Rhabdomyomas
and Rhabdomyosarcomas (RMS)

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Tumors of skeletal muscle: Rhabdomyomas and rhabdomyosarcomas

Embryonal muscle
uncommitted mesenchymal cell → myoblast
Cytologic myogenesis

myocyte fusion → myotube
Cytologic myogenesis

myotube

myofiber
Rhabdomyoma

- Benign soft tissue counterpart of RMS
- Rare (<2% of soft tissue neoplasms)
- Cardiac and non-cardiac types
  - Cardiac more common, associated with tuberous sclerosis
- Non-cardiac types
  - Fetal
  - Adult
  - Genital
Fetal Rhabdomyoma
Clinical Features

- Most patients <3 years of age
- More common in boys
- Sporadic or associated with Gorlin syndrome
- Most common in head and neck
  - Post-auricular region is favored site
- Much less common than rhabdomyosarcoma (1:50)
Fetal Rhabdomyoma
Histologic Features

- Parallel bundles of spindle cells and myoid tubules
- Separated by less differentiated cells
- Biphasic pattern
- No significant nuclear pleomorphism
- Low mitotic activity (<1/10 HPFs)
- Intermediate forms may resemble adult rhabdomyosarcomas and contain smooth and skeletal muscle
Fetal Rhabdomyoma Differential Diagnosis

- Spindle cell rhabdomyosarcoma
- Embryonal rhabdomyosarcoma
- Differential points
  - No cambium layer
  - RMS has higher mitotic rate (>5/10 HPFs)
  - Circumscription: RMS not well circumscribed
  - Should be PRE-treatment material for differential dx
Fetal Rhabdomyoma Immunohistochemistry

- Markers of differentiated muscle
  - Myoglobin
  - Desmin
  - Actin (smooth and skeletal muscle)
  - Not useful in distinction from RMS

- Negative:
  - Keratin
  - CD68 (useful for rhabdomyoma-like histiocytic tumors, sometimes desmin-positive)
Fetal Rhabdomyoma
Genetics

- Gorlin syndrome mutation: *PTCH1*
  - Negative regulator of hedgehog signaling pathway
  - Pathway may also be activated in sporadic, non-syndromic tumors
Adult Rhabdomyoma

- Rare benign neoplasm
- Composed of mature, differentiated muscle
- Typically occurs after adolescence
Adult Rhabdomyoma
Clinical Features

- Usually in
  - Oral cavity
  - Superficial soft tissue of head and neck
  - Origin from bronchial musculature?
- Mean age: 50 years
- Rare pediatric cases
- Up to 20% are multifocal
- Local recurrences possible, even years after operation
Adult Rhabdomyoma
Pathologic Features

- **Gross:** Brown lobulated mass
- **Micro:**
  - Large round and polygonal cells
  - Uniform cytology
- **PAS** positive due to glycogen
- Cross-striations may be seen.
Adult Rhabodyoma
Differential Diagnosis

- Granular cell tumor (S100 positive, desmin negative)
- Hibernomas (S100 positive, desmin negative)
- Crystal storing histiocytosis (CD68 positive, desmin negative, crystals on EM)
Genital Rhabdomyoma

- Benign myogenic tumor of female genital tract
- Possible origin from myogenic stem cells in subepithelial stroma
- Usually in vagina or cervix of reproductive age women
  - May be pregnancy-associated
- Male genital lesions occur, but more like fetal rhabdomyoma
- Female lesions resemble adult rhabdomyoma
  - No significant pleomorphism
  - Focal cross striations
Miscellaneous Benign Myogenous Tumors

- Neuromuscular choristoma ("benign Triton tumor")
  - A hamartomatous lesion of peripheral nerve
  - Muscle within perineurial sheath
  - Most in head and neck
  - May have associated rhabdomyoma
Benign Triton Tumor

Desmin and EMA
Miscellaneous Benign Myogenous Tumors

• Rhabdomyomatous mesenchymal hamartoma
  – Head and neck lesions
  – Affects skin of newborn and infant ages
  – Polypoid skin tags or mouth lesions containing benign skeletal muscle
    • Myotubes, cross-striations
Benign rhabdomyomatous hamartoma
Focal Myositis

- Solitary mass
- Degenerating and regenerating skeletal muscle
- Infiltrates of macrophages and lymphocytes
- Secondary to focal denervation?
- Relationship to polymyositis?
  - Only occasional association
Rhabdomyosarcoma

- Soft tissue tumor with features of embryonic or fetal myogenesis
- Most common soft tissue sarcoma in children
- Can be subclassified into multiple, distinct clinical and genetic entities
  - Embryonal
  - Alveolar
  - Spindle cell
  - Pleomorphic (adult)
Rhabdomyosarcoma
Introduction and Clinical Features: General

- Most present as painless mass
- Rarely have systemic problems, e.g. hypercalcemia
- Symptoms may relate to affected organ
  - Proptosis
  - Urinary retention
  - Bile retention
May be affected by genetic syndrome

- P53
- Beckwith-Wiedemann
- Neurofibromatosis 1
- Gorlin
- DICER mutation-associated (pleuropulmonary blastoma)
Rhabdomyosarcoma
Pathologic Features: General

• Only some arise in extremity skeletal muscle; most do not
• Histology resembles developing or disordered muscle
  – Rhabdomyoblast is key cell
  – Undifferentiated “blastoma” cells
  – Occasional multinucleated cells
  – Differentiated myoblasts (more common after therapy)
Embryonal Rhabdomyosarcoma

- A primitive soft tissue tumor with features of embryonic skeletal muscle
Embryonal Rhabdomyosarcoma
Clinical Features

- Over one half of rhabdomyosarcoma
- Most occur in children <10 years of age
- Rare in adults
- Botryoid type forms polypoid masses in vagina, bladder, mouth, or bile ducts
Embryonal Rhabdomyosarcoma
Histologic Features

• Haphazard arrangement with areas of myxoid stroma
• Compact areas
  – “Loose and dense” pattern resembling nascent muscle
• Some predominantly loose, others predominantly dense
• Much variation in cytology
  – Strap cells, spider cells, racket cells, etc., with bright eosinophilic cytoplasm
  – Undifferentiated, slightly spindled cells with oblong nuclei
• Cambium layer in botryoid variant
ERMS
Embryonal Rhabdomyosarcoma
Genetics

• No single specific mutation
• Recurring pattern of chromosome gains and losses
• Profound loss of heterozygosity on chromosome 11p
  – Affects Beckwith-Wiedemann locus (11p15.5)
  – Associated with imprinting abnormalities
  – Loss of maternal allele in syndromic cases
ERMS
Embryonal Rhabdomyosarcoma (ERMS) Differential Diagnosis

- Malignant peripheral nerve sheath tumor (MPNST)
  - Triton tumor contains ERMS-like foci
  - MPNST may be positive with some muscle markers
- Myofibroblastic tumors
  - Inflammatory myofibroblastic tumors (often ALK1 positive, but so is ERMS)
- Inflammatory or reactive processes
  - Eosinophilic cystitis, beware on frozen section
Spindle Cell/Sclerosing Rhabdomyosarcoma

- Spindle cell lesion resembling fibrosarcoma or smooth muscle neoplasm
- May be hyalinized with abundant collagen (sclerosing RMS)
Spindle Cell/Sclerosing Rhabdomyosarcoma
Clinical Features

• Predilection for paratesticular region in boys
• Head and neck
• Extremities
• Good prognosis in children (different tumor?)
• Bad prognosis in adults
Spindle Cell/Sclerosing Rhabdomyosarcoma
Histologic Features

- Spindle cells with elongate borders
- Must comprise >80% of tumor (overlap with ERMS)
- Should have definitive skeletal muscle phenotype
  - Some smooth muscle features
  - Some areas may be positive for smooth muscle actin
  - Isolated, well-differentiated cells with cross striations may be found
- Variable collagen
Spindle cell ERMS
Sclerosing rhabdomyosarcoma

- Hyalinizing collagen with entrapment of tumor cells defines sclerosing variant
- Osteoid-like
- Can have a small cell component that resembles an alveolar pattern
Sclerosing RMSA
Spindle Cell/Sclerosing Rhabdomyosarcoma
Genetics

• Adult spindle cell RMS:
  – 40% have activating mutations in MyoD1 gene (located in chromosome 11p)
• Infantile spindle cell RMS
  – May have NCOA2 rearrangements
  – Should be negative for PAX gene and FOXO1 rearrangement
Spindle Cell/Sclerosing Rhabdomyosarcoma
Differential Diagnosis

- Leiomyosarcoma (myogenin negative)
- Fibrosarcoma (desmin negative)
- Synovial sarcoma (positive for SS18 rearrangement, negative for myogenin, typically negative for desmin)
- Spindle cell carcinoma (usually adults)
- Osteosarcoma (vs sclerosing RMS, myogenin-negative)
- Angiosarcoma (CD31-positive)
Alveolar Rhabdomyosarcoma

- A small cell neoplasm
- Patternless sheets of cells or alveolar pattern
- Often (always?) positive for FOXO1 fusion
Alveolar Rhabdomyosarcoma
Clinical Features

• Usually extremity
• Head and neck (sinonasal tumors in particular)
• Parameningeal
• Metastasize to regional lymph nodes
• Predominate in older children, adolescents
  – Also occur in younger children, adults
• Incompletely excised lesions recur with drug resistance
• Rare lesions present as leukemia
ARMS
Alveolar Rhabdomyosarcoma
Pathologic Features

• Alveolar pattern
  – Cells lining a hollow space (L. *alveolus*, cavity)
  – Central floating clusters
  – Peripheral discohesion or cracking
  – Fibrous septa

• Solid pattern
  – Patternless sheets
  – No apparent alveolar spaces or septa
ARMS
ARMS, solid variant
Alveolar Rhabdomyosarcoma (ARMS)

Genetics

- $t(2;13)$
  - *PAX3-FOXO1* fusion
  - About 60% of cases
  - Overexpressed
- $t(1;13)$
  - *PAX7-FOXO1* fusion
  - About 20% of cases
  - Amplified
- PAX fusion negative
  - Are these truly ARMS?
t(2;13)
ARMS FISH
Fusion vs. histology (Davicioni et al).
Alveolar Rhabdomyosarcoma
Differential Diagnosis

- ERMS (fusion negative, with rare exceptions)
- Ewing sarcoma
- Lymphoma
- Neuroblastoma
- Synovial sarcoma
- Other round cell neoplasms
Pleomorphic Rhabdomyosarcoma

- A high grade sarcoma that usually arises in the extremities
- Features similar to other high grade adult sarcomas
- Should have definitive skeletal myogenesis, by definition
  - May require immunohistochemistry, i.e. myogenin stain
Pleomorphic Rhabdomyosarcoma
Clinical Features

- Lower extremity lesion most common
- Other sites, abdomen, chest wall, spermatic cord, arm, mouth, orbit
- Ages: 21-81 years (median 54 years)
- Clinical outcome: 70% die, mean survival 20 months
Pleomorphic Rhabdomyosarcoma
Pathologic Features

• Pleomorphic spindle cells and giant cells
• May have “malignant fibrous histiocytoma”-like (storiform) pattern
• Cells with eosinophilic cytoplasm
• Woven, streaming, or indistinct pattern
• Must demonstrate features of skeletal muscle
  – Myogenin and MyoD may be negative or focal in some cases
  – Desmin should be positive, but is non-specific
  – Cytological features should be present
Pleomorphic RMS
Pleomorphic Rhabdomyosarcoma Genetics

• Few good studies
• Regions of chromosomal gain and loss
• Regions of gene amplification
• Genetic features of osteosarcoma
Pleomorphic Rhabdomyosarcoma
Differential Diagnosis

- Undifferentiated pleomorphic sarcoma (MFH)
- Dedifferentiated liposarcoma (MDM2 expression, 12p12-15 region amplification)
- Dedifferentiated chondrosarcoma (bone tumor)
- Melanoma (HMB45, other melanocytic markers)
- Spindle cell carcinoma
- Carcinosarcoma
Epithelioid/Rhabdoid Rhabdomyosarcoma

- A newly-described RMS variant with features of carcinoma or rhabdoid tumor
- Rhabdoid tumor features more typical with children
- Probable variant of ERMS
  - Fusion-negative
  - Weak or focal myogenin
- Other differential diagnosis features
  - INI1 retained
  - Melanocyte markers negative (beware of desmin-positive melanoma)
Immunohistochemistry of Rhabdomyosarcoma

• General markers of muscle differentiation
  – Muscle actin
  – Desmin

• Specific markers of skeletal muscle differentiation
  – MyoD (myf3)
    • Must be nuclear stain to be positive
  – Myogenin (myf4)
  – Myoglobin (terminal differentiation)
Myogenin

ARMS

ERMS
Surrogate Markers of Fusion Status in Rhabdomyosarcoma

- **Strong expression**
  - Myogenin
  - NOS-1
  - AP2β
  - P-cadherin

- **Weak expression**
  - HMGA2
  - EGFR
  - Fibrillin-2
## Prognosis and Clinical Course of Rhabdomyosarcoma

### Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Sites</th>
<th>T</th>
<th>T Size</th>
<th>Node Status</th>
<th>Metastases</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Favorable site (orbit; head and neck, excluding parameningeal; and genitourinary, nonbladder/prostate)</td>
<td>T1 or T2</td>
<td>Any</td>
<td>N0, N1 orNX</td>
<td>M0</td>
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<tr>
<td>2</td>
<td>Unfavorable site (any site not listed above)</td>
<td>T1 or T2</td>
<td>&lt;5 cm</td>
<td>N0 or NX</td>
<td>M0</td>
</tr>
<tr>
<td>3</td>
<td>Unfavorable site</td>
<td>T1 or T2</td>
<td>&lt;5 cm</td>
<td>N1</td>
<td>M0</td>
</tr>
<tr>
<td></td>
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<td></td>
<td>&gt;5 cm</td>
<td>N0, N1 orNX</td>
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<tr>
<td>4</td>
<td>Any</td>
<td>T1 or T2</td>
<td>Any</td>
<td>N0, N1 orNX</td>
<td>M1</td>
</tr>
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</table>
Prognosis and Clinical Course of Rhabdomyosarcoma Group

- Group 1: Completely resected, non-metastatic
- Group 2: Microscopic residual disease
  - non-metastatic
  - resected nodal metastatic
- Group 3: Gross residual disease
- Group 4: Distant metastasis
**Prognosis and Clinical Course of Rhabdomyosarcoma**

**Prognostic groups**

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Stage/Group</th>
<th>Fusion Status</th>
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<tbody>
<tr>
<td>Low</td>
<td>Stage 1, Group III (orbit)</td>
<td>Negative</td>
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<tr>
<td></td>
<td>Stage 1, Group I-II</td>
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<tr>
<td></td>
<td>Stage 2, Group I-II</td>
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<tr>
<td>Intermediate, subset 1</td>
<td>Stage 1, Group III (non-orbit)</td>
<td>Negative</td>
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<tr>
<td></td>
<td>Stage 3, Group I-II</td>
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<td>Intermediate, subset 2</td>
<td>Stage 2-3, Group III</td>
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<td></td>
<td>Stage 1-3, Group I-III</td>
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<td>Intermediate, subset 3</td>
<td>Stage 4, Group IV</td>
<td>Negative</td>
</tr>
<tr>
<td>High</td>
<td>Stage 4, Group IV</td>
<td>Positive</td>
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</table>
Failure free survival

Log Rank Test: p<0.001
Summary

- Rhabdomyoma is a rare benign tumor of adults and children
- Rhabdomyosarcoma is more common, malignant, and usually affects children
- Diagnosis is improved with immunohistochemistry
- Prognosis depends on stage, group, and PAX fusion status