Selected Tumors Showing Melanocytic Differentiation in the Differential Diagnosis of Soft Tissue Tumors

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Overview
- Desmoplastic/ spindle cell melanoma
- Clear cell sarcoma
- Clear cell sarcoma-like tumor of the gastrointestinal tract
- Malignant melanotic schwannian tumor

Desmoplastic/ Spindle Cell Melanoma
- Approximately 4% of all melanomas
- Present in 6th to 7th decades
- Most commonly involve head and neck
- More than half clinically amelanotic
- Melanoma clinically suspected in minority of cases
- Potential for delayed diagnosis
Pathologic Features

- Sun-damaged skin
- Usually thick and deep at time of diagnosis
- Often lacks clear-cut melanoma in situ or conventional melanoma
- Hyperchromatic spindle cells; may be deceptively bland
- Packeted arrangement
- Deep nodular lymphoid aggregates
- Few mitoses
- Amelanotic
Immunohistochemistry

- S100 and SOX10 strongly positive
- Melanocyte-specific markers of limited utility (<5% positive)
- May contain many SMA-positive myofibroblasts; potential for confusion with myofibroblastic/myoid tumors
- Occasionally shows anomalous expression of keratins, desmin, neurofilament protein, synaptophysin
Outcome

- As compared with conventional melanoma:
  - Higher rate of local recurrence (10-50%)
  - Lower rate of lymph node metastasis
  - Comparable rate of visceral metastasis
  - Similar overall survival

- Adverse prognostic features
  - Depth of tumor > 4 mm; Clark’s level V
  - Mitotic rate >4/mm2
  - Ulceration
  - Head and neck location
  - Prior misdiagnosis
  - Narrow margins (< 1 cm)
Differential Diagnosis

- Neurofibroma
- Blue nevus
- Desmoplastic Spitz nevus
- Other sun damage-associated cutaneous spindle cell malignancies
- Superficial malignant peripheral nerve sheath tumor

When you make the diagnosis of superficial malignant peripheral nerve sheath tumor—you are almost always wrong

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; reported in essentially any location
- Associated with tendons and aponeuroses
- Relatively small (<5cm) at the time of diagnosis
- Often long pre-biopsy duration
Pathological Features

- Compact nests and fascicles, often organoid
- Surrounding collagenous bands
- Epithelioid to spindled cells with lightly eosinophilic to amphiphilic cytoplasm; truly clear cells are rare
- “Melanoma-like” cytology with prominent macronucleoli
- Pleomorphism is uncommon; rarely seen in recurrent and/or metastatic lesions
- Mitotic figures and necrosis are uncommon
- Occasionally contains melanin pigment
Immunohistochemistry

- S100 protein and SOX10 positive
- Approximately 85% express HMB45, Melan-A, tyrosinase, MiTF
- May be CD117 positive
- Negative for neuroendocrine markers
### Genetics

- \( t(12;22)(q13;q12) \) (EWSR1-ATF1): >90%
- \( t(2;22)(q32.3;q12) \) (EWSR1-CREB1): <10%
- Rare cases with FUS rearrangements

### Outcome

- 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

### Differential Diagnosis

- Conventional melanoma
- Perivascular epithelioid cell neoplasms
- Cellular blue nevus
- Epithelioid MPNST
- Malignant gastrointestinal neuroectodermal tumor (CCS-like tumor of gastrointestinal tract)
• BRAF mutations are found in many melanomas, but not in CCS
• EWSR1 and FUS rearrangements are not found in conventional melanoma

Epithelioid MPNST
• < 5% of MPNST
• Composed predominantly or exclusively of epithelioid Schwann cells
• M>F; 20–50 years of age
• Usually involve major nerves
• Less often NF1-associated than are conventional MPNST
• Most common subtype of MPNST arising within schwannomas
• Nests and cords of epithelioid cells with prominent nucleoli
• Variable myxoid change and a minor degree of spindling
• Intensely S100 protein-positive, abundant pericellular collagen IV, negative for melanoma-specific markers
• Frequently SMARCB1-deficient
• Aggressive tumors with 50% metastatic risk; may metastasize to lymph nodes
Malignant Gastrointestinal Neuroectodermal Tumor

CASE REPORTS

Malignant neuroendocrine tumor of the jejunum with osteoclast-like giant cells

Enzyme histochemistry distinguishes tumor cells from giant cells

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EWS-CREB1: A Recurrent Variant Fusion in Clear Cell Sarcoma—Association with Gastrointestinal Location and Absence of Melanocytic Differentiation

Cristina R. Antonescu, M.D.,
Kheoudija Nafa, M.D.,
Neil H. Segal, M.D.,
P. Polidoro Del Cin, M.D.,
and Marc Ladanyi, M.D., Ph.D.

Malignant Gastrointestinal Neuroectodermal Tumor: Clinicopathologic, Immunohistochemical, Ultrastructural, and Molecular Analysis of 16 Cases With a Reappraisal of Clear Cell Sarcoma-like Tumors of the Gastrointestinal Tract

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**Clinical Features**

- Fewer than 30 reported cases
- Young to middle aged adults
- Most often involve the small intestine but may occur anywhere in gastrointestinal tract
- Centered within muscularis propria
- Highly aggressive, with aggressive local recurrence, lymph node or visceral metastases, or death from disease in 75% of reported cases
- No known role for radio/chemotherapy

**Pathological Features**

- Solid, pseudopapillary and alveolar patterns
- Round to oval cells with clear to lightly eosinophilic cytoplasm
- Centrally located, round nuclei with irregularly dispersed chromatin and inapparent or small nucleoli
- Mitotic activity and necrosis
- Osteoclast-like giant cells identified in most
- Lack the nesting, spindling, macronucleoli and neoplastic giant cells seen in soft tissue CCS
Ancillary Studies

- Express S100 protein and SOX10
- Lack expression of HMB45, Melan A, MiTF and tyrosinase
- Variably SOX10, synaptophysin, CD57 and NSE positive
- CD117 (C-kit) negative
- \textit{EWSR1-CREB1} or \textit{EWSR1-ATF1} fusions
Differential Diagnosis

- Soft tissue-type clear cell sarcoma occurring in a gastrointestinal location
- Gastrointestinal stromal tumor

Comparison of CCS and MGNET

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<td>Morphology</td>
<td>Melanoma-like, neoplastic giant cells</td>
<td>Primitive cells without macronucleoli, osteoclast-like giant cells</td>
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<td>IHC</td>
<td>Expression S100 protein and melanocytic markers, lacks neuroendocrine markers</td>
<td>Expresses only S100 protein, frequently neuroendocrine marker positive</td>
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<td>Ultrastructure</td>
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<td>EWSR1-CREB1 and EWSR1-ATF1</td>
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Different Tumors-Identical Genetics

- "Psammomatous melanotic schwannoma" (Carney 1990)
- Mid aged adults of either sex
- History of Carney complex present in only a minority of patients
- Midline, usually paravertebral nerve roots
- Darkly pigmented

Pathologic Features

- Lobulated, partially encapsulated but infiltrative
- Spindled to epithelioid
- Fascicular, sheetlike and syncytial patterns
- Occasional cases with striking pleomorphism
- Psammoma bodies present in 40%
- Variable amounts of melanin
- Necrosis and mitotic activity >2/50 in a minority of cases
Outcome

- Local recurrences in 35%
- Distant metastases in 42%
- Death from disease in 27%
- Clinical behavior generally not predicted by pathologic features
- Should be considered a malignant neoplasm with unpredictable clinical behavior
- “Malignant melanotic schwannian tumor”
Genetic Features

- Gene expression profiling shows clear differences with melanoma and schwannoma
- Loss of PRKAR1A in many, even without clinical evidence of Carney Syndrome