Pediatric Fibroblastic, Myofibroblastic and Spindle Cell Tumors

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Pediatric Tumors of Fibroblastic & Myofibroblastic Origin

- Infantile Fibrosarcoma (uncommon)
- Myofibroma (common, includes infantile hemangiopericytoma)
- Myopericytoma [pericytic tumor with t(7;12) translocation, rare]
- Inclusion Body Fibromatosis (rare)
- Fibrous Hamartoma of Infancy (rare)
- Juvenile Hyaline Fibromatosis (rare)
- Fibrodysplasia Ossificans Progressiva (rare)

Pediatric Tumors of Fibroblastic & Myofibroblastic Origin: Uncommon

- Desmoid
- Fibromatosis Coli
- Gardner-Associated Fibroma
- Cardiac Fibroma
- Nodular Fascitis & Cranial Fascitis
- Inflammatory Myofibroblastic Tumor

Pediatric Tumors of Fibroblastic & Myofibroblastic Origin: Rare

- Calcifying Aponeurotic Fibroma
- Calcifying Fibrous Tumor
- Lipofibromatosis
- Solitary Fibrous Tumor (includes “adult hemangiopericytoma”)
- Hereditary Gingival Fibromatosis
- Juvenile Nasopharyngeal Fibroma

Pediatric Tumors of Fibroblastic & Myofibroblastic Origin: Malignant

- Infantile Fibrosarcoma (congenital)
- Myofibrosarcoma
- Rhabdomyofibrosarcoma (infantile RMS)
- Adult Fibrosarcoma
  - Classic Type
  - Low Grade Fibromyxoid Sarcoma
  - Hyalinizing Spindle Cell Tumor with Giant Rosettes
  - Sclerosing Epithelioid Fibrosarcoma
  - Acral Myxoinflammatory Fibrosarcoma
Triaging for Fibroblastic & Myofibroblastic Tumors
- Frozen Tissue Cryopreserved
- Routine Formalin-Fixed Tissue
- Immunocytochemistry
- RT-PCR for Translocation Identification
- Glutaraldehyde-Fixed Tissue for EM
- Fresh Tissue for Cytogenetic and Molecular Studies
- Cytologic Imprints for FISH, Cytogenetic Interphase Studies & Immunophenotype

Infantile Fibrosarcoma
- >50% Diagnosed During 1st Year of Life
- H&N, Trunk and Distal Extremities
- Asymptomatic, Bulky, Rapidly Growing
- Deep Soft Tissues
- Locally Invasive
- Metastasize Infrequently
- 5 Year-Survival: 90%

Infantile Fibrosarcoma
- Gross Appearance:
  - Infiltrative Fleshy Tumor
  - Lack of Well-Defined Borders
  - Lobulated with Mucinous to Myxoid Character
  - Areas of Necrosis, Cystic Degeneration and Hemorrhage
- Fibroblastic-Myofibroblastic Proliferation
- High Cellularity with Closely Packed Cells
- Prominent Mitotic Activity
- Herring-Bone Pattern
- Collagen Formation
- Desmin and/or Muscle Specific Actin in 20-30%
- Markedly Dilated and Branching RER
- Rare to Absent Basal Lamina
- Rare Extracellular Banded Collagen
- Irregular Nuclear Contours
- Extracellular Fibrillargranular Material
Extracellular Fibrillogranular Material

Infantile Fibrosarcoma: ETV6-NTRK3

Non-Resectable Infantile Fibrosarcoma
- Children's Oncology Group Protocols
- VAC-Based Therapy
- Excellent Response to Therapy
- Tumors Amenable to Resection
- “Myofibromatosis-like” Appearance on Resection

Infantile Rhabdomyofibrosarcoma
- Mimics Infantile Fibrosarcoma
- Considered a High Grade Sarcoma
- Fibroblastic and Rhabdomyoblastic Differentiation
- EM Important for Appropriate Diagnosis
- Monosomy Chromosomes 19 & 22
der(2) t(2;11)(q37;13)
Infantile Myofibromatosis

- Initially termed "Infantile Fibrosarcoma" (1954)
- Re-classified "Quickly" as Congenital Generalized Fibromatosis (Late 1950's)
- Renamed "Infantile Myofibromatosis" (1981)
  - Solitary (>50%)
  - Multicentric (33%)
  - Multicentric with Visceral Involvement (15%)

Solitary Form
- Cutaneous with Dermal and Subcutis Extension - Sometimes Muscle & Bone Involvement
- Bone Only
- Multicentric Form
  - Several Soft Tissue Sites
  - Multicentric Bone Lesions Possible
  - Visceral Involvement
  - Lung, Heart, Gastrointestinal System, Central Nervous System
- Familial (Autosomal Dominant)

Multicentric Form
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- Multicentric Bone Lesions Possible
- Visceral Involvement
- Lung, Heart, Gastrointestinal System, Central Nervous System
- Familial (Autosomal Dominant)

Nodular to Multinodular Pattern
- Peripheral Spindle Cells Organized into Fascicles
- Merge and Blend with Sheets of Ovoid to Polygonal Shaped Less Differentiated Cells

Infantile Myofibromatosis

Common Sites
- Head and Neck > Extremities > Trunk

Natural History and Prognosis
- Soft Tissue and Bone Lesions - Stabilize & May Undergo Spontaneous Regression
- Locally Aggressive Tumors - Unremitting Gradual Destruction of Adjacent Tissues
- Aggressive Tumors in Non-Resectable Sites May Require Chemotherapy
- Visceral Involvement - Up To 75% Mortality in Infants

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- Visceral Involvement - Up To 75% Mortality in Infants
- Areas of Necrosis and Calcifications
- "Vascular Invasion" – Subendothelial Growth
- Relatively High Mitotic Activity (not atypical)
- Nuclear Atypia
- No Bearing on Clinical Outcome
- Stromal Hyalinization

- Prominent Pericytoma Architecture
- More Common within Center of Tumor
- Misclassified as Infantile Hemangiopericytoma
- Tumors Lack Cytogenetic Features of “True Hemangiopericytoma” (Now SFTs by WHO)
- Myofibromas with Hemangiopericytoma-Like Pattern

- Myofibroblastic Differentiation
  - Prominent Rough Endoplasmic Reticulum
  - Longitudinal Filaments with Dense Body Attachment Plaques
  - Focal Basal Lamina

- Fibronexus Structures – Not Typically Present
- Intercellular Junctions – Sparse & Diminutive
- Pinocytotic Junctions, Basal Lamina & Intercellular Junctions Much More Common in Rhabdomyosarcoma

- "Leiomyomatous-Like"
Myopericytoma

**Pericytic Tumor with t(7;12)**

- May be Mistaken for HPC-like Myofibroma or Adult HPC (SFT)
- Age Range: 11-65 yrs
- M:F 2:1
- Most common locations: upper and lower extremities.
- Especially Distal Extremities: Leg/Knee, Forearm/Hand
- Multilobulation and Infiltrative Growth Around Thin-Walled Vessels

**Immunocytochemistry**

- CD34: Negative
- SMA, Laminin & Type IV Collagen: Positive
- Pericytic Features by EM
  - Attachment Plaques
  - Thin Filaments
  - External Lamina
- t(7;12)(p21-22;q13-15)
  - beta-Actin/GLI Oncogene

**Novel Translocation Between Beta-Actin Gene (ACTB) and GLI Oncogene [t(7;12)(p21-2;q13-15)]**

- Overexpression of GLI Oncogene by the Inclusion of the ACTB Promoter Region
- GLI: Essential in Sonic Hedgehog Signaling Pathway (cell cycle regulation, cell adhesion, apoptosis, signal transduction and cell proliferation)

**Infiltrative Growth Pattern**

- Subendothelial Insinuation (myopericytoma)

**Dorsal Aspect of Digits (hands & feet) in Young Children**

- Gradual Enlargement of Firm Broad-Based Nontender Nodule
- Interphalangeal Joint Deformity
- Erodes into Bone
- Recurrence in 50-60%
Inclusion Body Fibromatosis
- Inclusions
  - Trichrome, PTAH, Iron Hematoxylin
  - SMA & Vimentin
  - Granular & Filamentous Character
- Recent Association
  - Facial Pigmentary Dysplasia, Focal Dermal Hypoplasia, Metacarpal & Metatarsal Disorganization, & Limb Malformations

Juvenile Hyaline Fibromatosis
- Hereditary Disorder
  - Described in 1873 as Molluscum Fibrosum
  - Autosomal Recessive
  - Aberrant Collagen Synthesis & Deposition
- Severe Form: Infantile Systemic Hyalinosis
- Mild Form: Juvenile Hyaline Fibromatosis

Juvenile Hyaline Fibromatosis
- Progressive Increase in Number & Size of Subcutaneous & Deep Nodules
- Bone Lesions Lead to Osteolysis and Osteoporosis
- Deformity and Dysfunction
- Survival into Adulthood

Fibrodysplasia Ossificans Progressiva
- Rare Autosomal Dominant Disorder
- Congenital Malformation of Great Toes
- Progressive Heterotopic Ossification of Tendons, Ligaments, Fascia and Skeletal Muscle
- Progressive Fibrosis with Calcification
- Similar to Aggressive Juvenile Hyaline Fibromatosis (lacks calcification)

Juvenile Hyaline Fibromatosis
- Fibroblasts with Markedly Dilated RER Filled with Fibrillogranular Material
- Vesicles Appear to be in Direct Continuity with Surrounding Ground Substance

Juvenile Hyaline Fibromatosis
- Capillary Morphogenesis Gene-2 (4q21), CMG2/ANTXR2
- Protein Upregulated in Endothelial Cells During Capillary Formation
- Binds Laminin, Collagen IV and von Willebrand Factor Type A Domain
- Interference with Normal Cell Interaction with Extracellular Matrix
Fibrodysplasia Ossificans Progressiva

- Previously Known as Myositis Ossificans Progressiva
- Early Stage: Perivascular Lymphocytic Infiltrate
- Proliferation of Fibroblasts, Formation of Fibrous Tissue (Resemble JHF & Fibromatosis Coli)
- Ectopic Bone in Soft Tissues Adjacent to Skeletal Muscle

Fibrodysplasia Ossificans Progressiva

- Typical Active Fibroblasts
- Embedded in Ground Substance and Collagen Matrix
- Early Foci of Calcification Not Apparent in Proliferating Fibroblastic Areas

Fibrodysplasia Ossificans Progressiva

- Genetic Linkage
  - ACVR1 (ALK2) 2q24.1
  - 4q27-31 Unknown
  - 17q21-22 NOG
  - 14q22-23 BMP4
- Mast Cell Involvement
  - 40-150 Fold Increase
- 10-40 Fold Increase Compared with Inflammatory Myopathy
- Ossification: Minor Trauma
- Surgical Intervention “Fuels the Fire”

FOP: Towards A Cure-Inhibitors of ACVR1 (ALK2) Pathway

Fibrous Hamartoma of Infancy

- Primarily in 1st Year of Life (90%)
- More Common in Males (2.4M:1.0F)
- Axilla, Upper Arm & Trunk, Inguinal & Genital Areas
- Rapidly Growing Painless Nodule-Poorly Circumscribed
- 3 Components: Dense Fibrous Tissue, Primitive Mesenchyme & Mature Adipose Tissue
Fibrous Hamartoma of Infancy

- Admixture of Fibroblasts and Myofibroblasts
- Stroma Variable Collagen and Ground Substance
- Paucity of Organelles and Indistinct Cytoplasmic Borders
- Treatment: Surgical with Recurrence Rate of 12%

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EGFR 20 Mutation in FHI:
EGFR Inhibitors Available

Myogenin
Desmin
MyoD1

MyoD1 Mutation in RMS

MYOD1 (L12P) mutations are associated with spindle cell and advising rhabdomyosarcomas with aggressive clinical outcomes.

Recurrent MYOD1 Mutations in Pediatric and Adult Skeletally and Spindle Cell Rhabdomyosarcoma: Evidence for a Common Pathogenesis

Myogenin
Desmin
MyoD1
Pediatric Spindle and Sclerosing RMS
- VGLL2-CITED2
- VGLL2-NC0A2
- TEAD1-NC0A2
- PAX3/7-NC0A2
- SRF-NC0A2 (single case)

A Molecular Study of Pediatric Spindle and Sclerosing Rhabdomyosarcoma
Identification of Novel and Recurrent VGLL2-related fusions in infantile cases

Primitive Myxoid Mesenchymal Tumor of Infancy
- Rare Soft Tissue Neoplasm
- Locally Aggressive Mesenchymal Tumor
- Represents Primitive End of Spectrum of Fibroblastic-Myofibroblastic Tumors
- Usually Occurs During First Year of Life
- Long, Indolent Course Complicated by Frequent Relapses

Vimentin Positive; Myogenin and Desmin Negative

PMMTI
- Clinical Course Usually Prolonged with Frequent Local Recurrences, But Rare Metastases
- Radical Surgical Excision with Establishment of Negative Margins
- Tumor Unresponsive to Chemotherapy
- Radiation Therapy Not Effective
PMMTI with BCOR Internal Tandem Duplication

- 7 Cases with Age Range from 2 to 12 mos; 5 Males and 2 Females
- Sites: Paraspinal, Larynx, Abdominal Wall, Retroperitoneum, Abdominal Cavity, Paravertebral, Thigh
- BCOR ITD in 6 of 7 Tumors
- Followup in 3 of 7 Cases: 1 Metastatic Disease, DOD at 5 Yrs, Local Response at 5 mos