

# CD34-positive superficial myxofibrosarcoma: a potential diagnostic pitfall<sup>§</sup>

**Background:** Myxofibrosarcoma (MFS) arises most commonly in the proximal extremities of the elderly, where it may involve subcutaneous and dermal tissues and masquerade as benign entities in limited biopsy samples. We encountered such a case, in which positivity for CD34 and morphologic features were initially wrongly interpreted as a 'low-fat/fat-free' spindle cell/pleomorphic lipoma. Case series have not assessed prevalence of CD34 reactivity among cutaneous examples of MFS.

**Methods:** We performed a systematic review of our institution's experience, selecting from among unequivocal MFS resection specimens those superficial cases in which a limited biopsy sample might prove difficult to interpret. These cases were immunostained for CD34 and tabulated for clinicopathologic characteristics.

**Results:** After review of all MFS diagnoses over 5 years (n = 56), we identified a study group of superficial MFS for comparison to the index case (total n = 8). Of these, the index and three additional cases (4 of 8, 50%; 2 low, 2 high grade) demonstrated positive staining for CD34, with diffuse staining of spindled cells including cellular processes. Four additional cases showed no or equivocal/rare staining.

**Conclusions:** CD34 positivity should be recognized as prevalent among such cases and should not be inappropriately construed as inveighing against a diagnosis of MFS in favor of benign entities.

**Keywords:** fibroblasts, histopathology, myxofibrosarcoma, soft tissue tumors

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Myxofibrosarcoma (MFS) represents a tumor comprised of malignant spindle cells in a myxoid stroma. The entity was originally considered a myxoid variant of malignant fibrous histiocytoma.<sup>1,2</sup> As currently classified, MFS constitutes a distinctive entity with reproducible histomorphologic and clinical features.<sup>2</sup> Most distinguishing for MFS, low grade-cases are characterized histopathologically by low cellularity, predominantly myxoid stroma and

malignant fibroblastic cells demonstrating spindle cell morphology and cellular condensation around characteristic curvilinear blood vessels.<sup>3</sup> High-grade cases are typically more cellular and show large, pleomorphic atypical cells with abundant mitoses and necrosis and are essentially pleomorphic undifferentiated sarcomas with a myxoid stroma. Individual cases often show a continuum of microscopic grade. Clinically, MFS tends to occur

as masses in the proximal limb girdles of elderly patients where they may involve skeletal muscle, fascia, subcutaneous adipose and through their propensity for infiltrative growth, the dermis.<sup>4</sup> The difficulty of rendering a diagnosis in superficially sampled lesions has been recognized in scattered case reports<sup>5–8</sup> and small series.<sup>9,10</sup> We recently encountered just such a case, in which a superficial, low-grade component of a MFS was sampled by a superficial cutaneous biopsy. Immunoreactivity for CD34, along with other features, initially prompted an incorrect diagnosis of ‘fat-free/low-fat’ spindle cell/pleomorphic lipoma.<sup>11,12</sup>

The case concerned an incisional biopsy from the right upper posterior arm of an 85-year-old man, with requisition listing ‘five year history of lipoma’. The impression of the patient’s primary care provider was of a ‘benign cyst’, though a plastic surgery consultation described an indurated but mobile nodule, suggestive of lipoma arising in the subcutaneous tissue and pressing against the dermis. Grossly, the specimen was an unoriented skin ellipse, 3.0 cm × 1.0 cm. Sections demonstrated a predominantly well circumscribed lesion with myxoid stroma and mostly bland admixed spindle cells. Scattered foci of adipocytes were present and entrapped ‘ropey collagen’ was prominent, with scattered mast cells; a ‘low-fat/fat-free’ spindle cell/pleomorphic lipoma was suspected clinically and pathologically (Fig. 1A,B). A CD34 immunostain was ordered and demonstrated diffuse positivity among spindle cells within the lesion, highlighting its silhouette at low power (Fig. 1C,D), consistent with a spindle cell/pleomorphic lipoma.<sup>11–14</sup> However, close inspection identified curvilinear vessels with perivascular condensation of hyperchromatic spindle cells (Fig. 1E). On the basis of these worrisome findings, re-excision was recommended. Sections of the re-excision showed a deeper seated MFS with greater cellularity and atypia (Fig. 1F), extending to within 0.1 cm of the deep margin.

On the basis of this experience, awareness of the expanding spectrum of CD34-positive cutaneous entities,<sup>15,16</sup> and relative lack of published data on the prevalence of CD34 immunoreactivity among MFS in large,<sup>1–3,17</sup> recent<sup>4,18,19</sup> and cutaneous series, we undertook a review of our institutional experience with MFS. Cases with superficial involvement were selected for study and stained with CD34, with the intention of better characterizing this potential diagnostic pitfall.

## Materials and methods

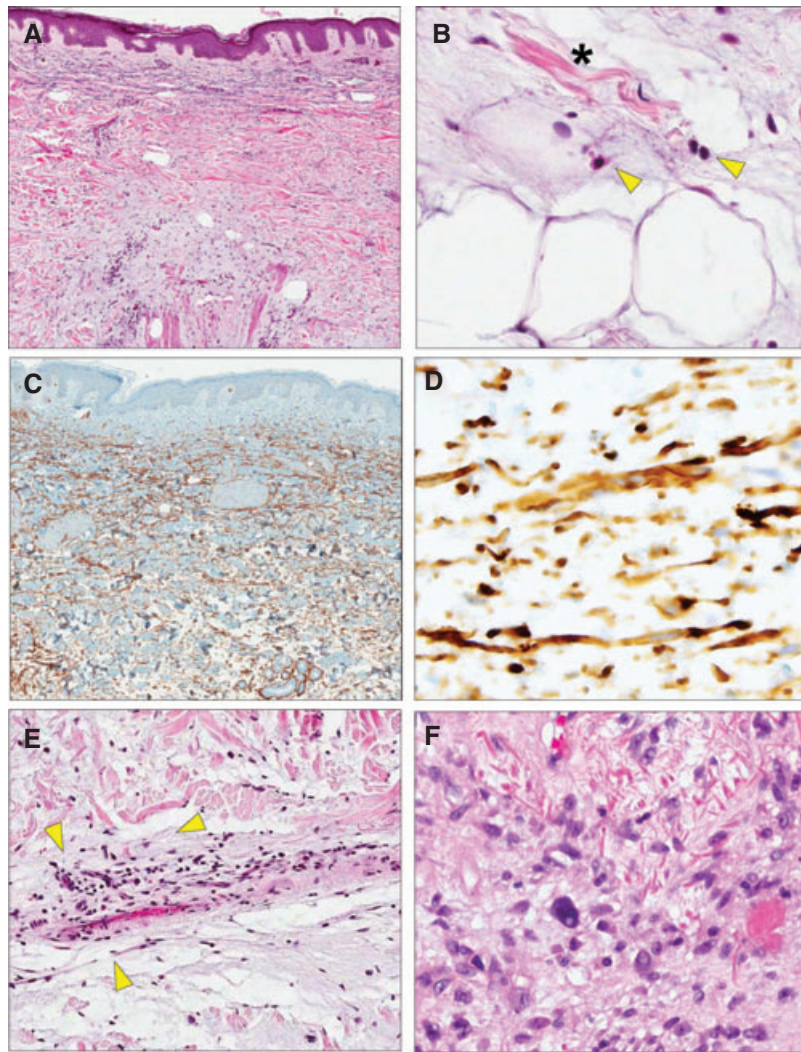
After encountering the index case described below during routine diagnostic practice, we undertook a

systematic review of our institutional experience with MFS. With approval of the University of Michigan Institutional Review Board, departmental records were searched for all cases with diagnosis of MFS from 2005–2010, resulting in identification of 56 candidate MFS corresponding to 44 patients (10 patients had  $\geq 2$  specimens evaluated). These cases were deidentified, reviewed to confirm diagnosis, and canvassed to identify cases where the MFS had arisen at, or extended to involve, dermis or superficial subcutaneous tissues (total  $n = 8$ ). The University of Michigan employs the grading system developed by the Fédération nationale des Centres de lutte contre le cancer (FNCLCC) for soft tissue sarcoma grading,<sup>20</sup> which is binarized for clinician use into low grade (FNCLCC Grade 1) or high grade (FNCLCC Grades 2 and 3) before formal diagnostic reporting. Herein, for ease of general understanding, each case was reviewed and the FNCLCC grade reported in Table 1. Appropriate sections were selected for CD34 immunohistochemical staining in the University of Michigan Clinical Immunohistochemistry Core. The antibody used was Clone QBEnd10 (Dako, Carpinteria, CA, USA) at 1/100 dilution for 32 min after pretreatment with CC1 buffer (Dako) for 30 min at 95°C, performed on a Benchmark Ultra autostainer (Ventana, Tucson, AZ, USA). Staining was evaluated by consensus by three pathologists (S.S., A.P., R.P.). For photomicrographs, the slides were scanned on a Scanscope XT whole slide scanner and photographed in ImageScope (both Aperio, Vista, CA, USA), at indicated magnifications.

## Results

Review of 56 cases from 2005 to 2010 confirmed the diagnosis in all cases and identified, among unequivocal resection specimens, 7 additional cases with superficial extension where a limited biopsy sample may have presented a similar diagnostic conundrum to the index case. Importantly, these cases presented clinicopathologic characteristics consistent with reported MFS cohorts<sup>1,3,4,18</sup> including age range (52–88 years), 4:3 male : female ratio and wide anatomic distribution (see Table 1). In 5 of 7 cases, benign disease was specifically favored in the relevant pre-procedural clinician notes; in no case was MFS suspected prior to pathologic diagnosis.

CD34 staining was unequivocally positive in three additional cases (Fig. 2A–J). Case 2 concerned a lesion on the left forearm of a 52-year-old male, clinically thought to be ‘benign’; this low grade MFS dissected along tissue planes in the superficial subcutis, with similar architectural and cytologic features to that of the index case (Fig. 2A). On higher power, diagnostic hyperchromatic, atypical



*Fig. 1.* Index case of CD34 positive myxofibrosarcoma masquerading as ‘fat-free/low-fat’ spindle cell/pleomorphic lipoma. A) Low-power micrograph demonstrating a bland spindle cell proliferation with myxoid stroma involving the dermis ( $\times 20$ ). B) High power micrograph showing a focus of mature adipose and ropey collagen (\*), with intervening scattered mast cells (arrows) ( $\times 400$ ). C) Low-power micrograph of CD34 immunostain ( $\times 200$ ). D) High power micrograph showing unequivocally positive CD34 in cytoplasm and cellular processes of spindled cells ( $\times 400$ ). E) Representative focus from deeper in the lesion, showing distinct curvilinear vessels with perivascular condensation of hyperchromatic stromal spindle cells ( $\times 10$ ). F) Representative micrograph showing a focus of greater cellularity and atypia from the final resection specimen from the case; definitive necrosis was not identified ( $\times 400$ ).

spindle cells can be appreciated (Fig. 2B). CD34 was diffusely positive throughout the lesion, with individual spindle cells showing varying degrees of expression of CD34 (Fig. 2C). Case 5 was an excision of a lesion clinically suspected to be a traumatically herniated muscle in the left lower leg of an 84-year-old male. Similar to Case 2, lower power sections of the lesion demonstrated a more cellular spindle cell myxoid lesion, dissecting through the subcutaneous connective tissue and extending superficially toward the dermis at excision margin (Fig. 2D). On higher power, mitotic activity was prominent, including atypical mitoses, signaling a Grade 2 lesion (Fig. 2E). CD34 was unequivocally positive among the atypical cells of these lesions (Fig. 2F). Case 6 was an excision

from the left torso of a 65-year-old male, on exam considered suspicious for a dermatofibrosarcoma protuberans (Fig. 2G–J). This case demonstrated areas of classic, low grade, infiltrative MFS as well as a nodule of higher grade, more cellular morphology (Fig. 2G–H). Areas within the lesion showed diffuse positivity for CD34 ranging from a light ‘blush’ with interspersed more intensely staining pleomorphic cells (Fig. 2I) to areas of diffuse moderate to intense stain (Fig. 2J).

Four additional cases showed negative staining (Fig. 3A–L) for CD34, encompassing a number of clinical presentations and grades. Of particular note was Case 3, a low grade MFS that was diagnosed entirely incidentally in the soft tissue of



Table 1. Characteristics of study cases

Case	Sex	Age	Site	Clinical diagnosis	Diagnosis	Overall grade*	CD34 stain	Months	Outcome
1, Index	M	85	R. upper arm	Lipoma	MFS	FNCLCC Grade 1	+, Spindled cells	15	NED
2	M	52	L. forearm	'Benign'	MFS	FNCLCC Grade 1	+, Subset of spindled and atypical cells	81	2 Recurrences (39 months, low grade; 43 months, high grade pleiomorphic) currently NED
3	M	53	R. thenar	Incidental finding, on carpal Tunnel surgery	MFS	FNCLCC Grade 1	(-), Vessels only	15	NED then LTF
4	F	88	R. forearm	'Growth'	MFS	FNCLCC Grade 2	(-), Rare positive cellular processes	17	NED
5	M	84	L. lower leg	'Herniated muscle'	MFS	FNCLCC Grade 2	+, Spindled and pleomorphic cells	3	Positive margins, follow-up elsewhere
6	M	65	L. torso	Dermatofibrosarcoma protuberans	MFS	FNCLCC Grade 2	+, Pleomorphic cells and diffuse spindle cell blush	2	NED then LTF
7	F	82	Central back	Lipoma	MFS	FNCLCC Grade 2	(-), Vessels only	71	NED
8	F	70	L. shin	Amelanotic melanoma	MFS	FNCLCC Grade 2	(-), Vessels only	2	NED

NED, no evidence of disease; LTF, lost to follow-up; MFS, myxofibrosarcoma.

\*Fédération nationale des Centres de lutte contre le cancer system grade, as reported.<sup>18</sup>

the right thenar eminence of a 53-year-old male, on carpal tunnel surgery (Fig. 3A–C). One case, Case 4, a 'growth' on the right forearm of an 88-year-old female, showed a number of foci where wispy cellular processes stained positive for CD34, though both the lower power appearance and our overall assessment were that it was negative for CD34. Case 8, a left shin lesion from a 70-year-old female considered clinically suspicious for amelanotic melanoma, showed prominent invasion of the dermis by MFS spindle cells (Fig. 3J–K), highlighting that these lesions may extend very superficially, even nearing the epidermis.

## Discussion

The observation of convincing CD34 positive staining among half of the representative cases of MFS with superficial involvement described herein emphasizes the high index of suspicion needed to make this diagnosis, especially when evaluating limited biopsy material. The differential diagnosis of a spindle cell and myxoid superficial lesion is broad, including, but not limited to, myxoid benign fibrous histiocytoma, cutaneous myxoma, superficial acral fibromyxoma, myxoid nerve sheath neoplasms, myxoid dermatofibrosarcoma protuberans, spindle cell/pleomorphic lipoma, myxoid solitary fibrous

tumor, myxoinflammatory fibroblastic sarcoma, and MFS. Moreover, a number of reports have described cases where low grade MFS has been mistaken for a number of benign and low-grade malignant entities, ranging from papular mucinosis<sup>7,21</sup> to myxoid neurofibroma<sup>22</sup> to cutaneous myxoma<sup>6</sup>; even pleomorphic hyalinizing angioectatic tumor (PHAT) has been considered.<sup>5,8</sup>

The potential to interpret a CD34 positive MFS as a low grade cutaneous neoplasm stems in part from the fact that an ever expanding number of cutaneous lesions have been reported to show frequent immunohistochemical expression of CD34.<sup>15</sup> In particular, Billings et al. and Sachdeva et al. highlighted this diagnostic difficulty in a series of 'fat-free/low-fat' spindle cell/pleomorphic lipomas, respectively, which are generally CD34 positive.<sup>11,12</sup> The overlapping CD34 positivity is important, especially given the spindle cell/pleomorphic lipoma-like features of the index case: the 'ropy collagen' proved to be disrupted dermal collagen. Moreover, the mast cells observed are also a non-specific feature often encountered whenever there are myxoid or mucinous changes within the dermis. Beyond pleomorphic/spindle cell lipoma and related lesions (mammary-type myofibroblastoma), the morphologic differential for several of the cases presented herein would have included

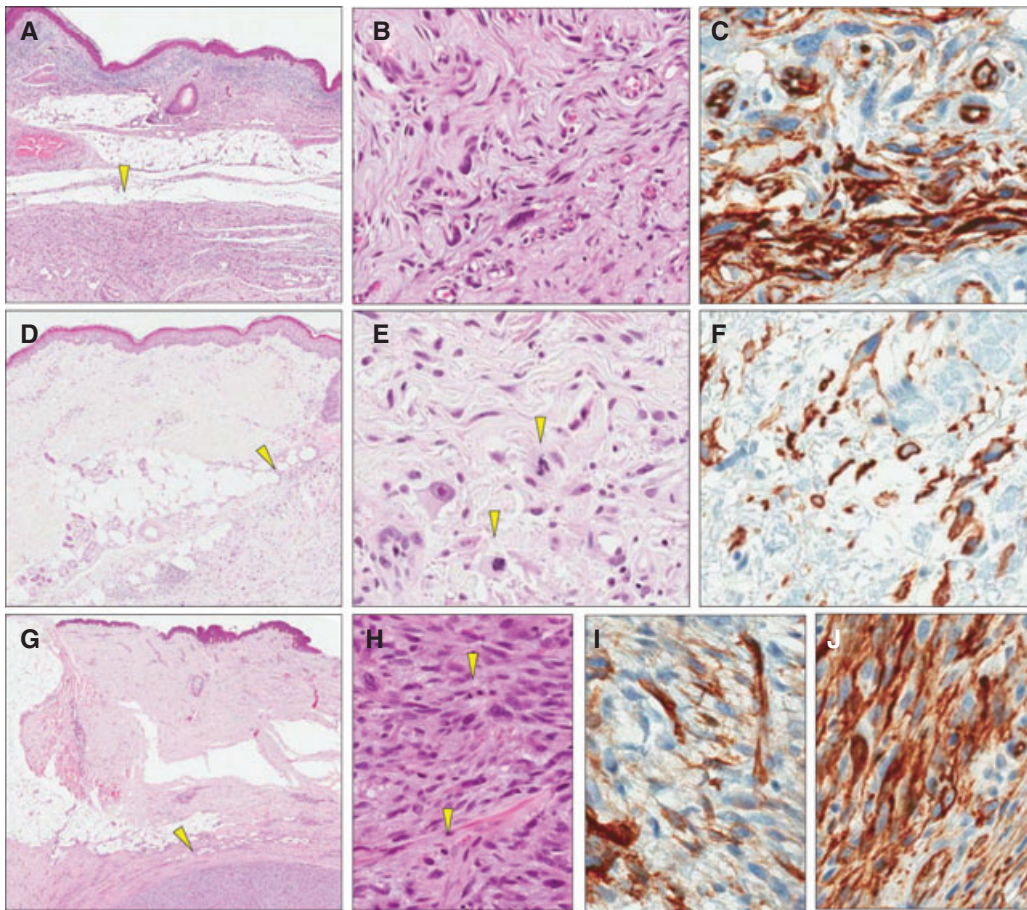


Fig. 2. Additional CD34-positive myxofibrosarcoma cases. CD34 was overall positive in Case 2 (low grade, A–C), Case 5 (high grade, D–F) and Case 6 (high grade, G–J) (A,D,G). Representative low-power micrographs for each lesion in first panels; arrows indicate lesions ( $\times 10$ – $\times 20$ ) (B,E,H). Representative intermediate power micrographs of lesions, arrows indicate mitoses ( $\times 200$ ) (C,F,I–J).

myxoinflammatory fibroblastic sarcoma, superficial acral fibromyxoma, and atypical neurofibroma with myxoid stroma. All of these entities may show varying CD34 immunoreactivity.<sup>15</sup>

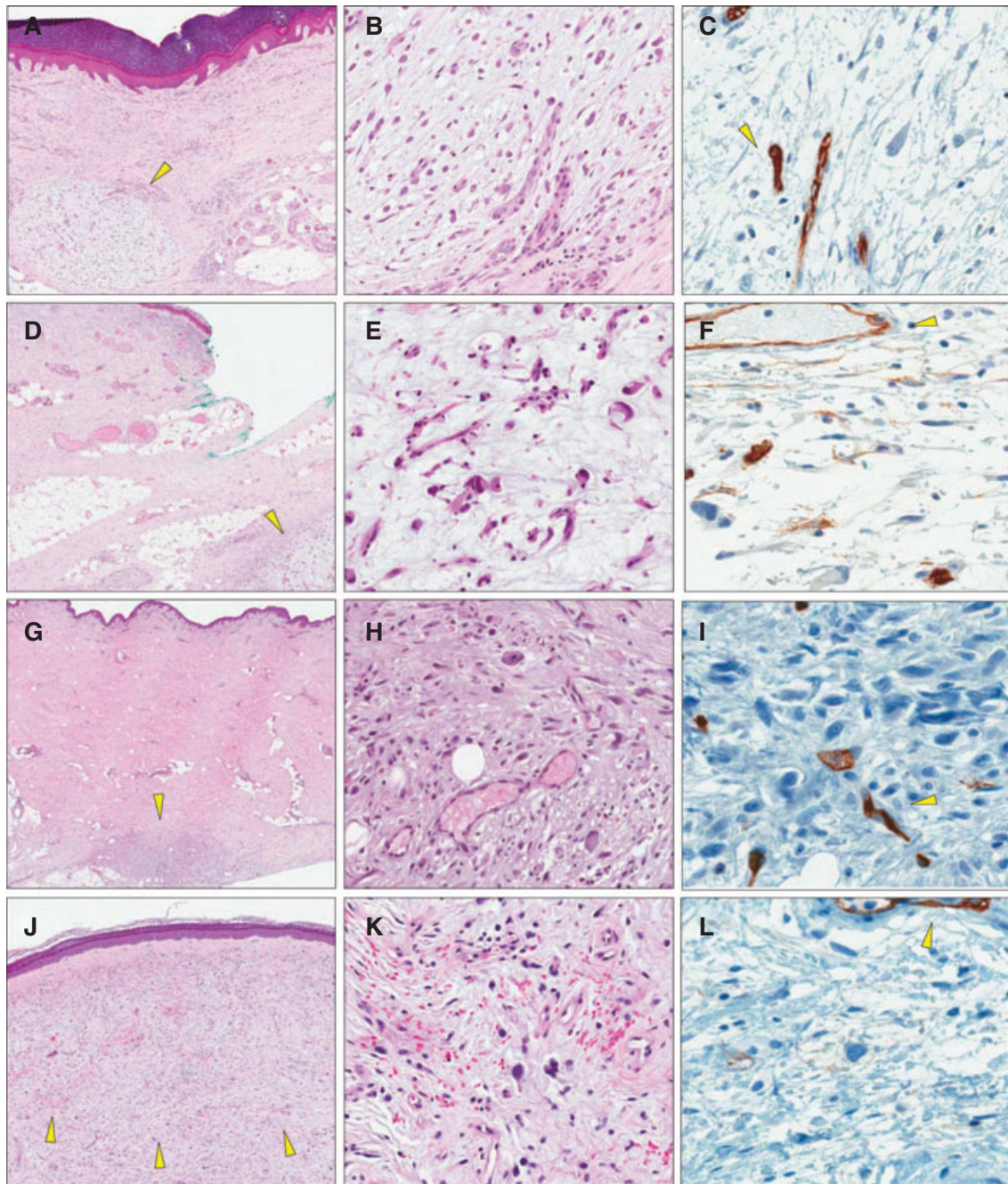
In contrast, in the workup of MFS, CD34 is neither salient nor generally considered to be of diagnostic value; it was a distraction from the appropriate diagnosis in the index case described herein. Of note, older reports, unselected for anatomical depth of the lesions, report positivity for the CD34 varying from approximately 14% in so-called MFH in general<sup>23</sup> to as much as 38% in myxoid MFH.<sup>24</sup> Thus, CD34 positivity in MFS is not unprecedented, with scattered prior reports having identified CD34 expression in MFS from several anatomic sites,<sup>25</sup> including skin in some<sup>9,26</sup> but not other<sup>6,7</sup> scattered case reports. We interpret the findings from our small cohort to be cautionary given the number of CD34 positive benign lesions in the differential diagnosis and the often bland appearance of superficially sampled MFS.

The caveats of these findings are several. Principally, the overall frequency of CD34 in MFS,

especially in MFS of deep soft tissues, remains untested in large contemporary cohorts and should not be extrapolated from these superficial cases. Certainly, to make a stronger argument, we would have preferred to report a greater number of cases, though we do note that our cohort is a sequential set of superficial MFS cases from our referral center. In any case, we intended to study a representative sample of cases illustrative of a potential diagnostic pitfall rather than perform an extensive assessment of MFS CD34 immunophenotype. Finally, we cannot exclude that a significant subset of the CD34 positive cells within these lesions may represent entrapped or reactive dermal fibroblasts; either way, this feature represents part of the potential diagnostic pitfall.

More important, then, are the lessons from these cases, especially from our experience of the index case. The feature in the biopsy that led to identification of the scattered, hyperchromatic spindled cells and diagnosis of low grade MFS, despite the puzzling CD34 stain, was the presence of several foci of the distinctive curvilinear vasculature of MFS (Fig. 1E). Classically, in low grade





*Fig. 3.* Additional CD34-negative myxofibrosarcoma cases. CD34 was overall negative in Case 3 (low-grade, A–C), Case 4 (high grade, D–F), Case 7 (high grade, G–I) and Case 8 (high grade, J–L) (A,D,G,J). Representative low-power micrographs for each lesion in the first panels; arrows indicate lesions ( $\times 10$ – $\times 20$ ) (B,E,H,K). Representative intermediate power micrographs of the lesions ( $\times 200$ ) (C,G,I,L). Representative high power micrographs showing CD34 immunostain for each case; arrows indicate microvasculature, internal positive control ( $\times 400$ ).

MFS, these vessels are elongate and arcuate, traversing a hypocellular myxoid matrix and showing perivascular condensation of spindled and or inflammatory cells. In the index case, these features were unequivocally present focally, particularly in the anatomically deeper areas of the sections, though the myxoid stromal change was more extensive. This pervasive stromal change, broadly involving lateral and deep margins, heralded the finding of a deeper,

more extensive lesion on re-excision and illustrates the infiltrative growth of these tumors.<sup>4,26</sup>

Cautionary too are the clinical impressions from the time of diagnosis, with benign processes favored in the majority of cases and two cases (carpal tunnel and muscle herniation surgery) presenting essentially an incidental diagnosis of sarcoma. The lack of clinical suspicion before diagnostic biopsies meant operationally that imaging was not available

for review at the time of diagnosis in any of these cases. However, we note that, if available, MRI may provide very helpful clues to the infiltrative growth of these lesions<sup>27</sup> and may be referenced or even recommended in difficult cases.

As always with soft tissue lesions, integrating as much clinical data as possible, from history to imaging to gross examination, aids in establishing the correct diagnosis. Essential in our experience is careful consideration of a broad differential and

review of microscopic sections of deeper levels, with at least a modicum of suspicion for more serious lesions, even when they are not suspected clinically. Based on our findings in these cases, awareness of the limits and pitfalls of popular adjunctive immunostains is invaluable.

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