Soft tissue tumors: Clear cell sarcoma

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Identity

Alias
Clear cell sarcoma of the tendons and aponeuroses
Malignant melanoma of the soft parts

Nests of clear polygonal cells delineated by fibrous septa (HE, 200x).
**Clinics and pathology**

![Image](image_url)

Cellular smear almost exclusively showing dispersed spindle cells. Their oval nuclei are only slightly irregular and contain a large nucleolus. The cytoplasm is rather scant (MGG, 400x) (Courtesy of Dr. J. Willems, Onze-Lieve-Vrouw Ziekenhuis Aalst, Belgium).

**Disease**
Soft tissue tumour, presenting as a slow growing mass intimately associated with tendons and aponeuroses, in young adults.

**Note**
To be distinguished from clear cell sarcoma of the kidney, to which it is unrelated.

**Embryonic origin**
Mesoderm.

**Epidemiology**
Rare sarcoma affecting primarily young adults

**Clinics**
Slowly growing tumour mass, causing pain or tenderness, particularly frequently (up to 95% of the cases) situated in the extremities, with a predilection for the foot and the ankle.

**Pathology**
Polygonal or spindle shaped cells with abundant eosinophilic or clear cytoplasm displaying a uniform, nested to fascicular growth pattern, delineated by fibrous septa. Melanin deposits can be demonstrated using specific stains, but is more readily detectable by immunoreactivity against melanoma antigens (e.g. S100 and HMB45) in the vast majority of the cases.

**Treatment**
Radical surgical resection, adjuvant radiotherapy should be considered in incomplete resections, large (>5 cm) tumours and/or high grade lesions. Clear cell sarcomas seem to display little sensitivity to conventional soft tissue sarcoma multi-agent chemotherapy protocols.
**Evolution**

Special attention should be paid to the occurrence of late recurrences (median time to recurrence: 4.2 years).

**Prognosis**

Generally, clear cell sarcoma is characterised by an adverse prognosis, only 40 to 50% of the patients being long-term survivors. As recurrences may occur late, 5-year survival rates tend to misjudge prognosis. Established prognostic features include: tumour size, necrosis and local recurrence.

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**Cytogenetics**

The t(12;22)(q13;q12), as identified by G-banding.

**Cytogenetics Morphological**

The cytogenetic hallmark of clear cell sarcoma is the presence of the t(12;22)(q13;q12). This translocation has been described in the majority of reported clear cell sarcoma cases, not however in other malignancies. The translocation is readily identifiable with G-, R- or Q-banding.

**Cytogenetics Molecular**

Fluorescence in situ hybridisation based approaches can be used to demonstrate the t(12;22), using chromosome painting probes or to demonstrate EWSR1 and ATF1 gene rearrangement, using gene specific probes.

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**Probes**

EWSR1 probes: 5’ EWSR1: G9 cosmid; 3’ ATF1 probe: CCS2.2

**Additional anomalies**

Although the t(12;22) has been reported as the sole chromosomal aberration in clear cell sarcoma, most cases display additional cytogenetic anomalies, including +7, +8 and structural and numerical aberrations of chromosome 22.

**Variants**

No variant translocations, creating EWSR1/ATF1 fusion transcripts, have been described.

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**Genes involved and proteins**

**EWSR1**

**Location**

22q13

**Note**

Also called EWS.
DNA / RNA
EWSR1 is transcribed from centromere to telomere at 22q12. The coding sequence contains 1971 bp, comprising 17 exons and spans approximately 32 kb. Alternative splicing creates the EWS-b variant, lacking exons 8 and 9.

Protein
The EWS protein contains a C-terminal RNA binding domain and has indeed been shown to display RNA binding properties. The functions of the EWS protein, however, largely remain elusive.

ATF1
Location
12q13
DNA / RNA
ATF1 is transcribed from centromere to telomere at 12q13. The coding sequence contains 816 bp, comprising 6 exons and spans approximately 43 kb.

Protein
ATF1 encodes a member of the CREB/ATF basic leucine-zipper type transcription factor family and binds to cAMP inducible promoters.

Result of the chromosomal anomaly

Hybrid Gene
Description
The EWS/ATF1 fusion transcript is detectable in up to 90% of the clear cell sarcoma cases. As described in other EWS rearrangements, the transcript fuses 5’ EWS to 3’ heterologous sequences. The reciprocal ATF1/EWS fusion probably does not contribute to malignant transformation since it is out of frame.

Transcript
Several alternatively spliced transcripts have been described, the more frequent being the type 1 fusion: EWS exon 8 fused to ATF1 exon 4.

Fusion Protein
Oncogenesis
The EWS/ATF1 oncoprotein converts ATF1 to a constitutive transcriptional activator that represses p53/CBP-mediated transactivation.

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Detection protocol: as described by Antonescu et al. (the data given are virtually identical to the Table 1 from the mentioned reference).

References
Speleman F, Delattre O, Peter M, Hauben E, Van Roy N, Van Marck E. Malignant melanoma of the soft parts (clear-cell sarcoma): confirmation of EWS and ATF-1 gene fusion caused by a t(12;22) translocation. Mod Pathol. 1997 May;10(5):496-9
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This article should be referenced as such: