Fibroblastic Lesions

Elizabeth Montgomery, MD

Case
An 52 year old male presented with a 5cm subcutaneous mass on the shoulder that was not present 1 month ago. The mass was excised and sent to pathology.
Diagnosis

Proliferative Fasciitis
Case
An 86 year old bed-ridden man presented with a large firm mass of his lower back. A needle biopsy was performed.
Diagnosis

Ischemic Fasciitis [Atypical Decubital Fibroplasia]

Fasciitides

1) Nodular Fasciitis
2) Proliferative Fasciitis
3) Ischemic Fasciitis/Atypical decubital fibroplasia
Nodular Fasciitis

- A fast growing, subcutaneous mass. Adults 20-40yrs. Rarely recurs.
- Zonation: myxoid, cellular, fibrotic phase.
- Fibroblasts in "tissue culture" pattern and vague storiform fascicles. Mits w/o atypia.
- Often with extravasated RBCs and lymphocytes.
- Variants: ossifying, intravascular.
- SMA (+), calponin (+), desmin (-), ALK (-), cytokeratin (-).

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Nodular Fasciitis: Zonation at low power

- Myxoid
- Fibrotic
- Cellular
- Granulation tissue-like
- Myxoid

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Nodular Fasciitis: Tissue culture fibroblasts, extravasated RBCs, and lymphocytes.
Nodular Fasciitis: Cellular phase

Nodular Fasciitis: Fibrotic phase with Keloid-like collagen

Nodular Fasciitis: Osteoclast-like Giant cells
Proliferative Fasciitis/Myositis

- Fast growing lesions in older (50-60) adults than nodular fasciitis
- Proliferative Fasciits: subcutaneous
- Proliferative myositis: intramuscular
- Nodular fasciitis-like pattern with ganglion-like cells
- "Vimentin-only" lesions **BUT NEVER DO VIMENTIN - ESP ON TINY SAMPLES - IT WASTES THE TISSUE**
Proliferative Fasciitis: Ganglion-like cells

Proliferative Fasciitis: Hypercellular

Proliferative Myositis: Lesion extends off fascia into skeletal muscle
Proliferative Myositis: "Checkerboard" infiltration into skeletal muscle

Proliferative Myositis: Ganglion-like cells in myxoid stroma in between bands of muscle

Proliferative Myositis: Entrapped degenerated multinucleated skeletal myocyte
Atypical Decubital Fibroplasia/Ischemic Fasciitis

- Classically described as a lesion of the elderly that arises over “pressure points”
  Montgomery & Enzinger 1992, Perosio & Weiss 1993
- Some cases lack the classic clinical profile
- Lobular arrangement in deep subcutis
- Zones of fibrinoid necrosis with ingrowth of fibroblasts having degenerative atypia

Ischemic Fasciitis: Lobular mass situated in the subcutis with hemorrhage and necrosis.

Fibrinoid Necrosis

Myxoid Cellular Interface
Ischemic Fasciitis: Ingrowth of plump Ganglion-like fibroblasts at cellular interface

Ischemic Fasciitis: Cellular:fibrinoid Interface

Ischemic Fasciitis: Atypical cells at the hypoxic interface
Case

A 73 year old female presented with a 5cm soft tissue mass on the upper arm. A distant history of prior radiation was given. The mass was excised and sent to pathology.
**Diagnosis**

**Extraskeletal Osteosarcoma (EO)**

**Case**

A 23 year old male presented with a rapidly growing 5cm soft tissue mass on the upper trunk. A history of recent trauma at the site was given. The mass was excised and sent to pathology.
Diagnosis

Myositis Ossificans (MO)
Myositis Ossificans

- Usually a rapidly growing mass within skeletal muscle in young, active adults
- Resembles nodular fasciitis with zonal patterns of fibroblastic cells, but with a peripheral rim of ossification
- Mitotically active, but little to no atypia
- Fibrodysplasia ossificans progressive
- Chief DD: Extraskeletal osteosarcoma

MO: Bone lines the periphery of the mass

EO: Bone extends toward the center of the mass
Myositis Ossificans

**Peripheral rim of well-formed bone**

**Osteoid**

**Spindle cells in myxoid stroma**

Myositis Ossificans: Longstanding lesions may develop fatty marrow elements

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Benign Fibroblastic Tumors

- Most examples are composed of dense collagen and bland spindle cells (hence the term “fibroma” or “fibromatosis”)
- Typically arise in subcutis from fascia or in association with tendons
- Although generally benign, some entities are prone recur locally
Collagenous/Desmoplastic Fibroma

- Solitary mass in subcutis, usually upper torso/extremities. 75% male.
- Well-circumscribed fibrotic mass. May infiltrate focally into fat or muscle
- Bland stellate cells, poorly vascularized
- Benign: does not recur or metastasize
- Chief DD: Low grade fibromyxoid sarcoma


Collagenous Fibroma: Bland stellate cells in a Densely fibrotic, poorly vascularized stroma
**Fibroma of Tendon Sheath**

- Typically small (2cm) nodule attached to tendon sheath on hands. 30-50yr. males
- Fingers, wrists, hands, 2-5cm.
- Well-margined, lobulated, attached to tendon sheath
- Bland stellate cells in fibrotic stroma with slit-like vessels. Fasciitis-like areas.
- Up to a quarter recur after excision
Fibroma of Tendon Sheath: Nodular fasciitis-like areas in myxoid matrix

Calcifying Aponeurotic Fibroma
- Children (first decade), typically attached to aponeurosis on palmar or plantar area, but may occur elsewhere
- Variably cellular fibrotic mass with central deposits of amorphous calcification
- Tends to recur. Rare fibrosarcomatous transformation with mets has been reported.

Calcifying Aponeurotic Fibroma: Cellular fibrous tissue with areas of calcification, attached to an aponeurosis
Calcifying Aponeurotic Fibroma: Cellular fibrous tissue with areas of calcification, attached to an aponeurosis

Calcifying Aponeurotic Fibroma: Osteoid and Chondroid metaplasia

Calcifying Fibrous Pseudotumor
- Multiple sites, multiple ages
- Soft tissue examples are often pediatric; visceral cases often in adults
- Typically circumscribed paucicellular fibroblastic lesion with plasma cells and psammomatous or dystrophic calcifications
- Seldom recurs
- CD34(+), ALK (-), actin (-)
Calcifying Fibrous Tumor: Subcutaneous soft tissue mass in the arm of a child.

Calcifying Fibrous Tumor: Densely fibrotic mass with inflammation and calcification.

Calcifying Fibrous Tumor: Dense collagen, inflammatory cells, and calcification.
Calcifying Fibrous Tumor: Wall of small bowel in an older patient

Calcifying Fibrous Tumor: Fibrotic, paucicellular, Psammomatous or dystrophic calcification

Calcifying Fibrous Tumor: Mild Atypia
Diagnosis
Low Grade Fibromyxoid Sarcoma

LGFS: swirling fascicles
Fibromatosis: sweeping fascicles
Diagnosis
Low Grade Fibromyxoid Sarcoma

LGFMS: stellate/triangular hyperchromatic nuclei without nucleoli
Fibromatosis: long, tapered hypochromatic nuclei with nucleoli

Case
53 year old female with a history of multiple colon polyps presents with small bowel outlet obstruction. A large mass involving the small bowel wall and mesentery was resected.
C-kit immunostain

Beta-catenin immunostain
Diagnosis
Mesenteric Fibromatosis

Deep Fibromatoses
- Slow growing infiltrative subfascial masses
- APC: sporadic or FAP/Gardner’s
- Extra-abdominal: young adults, proximal limb girdles, head/neck
- Abdominal wall (pregnancy)
- Intra-abdominal (mesenteric, retroperitoneal)
- Difficult to completely resect, high local recurrence rate (up to 50%)
- Nuclear beta-catenin (+), SMA (+)

Fibromatoses: Morphology
- Sweeping Fascicles of Fibroblasts
- Infiltrative Growth Pattern
- Characteristic Vascular Pattern
- Superficial and deep
Sweeping fascicles

Prominent vessels

Gaping vessels

Long, tapered nuclei
Open chromatin + nucleoli

Low-grade fibromyxoid sarcoma t(7;16)(q34;p11) translocation and fusion gene [FUS (TLS)-CREB3L2]
Low-grade fibromyxoid sarcoma – MUC4 stain

Superficial Fibromatoses
- Typically adult Caucasian males
- Palmar/Dupuytren’s contracture
- Plantar/Ledderhose’s disease
- Penile/Peyronie’s disease
- Infantile digital fibroma (inclusion body fibromatosis)
- No beta-catenin or association with FAP
Palmar Fibromatoses
- Common, approximately 1-2%
- Slowly growing small subcutaneous nodules or plaques that may lead to contractures
- May be bilateral, familial, and multiple
- Associations: alcoholism, epilepsy, diabetes, and chronic lung disease
- May coexist with other superficial types but not with deep fibromatoses
- Prone to locally recur
Palmar fibromatosis: Bland spindle cells in collagen

Palmar fibromatosis: Often also affects knuckle pads

Plantar Fibromatoses
- Younger age group, often bilateral
- Nodular fibrous proliferation of plantar aponeurosis
- Less likely to result in contractures
- May be hypercellular
- Carries a higher local recurrence rate
- Increased incidence in patients with palmar or penile fibromatosis
Plantar fibromatosis: Subcutaneous nodules

Palmar fibromatosis: Sweeping fascicles, bland spindle cells, prominent vessels

Palmar fibromatosis may show alarming hypercellularity, especially in younger patients
Peyronie’s disease

- Affects tunica albuginea of the penis
- Begins as an inflammatory disorder, leading to dorsal fibrous plaques and exaggerated curvature
- Plaques may become hyalinized, calcified, and even ossified
- Higher recurrence rate
- Uncommon, but increased incidence in patients with palmar or penile fibromatosis

Early Peyronie’s disease: Inflammatory process that expands and infiltrates over dorsum

Late Peyronie’s disease: The inflammatory process “burns out” resulting in sclerotic plaque
Late Peyronie's disease: Plaques may calcify and even ossify

Case

36 year old male with a ill-defined, multinodular lesion involving the dermis of the shoulder. An excisional biopsy was performed.
Diagnosis
Dermatofibrosarcoma protuberans
Case

29 year old male with a 2cm mass lesion involving the dermis of the neck. An excisional biopsy was performed.
Dermatofibrosarcoma protuberans (DFSP)
- Slowly growing dermal plaque, may become multinodular. M>F, 25-45yrs.
- Infiltrates dermis and subcutaneous fat imparting a “honeycomb” appearance
- A translocation sarcoma t(17;22)(q22;q13): uniform spindle cells in a monotonous storiform pattern
- Intermediate biologic potential: Recurs and rarely metastasizes (5%).
- Fibrosarcomatous transformation
- DD: Melanoma, SFT, cellular fibrous histiocytoma, AFX, leiomyosarcoma
- CD34(+), CD99(+), Bcl2(+), S-100(-), FllIX(-), desmin(-)
- Variants: myxoid DFSP, Bednar tumor, Giant cell fibroblastoma (pediatric)
DFSP: Extends up to epidermis and down into subcutaneous fat

DFSP: Hypercellular, monotonous, storiform

DFSP: Hypercellular, monotonous, storiform
DFSP: Extends up to epidermal layer

DFSP: Entrapped skin appendages

DFSP: Infiltration of fat in a honeycomb pattern
DFSP: Extension along fibrous septa away from main tumor mass

DFSP: Strong CD34 immunoreactivity
DFSP: Fibrosarcomatous transformation

Myxoid DFSP: cellular, no atypia or lipoblasts, S100(-)

Pigmented DFSP: Bednar Tumor
Giant Cell Fibroblastoma

- Pediatric patients <5yrs, M>F, proximal lower limbs and trunk
- Juvenile form of DFSP, same translocation
- Bland spindle cells in myxoid stroma, with characteristic tumor-lined pseudovascular spaces
- Like DFSP, CD34 (+)
- Often recurs, but no mets in pure form
Giant Cell Fibroblastoma: Bland spindle cells in matrix; some line pseudovascular spaces

Giant Cell Fibroblastoma: Tumor cells line pseudovascular spaces

Deep Fibrous Histiocytoma
- The deep counterpart of dermatofibroma
- Lower limbs, head/neck of adults
- Well-circumscribed, non-infiltrative
- Varying amounts of spindle cells, collagen, foamy histiocytes, blood lakes, hemosiderin, giant cells
- Prone to recur. Rare case reports of metastasis.
- Chief DD: cellular variant with DFSP
- FXIIIa(+), CD34 often stains the periphery
Fibrous histiocytoma: Circumscribed with grenz zone, hemosiderin, blood lakes, areas of fibrosis

Deep fibrous histiocytoma: plump spindle cells, blood, hemosiderin, giant cells, hyalinized vessels

Deep fibrous histiocytoma: plump spindle cells, blood lakes, hemosiderin, collagen, foamy histiocytes
Deep fibrous histiocytoma: entrapped collagen fibers are often found at the periphery of the lesion.

Deep fibrous histiocytoma: cellular variant.

Deep fibrous histiocytoma: FXIIIa.
Deep fibrous histiocytoma: CD34+ periphery

Deep fibrous histiocytoma: CD34 on the periphery

Deep fibrous histiocytoma: CD34 in the center

Deep fibrous histiocytoma: Be careful, S-100 protein may highlight numerous dendritic cells
**DFSP vs. Deep BFH**

- Deep BFH: pushing border, grenz zone, entrapped collagen. CD34(-), FXIIIa(+).
- DFSP: down into fat, up to epidermis, packed cells. CD34(+), FXIIIa(-).

**Solitary Fibrous Tumor**

- The tumor formerly known as hemangiopericytoma (among others)
- May arise at any site in the body
- Alternating hyper- and hypocellular regions, "patternless pattern", HPC vessels
- CD34(+), CD99(+), BCL2(+), beta-cat (+/-)
- Malignant criteria: frankly sarcomatous, >4 mit/10hpf, necrosis, packed cellularity
- However, benign appearing lesions may met
- Variants: fat-forming, giant cell-rich

**Solitary Fibrous Tumor: Well-circumscribed fibrotic mass involving the bladder**
SFT: Alternating cellularity, patternless pattern, vessels

Hypercellular

Hypocellular

Hypercellular

Hypocellular

Hypercellular
Fat-forming (lipomatous) SFT

Fat-forming (lipomatous) SFT: spindle cells intermixed with mature fat

Giant cell-rich SFT (Giant cell angiofibroma)
Giant cell-rich SFT (Giant cell angiofibroma)

SFT: Frank malignant transformation

Hypercellular
Hypocellular
Sarcomatous
SFT: Frank malignant transformation

Needle biopsy of fat-rich solitary fibrous tumor

Fat-rich solitary fibrous tumor - Wiry collagen, fat, "disorganized" pattern of cells

Inflammatory Myofibroblastic Tumor (IMT)

Pulmonary lesions called “inflammatory pseudotumors” have been recognized for many years and regarded as part of a spectrum of lesions called “plasma cell granulomas”
Subsequently, similar tumors were described in the abdomen and other soft tissue sites.

“Inflammatory Fibrosarcoma”
- AFIP series, [Meis and Enzinger 1991], mesentery, omentum and retroperitoneum (over 80% of cases).
- Systemic symptoms.
- Both solitary and multinodular (30%) tumors up to 20 cm in diameter.

Inflammatory Fibrosarcoma
- Myofibroblasts and fibroblasts in fascicles or whorls, and also histiocytoid cells.
- Variable but often marked inflammatory infiltrate
- Immunostaining: smooth muscle actin, cytokeratin.
- 37% recurred and 3 cases (11%) metastasized. A quarter of the patients died of disease.
Inflammatory Myofibroblastic Tumor [Extrapulmonary]

Coffin et al 1995
Mostly pediatric cases
Similar to cases reported by Meis and Enzinger

? – Metastatic potential v. multicentricity
Some cases DO behave aggressively and kill the patient
Lung Lesion

Thigh Lesion

Thigh Lesion

Thigh Lesion
IMT/Inflammatory Fibrosarcoma

- IMT and inflammatory fibrosarcoma of soft tissues have now been recognized as ends of a spectrum of tumors unified by a common molecular profile, which are relatives of lung lesions
  - Grouped together by the WHO

IMT; Important Discovery

- Griffin et al. [1999] reported 3 IMT with rearrangements at 2p23 involving ALK gene
- Subsequently, ALK shown to be rearranged in a subset of IMTs from many sites
- Identified partners including CLTC, RANBP2, TPM3, TPM4, CARS ATIC, and SEC1L1.

Inflammatory Myofibroblastic Tumor (Extrapulmonary), ALK1 stain
ALK FISH

The FISH test performed for ALK is a break apart rearrangement DNA probe. Different color fluorescent labels (orange and green) are hybridized to the DNA on either side of the 2p23 breakpoint on chromosome 2. The normal, or non-translocated chromosome, has the orange and green signals immediately next to each other, which are sometimes overlapped causing a yellow color to be observed, termed "fused signals or fusions". In the normal control specimen, there are 2 of these fusions (2F) - one for each copy of chromosome 2 - present in each of the nuclei.

Normal lymphocytes tested for ALK rearrangements

ALK FISH

- When the 2p23 breakpoint on chromosome 2 is rearranged (involved in a translocation), the orange and green signals are separated, and are visualized as distinct signals more than one signal width apart.

- The abnormal specimen thus has one fusion for the normal chromosome 2, and one orange and one green signal for the rearranged chromosome 2.
ALK rearrangement in an Inflammatory myofibroblastic tumor

Targeted Therapy

Crizotinib (PF-02341066, Pfizer) - orally bioavailable, ATP-competitive, small-molecule inhibitor of the receptor tyrosine kinases (RTKs) c-Met (also known as hepatocyte growth factor receptor) and anaplastic lymphoma kinase (ALK), Used in lung cancer (about 5% of lung cancers have ALK rearrangements) and now IMT!!


Ceritinib is a newer one (N Engl J Med 2014: 370: 1189)

More Targets for IMT

There are ROS1 rearrangements as well as ALK ones. 

ROS1 more likely in children (also targetable)
High grade form of IMT

Termed epithelioid inflammatory myofibroblastic sarcoma
Appears similar to epithelioid leiomyosarcoma (and probably some old "epithelioid leiomyosarcomas" are these)
Can have unusual ALK patterns on immunolabeling

Response to targeted therapy then the tumor loses responsiveness


Case - Gastric IMT
Aggressive recurrence a few years later – now epithelioid, far less inflamed, and more atypical with nucleoli that ate Detroit.
Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT) – colon mesentery and colon

Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT)

Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT), ALK stain
Epithelioid inflammatory myofibroblastic sarcoma (malignant IMT), peculiar nuclear membrane ALK distribution.
So let’s all get ready to target these lesions!

Thank you