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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. ■ **Mutiple 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**
Deramatofibroma (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: ○ **Cellular DF**→ most common type to be confused w/ DFSP ○ **Hemosiderotic**→prominent hemosiderin and small blood vessels ○ **Lipidized/xanthomatous**→ prominent foam cells ○ **Aneurysmal dermatofibroma** (sclerosing hemangioma)→dilated B.V, worrisome for **melanoma or angiosarcoma** ○ **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** ○ The **pigmented** variant of DFSP, Less than 5% of DFSPs ■ **Giant cell fibroblastoma** ○ Pediatric variant of DFSP according to the WHO classification ○ Boys ≫ girls; favors head/ neck ○ 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: ○ ↑ recurrence rate ○ ↑ metastasis to the lung ○ ↓ CD34 staining (weak or lost) ○ ↑ cellularity ○ ↑ mitoses ○ ↑ atypia intersecting fascicles in herringbone pattern

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Dermatomyofibroma	■ Young adults; F > M; solitary, well-circumscribed oval plaque r**esembling 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 pilar 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, Bart–Pumphrey 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 XIIIa+ fibroblasts **(hypocellular)**
Infantile Myofibromatosis	■ **Most common form of fibromatosis 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**

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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 disseminate→ 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 **pseudogranulomatous, 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

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