Case Report
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# Diagnostic Dilemma: A Case of Malignant Melanoma Mimicking Clear Cell Sarcoma

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## Abstract

Clear Cell Sarcoma (CSS) is an exceptionally rare cancer with a predilection for tendons, aponeurosis and fascia of the lower limbs. It may be a close mimic of the more common primary cutaneous Malignant Melanoma (MM) with which it shares many histological markers including S-100, SOX10, HMB-45 and Melan A expression. The differentiation of the two pathologies is important for both treatment and prognostication. Although widely used in the treatment of MM, systemic therapy has no established benefit in CCS. Prognosis in CCS is based primarily on tumour size, the thickness being the principal determinant in MM.

We report a case of MM of the anterolateral left leg of a 70-year-old male patient with an unusual clinical presentation that closely resembled sarcoma. While the histological appearance was not typical of clear cell sarcoma, the unusual clinical presentation prompted cytogenetic analysis to rule out CCS. The patient was successfully treated for MM following a negative karyotype for the EWS gene rearrangement and confirmation of the presence of the V600E BRAF mutation.

## Background

Clear Cell Sarcoma (CCS) is a very rare aggressive tumour of neural crest cell origin with melanocytic differentiation, which can be challenging to discern the more common Malignant Melanoma (MM). Based on case series, the incidence of CCS is estimated to be in the region of 1% of all soft tissue sarcomas, although the exact incidence is unknown [1].

CCS usually involves tendons, fascia and aponeuroses, displaying a preponderance for the lower limbs [1,2], with the majority of CCS cases presenting as painless masses which slowly increase in size before disseminating to the lymph nodes. Although CCS has a distinct genetic background from MM clinical and histological differentiation can be difficult since unusual histological variants of MM may mimic CCS upon routine examination.

Histology of CCS includes compact nests of uniform to minimally pleomorphic tumour cells which may be polygonal to fusiform in appearance with abundant pale eosinophilic or clear cytoplasm. Typically, the neoplastic cells display prominent central nucleoli or vesicular nuclei delineated by fibrous septa.

Ultimately, the distinct genetic background of CCS renders cytogenetic analysis extremely useful in differentiating it from MM. The translocation t(12;22) (q13;q12) is considered pathognomonic for CCS, since it has yet to be observed in MM, and can be detected in 40-70% of CCS cases [3,4].

It is vital that CCS is considered as a potential differential in patients presenting with histologically and clinically unusual MM. Although initial management is similar, with wide local excision and sentinel lymph node biopsy considered a mainstay for both, immunotherapy has shown significant survival benefits for MM [5]. Still, there is no well-evidenced benefit for those with CCS.

## Case Presentation

We present the case of a 70-year-old man who was referred to our care by his general practitioner with a six-month history of a slowly growing lump on his left lower leg.

Physical examination revealed a 3x3 cm diameter subcutaneous mass on the distal anterolateral left lower leg, with overlying erythema, but no pigmentation is seen clinically or dermoscopically (Figure 1). Full skin check revealed no other concerning lesions, and there was no palpable lymphadenopathy. His past medical history comprised of well-controlled hypertension. There was no personal or familiar history of cutaneous or other malignancy. On first attendance at our clinic,

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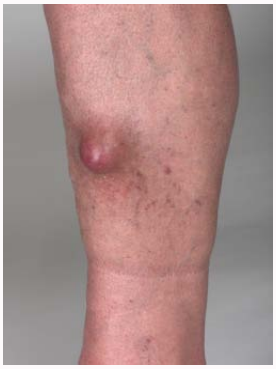

**Figure 1:** Subcutaneous nodule left lower leg.

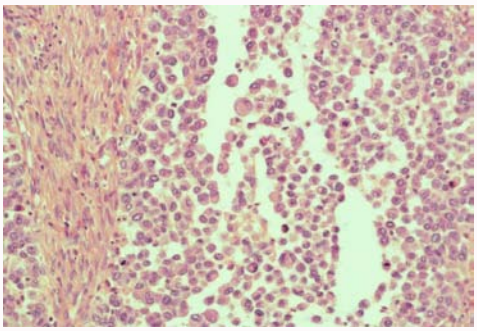

**Figure 2:** A Trucut biopsy showing infiltration by solid nests of large epitheloid cells, some of which had vacuolated cytoplasm and eccentrically located nuclei.

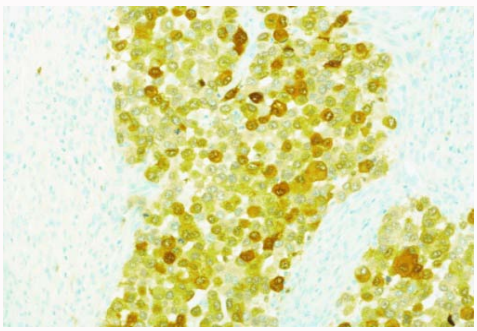

**Figure 3:** Immunohistochemistry demonstrated cells to be diffusely positive for S100.

an MRI of the left leg was arranged, revealing a solid 3.2 cm lesion superficial to the deep fascia, confined to subcutaneous soft tissues. The lesion displayed an intermediate signal on T1 images and had mixed-signal characteristic on T2 images, in addition to peripheral enhancement with intravenous gadolinium. It was felt that these images did not lend themselves to any particular histological diagnosis but were suspicious for sarcoma. Consequently, this gentleman was referred to our local sarcoma service. A Trucut biopsy was performed, demonstrating infiltration by solid nests of large epitheloid cells, some of which had vacuolated cytoplasm and eccentrically located nuclei (Figure 2). Immunohistochemistry showed lesional cells to be diffusely positive for S100 (Figure 3) and SOX10 and negative for HMB45 and Melan A.

A few weeks later he was referred back to our tertiary melanoma centre for management of his suspected melanoma; at time of re-

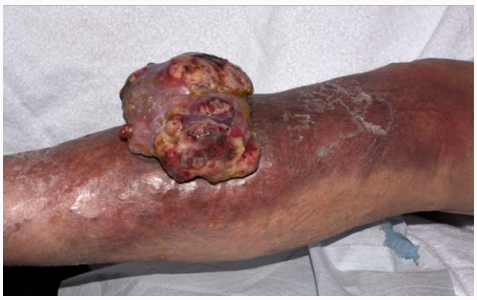

**Figure 4:** Evolution to an exophytic fungating lesion.

presentation, he had a large fungating 10 cm diameter mass on his left leg (Figure 4).

He underwent staging MRI brain and body Computed tomography scanning of his chest, abdomen and pelvis revealed prominent left inguinal and external iliac nodes, no evidence of other metastatic disease. The patient underwent a PET-CT scan which demonstrated uptake at the site of the initial lesion as well as the presence of a 1.5 cm diameter satellite lesion medially, with left inguinal and external iliac nodes again highlighted. Ultrasound-guided biopsy of these nodes suggested that they were reactive in nature, and this was confirmed later on open biopsy of his groin node. Given the unusual clinical and radiographic presentation, it was felt prudent to exclude clear cell sarcoma through Fluorescence *In Situ* Hybridization (FISH) analysis. No break apart signal (indicative of the pathognomonic t(12; 22) (q13; q12) translocation) was detected, thus excluding clear cell sarcoma as a differential. Subsequent PCR demonstrated the V600E BRAF mutation, in keeping with a diagnosis of melanoma.

## Treatment and Follow-Up

Prior to the cytogenetic analysis results, the patient underwent wide local excision of the left lower leg lesions, an open biopsy of the left inguinal node and application of Negative Pressure Wound Therapy (NPWT) dressing. 14 days later, with FISH analysis having ruled out clear cell sarcoma, and histology confirming clear excision margins, the NPWT device was removed, and the wound was closed with a split skin graft three weeks later. Two weeks postoperatively, the patient had 100% take of his skin graft and had begun to return to his activities of daily living independently.

## Discussion

The patient presented with a tumour on the left lower leg, which had been present for approximately six months. Due to its physical appearance and rapid growth, the lesion was felt to be suspicious for sarcoma. The location of the tumour on the lower extremity and its physical appearance raised the possibility of CCS. Following cytogenetic analysis, the proper diagnosis of malignant melanoma was confirmed.

Melanoma is one of the most aggressive cutaneous malignancies, responsible for more than 80% of dermatological cancer deaths [6]. BRAF and N-RAS are the two most common underlying mutations and result in abnormal melanocyte proliferation through activation of mitogen-activated protein kinases [7]. Histological diagnosis usually is sufficient to confirm clinical suspicion, although FISH may be used in rare instances to differentiate between subtypes or nevi [8]. Tumour thickness is considered the primary prognostic indicator,

but the stage, mitotic rate, ulceration as well as lymphatic, visceral and non-visceral spread are also of importance [9]. The prognosis of clear cell sarcoma, on the other hand, is primarily determined by tumour size [10]. It can be difficult to differentiate between MM and CCS, since up to 90% of CCSs express Melan A, a result of the fusion of the EWS and AFT1 genes occurring with the t(12; 22) (q13; q12) translocation. Confirmation can be achieved either through FISH to detect this rearrangement (which is considered pathognomonic for CSS) [4], or through detection of the V600E BRAF mutation which is present in more than 90% of MM cases but has not been reported in CCS [11]. CCS can closely resemble MM, and both should be considered when presentation fits the epidemiology of CCS (an apparently deep-seated tumour of the lower extremities, in younger adults) or if histology is suspicious. The importance of their differentiation lies in both treatment, where systemic therapy is of evidenced benefit for MM but not for CCS, and their prognostication, which is based on different factors.

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