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Superficial CD34-positive fibroblastic tumor: report of 18 cases of a distinctive low-grade mesenchymal neoplasm of intermediate (borderline) malignancy

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Fibroblastic mesenchymal tumors show a spectrum of biological behavior, from benign to fully malignant. We report our experience of two decades with a distinctive, previously undescribed low-grade fibroblastic tumor of the superficial soft tissues. Eighteen cases were identified within our consultation files, previously coded as 'low-grade sarcoma, not further classified' and 'malignant fibrous histiocytoma, low grade'. The tumors occurred in adults (median age 38 years, range 20–76 years) of either sex (10 males and 8 females), ranged in size from 1.5 to 10 cm (mean 4.1 cm), and were confined to the superficial soft tissues of the thigh ($N=5$), knee ($N=2$), and other sites. Histological features included a fascicular growth pattern of the neoplastic spindled cells with striking, often bizarre cellular pleomorphism and variably prominent nucleoli. Necrosis was seen in one case. All cases showed strong, diffuse CD34 positivity and 68% of tested cases demonstrated focal cytokeratin expression. Desmin, ERG, FLI-1, smooth muscle actin, and S100 protein were negative. TP53 overexpression was absent. Fluorescence *in-situ* hybridization studies for *TGFBR3* and/or *MGEA5* rearrangements were negative in all tested cases. Clinical follow-up was available in 13 patients (median duration of 24 months; range 1–104 months). Twelve of 13 patients had no disease recurrence. One patient had regional lymph node metastases, 7 years after incomplete excision of the primary tumor. All patients are currently alive and disease free. The unique clinicopathological features of superficial CD34-positive fibroblastic tumor define them as a novel subset of low-grade fibroblastic neoplasms, best considered to be of borderline malignancy.
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Most fibroblastic tumors of deep soft tissue fall into well-defined clinicopathological categories, such as desmoplastic fibroblastoma (collagenous fibroma),[1] adult fibrosarcoma,[2] low-grade fibromyxoid sarcoma,[3] and sclerosing epithelioid fibrosarcoma.[4] Although these tumors may also rarely occur in superficial (suprafascial) locations, superficially located fibroblastic tumors more often represent different entities, such as myxofibrosarcoma (myxoid malignant fibrous histiocytoma),[5,6] fibrosarcoma arising in dermatofibrosarcoma protuberans,[7] myxoinflammatory fibroblastic sarcoma (inflammatory myxohyaline tumor of distal extremities),[8,9] and pleomorphic hyalinizing angiectatic tumor.[10,11]

Over the past two decades we have seen in consultation a number of cases of a distinctive fibroblastic tumor of the superficial soft tissues, characterized in part by striking pleomorphism, very low mitotic activity, and CD34 immunoreactivity, and not clearly corresponding to a previously described entity. The present study was undertaken in order to more fully characterize the clinicopathological features of these rare lesions, which we have termed 'superficial CD34-positive fibroblastic tumor', and to evaluate their relationship, if any, to other superficial fibroblastic sarcomas, in particular undifferentiated pleomorphic sarcoma ('malignant

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fibrous histiocytoma'), myxofibrosarcoma ('myxoid malignant fibrous histiocytoma'), hemosiderotic fibrolipomatous tumor/'early' pleomorphic hyalinizing angiectatic tumor, classical pleomorphic hyalinizing angiectatic tumor, and myxoinflammatory fibroblastic sarcoma.

Materials and methods

The study was approved by the Mayo Clinic and Emory University Institutional Review Boards. The consultation archives of two of the authors (ALF and SWW) were searched for cases previously coded as 'low-grade sarcoma, not further classified' and 'malignant fibrous histiocytoma, low grade', yielding 18 cases. One case had previously been reviewed by another group of expert soft-tissue pathologists, and was considered to most likely represent an unusual variant of pleomorphic hyalinizing angiectatic tumor, lacking characteristic vascular changes. All available slides from these 18 cases were re-reviewed by three of the authors (JMC, SWW, and ALF). Clinical follow-up information was obtained from existing medical records and from the referring clinicians and pathologists.

Immunohistochemistry was performed on deparaffinized, rehydrated sections obtained from formalin-fixed, paraffin-embedded tissue, using antibody-specific epitope retrieval techniques with the Dako Envision (Dako, Carpinteria, CA, USA) automated system for detection of the following primary antigens: CD34 (QBEnd/10, 1:50, Leica Biosystems, Buffalo Grove, IL, USA), cytokeratins (OSCAR, >1:40, Covance, Princeton, NJ, USA), desmin (DE-R-11, 1:50–1:100, Leica) ERG (9FY, 1:50–1:100, Biocare Medical, Concord, CA, USA), FLI-1 (1:25–1:100, Cell Marque, Rocklin, CA, USA), Ki-67 (MIB-1, 1:75–1:150, Dako), TP53 (DO-7, prediluted, Ventana), SMARCB1 (BAF47/INI1; 25, BD Transduction Laboratories, Franklin Lakes, NJ, USA), smooth muscle actin (1A4, 1:50–1:100, Dako), and S100 protein (polyclonal, 1:400, Dako). Five cases were analyzed for rearrangements of *TGFBR3* and *MGEA5* in the laboratory of Dr Cristina Antonescu (Memorial Sloan Kettering Cancer Center, New York, NY, USA) by fluorescence *in-situ* hybridization (FISH) using previously described methods.[12]

Results

The clinicopathological features of the 18 cases of superficial CD34-positive fibroblastic tumor are summarized in Table 1. The lesions occurred exclusively in adults (median age 38 years, range 20–76 years) of either sex (10 males and 8 females) and typically presented as painless, slow-growing masses present for at least 1 year, ranging in size from 1.5 to 10 cm (mean 4.1 cm). The majority of cases (67%) occurred in the lower limb, including the thigh (six cases, 30%), the soft tissues around the knee (two cases, 11%), and the buttock, lower leg and foot (one case each). Other involved sites included the arm (two cases), groin (two cases), neck, shoulder, hip, and vulva (one case each). All tumors were confined to the superficial fibroadipose tissues, with minimal or absent involvement of the

Table 1 Clinicopathological features

Case No.	*Age (year)/ sex*	*Site/size (cm)*	*Preoperative duration*	*Depth*	*Treatment/margin status*	*Local recurrences*	*Outcome/follow-up duration (months)*
1	20/M	Thigh/3.1	Unknown	Suprafascial	Local excision, then interval regional lymphadenectomy/marginal	No, regional LN metastasis	ANED/104
2	21/F	Leg/2	Unknown	Suprafascial	Local excision/marginal	No	ANED/30
3	25/M	Groin/7.5	Unknown (rapid enlargement)	Suprafascial	Local excision/marginal	No	ANED/1
4	25/M	Foot/3.8	4 years	Suprafascial	Wide excision/wide	No	ANED/17
5	26/M	Thigh/6.5	Unknown	Suprafascial	Local excision, then wide excision/wide	No	ANED/7
6	26/M	Thigh/2.2	'Several years'	Suprafascial	Local excision/marginal	NA	NA
7	28/M	Thigh/1.5	Unknown	Suprafascial	Local excision/Marginal	No	ANED/24
8	32/M	Shoulder/ unknown	14 years	Suprafascial	Local excision/marginal	No	ANED/2
9	37/F	Vulva/10	Unknown	Suprafascial	Local excision/marginal	NA	NA
10	38/F	Neck/1.5	6 years	Suprafascial	Local excision/Marginal	No	ANED/38
11	44/F	Popliteal fossa/6.5	At least 1 year	Suprafascial	Local excision, then wide excisions[2] and RT/wide	No	ANED/20
12	45/M	Knee/ unknown	Unknown	Suprafascial	Local excision/marginal	NA	NA
13	46/M	Hip/2	Unknown	Suprafascial	Local excision/marginal	NA	NA
14	48/M	Arm/2.7	Unknown	Suprafascial	Local excision, preoperative RT, then wide excision/Wide	No	ANED/4
15	51/F	Arm/ unknown	Unknown	Suprafascial	Local excision/marginal	NA	NA
16	53/F	Groin/3.4	20 years	Suprafascial	Local excision, then wide excision/wide	No	ANED/53
17	57/F	Thigh/7.4	Unknown	Suprafascial	Local excision, then wide excision/wide	No	ANED/3
18	76/F	Buttock/2	'Many years'	Suprafascial	Local excision/marginal	No	ANED/3

Abbreviations: ANED, alive no evidence of disease; F, female; LN, lymph node; M, male; NA, not available; RT, radiotherapy.

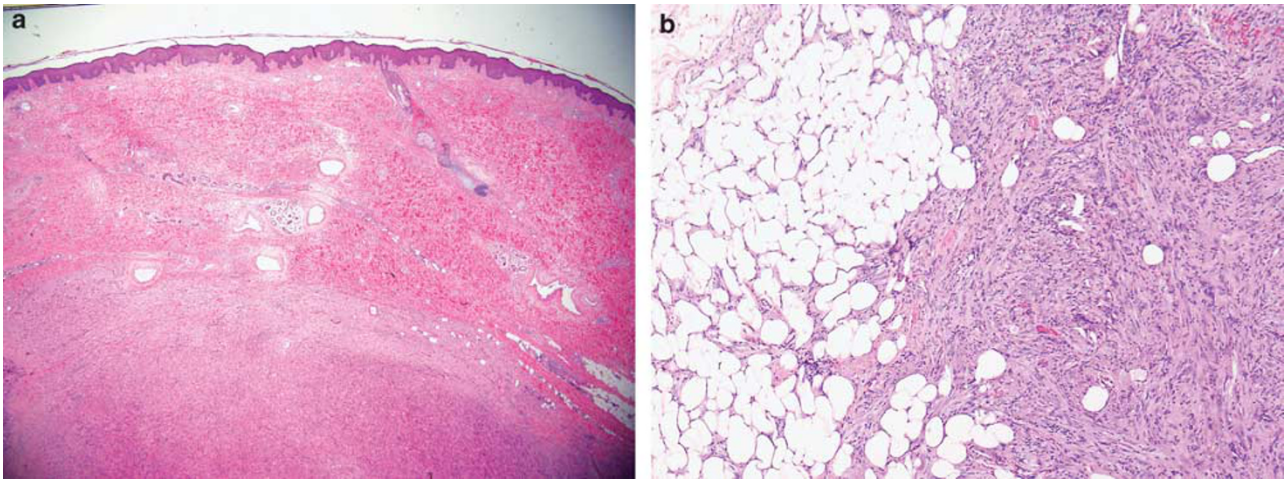

Figure 1 All tumors arose in suprafascial locations, as in this example showing involvement of the deep dermis and subcutaneous fat (**a**). Although the lesions had a relatively well-circumscribed appearance at low-power magnification (**a**), infiltrative growth into the surrounding fibroadipose tissue was invariably present, at least focally (**b**).

subjacent muscle. No patient had a history of a prior cutaneous neoplasm in the same location.

Grossly, the tumors were described as firm, yellow to tan, and variably gelatinous in appearance. Microscopically, they grew in a generally circumscribed but infiltrative fashion (Figures 1a and b), and were composed of moderately to sometimes highly cellular fascicles and sheets (Figures 2a–c) of spindled-to-epithelioid cells with an abundant granular, fibrillary, or glassy cytoplasm (Figures 3a–c). An arborizing capillary-sized vasculature was frequently present, particularly in areas showing a fascicular growth pattern. A sub-population of tumor cells showed xanthomatous change. Most cells displayed marked nuclear pleomorphism, with bizarre, lobated, hyperchromatic nuclei containing one or more large nucleoli, reminiscent of those seen in myxoinflammatory fibroblastic sarcoma (Figures 4a–c). Intranuclear cytoplasmic pseudoinclusions and a mixed chronic inflammatory cell infiltrate including numerous mast cells, as are seen in pleomorphic hyalinizing angiectatic tumor, were frequently present. However, other morphological features of pleomorphic hyalinizing angiectatic tumor and/or myxoinflammatory fibroblastic sarcoma such as ectatic, hyalinized blood vessels, myxoid zones with pseudolipoblasts, hyalinized areas with a 'burned out' appearance, and intracytoplasmic hemosiderin pigment were not present. Similarly, areas resembling conventional dermatofibrosarcoma protuberans or fibrous histiocytoma were entirely absent. Despite the moderate to occasionally high cellularity and marked nuclear atypia, mitotic figures were extremely uncommon, usually numbering $<1/50$ high-powered fields (HPFs; Figures 5a and b). Atypical mitotic figures were absent and necrosis was present in only one case. Mitotic activity of $>1/50$ HPF was seen in the re-excision specimen of one case.

By immunohistochemistry, all tumors showed strong, diffuse CD34 positivity (Figure 6a). Limited cytokeratin expression was seen in the neoplastic cells of 11 out of 16 tested cases (69%; Figure 6b). All tested cases lacked expression of FLI-1 and ERG proteins and showed retained expression of the *SMARCB1* tumor suppressor gene product (Figure 6c). S100 protein, desmin, and smooth muscle actin were negative in all tested cases. The Ki-67-labeling index was extremely low in all tested cases ($<1\%$ of cells). All tested cases lacked TP53 overexpression (Figure 6d). The five cases tested by FISH for *TGFBR3* and/or *MGEA5* rearrangements were negative (Figure 7).

Clinical follow-up was available for 13 of 18 (72%) patients, with a median duration of 24 months (range 1–104 months). Of these 13 patients, 12 are currently alive and are without evidence of disease. One patient with a superficial CD34-positive fibroblastic tumor of the thigh suffered metastasis to an external iliac lymph node, 7 years after marginal excision of his primary tumor (Figure 8). The morphological and immunohistochemical features of this metastasis were identical to those of the primary tumor. Imaging studies did not show any evidence of distant metastatic disease, and no additional positive lymph nodes were identified in a complete pelvic lymphadenectomy; this patient is presently disease free.

Discussion

Superficial CD34-positive fibroblastic tumor is, in our experience, a unique lesion, not corresponding to any previously described soft tissue neoplasm. We suspect that many cases have been historically diagnosed as representing undifferentiated pleomorphic sarcomas or myxofibrosarcomas, based

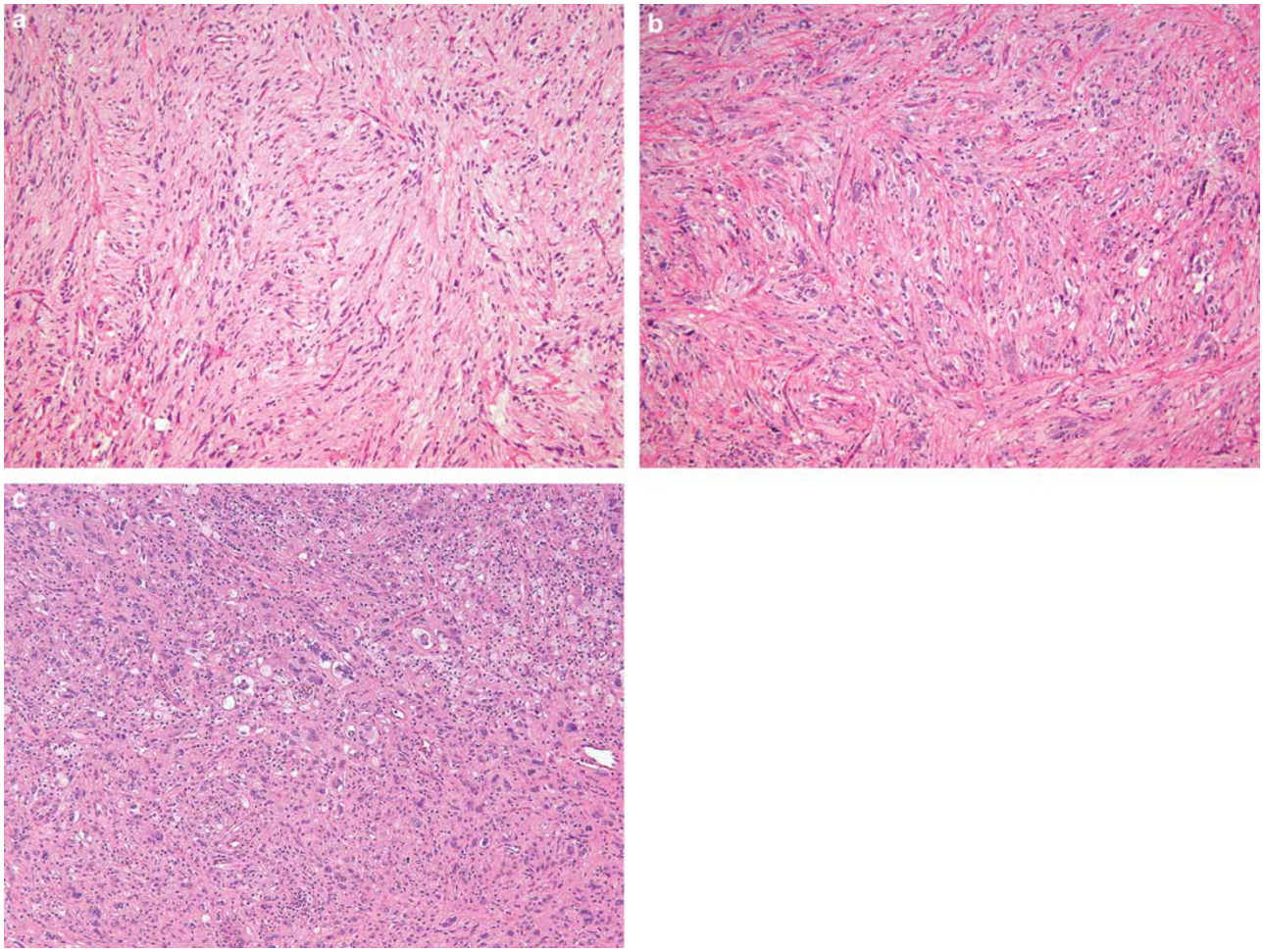

Figure 2 Most tumors consisted, at least in part, of relatively monomorphic spindled cells growing in intersecting fascicles, in association with an arborizing capillary vasculature (**a**). These relatively monomorphic areas gave way to larger areas showing greater pleomorphism and less well-formed fascicles (**b**) and to sheets of pleomorphic, epithelioid cells (**c**). Lipidized tumor cells were also commonly present.

chiefly on their very striking nuclear pleomorphism. Indeed, one of us (SWW) initially classified these tumors as 'low-grade malignant fibrous histiocytomas' before recognizing their unique clinical, morphological, and immunohistochemical features.

A number of features strongly suggest us that the lesions reported herein do not represent simply morphological variants of undifferentiated pleomorphic sarcoma, myxofibrosarcoma, or atypical fibroxanthoma. These tumors differ from undifferentiated pleomorphic sarcomas by virtue of their strikingly low mitotic rate and Ki-67-labeling index, their distinctive abundant granular to 'glassy'-appearing cytoplasm, and their robust expression of CD34, a marker not generally expressed in quite so uniform a pattern in the great majority of undifferentiated pleomorphic sarcomas. Superficial CD34-positive fibroblastic tumors also appear to occur exclusively in a suprafascial location, in contrast to the great majority of undifferentiated pleomorphic sarcomas. Although myxofibrosarcomas typically arise in the superficial soft tissues of the extremities of older adults, they are characterized by the presence of myxoid nodules displaying an arborizing, thick-walled vasculature, and they lack the distinctive cytoplasmic and nuclear features of the present lesions (eg, intranuclear inclusions), and show a much higher mitotic rate and Ki-67-labeling index.[5,6,13–15] Expression of CD34 may be seen occasionally in myxofibrosarcomas,[16] although not typically to this degree, in our experience; co-expression of CD34 and cytokeratins is not a feature of myxofibrosarcoma. Although granular cell variants of atypical fibroxanthoma have been reported, atypical fibroxanthomas generally lack CD34 expression, show brisk mitotic activity, and arise in the dermis of sun-exposed skin.[17–20] Finally, we did not detect TP53 overexpression in any studied case; TP53 overexpression is commonly present in high-grade pleomorphic sarcomas, myxofibrosarcomas, and atypical fibroxanthomas.[21–26]

The superficial location, striking pleomorphism, low mitotic rate, and chronic inflammatory cell infiltrate of superficial CD34-positive fibroblastic

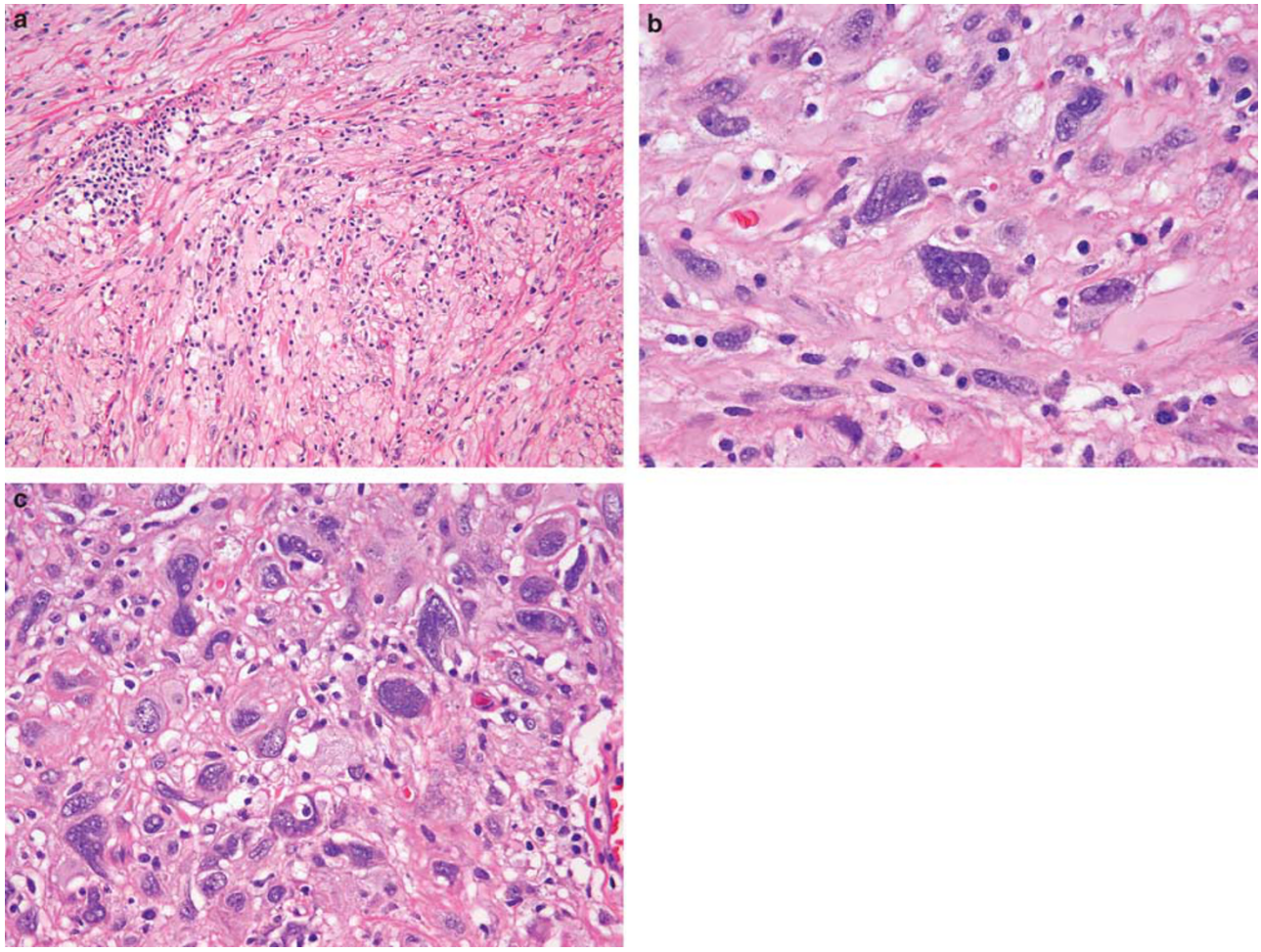

Figure 3 CD34-positive fibroblastic tumors were composed of spindled-to-epithelioid cells with abundant, eosinophilic cytoplasm, often having an unusual 'glassy' appearance (**a**). Higher-power view of 'glassy' eosinophilic cytoplasm (**b**). In some cases, the cytoplasm of the neoplastic cells showed a granular, rather than 'glassy' appearance (**c**).

tumor might also raise the question of a possible relationship to pleomorphic hyalinizing angiectatic tumor.[10,11] As noted above, one case from the present series was seen in consultation by other soft-tissue experts, and was thought to most likely represent a variant of pleomorphic hyalinizing angiectatic tumor. However, the present lesion lacks the low-grade, hemosiderin-rich spindle cell proliferation typically seen at the periphery of pleomorphic-hyalinizing angiectatic tumor, which we have termed 'early' pleomorphic-hyalinizing angiectatic tumor[11] and others have termed 'hemosiderotic fibrolipomatous tumor'.[27–30] In addition, superficial CD34-positive fibroblastic tumor lacks the ectatic blood vessels and striking hemosiderin deposition that typify pleomorphic-hyalinizing angiectatic tumor and often shows cytokeratin expression.

Myxoinflammatory fibroblastic sarcoma (inflammatory myxohyaline tumor of distal extremities) also shares some morphological features with superficial CD34-positive fibroblastic tumor, including bizarre-appearing cells with prominent nucleoli, a generally low mitotic rate, a prominent chronic inflammatory cell infiltrate, and rarely cytokeratin expression.[8,9,12] However, myxoinflammatory fibroblastic sarcoma typically involves acral locations, lacks cells with abundant granular cytoplasm, contains prominent myxoid and acellular hyaline zones, the former with pseudolipoblasts, lacks diffuse CD34 expression, and often shows rearrangements of the *TGFBR3* and *MGEA5* genes.[12,31,32] In addition, the degree of atypia shown by superficial CD34-positive fibroblastic tumor exceeds that typically seen in myxoinflammatory fibroblastic sarcoma.

The CD34 and cytokeratin co-expression shown by superficial CD34-positive fibroblastic tumor also raise the possibility of some relationship to epithelioid sarcoma or an epithelioid endothelial cell tumor. The morphological features of the present lesion are obviously quite different from those of epithelioid sarcoma of both classical and proximal type.[33,34] Furthermore, the lesions that we have described show retained expression of SMARCB1, unlike the great majority of epithelioid sarcomas.[35]

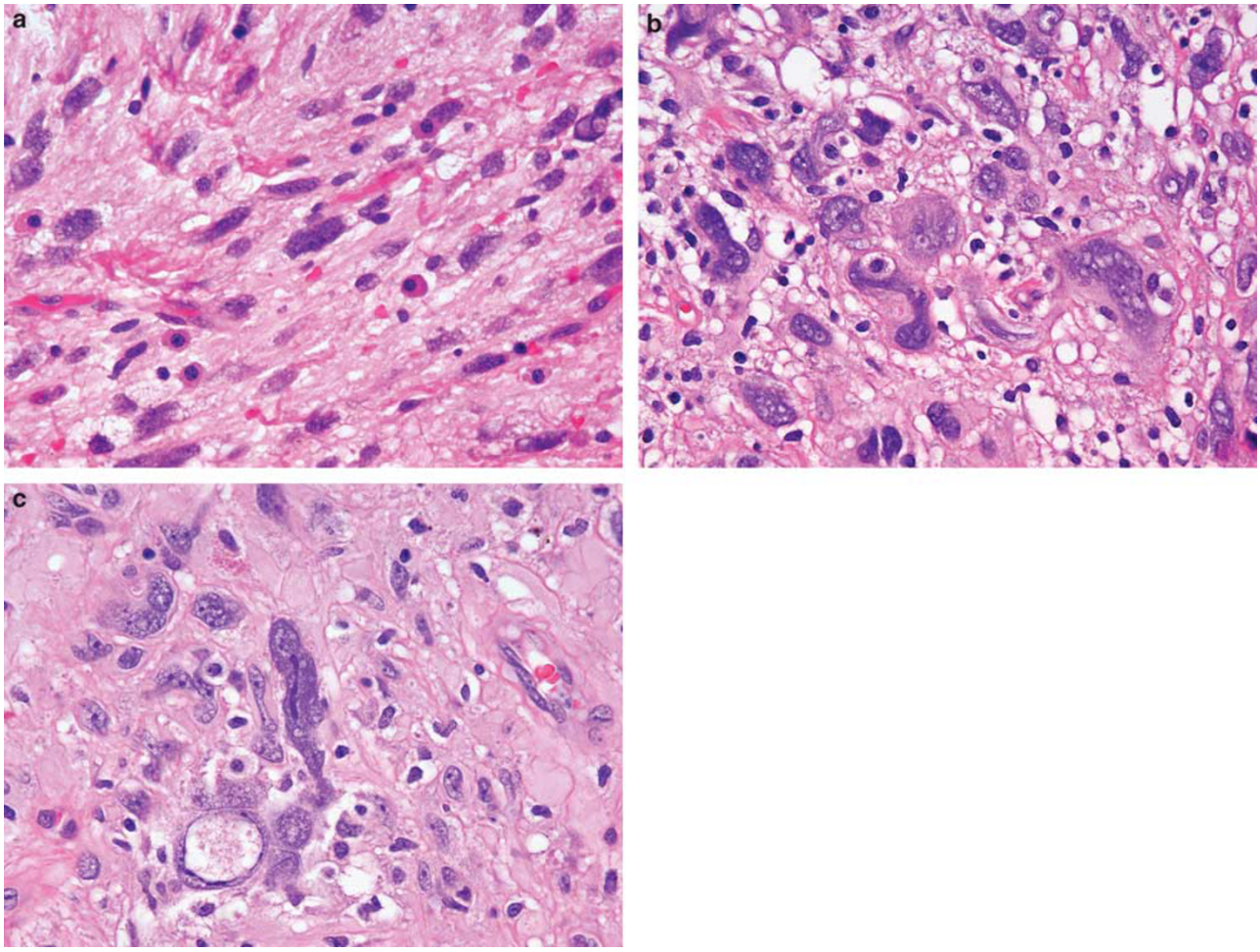

Figure 4 Although small areas with these tumors sometimes consisted of relatively monomorphic spindled cells (**a**), all tumors were notable for very striking nuclear pleomorphism, with enlarged, bizarre-appearing, hyperchromatic nuclei (**b**). Giant macronucleoli and intranuclear pseudoinclusions were also frequently present (**c**). Note also the mixed chronic inflammatory cell infiltrate present in all cases, including mast cells.

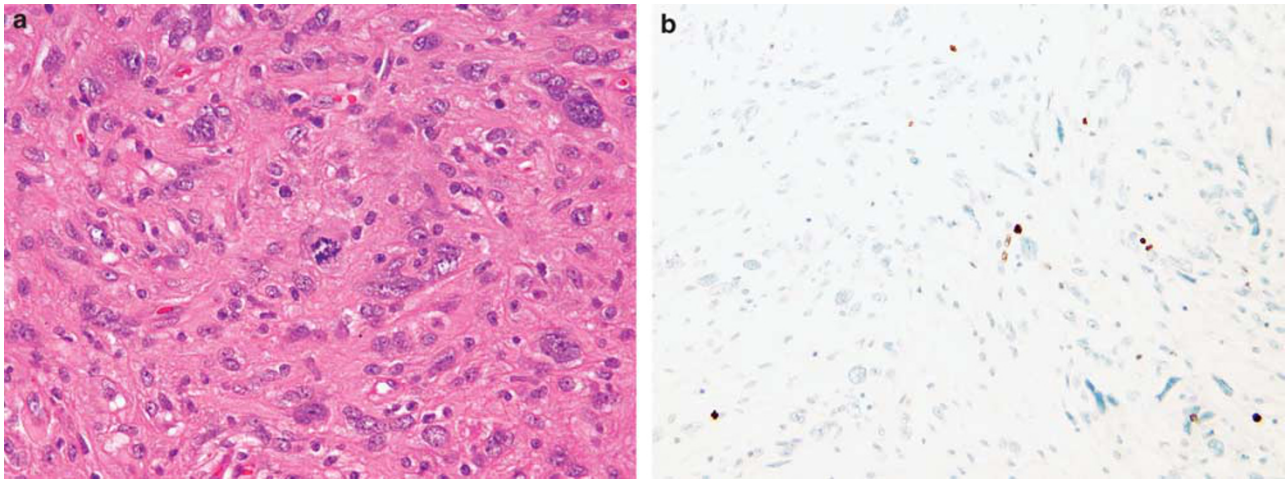

Figure 5 Despite their striking nuclear pleomorphism, CD34-postive fibroblastic tumors show an extremely low mitotic rate, invariably $<1/50$ high-powered fields (HPFs). One of the only mitotic figures identified is shown (**a**). Similarly, the Ki-67-labeling index was also extremely low (**b**).

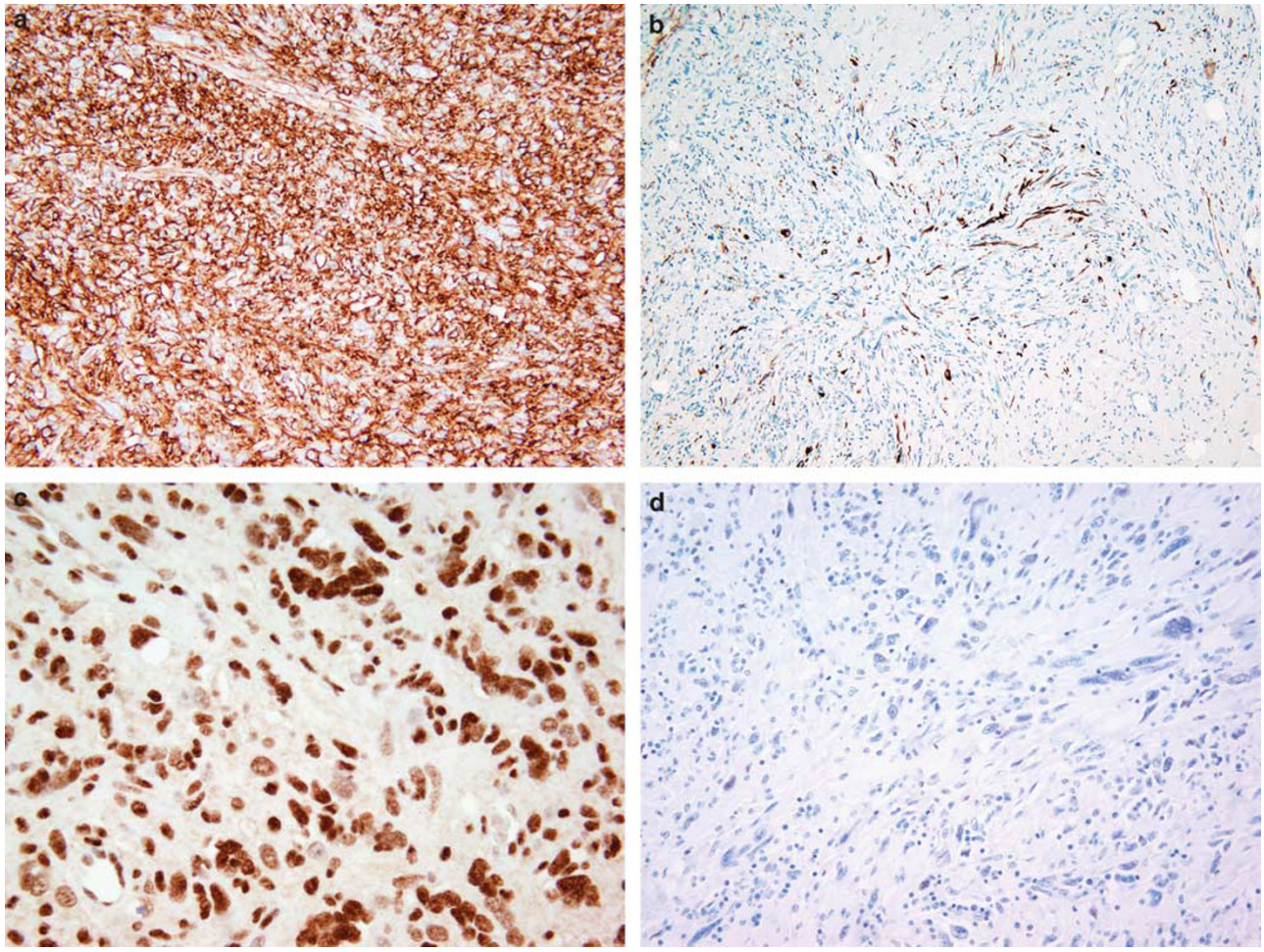

Figure 6 All tumors strongly expressed CD34 (**a**), and most of them were also positive for cytokeratins (**b**). In contrast, SMARCB1 expression was always retained (**c**) and p53 overexpression was absent.

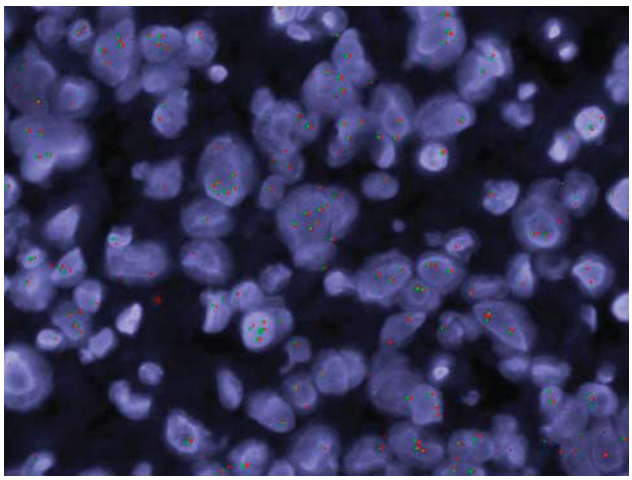

Figure 7 Negative fluorescence *in-situ* hybridization (FISH) for the myxoinflammatory fibroblastic sarcoma-associated *MGEA5* gene. All tested cases were negative for *MGEA5* and *TGFBR3* rearrangement.

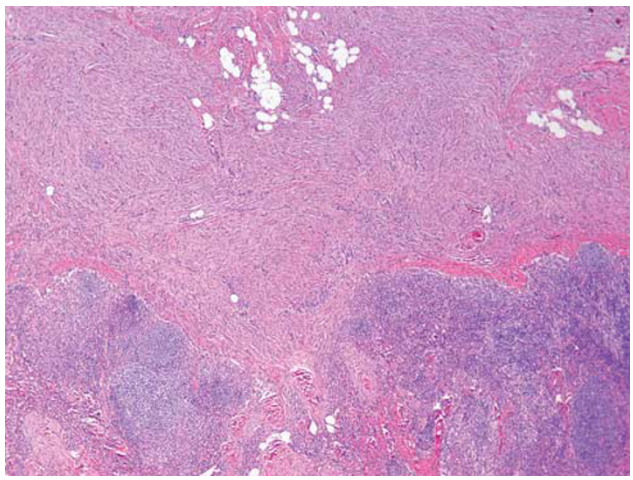

Figure 8 One case of CD34-positive fibroblastic tumor metastasized to a regional lymph node. Distant metastases were not seen.

Similarly, the morphological features of superficial CD34-positive fibroblastic sarcoma are quite dissimilar from those of epithelioid angiosarcoma,[36] epithelioid hemangioendothelioma,[37] and epithelioid sarcoma-like hemangioendothelioma,[38,39] and these tumors lack expression of the endothelial markers FLI-1 and ERG.[40–42]

The superficial location of these lesions might also raise the question of a possible relationship to dermatofibrosarcoma protuberans or cutaneous fibrous histiocytoma. Important points arguing against these possibilities include the subcutaneous (as opposed to dermal) location of these tumors, the lack of any history of a prior cutaneous tumor in the locations where these lesions arose, and the absence of any morphological features of dermatofibrosarcoma or fibrous histiocytoma at the periphery of the tumors. Fibrosarcomas arising in dermatofibrosarcoma protuberans typically show a herringbone pattern of growth, monomorphic cytology, brisk mitotic activity, and diminished CD34 expression, features very different than those of superficial CD34-positive fibroblastic tumor.

Finally, the abundant granular cytoplasm shown by these lesions might also suggest malignant granular cell tumor. Malignant granular cell tumors often show a component of pre-existing benign-appearing granular cell tumor, consist of a relatively monomorphic spindle cell sarcoma, resembling conventional malignant peripheral nerve sheath tumor, and are S100 protein positive[43]

In summary, we have reported the clinical, pathological, immunohistochemical, and molecular cytogenetic features of a novel mesenchymal tumor of the superficial soft tissues, which we have termed 'superficial CD34-positive fibroblastic tumor'. On the basis of available follow-up information, this tumor appears to behave as a mesenchymal tumor of intermediate malignancy (rarely metastasizing) to use current the World Health Organization nomenclature.[44] Longer-term follow-up and accrual of additional cases will be required to more fully understand the natural history of this distinctive lesion and whether it, like other low-grade fibroblastic mesenchymal tumors, has a characteristic molecular signature. Careful morphological evaluation and appropriate ancillary studies should allow for the distinction of superficial CD34-positive fibroblastic tumors from potential morphological mimics, in particular undifferentiated pleomorphic sarcoma.

Disclosure/conflict of interest

The authors declare no conflict of interest.

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