Cutaneous Neoplasms Showing $EWSR1$ Rearrangement

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Ewing sarcoma breakpoint region 1 (EWSR1)

- RNA binding protein
- Part of TET family (FUS, TAF15, others)
- Located on 22q12
- Ubiquitously expressed
- Most likely a housekeeping gene
Ewing Sarcoma / Primitive Neuroectodermal Tumor

- Rare sarcoma of bone or soft tissue
- Extremely rare cutaneous cases
- Any age; usually <30 years of age
- High-grade sarcomas with 60% 10 year survival in the modern era
- Fewer than 10 reported cases of primary cutaneous ES/PNET
  - May represent a clinically favorable subset, but follow-up is very limited
Pathologic Features

- Sheet-like to vaguely lobular, with well-developed capillary network
- Uniform population of small, round cells with clear to lightly eosinophilic cytoplasm, finely dispersed chromatin, small nucleoli
- Geographic necrosis
- Pseudorosettes in some (PNET)
- Very rare large cell, adamantinoma-like, sclerosing and spindled variants
- IHC: 100% CD99 (+), >75% FLI-1 (+) 25% LMWCK (+), occasionally S100 and/or synaptophysin (+), very rare cases desmin (+)
"Adamantinoma-like"
Genetics

<table>
<thead>
<tr>
<th>Translocation</th>
<th>Fusion</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>t(11;22)(q24;q12)</td>
<td>EWS-FLI1</td>
<td>95%</td>
</tr>
<tr>
<td>t(21;22)(q22;q12)</td>
<td>EWS-ERG</td>
<td>5%</td>
</tr>
<tr>
<td>t(7;22)(p22;q12)</td>
<td>EWS-ETV1</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>t(2;22)(q33;q12)</td>
<td>EWS-E1AF</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>t(1;22)(q42;q12)</td>
<td>EWS-?</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>t(2;22)(q33;q12)</td>
<td>EWS-FEV</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>t(17;22)(q12;q12)</td>
<td>EWS-ETV4</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>t(16;21)(p11;q22)</td>
<td>FUS-ERG</td>
<td>&lt;1%</td>
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</tbody>
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Differential Diagnosis

- Lymphoblastic lymphoma
- Small cell carcinoma
- Merkel cell carcinoma
- Small cell melanoma
- Poorly differentiated synovial sarcoma
- Alveolar rhabdomyosarcoma
- Other
Angiomatoid (malignant) fibrous histiocytoma

- Children and young adults
- Extremities, trunk, head and neck
- Arises in subcutis and deep dermis
- May have systemic symptoms: fever, weight loss, anemia
- Local recurrences common
- LN and distant metastases rare (2-5%) with complete cure and/or long survival still possible
- Adverse prognostic features include head/neck location, infiltrative margins, skeletal muscle involvement
Pathological Features

- Fibrous pseudocapsule with pericapsular lymphocytic infiltrate
- Fascicular and whorling pattern
- Pseudovascular spaces
- Generally bland histiocytoid cells, sometimes with hemosiderin pigment
- Traumatized cases may show extensive hemorrhage and fibrosis, obscuring tumor
- Positive for CD68, desmin (50%), EMA (50%)
- Negative for vascular markers, S100, MyoD1/myogenin
Genetic Characterization of Angiomatoid Fibrous Histiocytoma Identifies Fusion of the FUS and ATF-1 Genes Induced by a Chromosomal Translocation Involving Bands 12q13 and 16p11

Brenda L. Waters, Ioannis Panagopoulos, and Elizabeth F. Allen

Fusion of the FUS and ATF1 Genes in a Large, Deep-Seated Angiomatoid Fibrous Histiocytoma

Emad Raddaoui, M.D., Ludvik R. Donner, M.D., Ph.D., and Ioannis Panagopoulos, Ph.D.

EWSR1-CREB1 Is the Predominant Gene Fusion in Angiomatoid Fibrous Histiocytoma

Cristina R. Antonescu,1,2 Paola Dal Cin,2 Khedoudja Nafa,1 Lisa A. Teot,3 Urvashi Surti,4 Christopher D. Fletcher,1 and Marc Ladanyi,1,5

EWSR1-CREB1 and EWSR1-ATF1 Fusion Genes in Angiomatoid Fibrous Histiocytoma

Sabrina Rossi,1 Károly Szuhaí,3 Marije Išzenga,3 Hans J. Tanke,3 Lucia Zanatta,1 Raf Sciot,4 Christopher D.M. Fletcher,1 Angelo P. Dei Tos,1 and Pancras CW. Hogendoorn2

Fusion of the EWSR1 and ATF1 Genes Without Expression of the MITF-M Transcript in Angiomatoid Fibrous Histiocytoma

Kariina Hansén Hallo,1 Hedi Martens,1 Yves Legrand,1 Joanne M. Melin-Kindblom,2 Lars-Gunnar Kindblom,2 Mikael Behrendtz,1 Anders Kallen,1 Nils Mandal,1 and Ioannis Panagopoulos1
Differential Diagnosis

• Lymph node metastasis
• Rhabdomyosarcoma
• Follicular dendritic cell tumor
• Aneurysmal benign fibrous histiocytoma
Aneurysmal BFH
Myoepithelioma (Parachordoma)

Parachordoma is a tumor that was established and described by Laskowski in 1951. It is a rare tumor, which appears adjacent to tendons, synovium, and even osteous structures. It is lobular and pseudoencapsulated. Histologically, in some ways, it is compatible with the chordomas of bone with a constant fibrous tissue component. It grows slowly and is only locally invasive. If not adequately excised, it is prone to recur, but complete surgical removal is usually possible. Its exact histogenesis remains obscure. This tumor may have some relationship to the great vesicular cells of chordoid tissue described by Schaffer as "bläsige Zellen von chordoiden Gewebe" developing from special synovial cells. Ten cases collected over a period of 26 years at the Institute of Oncology in Warsaw are presented.


Myoepithelioma/ mixed tumor of soft parts described by Kilpatrick et al (1997); relatively large number of subsequent reported cases

The WHO currently considers both terms to be essentially synonymous

Parachordoma described initially by Laskowski (1951), and more fully by Dabska (1977); controversial and rare
Clinical Features

- Adults in 2\textsuperscript{nd}-4\textsuperscript{th} decades of life (mean 35-38 years)
- No sex predilection
- Subcutis or deep soft tissues of the thigh, calf, arm, head/neck
- Painless mass
- All have potential for recurrence and/or metastasis
  - Histologically benign tumors may metastasize
  - Histologically malignant tumors have a greater risk of distant metastases
- Wide excision; unclear role for adjuvant therapy
Pathological Features

- Circumscribed but often subtly infiltrative, vaguely lobular
- Cords, chains and nests of spindled to epithelioid cells in a myxoid/ chondroid matrix
- Hepatoid, glomoid, plasmacytoid and vacuolated ("physaliferous") cells
- Cytologic atypia, mitotic activity, vascular invasion, necrosis in a minority of cases
- Positive for cytokeratins and S100 protein; less often positive for muscle markers, p63 and GFAP; brachyury-negative
Genetics

- **EWSR1** rearrangements in 30 cases (45%), predominantly deeply situated
- **EWSR1-POU5F1** (5), **EWSR1-PBX1** (5), **EWSR1-ZNF444** (1), **EWSR1-??** (19)
- 1 case with **FUS** rearrangement
- All tumors with ductal differentiation were **EWSR1**-negative
- All salivary gland tumors were negative
Differential Diagnosis

- Cutaneous mixed tumor/ chondroid syringoma
- Extraskeletal myxoid chondrosarcoma
- Extra-axial chordoma
• *PLAG* rearrangements, characteristic of salivary gland pleomorphic adenoma, found only in “true” mixed tumors with ductal differentiation.
Cutaneous chordoma

Brachyury
Clear Cell Sarcoma

- Enzinger (1965)
  - Uncertain histogenesis
  - Fontana-positive pigment initially regarded as pitfall
- Hoffman and Carter (1973)
  - First to recognize melanosomes in CCS
- Chung and Enzinger (1983)
  - Proposed term “malignant melanoma of soft parts”
  - Recognized that CCS was clinically distinct from conventional melanoma
Clinical Features

- Very rare; <1% of all soft tissue tumors
- Young to middle aged adults of either sex
- Most often involves foot and ankle
- Typically deep, in association with tendons and aponeuroses
- Cutaneous involvement usually only in larger lesions
- Relatively small (<5cm) at the time of diagnosis
- Often long pre-biopsy duration
- Protracted clinical course with multiple local recurrences and late metastases (lung, bone, LNs)
- Up to 30% of patients present with metastases; 5-year (50%), 10-year (33%) and 20-year (10%) survival rates
- Not graded; consider “high-grade”
- Wide excision and adjuvant radiotherapy; unclear role for chemotherapy and/or immunotherapy
- Some advocate SLN biopsy and LN dissection
Cutaneous Clear Cell Sarcoma

- 10F, 2M
- Median 25 years of age
- Extremities (9), trunk (3)
- Small (1 cm)
- Typical pathologic and IHC features
- All FISH positive for EWSR1; one with EWSR1-CREB1 by RT-PCR
- F/U: 8 ANED, 2 AWD, 1 DOD; 2 LR, 3 MET

Cutaneous Clear Cell Sarcoma: A Clinicopathologic, Immunohistochemical, and Molecular Analysis of 12 Cases Emphasizing its Distinction from Dermal Melanoma

Markus Hantschke, MD,* Thomas Mentzel, MD,* Arno Rütten, MD,* Gabriele Palmexo, PhD,* Eduardo Calonje, MD,‡ Alexander J. Lazar, MD,‡ and Heinz Kutzner, MD*

Abstract: Clear cell sarcoma (CCS) of tendons and aponeuroses/malignant melanoma (MM) of soft parts is a rare tumor and in the majority of cases presents a characteristic reciprocal translocation t(12;22)(q13;q12) that results in fusion of the EWS and ATFI genes. Although the melanocytic differentiation of CCS is indisputable, its precise lineage remains unclear. Typically, the slowly growing tumor affects the extremities of cases by fluorescence in situ hybridization. Local recurrences and metastases developed in 2 and 3 patients, respectively, and 1 patient died of the disease.

Key Words: clear cell sarcoma, melanoma of soft parts, melanoma

(Am J Surg Pathol 2010;34:216–222)
Differential Diagnosis

• Conventional melanoma
• Dermal perivascular epithelioid cell neoplasm
• Other dermal melanocytic tumors
- **BRAF** mutations are found in many melanomas, but not in CCS
- **EWSR1** rearrangements are not found in conventional melanoma
EWSR1: A “Promiscuous” Gene

- Ewing sarcoma/ primitive neuroectodermal tumor
- Angiomatoid (malignant) fibrous histiocytoma
- Myoepithelioma of soft tissues
- Clear cell sarcoma
- Hyalinizing clear cell carcinoma of salivary gland
- Gastrointestinal clear cell sarcoma-like tumor
- Extra-skeletal myxoid chondrosarcoma
- Desmoplastic small round cell tumor
- Myxoid liposarcoma
- “Primary pulmonary myxoid sarcoma”
- Unusual undifferentiated sarcomas of bone and soft tissue
- Hidradenoma
- Mucoepidermoid carcinoma
Different Tumors-Identical Genetics

Detection and characterization of EWSR1/ATF1 and EWSR1/CREB1 chimeric transcripts in clear cell sarcoma (melanoma of soft parts)

Detection and characterization of EWSR1/ATF1 and EWSR1/CREB1 chimeric transcripts in clear cell sarcoma (melanoma of soft parts)

EWSR1-ATF1 Fusion Is a Novel and Consistent Finding in Hyalinizing Clear-Cell Carcinoma of Salivary Gland

EWSR1-CREB1 and EWSR1-ATF1 Fusion Genes in Angiomatoid Fibrous Histiocytoma

Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update

Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update

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Clear cell sarcoma of tendons and aponeuroses, and osteoclast-rich tumour of the gastrointestinal tract with features resembling clear cell sarcoma of soft parts: a review and update
Although molecular genetic studies have contributed immensely to our understanding of soft tissue tumors, and are increasingly important in their diagnosis, they must be interpreted in the context of traditional clinical and morphological findings.