**Testable fibrous and fibrohistiocytic proliferations of the skin: Facts and buzzwords**

by Mohammed Shanshal, MD

| Angiofibromas | Small, red to skin-colored papules, variants include:  
| | ■ **Fibrous papule**: solitary domed papule; nose/face of adults; mimics BCC  
| | ■ **Pearly penile papules**: multilayered and circumferential manner on the corona of glans penis in up to 30% of young adults.  
| | ■ **Multiple Facial angiofibromas**: a/w various syndromes → TS, MEN 1, Birt–Hogg–Dubé syndrome, and NF2  
| | ■ **Histology**: collagen oriented **concentrically around follicles** or oriented more perpendicular to the epidermis with **few dilated blood vessels**  
| | **Dermatofibroma**  
| | **(DF, benign fibrous histiocytoma)**  
| | ■ Firm dermal papules w/ **overlying pigmentation** and “**dimple**” sign (moves downward when pinched)  
| | ■ **F > M**: most commonly on **lower extremities**  
| | ■ Eruptive dermatofibromas → SLE, atopic dermatitis, HIV infection.  
| | ■ **Factor 13a positive**, **Stromelysin-3 positive**, CD34 = positive at the periphery while the center is usually negative (vs DFSP = homogeneously positive)  
| | ■ Dermal nodular proliferation of spindled fibroblasts with **collagen trapping** at the periphery. Can have multinucleated giant cells or Touton giant cells.  
| | ■ Testable DF variants:  
| | o **Cellular DF**: most common type to be confused w/ DFSP  
| | o **Hemosiderotic**: prominent hemosiderin and small blood vessels  
| | o **Lipidized/xanthomatous**: prominent foam cells  
| | o **Aneurysmal dermatofibroma**: (sclerosing hemangioma) → dilated B.V, worrisome for melanoma or angiosarcoma  
| | o **DF with “monster” cells**: large, bizarre, and highly pleomorphic cells but still has **benign behavior!**  
| | **Dermatofibrosarcoma protuberans (DFSP)**  
| | ■ Multinodular, firm plaque on the **trunk** (50–60%), proximal extremities (20–30%)  
| | ■ **t(17;22) → COL1A1-PDGFB fusion protein**  
| | ■ **CD34** strongly positive, factor XIIIa-negative  
| | ■ **Storiform** spindle cells with characteristic multilayered or “**honeycomb**” infiltration of fat  
| | ■ Can see accelerated growth during pregnancy and multiple DFSPs in children with **adenosine deaminase-deficient SCID**.  
| | ■ Mohs micrographic surgery → the standard treatment  
| | ■ **Imatinib**: targets the PDGF receptor → FDA-approved for unresectable, recurrent, and/or metastatic DFSP  
| | ■ **Subtypes of DFSP**:  
| | ■ **Bednar tumor**:  
| | o The **pigmented** variant of DFSP, Less than 5% of DFSPs  
| | ■ **Giant cell fibroblastoma**:  
| | o Pediatric variant of DFSP according to the WHO classification  
| | o **Boys >> girls**: favors head/neck  
| | o Histologically resembles DFSP, but has distinctive multinucleated giant cells lining vascular-like spaces  
| | **Fibrosarcomatous changes of DFSP**  
| | ■ Compared to the classical DFSP, it is associated with:  
| | o ↑ recurrence rate  
| | o ↑ metastasis to the lung  
| | o ↓ CD34 staining (weak or lost)  
| | o ↑ cellularity  
| | o ↑ mitoses  
| | o ↑ atypia intersecting fascicles in herringbone pattern

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# Testable fibrous and fibrohistiocytic proliferations of the skin: Facts and buzzwords

**Dermatomyofibroma**
- Young adults; F > M; solitary, well-circumscribed oval plaque resembling plaque type DFSP or DF; most commonly on upper trunk/neck
- SMA+ (tram-track); CD34 negative (vs DFSP), factor 13a negative (vs DF), and desmin negative (vs pilair leiomyoma)
- Histology → well-defined, long fascicles of spindle cells with east–west orientation (parallel to the skin surface), corkscrew (wavy) appearance of some myofibroblast nuclei.
  The adnexal structures are spared.

**Atypical fibroxanthoma (AFX) is considered superficial variant of undifferentiated pleomorphic sarcoma**
- Rapidly growing/ ulcerated red nodule occurs in elderly (70–80 years old)
- Chronically sun-damaged skin — head and neck #1
- Non-specific immunohistochemistry → stain positive for vimentin, CD68, CD99, procollagen-1 and strongly positive for CD10
- Histology → composed of both atypical spindle-shaped cells and overtly malignant large atypical cells with abundant pale- staining vacuolated cytoplasm. AFX never extensively infiltrates SQ fat (vs UPS)
- Treatment: Mohs > WLE
  - Patients should be followed as local recurrence rate of 25–30% and a metastatic rate of 10%

**Undifferentiated pleomorphic sarcoma (UPS)**
- The most common soft tissue sarcoma of middle and late adulthood, thigh or buttock are #1 site
- The pathologic features are similar to AFX but have deep subcutaneous invasion, necrosis, and/or lymphovascular or perineural invasion, pleomorphic cellular elements and bizarre mitotic figures are characteristic
- The prognosis is related to the site; deeper and more proximally located tumors have a poorer prognosis

**Fibromatosis**
- Superficial fascial fibromatosis:
  - Dupuytren disease = palmar fibromatosis → flexion contractures especially of the fourth and fifth fingers
  - Ledderhose disease = plantar fibromatosis → associated with trisomies 8 and 14
  - Peyronie disease = penile fibromatosis → penile bending deformity associated with pain and erectile dysfunction
  - Knuckle pads (holoderma) → extensor surfaces of the IP + MCP joints, Bar-Pumphey syndrome (knuckle pads+ PPK+ hearing loss+ leukonychia)
  - Pachydermodactyly → soft tissue swelling of the lateral aspects of the PIP joints of 2nd-4th fingers
- Deep musculoaponeurotic fibromatosis:
  - Desmoid tumor → deep /aggressive fibromatosis seen in abdominal wall, may be associated with Gardner’s syndrome, have β-catenin mutations, and stain β-catenin+
  - Histology → all forms demonstrate corkscrew-shaped myofibroblasts and collagen. Ledderhose disease tends to form large whorled nodules.

**Sclerotic fibroma**
- Very collagenous variant of fibroma → firm/pearly papule or nodule
- May be a marker for Cowden’s syndrome and also reported in MEN2A
- Histology → sclerotic collagen bundles arranged as intersecting stacks (“plywood” pattern, whorl-like or Starry night pattern), very few CD34+ and factor Xllla+ fibroblasts (hypocellular)

**Infantile Myofibromatosis**
- Most common form of fibromatoses in children
- Multiple skin–colored to purple, dermal or subcutaneous nodules in the head and neck or trunk
- Can involve the skeletal muscle and/or internal organs. Visceral involvement associated w/ high mortality
- Histology → Biphasic proliferation:
  - Hypocellular areas w/ fascicles of bland corkscrew myofibroblasts
  - Hypercellular areas and ectatic staghorn (“hemangiopericytoma-like”) vessels
- Stains confirm myofibroblastic derivation [SMA+, Vimentin +, actin +, and desmin negative]
- If limited to soft tissue and bone involvement → self-resolves; good prognosis
### Infantile digital fibroma (Inclusion body fibromatosis)
- Multiple firm papules on **dorsolateral fingers and toes** (spares thumb/first toe).
- Histology: criss-cross fascicles of *spindle cells*; on high power can see the pathognomonic **pink-red inclusion bodies** (same size as an RBC).
- The inclusions stain with PTAH and Masson’s trichrome. They are actin positive, PAS negative.
- Spontaneous regression within 2–3 years is the usual, surgery may indicated (50% recurrence rate).

### Nodular fasciitis (pseudosarcomatous fasciitis)
- Benign transient tumor (“transient neoplasia”) in young to middle aged adults.
- **Rapidly growing nodules on upper extremities (#1 site overall)** and *head/neck (#1 site in children)*.
- Histology: pseudo sarcoma = Proliferation of spindle shaped and plump fibroblasts arranged in a haphazard array with focally myxoid stroma (tissue culture-like appearance).
- MYH9-USP6 is the most common fusion product, FISH for USP6 can aid in diagnosis.

### Acral fibrokeratoma (Acquired digital/periungual fibrokeratoma)
- Pink exophytic papule arising from the dorsal surface of the finger, collarette at the base of the lesion is characteristic.
- Histology: digitated fibrovascular core with vertically arranged collagen bundles lined by epidermal hyperplasia.
- Important DDx:
  - supernumerary digit (has abundant nerve fascicles)
  - periungual fibroma (more vascular)

### Skin tags (Acrochordons)
- Very common, 50% have at least one skin tag.
- Birt–Hogg–Dubé syndrome and Cowden syndrome can have numerous skin tags.
- Histology: polypoid with loose to dense collagenous stroma and thinwalled blood vessels.

### Pleomorphic fibroma
- F > M, clinically resemble skin tags, neurofibromas, or intradermal melanocytic nevi.
- Histology similar to acrochordon, but has scattered hyperchromatic, bizarre, multinucleated, or stellate cells; lacks mitoses.

### Fibrous hamartoma of infancy
- Solitary subcutaneous nodule favors the axilla, shoulder and upper arm.
- Occasionally a/w hyperhidrosis and hypertrichosis.
- Histology: composed of triphasic proliferation:
  - Plump of *spindle cells* in fascicles associated with collagenous stroma
  - Small aggregates of *immature mesenchymal cells*
  - Mature fat
  - Organoid (compartmentalized) appearance and surrounding skin has “kid” skin appearance (delicate collagen bundles that stain deeply red with small lipocytes and adnexal structures).

### Giant cell tumor of tendon sheath (Tenosynovial giant cell tumor)
- Most common tumor of the hand, F > M.
- Subcutaneous nodule; most common on fingers.
- Histology: nodular proliferation of round polygonal cells and numerous *osteoclast-like giant cells* that have eosinophilic cytoplasm and from a few to 50 nuclei.

### Multinucleate cell angiohistiocytoma
- Grouped red to violaceous papules on dorsal hands or legs, resembling Kaposi sarcoma, granuloma annulare, or sarcoidosis clinically.
- Histology: resemble richly vascularized dermatofibroma with proliferation of dilated blood vessels, stellate and angulated giant cells.
- Stains like DF (factor 13a+ and S100 negative).
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Connective tissue nevus (collagenoma and elastoma)

- Syndromes a/w connective tissue nevi:
  - Shagreen patch → tuberous sclerosis = pebbly plaque with a "pigskin" appearance on the lower back
  - Pedunculated collagenomas → MEN-1
  - Dermatofibrosis lenticularis disseminata → Buschke–Ollendorf syndrome
  - Cerebriform plantar connective tissue nevi → Proteus syndrome
- Histology → Collagenoma: haphazard, thickened collagen bundles, Elastoma → elastic fibers; histologic changes may be very subtle → need VVG stain

Fibrosarcoma

- Slowly growing, large and deep subcutaneous nodules on the lower extremities (#1 site, followed by upper extremities)
- Classification of fibrosarcomas:
  - Adult-type (classic, sclerosing, myxoid, fibromyxoid fibrosarcoma)
  - Congenital or infantile fibrosarcoma
- Histology → densely hypercellular proliferation of atypical spindle-shaped in herringbone or fir tree pattern, variable mitotic rate and the nuclei may be large and hyperchromatic

Epithelioid sarcoma

- Two clinicopathologic subtypes:
  - The classic ("distal") form occurs on the extremities and has a pseudo-granulomatous, biphasic (transition between epithelioid and spindle cells) growth pattern.
  - The proximal-type ("large-cell") usually arises on the trunk or proximal extremities and is composed of nests and sheets of large epithelioid cells
- CD68 −, co-expression of keratins and vimentin with loss of INI1 expression

List of abbreviations:

- a/w = associated with
- TS = tuberous sclerosis
- MEN = multiple endocrine neoplasia
- NF = neurofibromatosis
- B.V = blood vessels
- T = translocation
- COL1A1-PDGFB = collagen type I alpha 1 gene with the platelet-derived growth factor beta chain
- SCID = Severe combined immunodeficiency
- WLE = wide local excision
- PTAH = Phosphotungstic acid haematoxylin
- VVG = Verhoeff-Van Gieson

References: