

## Clinicopathological features, diagnosis and treatment of clear cell sarcoma/melanoma of soft parts

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### Abstract

**Background:** Clear cell sarcoma of tendons and aponeuroses is a rare, high grade malignant soft tissue tumor resembling melanoma and soft tissue sarcomas.

**Clinical and Imaging Presentation:** The median age at presentation is 27 years and the most common location are the foot and the ankle. MR imaging typically shows a benign looking, well defined, homogenous mass; on T1-weighted MR images, it is usually homogeneous and isointense or slight hyperintense to muscle, whereas on T2-weighted MR images, it is usually more heterogeneous with variable signal intensity.

**Pathology:** Microscopically, the clear cell appearance is due to the accumulation of glycogen. The cells show no or minimal pleomorphism, and paucity of mitotic figures that is in concordance with the slow-growing behavior of the tumor. Scattered multinucleated giant cells are commonly present; areas of necrosis and melanin pigment may be identified. The reciprocal translocation t(12;22)(q13;q12) is observed in more than 90% of clear cell sarcoma cases. In addition, polysomy of chromosome 8 has been observed as a secondary abnormality in many cases of clear cell sarcoma. The differential diagnosis of clear cell sarcoma should include melanoma, epithelioid malignant peripheral nerve sheath tumor, melanotic schwannoma, paraganglioma-like dermal melanocytic tumor, perivascular epithelioid cell neoplasms (PEComas), cellular blue naevus, synovial sarcoma (monophasic type), alveolar soft part sarcoma, paraganglioma, epithelioid sarcoma and carcinomas.

**Treatment and Prognosis:** The treatment of choice for clear cell sarcoma is wide surgical resection. If complete excision is achieved, adjuvant treatments are not unnecessary. Chemotherapy is predominantly employed in patients with metastatic disease. The 5 to 20 year survival of the patients with clear cell sarcoma range from 67% to 10%. The rates of local recurrence ranges up to 84%, late metastases up to 63%, and metastases at presentation up to 30%. Hippokratia 2013; 17 (4): 298-302.

**Keywords:** Clear cell sarcoma; Melanoma of soft parts; Soft tissue sarcoma.

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### Introduction

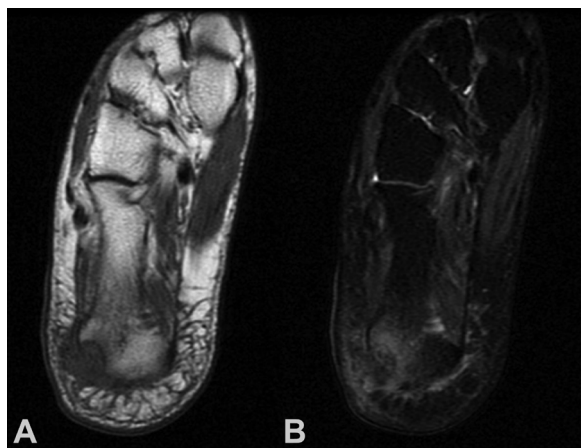
Clear cell sarcoma of tendons and aponeuroses was first described in 1965, as a rare malignant tumor originating from tendons and aponeurosis, with histological clear cell appearance due to the accumulation of glycogen<sup>1</sup>. In 1973, melanocytic differentiation was recognized by the presence of cytoplasmic melanosomes<sup>2</sup>. In 1983, the name “malignant melanoma of soft parts” was proposed due to its histological similarities to malignant melanoma<sup>3-10</sup>.

Currently, clear cell sarcoma is a well documented, distinct clinicopathological entity, resembling melanoma and soft tissue sarcomas. Like melanoma, clear cell sarcoma shows melanocytic differentiation in almost all instances as a result of the translocation t(12;22)(q13;q12), a genetic event not seen in melanoma. Like soft tissue sarcomas, it shows deep soft tissue primary location, lacks cutaneous invasion, and has preference for lymph node and pulmonary metastasis<sup>11-15</sup>.

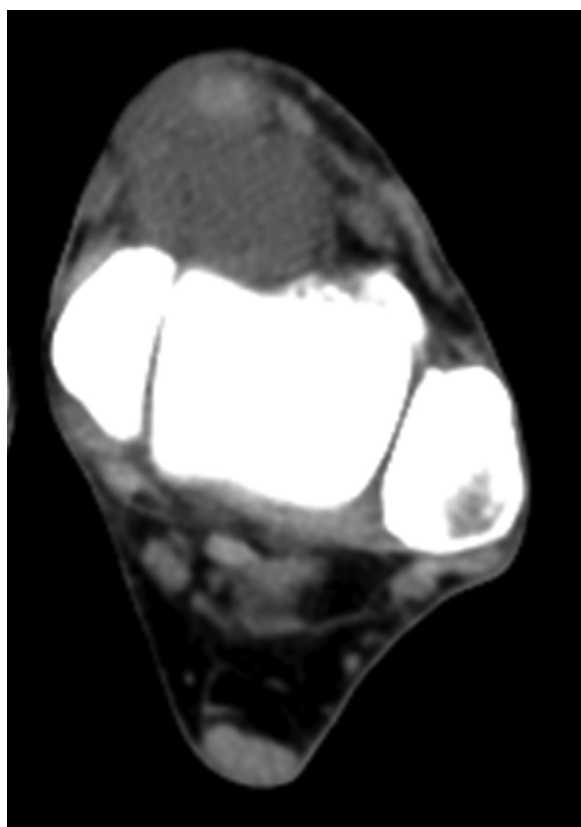
### Clinical and Imaging Presentation

Clear cell sarcoma accounts for less than 1% of all soft tissue tumors<sup>1-4,16-25</sup>. The tumor is typically a relatively small (<5 cm), deep soft tissue lesion, often juxtaposed to tendons, fascia, or aponeuroses<sup>1,3,17,18,26</sup>. It is more prevalent in Caucasians than in African Americans or Asians, without any gender predilection<sup>17,21,26</sup>. Patients' age at its presentation ranges from 7 to 83 years (median 27 years), with 2% occurring in children younger than 10 years<sup>3,14</sup>. The most common location are the foot and the ankle; other sites in the skeleton as well as location at the penis, retroperitoneum, kidney and gastrointestinal tract have also been reported<sup>14,24,27-33</sup>. Clear cell sarcoma of bone can be primary and metastatic (Figure 1)<sup>34-37</sup>. The distinction between clear cell sarcoma and melanoma, especially in metastatic presentation of an unknown primary tumor, often creates diagnostic challenge<sup>25</sup>.

Radiographs are usually reported as normal as intratumoral calcifications are rare<sup>26,38,39</sup>. Computed tomography (CT) (Figure 2) and magnetic resonance (MR) imaging



**Figure 1:** A 40-year-old woman with pain at the right calcaneus. Coronal (A) T1-weighted MR image showing an isointense to muscle lesion involving the calcaneus with soft tissue mass; (B) T2-weighted MR imaging showing heterogeneity of the lesion with foci of hypointensity. Biopsy showed clear cell sarcoma. Wide resection with partial calcaneectomy and local flap wound coverage was done, without evidence of local recurrence or distant metastases 3 years after diagnosis and treatment.



**Figure 2:** A 73-year-old man with pain and a palpable mass at the left distal tibia. Axial CT scan shows a homogenous, isointense to muscle lesion. Biopsy showed clear cell sarcoma. Marginal resection, brachytherapy (20 Gy) and external beam radiation therapy (34 Gy) was performed without evidence of local recurrence or distant metastases 2 years after diagnosis and treatment.

typically show a benign looking, well defined, homogeneous mass<sup>38-40</sup>. On T1-weighted MR images, it is usually homogeneous and isointense or slight hyperintense to muscle, whereas on T2-weighted MR images, it is usually more heterogeneous with variable signal intensity<sup>41</sup>. Foci of hypointensity may be present, corresponding to melanin and iron<sup>38,41</sup>.

### Pathology

Macroscopically, clear cell sarcoma is a tan-grey, firm, circumscribed mass<sup>10</sup>. Microscopically, the tumor is highly infiltrative and haphazardly organized into small compact nests and fascicles of neoplastic cells dissecting along the dense fibrous connective tissue of tendons, fascia, and aponeuroses. Biphasic differentiation is absent<sup>1,4,42</sup>. The cellular nests are divided into lobules by a fine fibrocollagenous framework of variable thickness that is contiguous with the fibrous connective tissue of the adjacent tendons and aponeurosis<sup>1,3,15</sup>. The neoplastic cells are polygonal to fusiform, with clear or pale, eosinophilic to amphophilic cytoplasm and have centrally located uniform, round to ovoid vesicular nuclei with prominent basophilic nucleoli, similar to melanoma. The clear cell appearance is due to the accumulation of glycogen. The cells show no or minimal pleomorphism, and paucity of mitotic figures that is in concordance with the slow-growing behavior of the tumor. Scattered multinucleated giant cells are commonly present; areas of necrosis and melanin pigment may be identified<sup>1,3,10,15,18,25,42-45</sup>.

Immunohistochemically, clear cell sarcoma shows a phenotype identical to that of conventional melanoma characterized by strong S100 protein expression in 100% of cases, and expression of HMB-45, Melan-A and MiTF in 97% to 81% of cases<sup>25</sup>. It may also express neuroendocrine and/or nerve sheath-related markers, including synaptophysin, CD56 and CD57 in 21% to 75% of cases; CD34 is generally negative<sup>25</sup>. Rarely, clear cell sarcoma may show anomalous expression of epithelial markers, including cytokeratins and epithelial membrane antigen.

### Cytogenetics

The reciprocal translocation  $t(12;22)(q13;q12)$  is observed in more than 90% of clear cell sarcoma cases, with chromosome analysis, reverse transcriptase polymerase chain reaction (RT-PCR), and fluorescent in situ hybridization (FISH)<sup>11</sup>. This translocation results in fusion of a portion of the Activating Transcription Factor gene (*ATF-1*) on the long arm of chromosome 12 (12q13) and the Ewing's sarcoma oncogene R1 (*EWSR1*) on chromosome 22 (22q12)<sup>11,13,22,25,30,33,46-49</sup>. Four types of *EWSR1/ATF1* fusion have been identified<sup>49</sup>, and one type of *EWSR1/CREB1* fusion, presumably representing the translocation  $t(2;22)(q32.3;q12)$ <sup>8,25,49</sup>. Recently, it has been shown that the *EWSR1/ATF1* fusion protein is capable of binding to and activating the melanocyte-specific microphthalmia-associated transcription factor (MiTF), which in the presence of the *sox10* transcription factor, results in expression of the melanocytic phenotype

and regulates the growth/survival of clear cell sarcoma cells<sup>50</sup>.

In addition to the diagnostic t(12;22)(q13;q12) translocation, polysomy of chromosome 8 has been observed as a secondary abnormality, in many cases of clear cell sarcoma<sup>46,51,52</sup>.

### Differential diagnosis

The differential diagnosis of clear cell sarcoma should include melanoma, epithelioid malignant peripheral nerve sheath tumor, melanotic schwannoma, paraganglioma-like dermal melanocytic tumor, perivascular epithelioid cell neoplasms (PEComas), cellular blue naevus, synovial sarcoma (monophasic type), alveolar soft part sarcoma, paraganglioma, epithelioid sarcoma and carcinomas<sup>15</sup>.

Compared to melanoma, clear cell sarcoma occurs in much younger patients, is deeply located, associated with tendons or aponeuroses, lacks epidermal involvement, tends to display less cellular pleomorphism, and may contain Touton-type neoplastic giant cells; these features are unusual for melanoma. In contrast, a primary cutaneous nodular melanoma is usually a dermal-based tumor that tends to be more pleomorphic and mitotically active, than clear cell sarcoma. Molecular genetic studies, for the EWS/ATF1 or EWS/CREB1 fusions, are required for definitive diagnosis<sup>8,11-13</sup>.

Malignant peripheral nerve sheath tumor is usually associated with a large peripheral nerve or neurofibromatosis, and is characterized by significant myxoid stroma, hyperchromatic nuclei, brisk mitotic activity, and negativity for HMB-45, melanocytic markers and cytogenetic abnormalities<sup>10</sup>. Melanotic schwannoma most often occurs in patients with Carney syndrome, in paraspinal or nerve plexus-related location, and frequently contains psammomatous calcifications and very abundant melanin pigment<sup>15</sup>. In contrast to clear cell sarcoma, paraganglioma-like dermal melanocytic tumor is primarily a tumor of the extremities of females, presents as a dermal nodule, and it has distinct histological appearance and absence of

*EWS* gene cytogenetic abnormalities<sup>53</sup>.

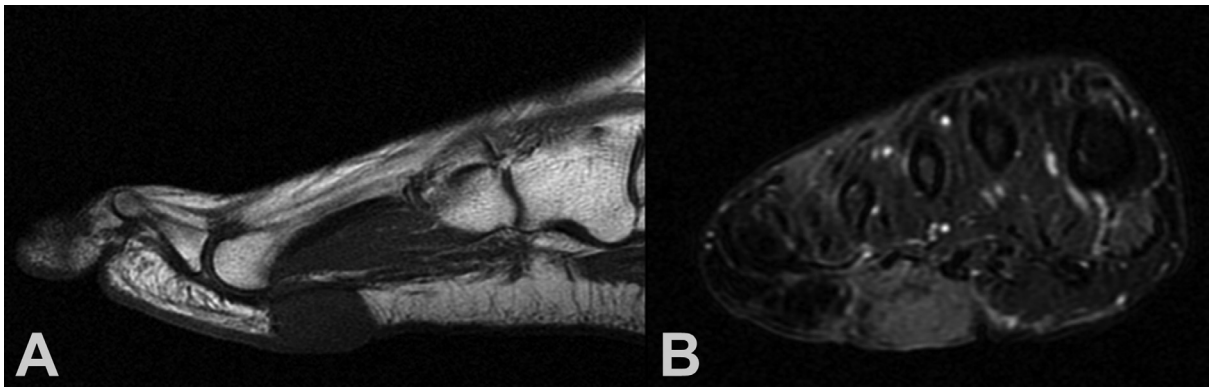
Perivascular epithelioid cell neoplasms commonly arise within the abdomen of young patients with predilection for the falciform ligament and ligamentum teres of the liver, and are characterized by fascicular and nested proliferation of uniform spindle cells, less prominent nucleoli and lack of multinucleation, and expression of smooth muscle actins and melanocytic markers in immunohistochemical studies<sup>10,54</sup>. Cellular blue naevi lack cytological atypia, frequently grow in a dumbbell-shaped configuration and are negative for the EWS-ATF1 gene fusion<sup>15</sup>. Synovial and epithelioid sarcomas, and carcinomas lack the distinctive nested growth pattern of clear cell sarcoma, and express cytokeratins, but not S100 protein<sup>10,15</sup>.

### Treatment

The treatment of choice for clear cell sarcoma is wide surgical resection<sup>14,21,24,55-57</sup>. If complete excision is achieved, adjuvant treatments are not necessary<sup>57</sup>. Amputation is not justified, unless there is vascular or neural impairment of the limb, as the survival is similar to that of wide resection<sup>19,56</sup>. Intralesional or marginal excision is associated with high local recurrence rates (Figure 3)<sup>21</sup>. In case of close resection margins, postoperative radiation therapy is indicated to improve local tumor control<sup>26,55,56</sup>.

Chemotherapy is predominantly employed in patients with metastatic disease<sup>14,17,21,24,55,57,58</sup>. Doxorubicin-based chemotherapy has not been effective<sup>21,26,57</sup>. In contrast, cisplatin-based chemotherapy and caffeine-assisted chemotherapy with doxorubicin and cisplatin, may elicit a tumor response, especially in patients with metastatic disease, or tumors more than 5 cm in maximum diameter<sup>24,59</sup>. Complete local response after isolated limb perfusion<sup>60</sup>, and intralesional injection of interferon alpha 2B has also been reported<sup>58</sup>.

Ten to 14% of patients with clear cell sarcoma will develop regional lymph node metastasis; the majority of these patients will develop distant metastasis, most often to lung and bone<sup>1,3,14,18-21,24-26</sup>. Although lung metastases-



**Figure 3:** A 47-year-old woman with pain and a palpable mass at the plantar aspect of the right forefoot. She had marginal resection for clear cell sarcoma at this location 9 years before. (A) Sagittal T1-weighted MR image showing a isointense to muscle lesion. (B) Coronal T2-weighted MR image showing a relative hyperintense to muscle lesion. Biopsy showed recurrent clear cell sarcoma. Wide resection and local flap wound coverage was performed without evidence of local re-recurrence 2 years after diagnosis and treatment of the recurrent tumor.

tomy is not recommended due to the aggressive clinical course of the metastatic disease, the role of therapeutic lymphadenectomy for locoregional disease control is unclear<sup>3,14,55,57,61</sup>. Most authors suggest regional lymphadenectomy, only in case of clinically and fine needle aspiration (FNA) cytologically confirmed regional lymph node involvement<sup>55,57,61</sup>. Early detection of occult regional lymphatic metastases by lymphatic mapping using lymphoscintigraphy and blue dye, and sentinel lymph node biopsy (SLNB) may improve staging of the regional disease, and guide the extent of surgery and decision for adjuvant treatments<sup>62</sup>.

### Prognosis

The rates of 5-year, 10-year and 20-year-survival of the patients with clear cell sarcoma, range from 67% to 100%<sup>1,3,14,18-21,24-26</sup>. The rates of local recurrence range up to 84%, late metastases up to 63%, and metastases at presentation up to 30% of patients<sup>1,3,4,18-21,24,25</sup>. Metastases may occur early, or as late as 29 years after diagnosis and surgical treatment<sup>3,14,21,26</sup>.

Prognostic factors in patients with clear cell sarcoma are tumor size, site, necrosis, mitoses, DNA content, and resection margins<sup>18,19,21,26,57</sup>. Tumors <5 cm are much less likely to recur or metastasize, whereas those >5 cm are more commonly associated with metastatic disease<sup>18-22,24-26</sup>. Probably, patients with tumors >5 cm have micrometastases at diagnosis<sup>24</sup>. Focal or diffuse tumor necrosis also correlates with a worse prognosis, independent of tumor size<sup>19</sup>. Lymph node metastasis is also associated with a poor prognosis, since patients with regional metastasis eventually will develop distant metastasis<sup>1,18,19,26</sup>.

### Conclusion

Clear cell sarcoma is a rare highly malignant soft tissue tumor, which resembles melanoma and soft tissue sarcomas. Wide resection is the treatment of choice. Adjuvant radiation is required if resection is close to resection margins; the role of chemotherapy is unclear. Long-term follow-up is necessary because of late local recurrences and regional lymph node or distant metastases.

### Conflict of Interest

Authors declare no conflict of interest

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