Fibrous Tumors of Infancy and Childhood: An Update
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Introduction
Fibroblastic and myofibroblastic neoplasms account for approximately 12% of soft tissue tumors in the first two decades of life, excluding the pseudosarcomas such as nodular fasciitis and related lesions and inflammatory myofibroblastic tumor (1-8). The histologic similarities, differences in biologic potential, and clinical and molecular genetic variations among this group of lesions create clinical, diagnostic and therapeutic challenges. The histologic spectrum encompasses reactive, malformative, pseudosarcomatous, and neoplastic lesions. In recent decades, the concept of intermediate or borderline fibroblastic-myofibroblastic tumors has been refined for neoplasms with a tendency for local recurrence or rare metastases. This presentation focuses on recently described fibroblastic neoplasms or new advances in the knowledge about these lesions in young patients.

Gardner Fibroma and Desmoid Fibromatosis
Gardner fibroma is a benign plaque-like mass with a predilection for children and young adults, and a strong association with APC mutation and familial adenomatous polyposis (9 and 10). It is associated with concurrent or subsequent development of desmoids. The mass is composed of coarse collagen fibers separated by clear clefts and interspersed with bland spindle cells and sparse mast cells. Although it is unknown whether Gardner fibroma represents an overgrowth or a neoplasm, nuclear beta-catenin reactivity has been observed in a subset of cases. There is over expression of beta-catenin and other proteins in the APC and WNT pathways. The optimal therapeutic approach to Gardner fibroma is not fully understood, since surgery may promote the growth of a subsequent desmoid in the region of a Gardner fibroma.

Desmoid tumors are relatively frequent in children although they are categorized among the so-called “adult fibromatoses” (11-16). Approximately 15-40% of desmoids occur in patients in the first two decades of life, and 19-60% of pediatric fibroblastic-myofibroblastic tumors are desmoids. Multiple desmoids occur in 3-12% of cases. The trunk and extremities are the most common sites, although desmoids can occur in soft tissue anywhere in the body. The grossly circumscribed mass is composed of sheets and fascicles of fibroblasts and myofibroblasts in a variably collagenized and myxoid background. The microscopic borders are often infiltrative. A pattern of elongated
slender blood vessels at the periphery of fascicles is distinctive. Nuclear beta-catenin reactivity is frequently demonstrated. The recurrence rate in children and adolescents is 60% overall, and 20% of patients have multiple recurrences. Fewer than 2% die of local complications. Up to 25% of young patients have adenomatous polyposis coli. This may be an underestimate of the frequency of APC mutation since other manifestations of APC may not be obvious in children and adolescents. Other genetic aberrations in desmoids include beta-catenin mutations, chromosome 5q deletion, and trisomies 8 and 20. Desmoid fibromatoses are treated with surgery; chemotherapy may be effective in selected cases.

**Lipofibromatosis**
Lipofibromatosis is a recently described intermediate, locally recurrent neoplasm (17-19). It has a predilection for infancy and early childhood, and approximately 25% are congenital. The distal extremities are the favored site. Lipofibromatosis has a male predilection. The poorly circumscribed mass is composed of slender interfacing bundles of mature fibroblasts interspersed with mature adipose tissue. 75% recur locally. Little is known about the cytogenetics or molecular genetic aspects of lipofibromatosis, although a complex translocation involving chromosomes 4, 6, and 9 has been reported in one case.

**Infantile Fibrosarcoma**
Infantile fibrosarcoma is an intermediate rarely metastasizing neoplasm that occurs mainly in infancy and very early childhood (20-29). Approximately 50% are congenital and the sex distribution is equal. Infantile fibrosarcoma can arise on the extremities, trunk, or head and neck as a rapidly growing tumor that reaches a very large size in proportion to the size of the child. Histologically, spindle, primitive angulated, and round cell patterns may be seen, and zonal necrosis is frequent. A translocation between chromosomes 12 and 15 with an ETV6-NTRK3 gene fusion is considered characteristic. In addition, gains of chromosomes 8, 11, 17, and 21 may be observed. Surgery and chemotherapy are effective treatments. It is now recognized that infantile fibrosarcoma and cellular congenital mesoblastic nephroma are histologically identical tumors with the same gene fusion and the same response to treatment.

**Primitive Myxoid Mesenchymal Tumor of Infancy**
Primitive myxoid mesenchymal tumor of infancy is a rare recently described primitive tumor of infancy that occurs on the trunk, extremities, and head and neck (29). The multinodular growth is composed of primitive cells with a myxoid background and lacks characteristic immunohistochemical features. Recurrence and metastasis occur. No information is yet available about cytogenetic or molecular genetic features. Primitive myxoid mesenchymal tumor has been provisionally included among the intermediate or low grade malignant potential fibroblastic-myofibroblastic tumors because of its tendency for recurrence, rare frequency of metastasis, and ultrastructural features of primitive fibroblasts.

**Low Grade Fibromyxoid Sarcoma**
Low grade fibromyxoid sarcoma is a specific subtype of fibrosarcoma with a low frequency of metastasis (30-36). Approximately 20% occur in the first two decades of life. Although the proximal extremities and trunk are the most common sites, the head and neck is a preferred site in children. The tumor may be superficial or deep, although pediatric cases are more frequently located in superficial soft tissue. A variety of histologic variants have been reported, including myxoid and cellular variants, hyalinizing spindle cell with giant collagen rosettes, and perhaps sclerosing epithelioid fibrosarcoma. A translocation between chromosomes 7 and 16 with a **FUS-CREB3L2** gene fusion has been reported. The recurrence rate is 10%. Approximately 6% of patients have late metastases. Complete surgical excision is effective treatment.

**Inflammatory Myofibroblastic Tumor**

Inflammatory myofibroblastic tumor is a distinctive lesion composed of myofibroblastic spindle cells accompanied by an inflammatory infiltrate of plasma cells, lymphocytes and eosinophils, according to the current WHO classification (2, 37-48). It is currently regarded as an intermediate, rarely metastasizing neoplasm. The age distribution is wide, but inflammatory myofibroblastic tumor is most frequent in the first three decades of life. It can arise in the mesentery, omentum, retroperitoneum, lungs, mediastinum, head and neck, live, and genitourinary tract as a solitary or multinodular mass. Up to 25% of patients have a clinical syndrome of fever, weight loss, growth failure, anemia, thrombocytosis, polyclonal hyperglobulinemia, and elevated inflammatory markers.

Genetic abnormalities have been reported including chromosome 2p23 abnormalities with **ALK** gene rearrangements in 50-70% of inflammatory myofibroblastic tumors. The fusion oncogenes are numerous and include tropomyosin, clathrin, RAN binding protein 2, and other oncogenes. Detection of the **ALK** abnormality with immunohistochemistry has high sensitivity and specificity. The **ALK** rearrangement can be demonstrated with conventional tumor karyotype, fluorescent in situ hybridization, and RT-PCR. Local recurrence has been reported in up to 25% of extrapulmonary inflammatory myofibroblastic tumors. Metastases are rare. Although surgery is the standard treatment, and chemotherapy may be effective, small molecule inhibitors of **ALK** are a recent therapeutic option for inflammatory myofibroblastic tumor with an **ALK** gene rearrangement.

Prognostic indicators have been elusive. Recent finding of clinical and prognostic importance is the recognition of the round cell variant of inflammatory myofibroblastic tumor. Round cell inflammatory myofibroblastic tumor is **ALK** positive with a distinctive membranous and dot-like pattern of **ALK** reactivity and a gene fusion between **ALK** and **RANBP2**, which has a predilection for males, involves intraabdominal sites, and has a mean age of 35 years, with an age range of infancy to the sixth decade. The majority of patients reported thus far with round cell inflammatory myofibroblastic tumor have experienced rapid local recurrence, a metastatic rate of 25%, and a death rate of 38%.

One of the most important aspects of the diagnosis of inflammatory myofibroblastic tumor is recognizing it from its many mimics. Many different reactive infections, fibroinflammatory, and neoplastic conditions can simulate inflammatory myofibroblastic tumor. Although the term “inflammatory pseudotumor” is embedded in the literature, we recommend abandoning this term because of its lack of specificity and
the significant potential for confusion about pathologic classification. IgG4-related sclerosing disease encompasses a clinical syndrome with multiorgan system involvement by a diffuse fibroinflammatory proliferation and is distinguished by its infiltrative growth pattern, presence of abundant lymphoid aggregates, and obliterative phlebitis. The IgG4/IgG plasma cell ratio in inflammatory myofibroblastic tumor can overlap with IgG-related sclerosing disease and is not a reliable test for distinguishing between the two lesions. There are many neoplastic mimics of inflammatory myofibroblastic tumor, such as lymphoma (Hodgkin’s disease, anaplastic large cell lymphoma, other lymphomas, and extramedullary myeloid sarcoma), dendritic cell neoplasms (especially follicular dendritic cell tumor arising in the context of Castleman disease), sarcomatoid carcinomas, malignant melanoma, plexiform fibromyxoma, and other sarcomas (inflammatory liposarcoma, inflammatory leiomyosarcoma).

At this point in time, understood that inflammatory myofibroblastic tumor is regarded as an intermediate rarely metastasizing neoplasm, and in 50-70% of cases it is an ALKoma with the potential for targeted treatment with small molecule inhibitors. It is also well recognized that inflammatory myofibroblastic tumor has a predilection for younger patients and an origin in body cavities. Ongoing challenges include identification of prognostic markers, optimal treatment, and appropriate classification of ALK-negative inflammatory myofibroblastic tumors. The pathologic paradox is the neoplastic proliferation of spindled myofibroblastic cells combined with the prominent inflammatory infiltrate.

Summary and Conclusions

Fibroblastic-myofibroblastic tumors in young patients are an important and challenging group of lesions with extensive histologic and immunohistochemical similarities. Cytogenetic and molecular genetic identification of mutations, deletions, gene rearrangements, and alterations in receptor tyrosine kinases has yielded new insights about this group of tumors. Whether non-round cell undifferentiated sarcomas in young patients will eventually be recognized as primitive fibroblastic neoplasms and included among the fibroblastic-myofibroblastic tumors in young patients is an important point for future consideration. It is also evident that many tumors previously classified as fibrohistiocytic tumors could be subsumed into the fibroblastic-myofibroblastic category because of their cellular characteristics and phenotypes. Finally, the extent to which treatment can be tailored to these individual tumors and to the individual patients will be an important area for further investigation. The time will soon come for a revised morphologic-genetic-managerial classification.
References


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Key Facts and Challenges

• >10% of soft tissue tumors in newborns to 20 year olds have a fibroblastic-myofibroblastic phenotype
• The clinicopathologic spectrum encompasses reactive, malformative, benign, intermediate, 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 discuss evolving knowledge and ongoing challenges of inflammatory myofibroblastic tumor (IMT)
Classification

• Benign
  Malformations/ overgrowths
  Pseudosarcomas
  Fibromas
  Fibromatoses, juvenile and adult
• Intermediate fibroblastic-myofibroblastic neoplasms (locally recurrent vs. rarely metastasizing)
• Fibroblastic-myofibroblastic sarcomas
Gardner Fibroma

• Benign plaquelike mass
• Predilection for children and young adults
• Strong association with FAP/APC
• Overexpression of beta-catenin and other proteins in the APC and Wnt pathways
• Association with concurrent or subsequent desmoids
• Surgery vs. no treatment?
• Overgrowth or neoplasm?
Juvenile Desmoid Tumors

- 15-40% of desmoids occur in NB – 20 y.o
- 3-12% are multiple
- Trunk and extremities are most common sites
- 60% recur; 20% have multiple recurrences
- Death in < 2%
- APC known in 25%
Lipofibromatosis

- Intermediate, locally recurrent neoplasm
- Infancy and childhood; 25% congenital
- Distal extremities favored site
- Male predilection
- 75% local recurrence rate
- t(4;6;9) in one case
Infantile Fibrosarcoma

- Intermediate, rarely metastasizing neoplasm
- Infancy; 50% congenital
- Extremities, trunk, head/neck
- Rapid growth, large size
- t(12;15) with *ETV6-NTRK3* fusion
- Gains of chromosomes 8,11,17,21
- Surgery, chemotherapy effective
Primitive Myxoid Mesenchymal Tumor of Infancy

- Rare primitive tumor of infancy
- Trunk, extremities, head, and neck
- Multinodular growth
- Recurrence, metastasis
- Intermediate or low grade malignant potential
Low Grade Fibromyxoid Sarcoma

- A specific subtype of fibrosarcoma
- 20% in first two decades of life
- Proximal extremities and trunk most common sites, superficial or deep
- Predilection for head/neck and superficial sites in children
- Histologic variants
- Recurrence in 9%, metastases in 6% (late)
- t(7;16)(q34;p11) with *FUS-CREB3L2* gene fusion
Inflammatory Myofibroblastic Tumor

- Intermediate, rarely metastasizing neoplasm
- Infancy to adulthood, most frequent in first 3 decades
- Mesentery, omentum, retroperitoneum, lung, mediastinum, head/neck, liver, GU tract
- Clinical syndrome: fever, weight loss, growth failure, anemia, thrombocytosis, polyclonal hyperglobulinemia, elevated ESR
- Local recurrence in 25%; metastasis rare
- Prognostic indicators elusive
Genetic Abnormalities

- Chromosome 2p23 abnormalities with ALK gene rearrangements in 50-70% of IMTs
- Fusion oncogenes: tropomyosin (TPM3, TPM4), clathrin (CLTC), Ran-binding protein 2 (RANBP2), CARS, ATIC, SEC31L1
- Detection: immunohistochemistry, FISH, RT-PCR
- Small molecule ALK inhibitors: a new therapeutic option
Round Cell IMT: A Morphologic-Prognostic- Molecular Subtype?

- Males
- Intraabdominal
- Mean age 35 yr. (7mo.- 59 yr.)
- Rapid local recurrence in 100%
- Metastases in 25%
- Death in 38%
- ALK- positive with RAN-BP2 fusion
IMT: What It Is Not

- A “pseudotumor” (abandon the term!)
- IgG4- related sclerosing disease
- Lymphoma, dendritic cell neoplasm, carcinoma, melanoma, other sarcomas
IMT: What It Is

- An intermediate (rarely metastasizing) neoplasm
- An ALKoma with potential for targeted treatment (sometimes)
- A tumor with a predilection for body cavities and younger patients
- A pathologic paradox
- An ongoing challenge
Rethinking the Fibroblastic-Myofibroblastic Tumors

- Mutations, deletions, rearrangements, receptor tyrosine kinases, and more?
- Is it time for a revised morphologic-genetic-managerial classification?
- Will non-round cell undifferentiated sarcomas in young patients eventually be recognized as primitive fibroblastic neoplasms?
- To what extent can treatment be tailored to tumors and to individual patients?
“There is a bright future for complexity, what with one thing leading to another.”

E.B. White