Don't call this a high-grade sarcoma! A case of superficial CD34-positive fibroblastic tumour

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Abstract

Described is a case of a superficial CD34-positive fibroblastic tumour, a rare atypical mesenchymal lesion of fibroblastic origin, in a female patient in her 40's. The common clinical, histological and molecular features are discussed with an emphasis on the pathologist's role in diagnosis, differentiation and MDT discussion.

Keywords Fibrosarcoma; PRDM10; sarcoma; soft tissue neoplasms; superficial CD34-positive fibroblastic tumor

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Case report

A female in her early 40s, normally fit and well, presented to her general practitioner with a 9-month history of a slowly growing mass on her lateral right thigh. There was no history of trauma to the area. The growth was not inherently painful but was uncomfortable when pressure was applied (e.g. in bed).

On examination there was a 4 x 3 cm non-mobile mass on the outer thigh which was thought to be tethered to the deep structures. No lymphadenopathy was detected clinically. An MRI scan was performed that revealed a well-defined 31 x 18 x 28 mm non-specific mass in the lateral aspect of the right mid-thigh (Figure 1) within the subcutaneous fat abutting the deep fascia. No adipose component was identified and there was no lymphadenopathy. The ultrasound confirmed an ovoid hypoechoic lesion in the deep subcutaneous fat that, in places, extended below the deep fascia of the vastus lateralis as was identified on the MRI scan. The lesion contained prominent neovascularity. Four 16-gauge cores were taken.

Microscopy showed neoplastic tissue formed of a cellular haphazard sheet arrangement of tapered spindle and plumper ovoid cells (Figure 2a). The eosinophilic cytoplasm was abundant and strikingly granular/glassy in sections (Figure 2b). Nuclear pleomorphism was prominent with the presence of often bizarre hyperchromatic irregular bordered nuclei (Figure 2c). A mixed inflammatory population of mast cells, eosinophils and lymphocytes were interspersed amongst the neoplastic tissue (Figure 2c). The lesional vasculature consisted of small calibre rounded vessels. No mitotic figures or areas of necrosis were identified in the biopsy material.

Immunohistochemistry demonstrated strong membranous and cytoplasmic staining of antibodies raised against CD34 (Figure 2d) with focal staining of AE1/3 cytokeratin of the neoplastic tissue. There was no expression of SMA, desmin, H-caldesmon, ERG, CD31, S100, SOX10, EMA, CD30, MNF116, MUC4, STAT6, p40 and CD45. INI1 was retained. The proliferative index, assessed by MIB1/Ki67, was low at between 5 and 10%. MDM2/CEP12 FISH demonstrated no amplification of the MDM2 gene.

Overall, the features were those of an atypical mesenchymal tumour with a diagnosis of a superficial CD34-positive fibroblastic tumour being favoured. Although with the caveat that on biopsy alone, confidently making this diagnosis is difficult. Due to the borderline behaviour of this neoplasm the patient was discussed at the local sarcoma MDT and wide local excision was performed. The appearances on the biopsy were recapitulated in this specimen with involvement of the subcutaneous tissues and deep fascia. The striking nuclear pleomorphism was once again noted however no necrosis was present, and the mitotic index was one mitosis per 10 high power fields. The lesion had a well circumscribed border although there was infiltration through the deep fascial layer with involvement of the deep margins (Figure 2e). A re-excision was performed with only post-surgical histological changes seen. Interval MRI scans showed no local recurrent or distant disease over a year later.

Discussion

Superficial CD34-positive fibroblastic tumour was reported as a distinct entity in 2014 after Carter et al.'s seminal work and was

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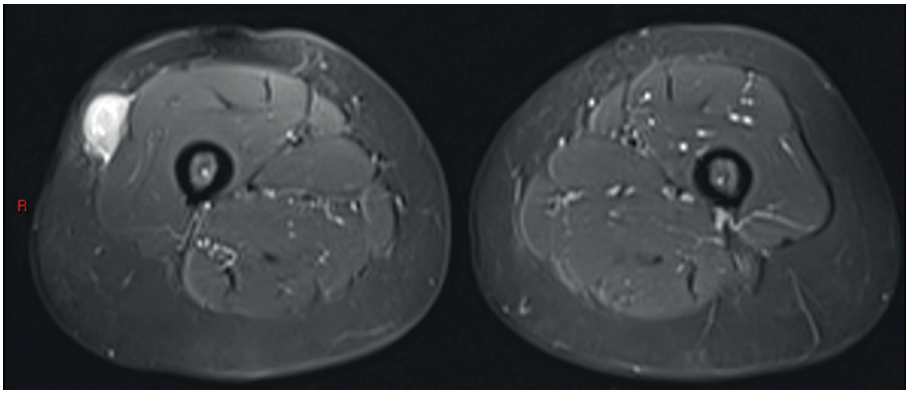

Figure 1 Short tau inversion recovery (STIR) magnetic resonance imaging of the lesion in the right thigh. This fat suppression MRI mode demonstrates no fatty component of the lesion. A bright well circumscribed enhancement is seen in the subcutis abutting but not invading the vastus lateralis muscle.

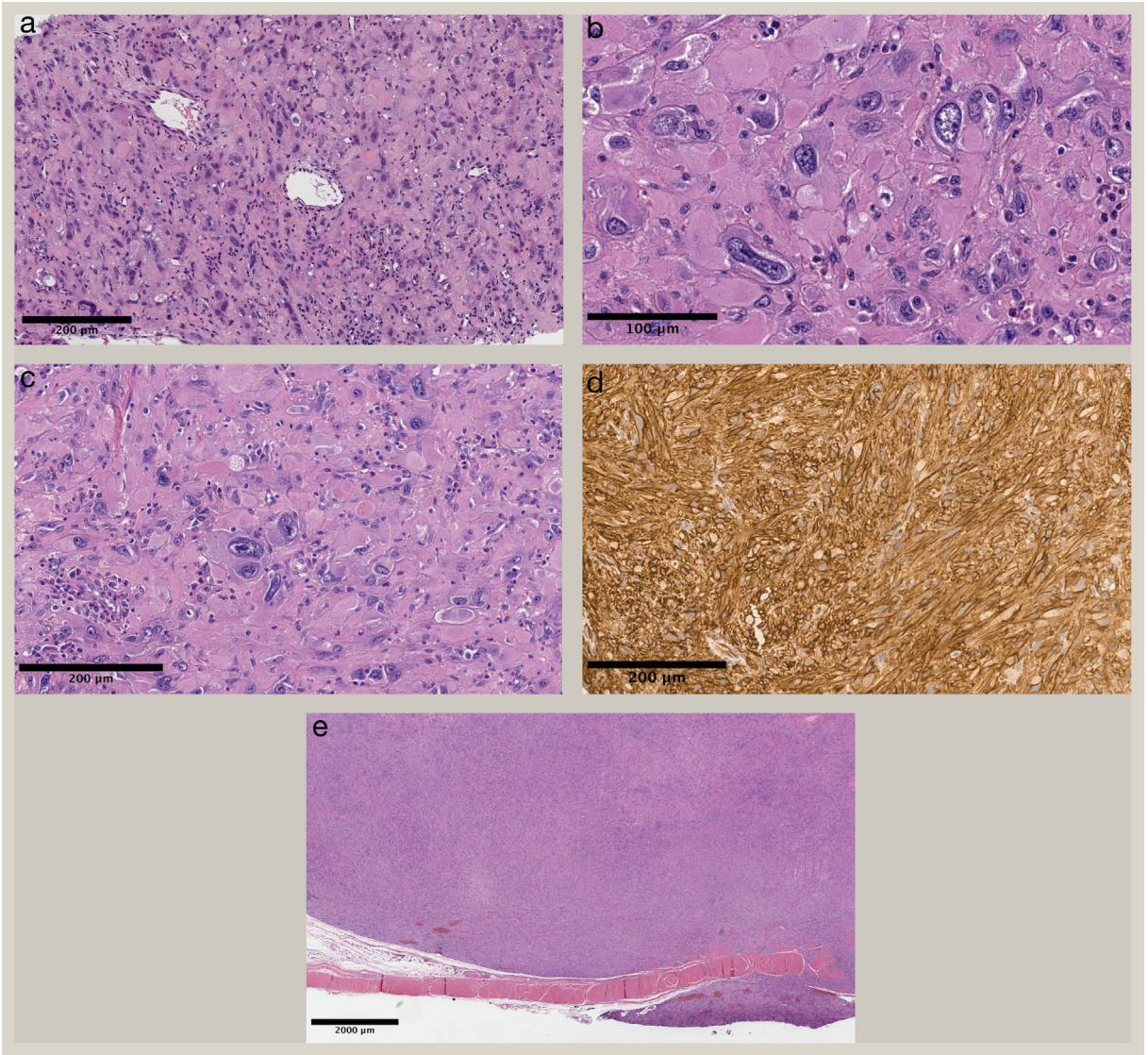

Figure 2 (**a**) Cellular haphazard sheets of spindle and plump ovoid cells with occasional thin-walled vessels. 15x magnification. (**b**) Cytoplasmic detail showing abundant eosinophilic granular/glassy cytoplasm. 35x magnification. (**c**) Occasional pleomorphic cells with large irregular nuclei and prominent nucleoli. A mixed inflammatory infiltrate is seen. 20x magnification. (**d**) Strong and diffuse membranous and cytoplasmic cytokeratin AE1/3 immunohistochemistry. 20x magnification. (**e**) Excision specimen showing a well circumscribed lesion in the subcutis abutting and infiltrating through the fascia to be present at the deep margin.

Key differential diagnoses in CD34-positive fibroblastic tumours (non-exhaustive, aide-memoire)

Entity	Clinical considerations	Morphology	Immunohistochemistry	Molecular characteristics
SCPFT	Young (20—30s), Indolent, lower limbs	'Glassy' cytoplasm, occasional pleomorphism, mitotic activity low	Strong, diffuse CD34+, occasional CK (particularly AE1/3)	—
UPS	Older patients, aggressive, sub-fascial location	Pleomorphism, necrosis, mitotically active	Weak/patchy CD34	—
Myxofibrosarcoma	Older patients (rare under 30), high grade aggressive	Myxoid stroma, often pleomorphism, mitotically active, infiltrative growth pattern. Low or high grade	Weak/patchy CD34, nonspecific staining of other markers	—
MIFS	Distal extremities, common local recurrence, middle aged	Myxoid stroma, dense inflammatory infiltrate, often pleomorphism, emperipolesis	CD10, BCL-1, factor XIIIa occasional/patchy CD34	—
PHAT	Distal lower extremities, locally aggressive, middle aged	Clusters ectatic vessels, haemosiderin, spindle cells, pleomorphism, necrosis and mitoses rare	Focal to diffuse CD34 expression	—
DFSP	Locally aggressive, young to middle aged	Generally bland, cellular, spindle cells storiform pattern, subvariants	CD34 lost in fibrosarcomatoid areas	COL1A1::PDGFB
SFT	Wide range of locations, prognosis dependent on location and risk stratification	Haphazard spindle cells, staghorn like vessels, collagenous stroma	CD34 often diffuse. STAT6 nuclear staining	NAB2::STAT6
AFX	Low grade dermal neoplasm, sun-exposed regions, elderly	Bizarre, atypical cells, necrosis and mitoses absent (deep located and high-grade think PDS)	Generally, CD34 negative. Nonspecific staining of other markers	—
LGFS	Thigh most common site, trunk. Fairly high recurrence/ metastasis rate	Generally bland, cellular, spindle cells, myxoid component	MUC4 positive	FUS::CREB3L2

SCPFT, superficial CD34-positive fibroblastic tumour; UPS, undifferentiated pleomorphic sarcoma; MIFS, myxoinflammatory fibroblastic sarcoma; PHAT, pleomorphic hyalinizing angiectatic tumor; AFX, atypical fibroxanthoma; PDS, pleomorphic dermal sarcoma; LGFS, low-grade fibromyxoid sarcoma; -, not used clinically.

Table 1

subsequently added to the 5th edition to the WHO Classification of Tumours.[1] To date, fewer than 70 cases of this entity have been reported in the literature.[2] The median age is early to mid-thirties with a male predominance and two thirds being found in the lower limbs.[3] It is likely there is underdiagnosis due to its rarity, the disconcerting pleomorphism and only recent official recognition. In fact, the original paper noted that many reviewed cases were originally designated as undifferentiated pleomorphic sarcomas, myxofibrosarcomas or myxoinflammatory fibroblastic sarcomas.[1] However, there were several features that pointed towards a separate entity. Superficial CD34-positive fibroblastic tumours, as the name suggests, are located superficially with no reported muscle invasion. Within the initial case series and subsequently published literature, there is reported universally strong diffuse expression of CD34 with occasional cases showing a degree of cytokeratin staining. Other immunohistochemical markers have been described as focal or absent. Importantly, cases note that despite the cytological pleomorphism, mitotic and proliferative counts were surprisingly low, and necrosis is not prominently described. The very classical granular/glassy/glazed eosinophilic cytoplasm is another commonly seen feature.

Of the published cases, instances of local recurrence are recorded, usually related to incomplete or marginal excisions. Only one case in the literature to date shows lymph node metastasis seven years following marginal excision, but following pelvic lymphadenopathy the patient remained disease free.[1] It is therefore favoured that these lesions are generally indolent but are designated 'borderline malignant' with particular focus on ensuring a wide margin of excision is completed.

With regards to the molecular landscape of these tumours, small series have shown a proportion of tumours have a PRDM10 rearrangement with various fusion partners.[4] Other neoplasms have demonstrated PRDM10 fusions including a small subset of

undifferentiated pleomorphic sarcoma (UPS), pleomorphic liposarcoma and pleomorphic hyalinizing angiectatic tumor (PHAT).[5,6] Of these rearranged cases, overlapping morphological and prognostic features seem to exist (spindle cells, often pleomorphic, low proliferative index and indolent nature). PRDM10-rearranged Soft Tissue Tumour has been proposed as a distinct entity which seems to have significant overlap with superficial CD34-positive fibroblastic tumours.[6] However, these are currently not recognized by the WHO, but as further molecular profiling studies come to light, nomenclature and classification may still alter.

The key challenge faced by the pathologist in these cases is a) awareness of this very rare neoplasm and b) the potential wide differential diagnosis particularly in biopsy material, which may just show concerning pleomorphic cells. Key differential diagnoses to consider when superficial CD34-positive tumour is being considered are myxoinflammatory fibroblastic sarcoma, myxofibrosarcoma, UPS, atypical fibroxanthoma, PHAT, and dermatofibrosarcoma. Key considerations are summarized in Table 1.

Conclusion

This case marks the second case of superficial CD34-positive fibroblastic tumour to have a confirmed diagnosis through the Scottish Sarcoma Network. It is a very rare tumour which should only be considered once more common alterative/higher grade diagnoses are ruled out.

Note

Given the rare nature of this diagnosis, fully informed signed patient consent was obtained. ◆

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Practice points

- Superficial CD34-positive fibroblastic tumour is a very rare lesion of fibroblast lineage with a strong preponderance for the lower limb
- It is characterized by a classical 'glassy' eosinophilic cytoplasm and often striking nuclear pleomorphism with a low mitotic/proliferative index. Radiology will support a superficial location, and deeper lesions should warrant alternative diagnoses
- Diffuse strong expression of CD34 is the hallmark of the entity with occasional cytokeratin expression (particularly the AE1/3 clone). Expression of other immunohistochemical stains and common molecular aberrations of low-grade sarcomas are absent
- Although the literature is limited, the lesion is best regarded as a tumour of borderline malignant potential with local recurrence happening following incomplete excision and one incidence of inguinal lymph node metastasis seven years following marginal excision
- The pathologist must a) rule out a low- or high-grade sarcoma and b) convey the borderline status to the surgical team to ensure adequate excisional margins are taken and suitable follow-up arranged

Multiple choice questions

1. Which of the following statements is true about superficial CD34-positive fibroblastic tumours?

A) They are entirely indolent with no recurrence or metastatic potential.
B) They always show diffuse strong cytokeratin staining.
C) Abundant mitoses and necrosis would help to support the diagnosis.
D) Glassy granular eosinophilic cytoplasm is a pathognomonic feature.
E) They most commonly arise on the lower limbs.

Answer: E). Two thirds of superficial CD34-positive fibroblastic tumours are found in the lower limbs. They are regarded as having borderline malignant potential due to their local recurrence risk and isolated described case of regional lymph node metastasis. Cytokeratin staining is usually weak and patchy, CD34 is diffuse and strong. High mitotic activity and necrosis would point away from a diagnosis of superficial CD34-positive fibroblastic tumour. Glassy cytoplasm is often seen and can be striking, but it is not pathognomic.

2. Which of the following translocations has been described in superficial CD34-positive fibroblastic tumours?

A) FGFR2::BICC1.
B) PRDM10::MED12.
C) COL1A1::PDGFB.
D) NAB2::STAT6.
E) FUS::DDIT3.

Answer: B). PRDM10::MED12, a subset of superficial CD34-positive fibroblastic tumours show rearrangements of the PRDM10 gene, but currently these are not used routinely for diagnostic purposes. FGFR2::BICC1 fusions are seen in a subset of cholangiocarcinomas. COL1A1::PDGFB fusions are seen in some dermatofibrosarcomas. NAB2::STAT6 fusions are seen in solitary fibrous tumours. FUS::DDIT3 fusions may be seen in myxoid liposarcomas.

3. With regards to superficial CD34-positive fibroblastic tumours, which of the following is the most important for the pathologist to convey in an MDT following a suspected biopsy?

A) Focal cytokeratin AE1/3 staining.
B) The possible risk for local recurrence and lymph node metastasis.
C) MIB1/Ki67 proliferative index of 5%.
D) Glassy/granular cytoplasm.
E) Bizarre pleomorphic cells.

Answer: B). The borderline malignant potential of these lesions should be conveyed to the MDT. Although regarded as indolent, local recurrence and lymph node metastases have been reported. Pleomorphism, glassy cytoplasm and focal cytokeratin staining and common descriptors and will aid the pathologist towards a diagnosis. The lesions are expected to have a low proliferative index.