Pigmented clear cell sarcoma of soft tissue: an important diagnostic mimic

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Abstract

Clear cell sarcoma of soft tissue (CCSST) is a rare and aggressive soft tissue tumour associated with tendons and aponeuroses of the lower extremities. Due to its melanocytic differentiation, distinguishing CCSST from melanocytic neoplasms and other pigmented lesions can be challenging. We report a peculiar case of CCSST and discuss the histological, immunohistochemical and molecular features which can aid in accurate diagnosis of this entity.

Keywords clear cell sarcoma; differential diagnosis; EWSR1; melanocytic

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Case report

An 80 year old male presented with a two year history of a painless, discoloured mass on his left lower leg. Imaging demonstrated a 45 mm nodular lesion with a benign appearance involving the dermis and subcutaneous tissue. A biopsy revealed nests and sheets of monotonous plump spindle cells with vesicular nuclei and prominent nucleoli (Figure 1). Intracytoplasmic melanin pigment and pigment-laden macrophages were present throughout the lesion. Occasional non-atypical mitoses were identified, and no tumour necrosis was seen. The tumour focally abutted the dermal-epidermal junction, however no connection to or involvement of the epidermis was identified. A definitive diagnosis was not made and the differential diagnosis included an unusual dermatofibrosarcoma protuberans (Bednar tumour), a melanocytic tumour or a tenosynovial tumour. The lesion was closely excised without morbidity.

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Several years later the tumour recurred, with an MRI showing a poorly defined lesion in contact with an underlying tendon. Review of both the original and recurrent lesions revealed the tumour cells to be immunoreactive for Melan-A and HMB45 (Figure 1), and negative for CD34, S100 and MNF116. These findings prompted molecular studies which demonstrated an *EWSR1* rearrangement by fluorescence in-situ hybridisation (FISH) leading to a final diagnosis of a clear cell sarcoma. This resulted in aggressive management of the recurrence with wide local excision and adjuvant radiotherapy.

Discussion

Clear cell sarcoma of soft tissue (CCSST), historically known as melanoma of soft parts due to its melanocytic phenotype, is a rare soft tissue tumour associated with tendons and aponeuroses. CCSST accounts for less than 1% of all sarcomas, and generally occur in adults under the age of 40 with a slight female predominance.[1,2] The vast majority arise in the distal lower extremities and present as painless slow-growing masses. Importantly, CCSSTs often have a misleadingly benign appearance on imaging.[3]

Morphologically CCSSTs are variably comprised of nests, sheets and fascicular areas. Tumour cells are spindled to epithelioid in appearance with clear or pale eosinophilic cytoplasm.[1] Intracytoplasmic melanin pigment can be present, but is typically focal.[2] Tumour nuclei are vesicular and commonly display prominent nucleoli. Most CCSSTs show no more than moderate nuclear pleomorphism and a deceptively low mitotic rate for the aggressiveness of this tumour. Occasional rhabdoid cells and Touton-like giant cells may also be observed in these tumours.[1,4]

Immunohistochemistry can be useful in establishing the diagnosis of CCSSTs but may also lead to misdiagnoses if interpreted in isolation. In keeping with melanocytic differentiation, CCSSTs characteristically express Melan-A, HMB45, S100, and MITF, albeit at more variable intensity than seen in malignant melanoma.[1,2] Additionally, diffuse expression of BCL2 is common,[2] and subsets of tumours express neuroendocrine markers, and occasionally EMA. Pancytokeratins, desmin and smooth muscle actin are typically negative.

Malignant melanoma is the top diagnostic mimic of CCSST given the similar histological and immunohistochemical profile, but unlike CCSST often comprises an intraepidermal component

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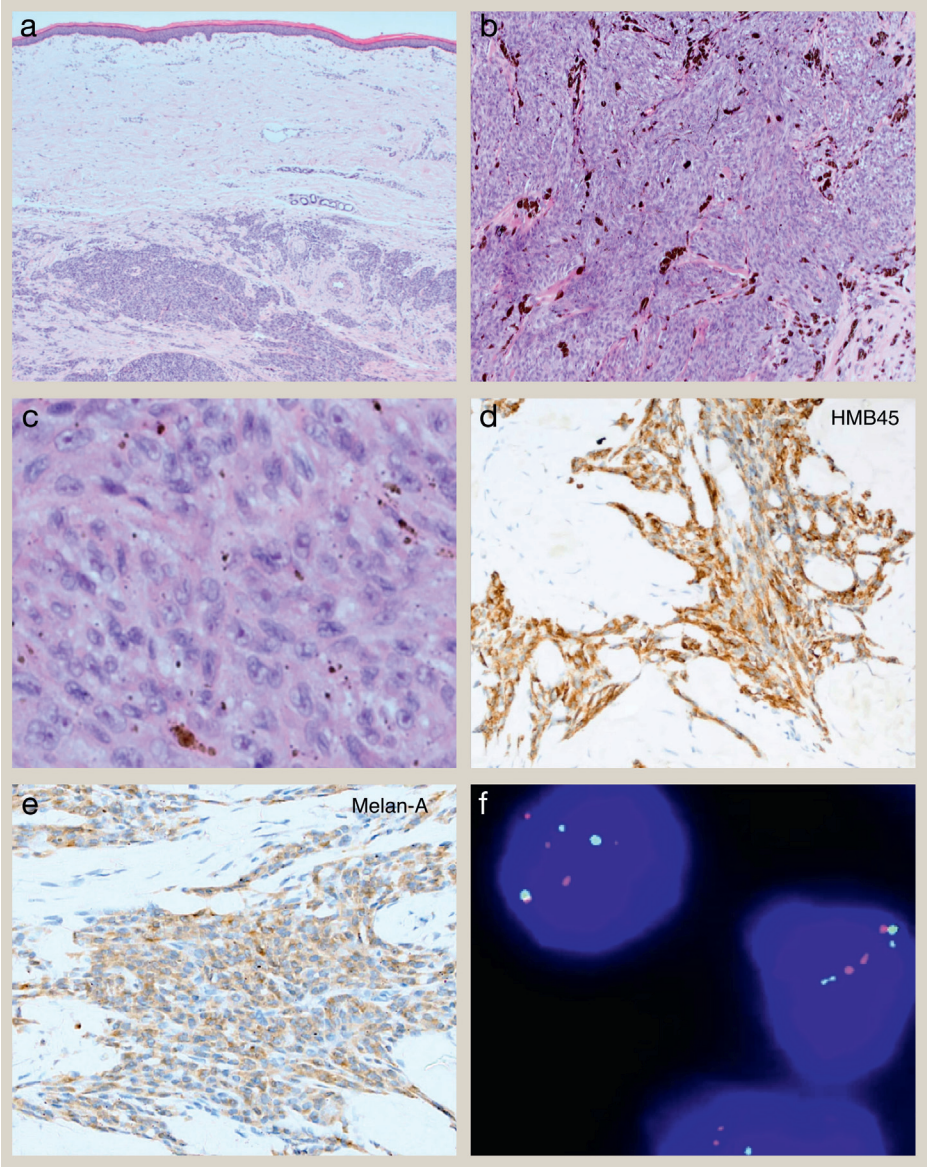

Figure 1 Histological appearances of unusual pigmented tumour with (**a**) tumour nests invading the dermis. (**b**) Confluent nests and sheets were present with numerous pigment laden macrophages. (**c**) Tumour cells display prominent nucleoli and intracytoplasmic pigment. Melanocytic markers (**d**) HMB45 and (**e**) Melan-A were both diffusely positive. (**f**) EWSR1 break-apart signal was demonstrated on interphase FISH.

and does not contain Touton-like giant cells. Other melanocytic lineage or pigmented lesions may also be considered such as perivascular epithelioid cell neoplasm (PEComa), atypical naevi, pigmented dermatofibrosarcoma protuberans (Bednar's tumour) and melanotic schwannomas/nerve sheath tumours. In its non-pigmented form, the differential also includes epithelioid mesenchymal tumours such as epithelioid sarcoma, epithelioid malignant peripheral nerve sheath tumour, and paraganglioma.

CCSST belongs to the diverse family of tumours harbouring fusion genes *EWSR1-ATF1* and *EWSR1- CREB1*[5] (Table 1), with the majority of cases demonstrating the former. Identification of an *EWSR1* rearrangement by FISH or RNA panel is often essential for distinguishing CCSSTs from melanoma and other diagnostic mimics.

Treatment of CCSST primarily involves surgical excision with wide margins and adjuvant radiotherapy in cases of incomplete

Tumours harbouring EWSR1-ATF1 and EWSR1-CREB1 fusion genes

Epithelial differentiation	Mesenchymal differentiation
Hyalinising clear cell carcinoma of the salivary gland ■	Angiomatoid fibrous histiocytoma (AFH) ■
Clear cell odontogenic carcinoma ■	Clear cell sarcoma of soft tissue ● ■
	Malignant gastrointestinal neuroectodermal tumour ● ■
	Primary pulmonary myxoid sarcoma ●
	Intracranial myxoid mesenchymal tumours (Intracranial AFH) ●

● EWSR1-CREB1 fusion; ■ EWSR1-ATF1 fusion.

Table 1

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excision. Patients with CCSST experience high rates of local relapse and metastatic disease, which is managed with multi-agent chemotherapy although response to systemic therapies is generally poor.[6] Long-term follow up is therefore necessary. Lymph node involvement, a rare occurrence in soft tissue tumours, occurs in almost 50% of cases of CCSST.[7] Five year overall survival ranges from approximately 70% in patients with localized disease at presentation to less than 40% in those presenting with disseminated CCSST.[1,7] Adverse prognostic factors include tumour size larger than 5 cm, truncal location, presence of tumour necrosis, a mitotic rate of ≥10 per 10 high-power fields, and positive margin status on resection. Clinical trials are currently underway to determine the utility of immunotherapies in patients with advanced CCSST.[6]

Conclusion

This case report highlights CCSST as an uncommon but important differential in pigmented lesions of the dermis and soft tissue. We outline key histological, immunohistochemical and molecular features which can aid in discriminating these tumours from melanoma and other mimics in challenging scenarios. ◆

REFERENCES

1 WHO Classification of Tumours Editorial Board. WHO classification of tumours soft tissue and bone tumours. 5th ed. Lyon, France: IARC Press, 2020.
2 Hisaoka M, Ishida T, Kuo TT, et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis of 33 cases. *Am J Surg Pathol* 2008; **32:** 452–60.
3 De Beuckeleer LH, De Schepper AM, Vandevenne JE, et al. MR imaging of clear cell sarcoma (malignant melanoma of the soft parts): a multicenter correlative MRI-pathology study of 21 cases and literature review. *Skeletal Radiol* 2000; **29:** 187–95.
4 Antonescu CR, Tschernyavsky SJ, Woodruff JM, Jungbluth AA, Brennan MF, Ladanyi M. Molecular diagnosis of clear cell sarcoma: detection of EWS-ATF1 and MITF-M transcripts and histopathological and ultrastructural analysis of 12 cases. *J Mol Diagn* 2002; **4:** 44–52.
5 Thway K, Fisher C. Tumors with EWSR1-CREB1 and EWSR1-ATF1 fusions: the current status. *Am J Surg Pathol* 2012; **36:** e1–11.
6 Smrke A, Frezza AM, Giani C, et al. Systemic treatment of advanced clear cell sarcoma: results from a retrospective international series from the World Sarcoma Network. *ESMO Open* 2022; **7**: 100522.
7 Bianchi G, Charoenlap C, Cocchi S, et al. Clear cell sarcoma of soft tissue: a retrospective review and analysis of 31 cases treated at Istituto Ortopedico Rizzoli. *Eur J Surg Oncol* 2014; **40:** 505–10.

Self assessment

1. Which feature of clear cell sarcoma of soft tissue is NOT commonly seen in malignant melanoma?

a) Spindled to epithelioid tumour cells
b) Focal intracytoplasmic melanin
c) Touton-like giant cells and rhabdoid cells
d) Expression of neuroendocrine markers

Correct answer: c) Touton-like giant cells and rhabdoid cells.

2. Which immunoprofile BEST represents a clear cell sarcoma of soft tissue?

a) MNF116 (-), Melan-A (+), S100 (-), BCL2 (-), CD56 (-)
b) MNF116 (-), Melan-A (+), S100 (+), BCL2 (+), CD56 (+)
c) AE1/AE3 (+), Melan-A (+), S100 (+), BCL2 (+), CD56 (-)
d) MNF116 (+), HMB45 (+/-), S100 (-), BCL2 (+), CD56 (-)

Correct answer: b) MNF116 (-), Melan-A (+), S100 (+), BCL2 (+), CD56 (+).

3. Which of the following statements is TRUE for clear cell sarcoma of soft tissue?

a) CCSSTs appear benign on imaging but have high mitotic rates and extensive tumour necrosis
b) CCSSTs most commonly harbour EWSR1-CREB1 fusions
c) CCSSTs rarely metastasize to lymph nodes
d) Larger tumours and tumours located on the trunk have a higher risk of adverse outcomes

Correct answer: d) Larger tumours and tumours located on the trunk have a higher risk of adverse outcomes.

Practice points

- CCSST is a rare soft tissue tumour which due to its melanocytic lineage can mimic melanoma and other skin and soft tissue tumours.
- CCSSTs are characterized by EWSR1-ATF1 and less commonly EWSR1-CREB1 fusions, which are also detected in many other cancer types.
- Although CCSSTs may display benign appearances on imaging and pathological examination, local recurrence and metastatic disease are common and patients require long term follow up.

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