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Clear Cell Sarcoma: A Case Report with Radiological and Pathological Features of an Atypical Case

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Key Words

Clear cell sarcoma of soft tissue · Malignant melanoma · Soft tissue tumor

Abstract

Clear cell sarcoma of soft tissue is a rare, aggressive soft tissue tumor, which is morphologically similar to malignant melanoma but has no precursor skin lesion and, instead, has a characteristic chromosomal translocation. It is critical, yet challenging, to recognize clear cell sarcoma of soft tissue because the outcome is very different to that of metastatic melanoma. We report a case of clear cell sarcoma of soft tissue arising in the left foot of a 35-year-old African-American woman.

Introduction

Clear cell sarcoma of soft tissue (CCSST) was first reported by Dr. Franz Enzinger in 1965 [1], who recognized it as a distinct entity of tendons and aponeuroses in young adults with a propensity to the lower extremity and described its morphological similarity to malignant melanoma [1, 2]. About 40% of cases are deeply located in foot and ankle, with no skin association [3]. The tumor was formerly termed ‘malignant melanoma of soft parts’ because of its morphological and immunohistochemical similarity to melanoma. The finding of a chromosomal translocation EWSR1-ATF1 gene fusion as a result of the t(12:22)(q13;q12) chromosomal translocation distinguishes it from melanoma [4, 5].

Case Presentation

A 35-year-old African-American female presented with a painful lump at the distal third metatarsal of the left forefoot that had been present for approximately 1 year. There was neither an overlying skin lesion nor a history of previous skin excision.

A preoperative MRI showed a $1.0 \times 1.0 \times 0.8$ cm soft tissue mass dorsal to the mid-diaphysis of the left third metatarsal, partially surrounding the extensor digitorum tendon. T1-weighted images showed a predominantly T1-hyperintense mass, while T2-weighted images showed predominant T2 hyperintensity, with several small hypointense foci within the mass ([fig. 1](#)).

Surgical excision revealed a soft tissue mass completely encasing the extensor digitorum longus tendon and slightly extending to the third interspace. The mass measured $2.9 \times 1.5 \times 1.1$ cm and appeared multilobulated. The cut surface of the mass was grey-tan, firm, and homogenous, with no hemorrhage, necrosis, or cystic changes. Microscopically, the tumor was partially encapsulated and extended to the inked resection margin. The tumor cells were polygonal or spindle-shaped with clear or slightly eosinophilic cytoplasm and exhibited a nested or fascicular growth pattern with thin fibrous septa ([fig. 2a](#)). The nuclei were vesicular with prominent nucleoli ([fig. 2b](#)). There was low mitotic activity. Wreath-like Touton giant cells were present. Melanin was not seen on both the HE and Fontana-Masson stains. The tumor was strongly positive for vimentin, S-100 ([fig. 3a](#)), and HMB-45 ([fig. 3b](#)). It was focally positive for AE1/AE3 ([fig. 3c](#)) and negative for epithelial membrane antigen (EMA), muscle-specific actin, desmin, and CD45. EWSR break-apart FISH analysis was performed on the paraffin section, showing positive break-apart signals in >20% of the cell population. This finding, together with the immunohistochemical study and tumor morphology, confirmed the diagnosis of CCSST.

Our patient had an initial resection, followed by re-excision to obtain wider margins. Follow-up MRI performed 8 months after surgery showed no evidence of a local recurrent or residual mass and no evidence of distal metastasis. Written informed consent was obtained from the patient for publication of this case report and accompanying images.

Discussion

CCSST is rare, accounting for approximately 1% of all soft tissue sarcomas. It typically involves extremities, especially tendons and aponeuroses of the foot and ankle. The exact histogenesis is obscure, but the presence of intracellular melanin in two thirds of cases supports an origin from migrated neural crest cells that have the capacity to produce melanin.

The diagnosis of clear cell sarcoma is challenging. The differential diagnosis includes malignant peripheral nerve sheath tumor, monophasic synovial sarcoma, deep-seated epithelioid sarcoma, adult fibrosarcoma, psammomatous melanotic schwannoma, and metastatic malignant melanoma. All these tumors can involve deep soft tissues of extremities and bear similar microscopic morphology as CCSST. Immunohistochemical study plays an important role for the differentiation. CCSST is usually immunopositive for S-100, HMB-45, melan-A, microphthalmia transcription factor, bcl-2, and vimentin, viable positive for synaptophysin, CD56, and EMA, rarely positive for AE1/AE3, and immunonegative for smooth muscle actin (SMA), desmin, and CAM5.2 [5]. Our case shows focal staining for AE1/AE3, which is seldom reported positive in the published data [5]. The variable immunoprofile can confuse CCSST with other soft tissue tumors. Malignant peripheral nerve sheath tumor is immunopositive for S-100, but the staining is usually only focal. Moreover, it is negative for HMB-45 and melan-A. Synovial sarcoma is generally positive for cytokeratin, EMA, bcl-2, CD99, and calponin. S-100 protein may be detectable in 30% of synovial sarcomas. It is characterized by the

SYT-SSX1 or SYT-SSX2 fusion, detectable by either RTPCR or FISH. Epithelioid sarcoma is immunoreactive for vimentin, low- and high-molecular-weight cytokeratins, and EMA, partial active for CD34, occasional active for SMA and S-100, and frequently negative for INI1. Adult fibrosarcoma is positive for vimentin and negative for S-100. The immunohistochemical appearance of CCSST resembles that of psammomatous melanotic schwannoma. However, psammomatous melanotic schwannoma has widespread psammoma bodies and usually affects spinal nerves, paraspinal ganglia, and autonomic nerves of viscera, which is not typical for CCSST. The most troubling differential is metastatic malignant melanoma, which has a similar deep soft tissue location as well as an identical microscopic morphology and immunohistochemical profile as CCSST. Moreover, metastatic melanoma, similar to CCSST, may not show a primary skin lesion (that may have been removed, sloughed off, or be in a difficult to find location such as within the mucosal membranes). The definitive diagnosis of CCSST relies on detecting its unique translocation by FISH study. More than 90% of CCSST are associated with a distinct t(12;22)(q13;q12) chromosomal translocation, resulting in the formation of a fusion protein, EWS-AFT1, which is absent in metastatic malignant melanoma [4, 5] and psammomatous melanotic schwannoma.

MR imaging is an important tool to diagnose soft tissue tumors. Because of T1 shortening caused by the paramagnetic effect of intralesional melanin, high signal intensity on T1-weighted images and low signal intensity on T2-weighted images has been the classic description in CCSST [6]. However, a literature review of MR imaging for CCSST showed highly variable results. In a review of 31 CCSST cases [7–13], MR images showed T1-hypointense signal in 33%, isointense signal in 19%, and T1-hyperintense signal in 48% of cases. The T2 characteristics showed T2 hypointensity in 22% of cases, isointense signal in 26%, and T2-hyperintense signal in 52% of these cases. The variable MR signal characteristics for CCSST cannot be explained only by melanin content. Tumors with similar melanin content can have quite different MR signals. In a case reported by Isoda et al. [9], both T1- and T2-weighted images exhibited hypointense signals, and no intracellular melanin was observed microscopically. Our case also did not show melanin microscopically, but presented with mildly hyperintense signal on T1-weighted images and predominantly hyperintense T2 signal with scattered foci of low signal intensity. The role of MR imaging in the diagnosis of CCSST may therefore be limited.

The prognosis of metastatic malignant melanoma is dismal. Comparatively, the outcome in CCSST, although poor, is more protracted with high local recurrence, distant metastasis, and death from tumor. The survival rate for CCSST at 5, 10, and 20 years was 67, 33, and 10%, respectively, in one study [14]. Patients with CCSST should therefore have a long follow-up.

Conclusions

CCSST is a rare, highly malignant soft tissue tumor. It has been a diagnostic difficulty for radiologists, podiatrists, and pathologists due to its rarity. The limited role of MR imaging in the diagnosis of CCSST and the variable immunoprofile, i.e. focally positive AE1/AE3 staining as shown in this paper, which is extremely rare, further complicate the diagnosis. When a slow-growing, nodular lesion is detected in a tendon or

aponeurosis of a young to middle-aged patient, it should always raise the concern for CCSST. Awareness of this rare tumor is crucial because it can be mistaken for other types of soft tissue tumors, especially metastatic malignant melanoma, an entity with an entirely different prognosis and management.

Acknowledgements

We acknowledge the cooperation of our patient. This paper is not funded by any external source.

Disclosure Statement

The authors declare that they have no competing interests.

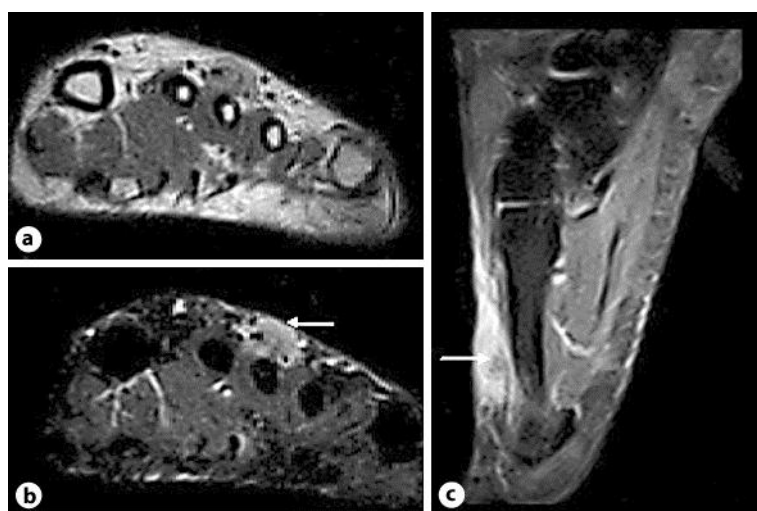


Fig. 1. **a** Short-axis T1-weighted image shows an iso- to mildly hyperintense soft tissue mass partially enveloping the extensor digitorum tendon, with well-defined margins. **b** Short-axis fat-suppressed fast spin-echo T2-weighted image shows that the lesion is T2 hyperintense, with foci of low signal that may represent melanin (arrow). **c** Sagittal fat-suppressed fast spin-echo T2-weighted image shows that the lesion is predominantly hyperintense, with foci of low signal intensity that may represent melanin (arrow).

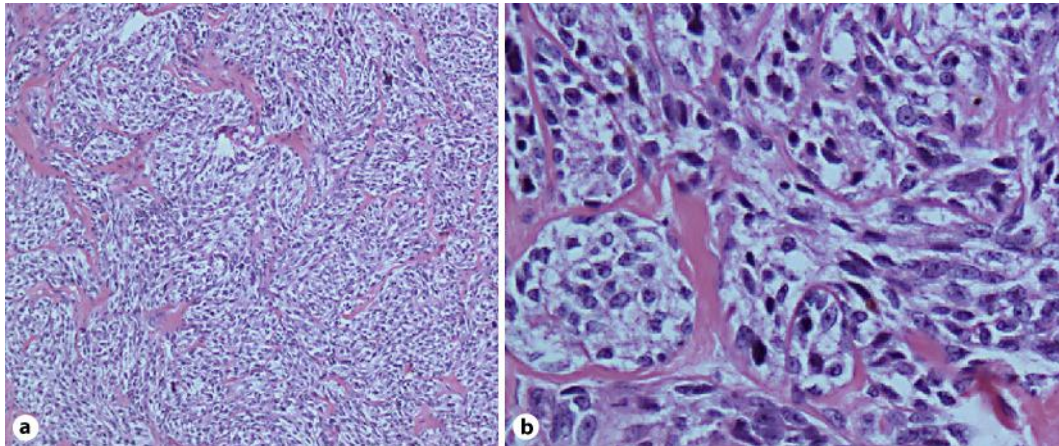


Fig. 2. **a** Polygonal or spindle-shaped tumor cells with clear or eosinophilic cytoplasm growing in nested to fascicular pattern with thin fibrous septa (original magnification, 100×). **b** Tumor cells with vesicular nuclei and prominent nucleoli (original magnification, 400×).

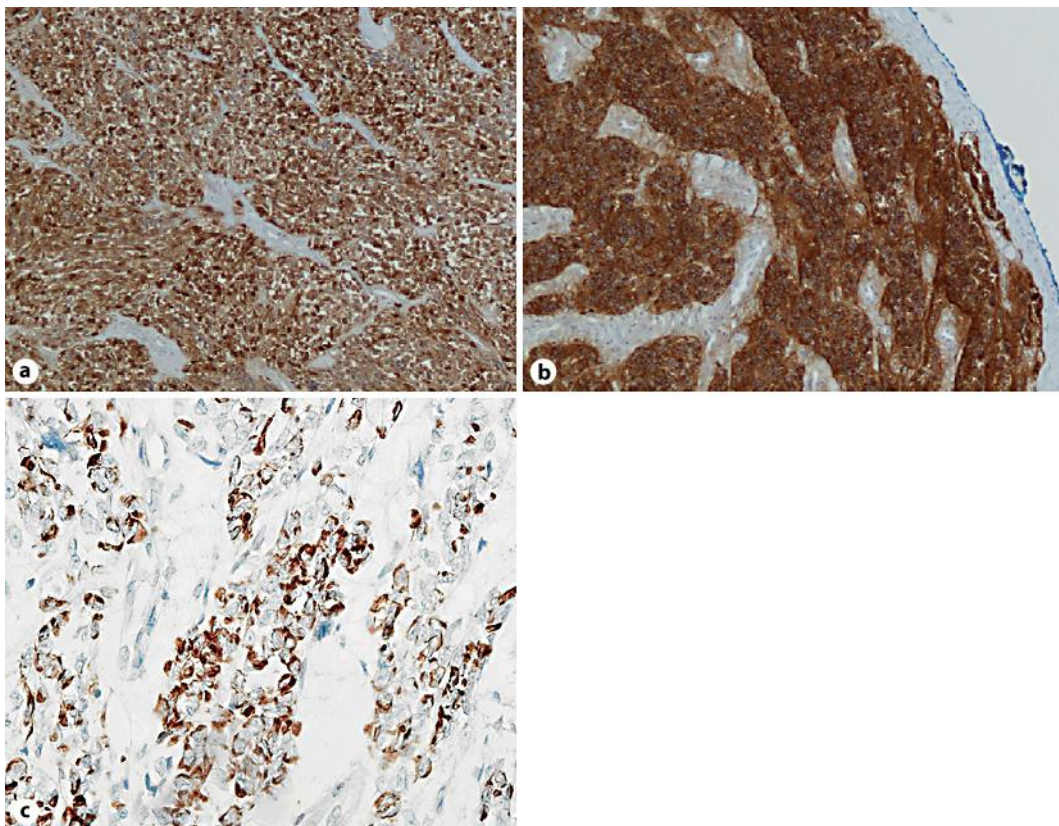


Fig. 3. The tumor cells are strongly immunoreactive to S-100 (**a**) and HMB-45 (**b**), and focally positive for AE1/AE3 (**c**) (original magnification, 100× for **a** and **b**, 400× for **c**).

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