Clear cell sarcoma: a rare cause of a lump in the foot

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Abstract

Clear cell sarcoma of soft tissue is a rare aggressive soft tissue malignancy primarily affecting the extremities of young adults and is characterised by an *EWSR1*::ATF1 fusion gene. The tumour has a high rate of local recurrence and metastasis and as such often has a poor prognosis.

Keywords ATF1; clear cell sarcoma; EWSR1; FISH; fusion; sarcoma

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Case report

A 36-year-old female presented with a 4 year history of a slow growing painless lump on the medial aspect of the left foot (Figure 1). A core needle biopsy of the lesion showed tendinous tissue infiltrated by nests and short fascicles of ovoid cells with eosinophilic cytoplasm showing focal clearing (Figure 2a). Immunohistochemistry showed diffuse strong positivity for SOX10, HMB45, and S100 (Figure 2b–d). The cells were negative for desmin, SMA, and MNF116. Interphase fluorescence in situ hybridisation (FISH) was performed which demonstrated an *EWSR1* rearrangement (Figure 3). Analysis of RNA sequencing data showed an *EWSR1::ATF1* fusion gene (Figure 4). The patient received a wide local excision (Figure 1) and post-operative radiotherapy. One year later, she developed an inguinal lymph node metastasis which was resected. The following year lung metastases were identified, and she commenced treatment with the multi-kinase inhibitor Pazopanib. Despite treatment, her disease progressed, and she died the following year approximately 3.5 yrs after initial diagnosis.

Discussion

Clear cell sarcoma of soft tissue (CCS) is a rare sarcoma that predominantly affects young adults in the third or fourth decade with a median age of 39. There is an equal sex predominance. Once known as melanoma of soft parts, the most common site is the extremities particularly the foot and ankle. This tumour has high rates of recurrence and lymph node metastases (unusual for soft tissue sarcomas), along with distal metastases most frequently to the lungs. The 5- and 10-year overall survival rates have been reported to be between 50%–59% and 38%–41%, respectively.[1–4]

Histologically the tumour has the classical appearance of a nested or sometimes fascicular architecture which infiltrates through dense fibrous tissue (Figure 5a and b). The nests of epithelioid to spindled cells are arranged in groups that are separated by intervening fibrous tissue. While occasionally they show cytoplasmic clearing from the accumulation of glycogen, more often the cells have pale eosinophilic cytoplasm. The nuclei are most often uniform with mild nuclear pleomorphism, vesicular, and contain macronucleoli. Multinucleated tumour giant cells are frequently identified (Figure 5c). Melanin pigment can be seen. The mitotic index is usually low (<5 mitoses per 10 hpf) (Figure 5d).[4,5]

The tumours harbour in nearly all cases an *EWSR1* gene fusion (Table 1).[4,6] The t(12; 22)(q13; q12) reciprocal translocation leads to a *EWSR1::ATF1* fusion protein in more than 90% of patients. As seen in this case the most common isoform arises from the fusion of *EWSR1* exon 8 with *ATF1* exon 4 (Figure 4). Rarer cases of t(2; 22)(q34; q12) *EWSR1::CREB1,* or *EWSR1::CREM* fusion genes have been identified.[4,6] The new fusion protein acts as an oncogenic transcription factor with the EWSR1 domain retargeting either the ATF1 or more rarely the CREB1 DNA binding domain to different genomic regions, subsequently resulting in chromatin remodelling and the activation of neural crest-related developmental programmes.[7] These transcriptional and differentiation programmes overlap with malignant melanoma which may help explain their morphological and immunohistochemical similarity.[7] Unlike melanoma, only rare cases of CCS have been reported with mutations in *BRAF*.[4]

Surgery is the primary treatment modality with radiotherapy offered in certain clinical situations. Chemotherapy has little benefit as patients show a poor response. Multi-kinase inhibition using drugs that target VEGFR and PDGFR such a pazopanib have been shown to have some effect, however the sample size in clinical trials is small and further prospective studies are needed. Clinical trials are underway involving immunotherapy along with inhibitors of mitochondrial metabolism, histone deacetylase, BRAF and Her 3.[4]

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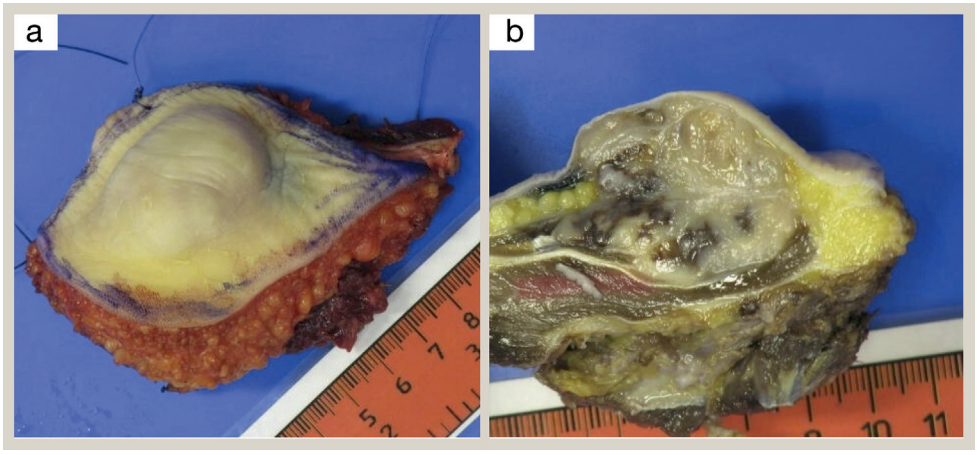

Figure 1 Resection of left foot tumour. (**a**) Skin ellipse with a central visible dome shaped mass. (**b**) Grey subcutaneous tumour measuring 40 x 35 x 32 mm extending into underlying skeletal muscle.

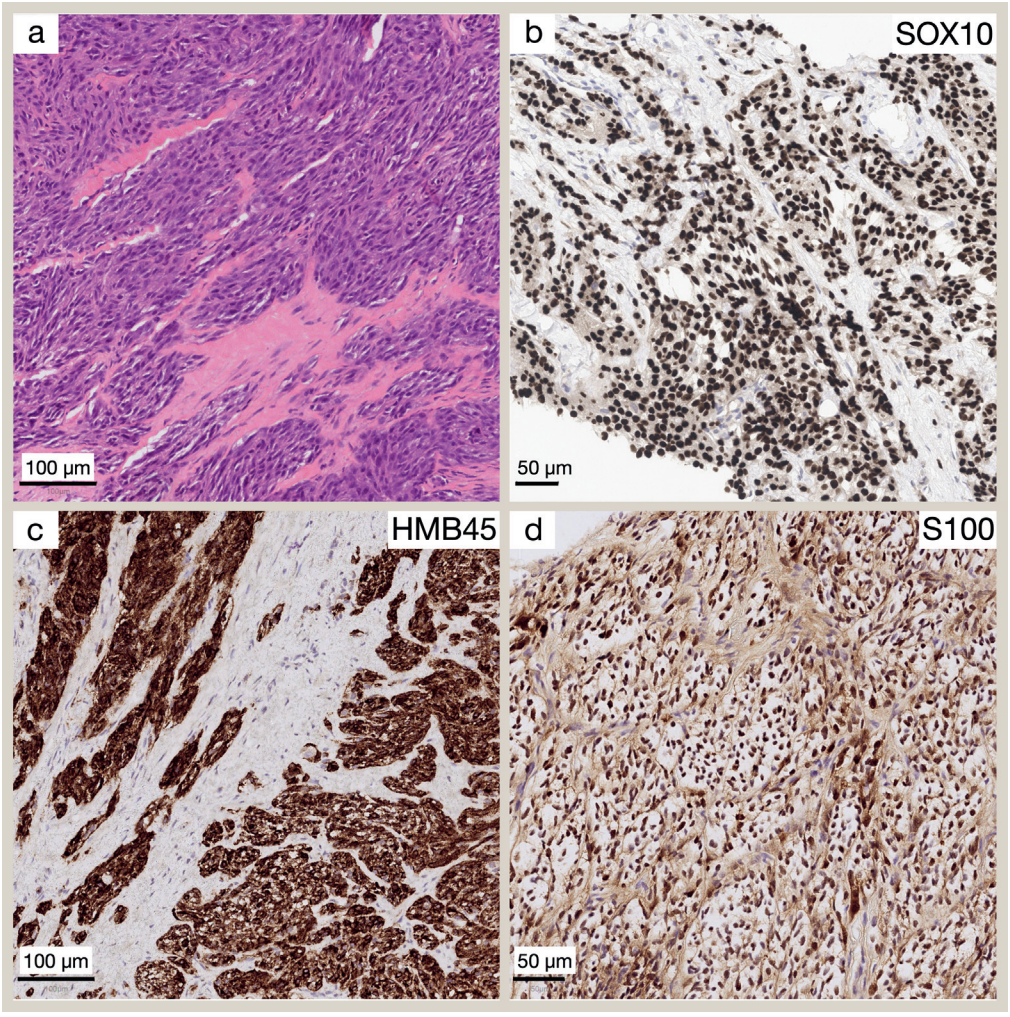

Figure 2 Histological appearance of the biopsy. (**a**) H&E straining showing nests of uniform spindled cells infiltrating dense fibrous tissue. The tumour was positive for the immunohistochemical markers (**b**) SOX10 (**c**) HMB45 and (**d**) S100.

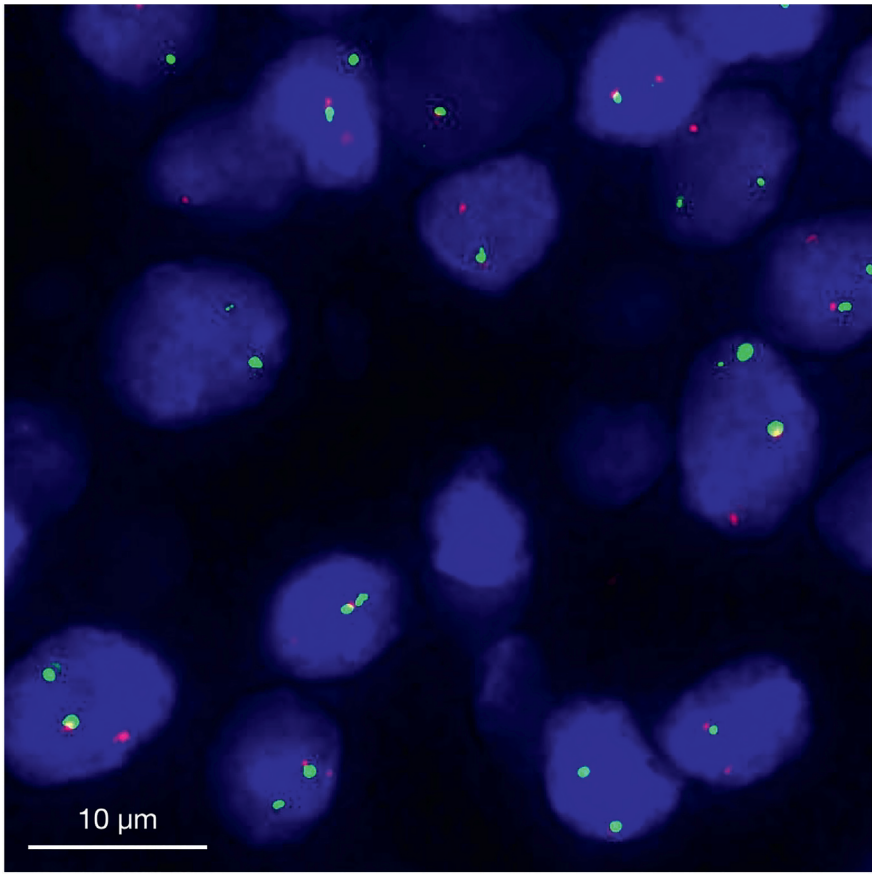

Figure 3 Interphase FISH demonstrating *EWSR1* gene break apart signals. The red and green probes are designed to bind to the *EWSR1* gene and in normal nuclei should produce an overlapping yellow signal. In many of these nuclei no yellow signal is seen, and the red and green signals are distant from each other. This indicates that an *EWSR1* fusion event has likely occurred.

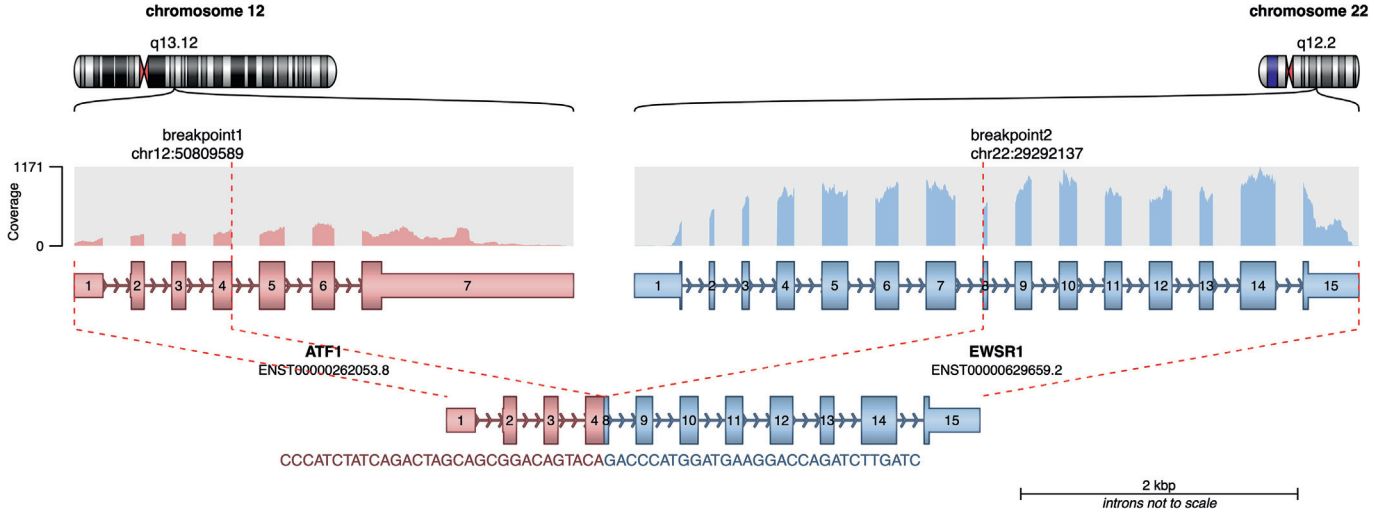

Figure 4 RNA sequencing demonstrates an *EWSR1::*ATF1 fusion gene resulting from the fusion of exons 1–4 from *ATF1* with exons 8–15 from *EWSR1.*

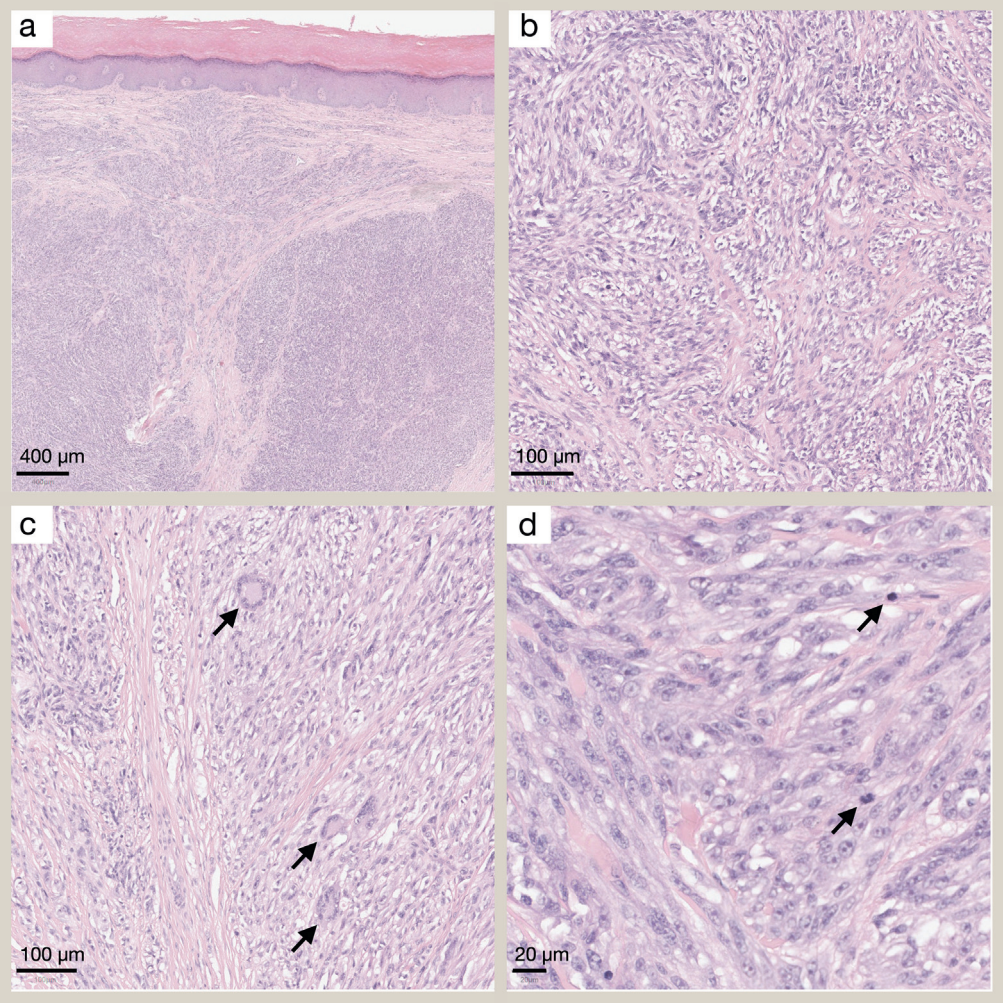

Figure 5 Histological appearance of the resection. (**a**) Acral skin with underlying deeply invasive tumour. (**b**) Higher magnification shows a typical appearance of this tumour with nests of uniform spindled cells with pale eosinophilic to clear cytoplasm. (**c**) Wreath-like multinucleated tumour giant cells are a common finding (arrows). (**d**) The vesiculated nuclei contain macronucleoli and occasional mitotic figures are seen (arrows).

Other tumours associated with *EWSR1::ATF1, EWSR1::CREB or EWSR1::CREM* fusion genes

EWSR1::ATF1	***EWSR1::CREB1***	***EWSR1::CREM***
Clear cell sarcoma of soft tissue	Clear cell sarcoma of soft tissue	Clear cell sarcoma of soft tissue
Angiomatoid fibrous histiocytoma	Angiomatoid fibrous histiocytoma	Primary pulmonary myxoid sarcoma
Hyalinizing clear cell carcinoma of the salivary gland	Malignant gastrointestinal neuroectodermal tumour	Malignant mesothelioma
Malignant gastrointestinal neuroectodermal tumour	Primary pulmonary myxoid sarcoma	Intracranial myxoid mesenchymal tumour
Primary pulmonary myxoid sarcoma	Intracranial myxoid mesenchymal tumour	
Malignant mesothelioma		
Myoepithelial carcinoma		
Clear cell odontogenic carcinoma		
Intracranial myxoid mesenchymal tumour		

Table 1

Conclusion

The diagnosis of Clear cell sarcoma of soft tissue relies on integrating the histological, immunohistochemical, and molecular findings in the appropriate clinical context. Given the histological and immunohistochemical similarity to malignant melanoma, and that *EWSR1* rearrangements can be found in other tumour types; care needs to be taken to avoid misdiagnosis to ensure appropriate management. ◆

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Acknowledgements

The macroscopic and microscopic images have been kindly provided by the Royal National Orthopaedic Hospital NHS trust histopathology department.

The genomic data used in generation of this case report was generously supported by a philanthropic donation from the Edward Showler Foundation which supports research into Clear cell sarcoma of soft tissue. www.edwardshowlerfoundation.com.

Practice points

- Given the histological and immunohistochemical similarity between melanoma, clear cell sarcoma should always be considered in the differential of a lesion with melanocytic differentiation particularly in extremities of a young person, particularly if the tumour is located in deep soft tissue
- Molecular testing either through FISH or targeted RNA sequencing to identify an *EWSR1* rearrangement should be done to confirm the diagnosis. This is especially important for tumours that are positive for melanocytic markers for which there is no identifiable in situ cutaneous or mucosal lesion
- Long term follow up is required for these patients given the high risk of relapse and metastasis

Multiple choice questions

1. What is the most common primary site of CCS?

A. Head and neck
B. Lung
C. Foot
D. Abdomen

Correct answer: C

2. What is the most common fusion gene identified in CCS?

A. *ESWR1::FLI1*
B. *ESWR1::ETV1*
C. *EWSR1::ATF1*
D. *ESWR1::WT1*

Correct answer: C

3. Which of the following immunohistochemical stains is negative in CCS?

A. Melan A
B. Desmin
C. S100
D. SOX10

Correct answer: B