NCOA2, AHRR, Cytogenetics

Introduction

Angiofibroma of soft tissue (AFST) is a rare benign mesenchymal neoplasm first described by Mariño-Enríquez and Fletcher (2012). It belongs to the fibroblastic/myofibroblastic tumor group according to the 5th edition of World Health Organization Classification of Soft Tissue and Bone Tumors (Mariño-Enríquez et al., 2020). AFST can show a morphological overlap with a variety of intermediate and malignant soft tissue tumors such as solitary fibrous tumor (SFT), low-grade fibromyxoid sarcoma (LGFMS), myxoid liposarcoma (MLS) and myxofibrosarcoma (MFS) (Nishio, 2013). Advances in knowledge of the histopathology and genetics of AFST are leading to more accurate diagnosis and appropriate treatment. This review highlights the clinical, histological, immunohistochemical and molecular genetic features of AFST. In addition, we will discuss the differential diagnosis of this recently described entity.

Clinical features

AFST has a peak incidence in the sixth decade of life (age range 6-86 years) with a slight female predominance (Mariño-Enríquez and Fletcher, 2012). It typically presents as a slow-growing, painless mass of variable

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Abbreviations. ABL1, ABL proto-oncogene 1; AFST, angiofibroma of soft tissue; AHRR, aryl hydrocarbon receptor repressor; ARNT, aryl hydrocarbon receptor nuclear translocator; BFH, benign fibrous histiocytoma; BRAF, B-Raf proto-oncogene; CREB3L1, cAMP responsive element binding protein 3 like 1; CREB3L2, cAMP responsive element binding protein 3 like 2; CYP1A1, cytochrome P450 family 1 subfamily A member 1; DDIT3, DNA damage-inducible transcript 3; EMA, epithelial membrane antigen; ER, estrogen receptor; ETV4, ETS variant transcription factor 4; EWSR1, EWS RNA binding protein 1; FUS, FUS RNA binding protein; GAB1, GRB2 associated binding protein 1; GTF2I, general transcription factor IIi; LGFMS, low-grade fibromyxoid sarcoma; MFS, myxofibrosarcoma; MLS, myxoid liposarcoma; MRI, magnetic resonance imaging; MUC4, mucin 4; NAB2, NGFI-A binding protein 2; NCOA2, nuclear receptor coactivator 2; P4HA2, prolyl 4-hydroxylase subunit alpha 2; PRKCB, protein kinase C beta; PRKCD, protein kinase C delta; Rb, retinoblastoma; SLC37A3, solute carrier family 37 member 3; SFT, solitary fibrous tumor; SMA, smooth muscle actin; SCL, spindle cell lipoma; STAT6, signal transducer and activator of transcription 6; TBCK, TBC1 domain containing kinase; TRIO, Trio Rho guanine nucleotide exchange factor; ZNF558, zinc finger protein 558.

duration. AFST shows a broad anatomic distribution but most frequently occurs in the lower extremities. Unusual anatomic sites include the back, abdominal wall, pelvic cavity and breast (Mariño-Enríquez et al., 2020). Although extremely rare, intra-articular involvement has been described (Hashino et al., 2017). The diameter ranges from 1.2 to 12 cm (median of 3.5 cm). Simple excision is the treatment of choice. Five cases of local recurrence have been reported in the literature (Mariño-Enríquez and Fletcher, 2012; Yamada et al., 2016). There is no documented risk for distant metastasis.

There is only limited description of the imaging appearance of AFST (Zhao et al., 2013; Fukuda et al., 2014; Lee et al., 2014; Song et al., 2014; Bekers et al., 2017; Hashino et al., 2017; Jeong et al., 2017). In our limited experience, radiographs are usually normal or reveal a non-specific soft tissue mass without calcification. Osseous erosion or invasion has not been reported. On magnetic resonance imaging (MRI), AFST shows a relatively well-defined mass with iso- to slightly-low signal intensity relative to skeletal muscle on T1-weighted sequences and heterogeneous high signal intensity on T2-weighted sequences. Strong enhancement is typically seen following intravenous contrast administration, but the enhancement pattern is variable.

Histological and immunohistochemical characteristics

Grossly, AFST usually appears as a well-circumscribed, nodular or multinodular mass with a white to yellow-tan cut surface (Fig. 1). Cystic or hemorrhagic areas may be seen (Mariño-Enríquez et al., 2020). Histologically, AFST consists of a proliferation of bland spindle cells in a fibromyxoid stroma with a prominent vascular network (Fig. 2). The lesion is usually well-circumscribed and surrounded by a fibrous capsule, but an infiltrative pattern into adjacent soft tissues can be found. The vascular component forms a complex arrangement of small, thin-walled branching blood vessels. Thick collagen bundles and inclusion of mature adipocytes can be observed (Bekers et al., 2017). Perivascular collagen deposition and hyalinization of vessel walls may be seen (Mariño-Enríquez and Fletcher, 2012). Cytological atypia and necrosis are

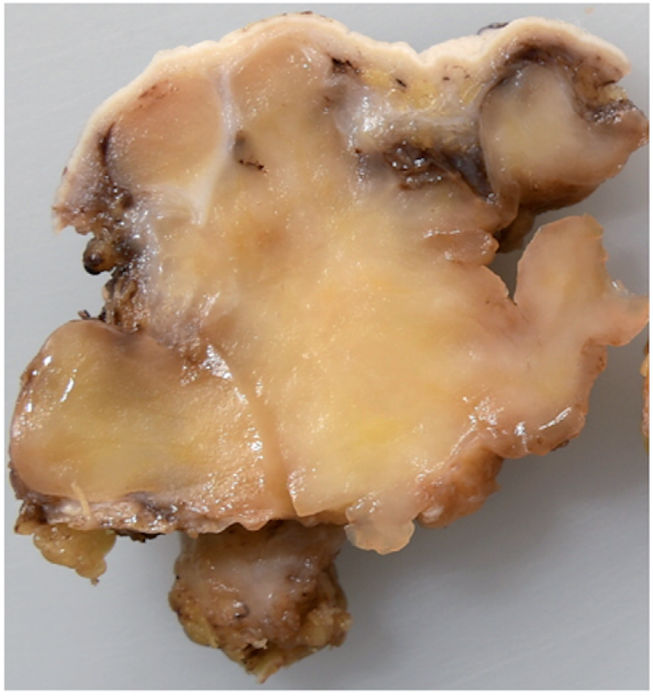

Fig. 1. Gross appearance of angiofibroma of soft tissue showing a well-circumscribed mass with a yellow-tan cut surface.

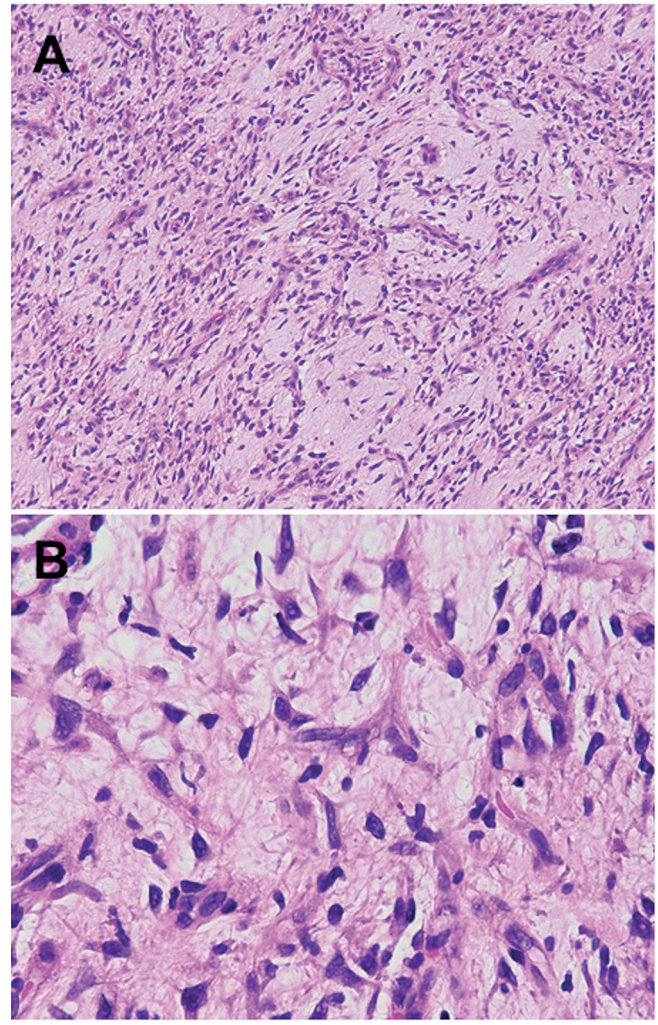

Fig. 2. Histological features of angiofibroma of soft tissue. **A.** The tumor is composed of bland spindle cells in a fibromyxoid stroma. Small, thin-walled branching blood vessels can be seen (hematoxylin and eosin staining). **B.** The spindle cells have a pale eosinophilic cytoplasm and short ovoid or tapering nuclei (hematoxylin and eosin staining). A, × 100; B, × 400.

generally absent. Mitotic activity is low and does not usually exceed 1 per 10 high-power fields (Bekers et al., 2017; Mindiola-Romero et al., 2020). Immunohistochemically, the neoplastic cells are variably positive for epithelial membrane antigen (EMA) (Fig. 3A), desmin, smooth muscle action (SMA), CD34 and CD68 (Fig. 3B) (Yamada et al., 2016; Mindiola-Romero et al., 2020). Moreover, the expression of CD163 (Fig. 3C) and estrogen receptor (ER) (Fig. 3D) has been observed in 100% of cases (Yamada et al., 2016). More recently, Bekers et al. reported that all cases analyzed showed nuclear expression of nuclear receptor coactivator 2 (NCOA2) (Bekers et al., 2017). However, NCOA2 staining is not specific for AFST because it may also occur in histological mimics of AFST, in particular SFT, LGFMS, MLS and MFS (Bekers et al., 2017). Immunostains for S-100 protein and cytokeratins are typically negative.

Molecular genetic features

AFST displays near-diploid karyotypes with a recurrent translocation t(5;8)(p15;q13), resulting in a fusion of aryl hydrocarbon receptor repressor (AHRR) (5p15) and NCOA2 (8q13) (Jin et al., 2012). AHRR is a putative tumor suppressor and regulates the activity of AHR. NCOA2 functions as a transcriptional coactivator for nuclear hormone receptors. AHRR has not previously been implicated in oncogenic gene fusions, whereas NCOA2 is the 3' partner in fusions involved in other bone and soft tissue tumors such as mesenchymal chondrosarcoma, alveolar rhabdomyosarcoma, congenital/infantile spindle cell rhabdomyosarcoma, biphenotypic sinonasal sarcoma and uterine sarcoma

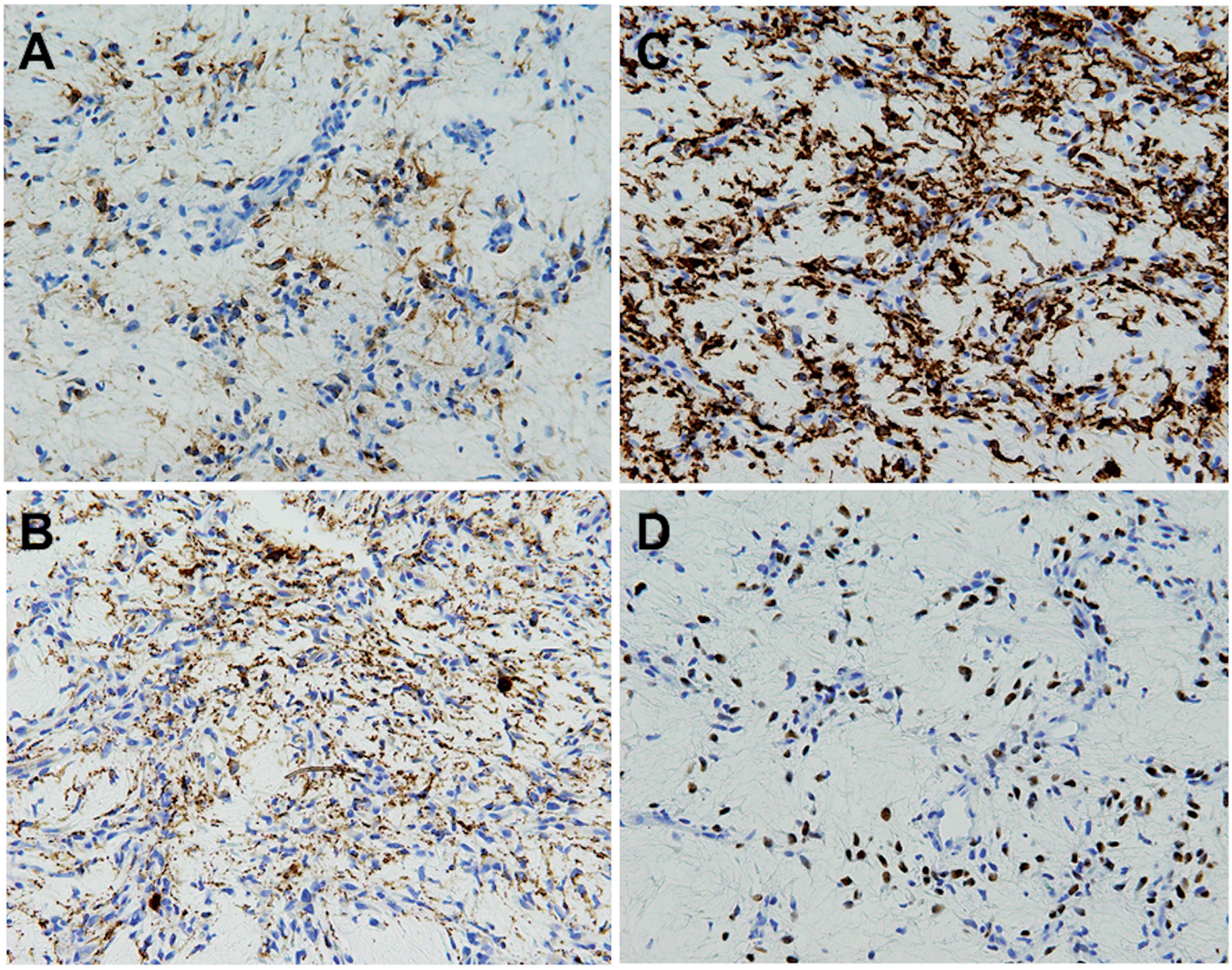

Fig. 3. Immunohistochemical features of angiofibroma of soft tissue. The neoplastic cells are focally positive for epithelial membrane antigen **(A)** and diffusely positive for CD68 **(B)** and CD163 **(C)**. **D.** The neoplastic cells show nuclear immunoreactivity for estrogen receptor. × 200.

with variable sex-cord differentiation (Mindiola-Romero et al., 2020). The AHRR-NCOA2 fusion is found in about 60-80% of cases (Mariño-Enríquez et al., 2020). NCOA2 rearrangement is detected in almost all cases, but in only a small population of tumor cells (Sugita et al., 2014; Yamada et al., 2016). The AHRR-NCOA2 chimera is predicted to upregulate the AHR/ARNT (AHR nuclear translocator) signaling pathway (Jin et al., 2012). Indeed, global gene expression analysis reveals upregulation of CYP1A1 (cytochrome P450 family 1 subfamily A member 1) as well as other well-known AHR target genes (Jin et al., 2012).

Two additional gene fusions, GTF2I (general transcription factor IIi)-NCOA2 and GAB1 (GRB2 associated binding protein 1)-ABL1 (ABL proto-oncogene 1), have also been identified in isolated cases of AFST (Arbajian et al., 2013; Bekers et al., 2017). Moreover, Panagopoulos et al. demonstrated several gene fusions, NCOA2-ETV4 (ETS variant transcription factor 4), ETV4-AHRR, P4HA2 (prolyl 4-hydroxylase subunit alpha 2)-TBCK (TBC1 domain containing kinase) and TBCK-P4HA2, in an AFST with the t(4;5)(q24;q31) and t(5;8;17)(p15;q13;q21) chromosomal translocations (Panagopoulos et al., 2016).

Most notably, these gene rearrangements have not been identified in other histologically similar fibrovascular tumors (Nishio, 2013; Sugita et al., 2014). Therefore, molecular genetic testing can be used to distinguish AFST from its histological mimics, especially on limited tissue samples.

Differential diagnosis

The differential diagnosis for AFST is broad and includes both benign and malignant entities (Mariño-Enríquez and Fletcher, 2012). It is particularly important to distinguish between AFST and intermediate and malignant soft tissue tumors to avoid unnecessary overtreatment.

In our opinion and experience, the most histologically significant differential diagnosis is SFT, which manifests an intermediate type of behavior. SFT can occur at any anatomical location and has a peak incidence in middle-aged adults with no gender predilection (Demicco et al., 2020). It usually presents as a slow-growing, painless mass. On MRI, a useful distinguishing imaging feature of SFT is the presence of large collateral feeding vessels (Wignall et al., 2010). Histologically, SFT is characterized by ectatic, branching staghorn-shaped vessels and a patternless distribution of spindle cells in a variably collagenous stroma. However, SFT lacks the abundant small-sized vessels characteristic of AFST. Immunohistochemically, SFT shows strong and diffuse expression of CD34 and signal transducer and activator of transcription 6 (STAT6). CD34 immunoreactivity is seen in 14% of AFST cases (Mariño-Enríquez and Fletcher, 2012). Such examples may be difficult to distinguish from SFT; however, AFST is typically negative for STAT6. SFT is genetically characterized by a NAB2 (NGFI-A binding protein 2)-STAT6 gene fusion, resulting from a paracentric inversion involving chromosome 12q13 (Robinson et al., 2013).

Some myxoid soft tissue sarcomas with hypervascularity should also be considered in the differential diagnosis of AFST, including LGFMS, MLS and low-grade MFS (Nishio et al., 2011).

LGFMS is a malignant fibroblastic neoplasm and typically arises in young adults with a slight male predominance. It usually presents as a slow-growing, painless, deep-seated mass in the proximal extremities and trunk (Doyle and Mertens, 2020). Histologically, LGFMS shows alternating collagenous and myxoid areas with bland spindle cells arranged in a whorled growth pattern. LGFMS tends to be less cellular than AFST and lacks the prominent vascularity (Mindiola-Romero et al., 2020). Immunohistochemically, LGFMS shows diffuse and strong cytoplasmic expression of mucin 4 (MUC4) (Doyle et al., 2011). In contrast, AFST is negative for MUC4 (Song et al., 2014). LGFMS is genetically characterized by a FUS (FUS RNA binding protein)-CREB3L2 (cAMP responsive element binding protein 3 like 2) gene fusion, resulting from a balanced translocation t(7;16)(q33;p11). Variant FUS-CREB3L1 (cAMP responsive element binding protein 3 like 1) or EWSR1 (EWS RNA binding protein 1)-CREB3L1 fusions have been identified in only a small subset of LGFMS (Mertens et al., 2005; Lau et al., 2013).

MLS most commonly arises in the deep soft tissues of proximal lower extremities and has a peak incidence in the fourth and fifth decades of life with no gender predilection. It usually presents as a large, painless mass. Local recurrence occurs in 12-25% of cases and distant metastases develop in about 30-60% of cases (Thway and Nielsen, 2020). Histologically, MLS is composed of round or slightly fusiform cells and a variable number of small lipoblasts in a prominent myxoid stroma. A delicate, arborizing capillary vascular network is present and may be confused with AFST. However, even the smallest vessels in AFST have thicker walls and are more numerous than the delicate capillary vessels of MLS (Mariño-Enríquez and Fletcher, 2012). DNA damage-inducible transcript 3 (DDIT3) positivity by immunohistochemistry is a sensitive marker for MLS (Scapa et al., 2021) and is expected to be negative in AFST. MLS is genetically characterized by a FUS-DDIT3 gene fusion, resulting from a balanced translocation t(12;16) (q13;p11). A variant EWSR1-DDIT3 gene fusion has also been identified in about 3% of MLS (Thway and Nielsen, 2020).

MFS primarily arises in the dermal and subcutaneous tissues of the extremities and has a peak incidence in the sixth to eighth decades of life with a slight male predominance (Huang et al., 2020). It usually presents as an enlarging, painless mass over several

months' duration. MFS is characterized by an infiltrative growth pattern and a high risk of local recurrence. Histologically, MFS is composed of spindle-shaped to polygonal cells with slightly eosinophilic cytoplasm and nuclear atypia in a variably myxoid stroma. A characteristic finding is the presence of elongated, curvilinear vessels which bear little/no resemblance to the abundant vascular network of AFST (Mentzel et al., 1996; Mariño-Enríquez and Fletcher, 2012). Immunohistochemistry plays little role in the diagnosis of MFS. In general, MFS displays highly complex karyotypes lacking specific structural aberrations (Nishio et al., 2011). A recent integrative genetic and epigenetic analysis of MFS has indicated a predominance of somatic copy number alterations (Ogura et al., 2018). In that analysis, a SLC37A3 (solute carrier family 37 member 3)-BRAF (B-Raf proto-oncogene) gene fusion has been identified in a single case of MFS. Moreover, a TRIO (Trio Rho guanine nucleotide exchange factor)-ZNF558 (zinc finger protein 558) gene fusion has also been detected in one MFS (Delespaul et al., 2017).

Other possible differential diagnoses are spindle cell lipoma (SCL) when mature adipocytes are included and benign fibrous histiocytoma (BFH) when the lesions are more cellular. SCL typically occurs in the posterior neck or upper back rather than the extremities. Unlike AFST, a vascular network is not prominent although clefts or pseudovascular spaces may be seen. SCL is cytogenetically characterized by 13q deletions with loss of nuclear retinoblastoma (Rb) protein expression (Billings and Ud Din, 2020). BFH, also known as dermatofibroma, is a distinctive tumor entity that usually occurs in the skin. The most common form of BFH is a small cutaneous papule or nodule. Unlike AFST, a storiform pattern is prominent. Rearrangements involving either PRKCB (protein kinase C beta) or PRKCD (protein kinase C delta) have been detected in all histological subtypes of BFH (Plaszczyca et al., 2014; Jo, 2020). A combination of clinical features and molecular alterations can help to distinguish AFST from SCL and BFH.

Conclusions

AFST is a distinctive benign fibroblastic neoplasm and simple excision is usually curative. Although it is associated with characteristic features of uniform bland spindle cells within a fibromyxoid stroma and a prominent vascular network, there is a morphological overlap with a variety of intermediate and malignant soft tissue tumors. By immunohistochemistry, AFST is variably positive for EMA, desmin, SMA, CD34, CD68, CD163 and ER. AFST is genetically characterized by an AHRR-NCOA2 gene fusion through a recurrent translocation t(5;8)(p15;q13). Identification of the AHRR-NCOA2 chimera would be helpful diagnostically for AFST in more difficult cases.

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Competing interests. The authors declare that they have no competing interests.

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