Update on Fibroblastic and Myofibroblastic Tumors in Young Patients

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Key Facts and Challenges

- >10% of soft tissue tumors in newborns to 20 year olds have a fibroblastic-myofibroblastic phenotype
- Clinicopathologic spectrum encompasses reactive, malformative, benign, locally aggressive, rarely metastasizing, and malignant lesions
- Morphologic and immunohistochemical similarities
- Biologic, genetic, and therapeutic diversity
Objectives

• To review the current classification of fibroblastic-myofibroblastic tumors
• To summarize new information and recently described lesions
• To review the re-emergence of fibrosarcoma as an entity
Fibroblastic – Myofibroblastic Masses

• Benign
  Malformations/ overgrowths
  Reactive processes
  Pseudosarcomas
  Fibromas
  Fibromatoses, juvenile and adult
• Locally recurrent/rarely metastasizing neoplasms
• Fibroblastic and myofibroblastic sarcomas
2013 WHO Classification of Fibroblastic-Myofibroblastic Tumors

- 32 entities
- 18 benign
- 10 locally recurring and/or rarely metastasizing
- 4 malignant (true sarcomas)
Gardner Fibroma: A Sentinel Lesion for APC and Desmoids

- Benign plaquelike mass: overgrowth or neoplasm?
- Children and young adults
- Association with FAP/APC and desmoids-to what extent?
- Overexpression of beta-catenin and other proteins in the APC and Wnt pathways
- Surgery vs. no treatment?
- Any association with CTNNB1 mutation?
Gardner fibroma and desmoid
Juvenile Desmoid Tumors: A Potential Harbinger of APC

- 15-40% of desmoids occur in NB – 20 y.o
- APC in at least 25%; GAF in a subset
- 3-12% are multiple
- Trunk and extremities
- 60% recur; 20% multiple recurrences
- Death in < 2%
- Surgery, chemotherapy more effective than radiotherapy
Desmoid
Genetic Aberrations in Desmoids

- Monoclonal
- *APC* mutation
- *Beta-catenin* mutations
- 5q loss, 6q loss, 20q gain, trisomy 8
- Mesenchymal stem cell markers
APC Mutations and Desmoids

- APC mutations occur in both FAP-associated and sporadic desmoids
- In FAP: 10-15% of patients develop desmoids
  - 852-fold increased risk
- Intrafamilial phenotypic variation
- Germline APC mutations
- In sporadic desmoids, somatic APC mutations
- FAP-associated desmoids have more intratumoral genetic aberrations (losses of 5q22, 6q15-q22.3, 13q14.11 – q34)
Beta-Catenin Mutations and Desmoids

• 19-87% of sporadic desmoids harbor a *CTNNB1* mutation at 3p22 (codons 41A, 45F, 45P); ethnic/geographic variability

• *CTNNB1* codon 45F mutation seems to be associated with higher recurrence risk

• *CTNNB1* mutations are more frequent than APC mutations in pediatric desmoids (66% vs. 18%)
Lipofibromatosis: A Bland But Locally Aggressive Neoplasm

- Infancy and childhood; 25% congenital
- Distal extremities favored site
- Male predilection
- 75% recur locally
- t(4;6;9) in one case
- What about “infantile fibromatosis”?
Lipofibromatosis
Giant Cell Fibroblastoma: A Locally Aggressive Neoplasm Related to DFSP

- Superficial soft tissue mass
- Male predominance (⅔)
- 50% before 5 years; 90% before 12 years
- Median age 6 years
- Chest wall, back, axilla, inguinal region, thigh
- Local recurrence rate 50%
- $COL1A1$-$PDGFB$ gene fusion
Giant cell fibroblastoma
Giant cell fibroblastoma
Myxoid giant cell fibroblastoma
Dermatofibrosarcoma Protuberans: An Aggressive “Mature” Form of GCF?

- Superficial soft tissue nodular or multinodular mass
- Slight male predominance
- 10-30% in newborns-20 year olds
- Trunk, proximal extremities, head and neck
- Recurrence rate 20-50%
- Rapid enlargement signals progression to fibrosarcomatous DFSP
- Metastasis rare, associated with fibrosarcomatous DFSP
- \( \text{COL1A1-PDGFB} \) gene fusion
Myxoid DFSP, CD34
DFSP: myoid nodules
SMA in myoid nodule, DFSP
DFSP with fibrosarcoma
Genetics: GCF and DFSP

- GCF: t(17;22)(q21.3;q13.1) balanced or unbalanced, with \(COL1A1-PDGFB\) gene fusion
- DFSP: supernumerary ring chromosome composed of sequences from chromosomes 17 and 22 or unbalanced t(17;22)(q21.3;q13.1) in pediatric cases, with \(COL1A1-PDGFB\) gene fusion; trisomies 5 and 8
- Responsive to imatinib: when should it be used?
- Is distinction between GCF and DFSP necessary?
Extrapleural Solitary Fibrous Tumor: A Rarely Metastasizing Tumor Whose Classification is Evolving

- Terminology encompasses hemangiopericytoma, lipomatous hemangiopericytoma, giant cell angiofibroma
- Rare in children and adolescents
- Orbital, nasal, and other sites
- Recurrence and metastasis possible
- Prognostic indicators elusive
- What about CNS and sinonasal hemangiopericytoma?
Solitary fibrous tumor, classic
Solitary fibrous tumor, myxoid
Solitary fibrous tumor

- CD34
- CD99
- Bcl-2
- SMA
Solitary fibrous tumor, variants
Infantile Fibrosarcoma (IFS): A Locally Aggressive, Rarely Metastasizing Tumor

- Intermediate, rarely metastasizing neoplasm
- Infancy; 50% congenital
- Rapid growth, large size
- Extremities, trunk, head/neck, kidney (CCMN)
- t(12;15) with $ETV6-NTRK3$ fusion
- Gains of chromosomes 8, 11, 17, 21
- Surgery, chemotherapy effective
- To what extent is genetic testing necessary?
Infantile fibrosarcoma
Infantile fibrosarcoma
Infantile fibrosarcoma
Inflammatory Myofibroblastic Tumor

- IMT is a distinctive neoplasm composed of myofibroblastic and fibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes, and/or eosinophils. It occurs primarily in soft tissue and viscera of children and young adults. (WHO, 2013).
- Clinical and laboratory syndrome
- 150-200 cases per year in U.S.
- Local recurrence in 25%; metastasis rare
- Activating ALK gene rearrangements in 50-60%
- Potential for targeted treatment
The Re-Emergence of Fibrosarcoma As An Entity

- With enhanced ability to diagnose monophasic synovial sarcoma and MPNST with adjunct tests, fibrosarcoma seemed to be a disappearing entity
- In the past decade or so, specific fibrosarcomas and myofibroblastic sarcomas have been recognized
- “True” fibrosarcoma now includes 4 subtypes: adult fibrosarcoma, low-grade fibromyxoid sarcoma, sclerosing epithelioid fibrosarcoma, and myxofibrosarcoma
- To what extent is distinction among these types necessary?
Low Grade Fibromyxoid Sarcoma

- A specific subtype of fibrosarcoma
- 20% in NB-20 y.o.
- Proximal extremities and trunk, superficial or deep
- Head/neck and superficial sites favored in children
- Recurrence in 9%, metastases in 6% (late)
- Histologic variants
- t(7;16)(q34;p11) with $FUS$-$CREB3L2$ gene fusion
Low grade fibromyxoid sarcoma
Low grade fibromyxoid sarcoma
Low grade fibromyxoid sarcoma
Adult Fibrosarcoma
Sclerosing Epithelioid Fibrosarcoma
Myxofibrosarcoma
Persistent Questions

• When is it important to distinguish among these similar-appearing tumors?
• With 32 entities in the 2013 WHO classification, and others too rare for inclusion, will the group of fibroblastic-myofibroblastic tumors continue to expand? How will classification change in the future?
• How can the surgical pathologist contribute to the diagnosis, clinical management, and improved understanding of these challenging tumors?
• To what extent can treatment be tailored to individual tumors and individual patients?