Update in cutaneous fibrohistiocytic tumors

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“fibrohistiocytic” tumors

- Fibrohistiocytic tumors are among the most frequent soft tissue tumors encountered in the skin.
- “Fibrohistiocytic” is an entirely descriptive term devised to designate a group of heterogeneous tumors resembling both normal fibroblasts and histiocytes.
- Unlike most similar designations (adipocytic, vascular,...), it does not cover a definitive line of differentiation.
- Most tumors in this category are of ‘uncertain histogenesis’.
- Based on their histological features, cutaneous fibrohistiocytic tumors fall into benign, intermediate and malignant subcategories.
Benign fibrohistiocytic tumors

• **Benign fibrous histiocytoma & variants**
  - cellular fibrous histiocytoma
  - aneurysmal fibrous histiocytoma
  - epithelioid fibrous histiocytoma
  - atypical fibrous histiocytoma

• **Cellular neurothekeoma**
Benign fibrous histiocytoma (BFH)

• Most commonly encountered as a solitary polypoid, flat or depressed lesion in the extremities of young to middle-aged adults, more frequently females

• Over the course of years it has been debated whether BFH is of neoplastic or inflammatory origin

• Recently, recurrent fusions of genes encoding membrane-associated proteins (podoplanin, CD63 and LAMTOR1) with genes encoding certain protein kinase C isoforms have been reported in a proportion of cases, setting a strong argument for the true neoplastic origin of BFH*

Benign fibrous histiocytoma (BFH)

• Most BFH are located superficially (hence the synonymous term ‘dermatofibroma’), and centred in the mid dermis
• BFH are composed of a polymorphous population of oval to spindled cells with fibroblastic and histiocytic features, arranged in short, storiform fascicles, intermediate fascicles or sheets, characteristically interdigitating between dermal collagen fibres (so-called ‘collagen trapping’), most apparent at the tumor periphery
• Frequently, the tumor contains hemosiderin pigment and inflammatory cells in varying quantities
• Many BFH induce epidermal hyperplasia and increased melanin production
Benign fibrous histiocytoma

• The list of histological appearances is exhaustive and includes variants such as:
  cellular, aneurysmal, epithelioid, atypical, hemangiopericytoma-like, lipidized, myofibroblastic, sclerotic, palisaded, clear cell, granular cell, balloon cell, myxoid, ossified, giant, metastasizing and other.....
Cellular fibrous histiocytoma

• Cellular fibrous histiocytoma differs from classical benign fibrous histiocytoma by several key histological features:
  - more cellular with a more uniform population of spindled cells with a predominantly fascicular growth pattern
  - larger and more deeply located
  - frequently shows some infiltration into the subcutis, typically in a limited lace-like pattern

• Cellular fibrous histiocytoma maintains low power features of conventional benign fibrous histiocytoma, including relative circumscription and peripheral collagen trapping

• Cellular fibrous histiocytoma may show immunoreactivity for SMA and is often negative for FXIIIa. Cellular fibrous histiocytoma shows relatively frequent (32%) desmin positivity and some positivity for CD34 in a minority (6%)*

• Recognition of this variant is important, as it has greater propensity (up to 25%) for local recurrence

*Volpicelli ER, Fletcher CD. J Cutan Pathol 2012;39:747-752
Cellular fibrous histiocytoma: differential diagnosis

• Dermatofibrosarcoma protuberans (DFSP)

• Nodular fasciitis

• Cutaneous (pilar) leiomyoma

• Cellular neurothekeoma (spindle cell variant)
Aneurysmal fibrous histiocytoma

• A relatively small proportion (1-2%) of benign fibrous histiocytoma develops central cystic hemorrhage

• Clinically, they are characterized by rapid growth and blue/black discolouration, being frequently mistaken for a haemangioma or a melanocytic lesion

• On histology, they contain prominent blood-filled spaces devoid of an endothelial lining, accompanied by abundant siderophages, copious hemosiderin deposition, giant cells and lipidized cells

• Aneurysmal fibrous histiocytoma has a higher local recurrence rate (up to 20%)

• Aneurysmal fibrous histiocytoma ≠ angiomatoid fibrous histiocytoma!
**Epithelioid fibrous histiocytoma**

- Epithelioid fibrous histiocytoma typically grows as a **polypoid nodule with an epidermal collarette**

- It is composed of **polygonal to rounded epithelioid cells** with vesicular nuclei, small nucleoli and abundant eosinophilic cytoplasm; **binucleate or multinucleate cells** are common

- A **dilated capillary vasculature** is often present, especially at the tumor periphery

- **ALK** rearrangement by FISH and ALK immunohistochemical expression have been demonstrated in close to 90% of cases

  Doyle LA, Marino-Enriquez A, Fletcher CD, Hornick JL. Mod Pathol 2015;28:904-912
  Felty CC, Linos K. Am J Dermatopathol 2018
  Dickson BC, Swanson D, Charames GS, et al. Mod Pathol 2018;31:753-762
Epithelioid fibrous histiocytoma: differential diagnosis

• Melanocytic lesion (Spitz tumor)

• Epithelioid sarcoma

• Syncytial myoepithelioma*/**

• Epithelioid perineurioma***/

* Doyle LA, Marino-Enriquez A, Fletcher CD, Hornick JL. Mod Pathol 2015;28:904-912


“Chondroblastoma-like” epithelioid fibrous histiocytoma: A previously undescribed and potentially confusing variant

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Background: Epithelioid benign fibrous histiocytoma has been considered a variant of fibrous histiocytoma, but is now considered a distinct entity, typically showing ALK expression. Most show typical morphological features, including an epidermal collarette and large, bland, epithelioid cells. We have recently encountered 2 examples showing an unusual pattern of pericellular calcification, a previously unreported finding.

Methods: Available slides were reviewed and clinical follow-up was obtained.

Results: These lesions occurred on the chins of a 16-year-old and 19-year-old female and showed prominent pericellular calcification in addition to otherwise-typical features of epithelioid fibrous histiocytoma. By immunohistochemistry, both lesions were intensely positive for ALK protein. Clinical follow-up (available for 1 case) showed the patient to be disease-free 5 months after excision.

Conclusions: To the best of our knowledge, epithelioid fibrous histiocytomas showing “chondroblastoma-like” calcification have not been previously reported. The chief significance of this finding seems to be in its potential for confusion with other calcifying tumors of the skin and subcutis. Awareness that epithelioid fibrous histiocytomas may show this unusual morphological finding, careful morphological evaluation and ancillary immunohistochemical studies, including ALK protein, should allow for their confident diagnosis in essentially all instances.

Keywords
ALK, chondroblastoma, epithelioid fibrous histiocytoma, immunohistochemistry, skin tumors
A. Epithelioid fibrous histiocytoma, presenting as a small nodule with an epidermal collarette on the chin of a 16-year-old female (H&E, x40). B. At medium power magnification, areas of typical epithelioid fibrous histiocytoma, characterized by bland, plump cells with abundant eosinophilic cytoplasm, are seen as are foci showing an unusual pattern of pericellular calcification (H&E, x100). C. Higher power magnification, showing the "chondroblastoma-like" pattern of pericellular calcification, and occasional reactive osteoclast-like giant cells (H&E, x200). D. ALK immunohistochemistry was diffusely positive, confirming the diagnosis of epithelioid fibrous histiocytoma (H&E, x200)
Atypical fibrous histiocytoma

• A small proportion of fibrous histiocytomas show **marked nuclear atypia and pleomorphism**, and have also been termed ‘dermatofibroma with monster cells’

• **Mitotic activity** can be quite high, up to 15 mitoses/HPF, including atypical forms

• Histologically, **atypia** is not spread throughout the lesion but instead **arises within a well-defined background of a classic benign fibrous histiocytoma**

• Up to a third of cases involve subcutaneous tissue as well as the dermis

• Differential diagnosis: atypical fibroxanthoma

• Follow-up in one large series showed local recurrence in 14%*

Metastasizing fibrous histiocytoma

- Metastasis is a very rarely documented event which can occur in benign-appearing fibrous histiocytomas
- Doyle and Fletcher reported on 16 patients: none of the cases represented classic benign fibrous histiocytoma; 9 were cellular, 2 aneurysmal, 2 mixed atypical and cellular, 2 atypical and 1 epithelioid fibrous histiocytoma
- Mentzel et al reported 7 patients, one of which had features of classic benign fibrous histiocytoma
- Most of the cases in both series exhibited a higher mitotic activity than the one typically encountered in classic benign fibrous histiocytoma, and some cases had foci of necrosis
- Based on these 2 series, metastatic fibrous histiocytoma follows a clinically aggressive course, with nearly half of the patients dying from disease
- Metastasizing examples demonstrate more genomic aberrations on comparative genomic hybridization than non-metastasizing cellular or atypical fibrous histiocytoma
- However, no consistent genetic abnormality or histologic feature predictive of metastasis has been identified
- It should be emphasized that metastasis is such rare event in this group of tumors, that they still considered fundamentally benign

Cellular neurothekeoma

• Cellular neurothekeoma is a tumor most frequently encountered on the head (especially the face), shoulder and arm of young adults, with female predominance.

• Cellular neurothekeoma typically grows slowly and rarely recur (in less than 10% of cases).

• Atypical cases have been described but without adverse outcome.

Stratton J, Billings SD. Mod Pathol 2014;27:701-710
Cellular neurothekeoma

- On histology, cellular neurothekeoma is classically composed of a nested, multinodular proliferation of epithelioid to spindled cells with round to oval vesicular nuclei and relatively abundant eosinophilic cytoplasm embedded in a variably collagenous to slightly myxoid stroma.
- The tumor nests sometimes have osteoclasts and haemorrhage.
- Reported mean mitotic activity is 2/mm².
- **Focal atypia** is common and rare cases show prominent nuclear atypia.
- Cellular neurothekeoma exhibits positivity for NKI/C3, CD10 and MITF in 60-80%. Variable immunoreactivity for SMA and calponin has also been reported.
- Cellular neurothekeoma is **consistently negative for S100, SOX10 and GFAP**.
Cellular neurothekeoma: differential diagnosis

- Dermal nerve sheath myxoma (myxoid neurothekeoma)
- Melanocytic neoplasms
- Cellular fibrous histiocytoma
- Plexiform fibrohistiocytic tumor
- Epithelioid sarcoma
Fibrohistiocytic tumors of intermediate malignancy

- Dermatofibrosarcoma protuberans
- Angiomatoid fibrous histiocytoma
- Plexiform fibrohistiocytic tumor
Dermatofibrosarcoma protuberans (DFSP)

• DFSP is typically a multinodular cutaneous mass presenting in early or middle adult life
• Approximately 50% of the tumors arise in the trunk, while the rest are equally distributed between head and neck, the upper and the lower extremity
• Most recurrences occur within 3 years, but long term follow-up is nevertheless suggested, as late recurrence can happen
• The likelihood of metastasis is 2-5%. Distant metastases are usually found following recurrences and are essentially restricted to cases with fibrosarcomatous transformation
• About 25% of the metastases are found in the lymph nodes, while the rest are hematogenous, mostly to the lungs
• Wide local excision is imperative in the treatment of DFSP
Dermatofibrosarcoma protuberans (DFSP)

• The prototypical feature of DFSP is its storiform pattern and infiltrative growth with monomorphous cytomorphology
• DFSP typically **diffusely involves the dermis with extensive infiltration into the underlying subcutis**
• Less commonly, DFSP is limited to the subcutis, such cases show a predilection for the scalp area
• The overlying epidermis does not usually exhibit epidermal hyperplasia or a ‘grenz’ zone typical of benign fibrous histiocytoma
• Cutaneous adnexa are spared, **and involvement of the subcutaneous fat produces a characteristic ‘honeycomb’ pattern** of tumor cells encircling individual adipocytes
• The tumor cell population is strikingly **monotonous** (when compared to other fibrohistiocytic neoplasms), composed of slender, uniform, spindled cells arranged in a **storiform** to sometimes fascicular pattern
• The mitotic rate is usually low (<5 mitoses/10HPFs)
Dermatofibrosarcoma protuberans (DFSP)

• The immunophenotype of DFSP is characterized by positivity for **CD34**, negative for S100, SOX10, desmin, keratins and EMA

• Areas with fibrosarcomatous transformation tend to be less consistently positive for CD34 than conventional areas*

• **Apo D protein** is expressed highly and relatively specifically in DFSP, in contrast to benign fibrous histiocytoma**

• The defining genetic alteration of DFSP is the **fusion** between various exons of collagen type 1 α1 (**COL1A1**) and exon 2 of the platelet-derived growth factor β-chain (**PDGFB**) gene***


Alternative PDGFD rearrangements in dermatofibrosarcomas protuberans without PDGFB fusions

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Abstract
Dermatofibrosarcoma protuberans is underlined by recurrent collagen type I alpha 1 chain-platelet-derived growth factor B chain (COL1A1-PDGFB) fusions but only 4% of typical dermatofibrosarcoma protuberans remain negative for this translocation in routine molecular screening. We investigated a series of 21 cases not associated with the pathognomonic COL1A1-PDGFB fusion on routine fluorescence in situ hybridization (FISH) testing. All cases displayed morphological and clinical features consistent with the diagnosis of dermatofibrosarcoma protuberans. RNA-sequencing analysis was successful in 20 cases. The classical COL1A1-PDGFB fusion was present in 40% of cases (n = 8/20), and subsequently confirmed with a COL1A1 break-apart FISH probe in all but one case (n = 7/8). 55% of cases (n = 11/20) displayed novel PDGFD rearrangements. PDGFD being fused either to the 5’ part of COL6A3 (2q37.3; n = 9/11) or Emilin2 (18p11; n = 2/11). All rearrangements led to in-frame fusion transcripts and were confirmed at genomic level by FISH and/or array-comparative genomic hybridization. PDGFD-rearranged dermatofibrosarcoma protuberans presented clinical outcomes similar to typical dermatofibrosarcoma protuberans. Notably, the two Emilin2-PDGFD cases displayed fibroblastomatous transformation and homoyzygous deletions of CDKN2A at genomic level. We report the first recurrent molecular variant of dermatofibrosarcoma protuberans involving PDGFD, which functionally mimic bona fide COL1A1-PDGFB fusions, leading presumably to a similar autocrine loop-stimulating PDGFβR. This study also emphasizes that COL1A1-PDGFB fusions can be cytogenetically cryptic on FISH testing in a subset of cases, thereby representing a diagnostic pitfall that pathologists should be aware of.
Dermatofibrosarcoma protuberans: fibrosarcomatous transformation

• Fibrosarcomatous transformation is characterized by an abrupt transition from conventional DFSP to a more cellular tumor with herringbone pattern of atypical hyperchromatic spindle cells

• The fibrosarcomatous component has an increased mitotic rate (≥5/10 HPFs) and often, though not always, shows diminished immunoreactivity for CD34

• Very infrequently, DFSP can show transition to areas resembling undifferentiated pleomorphic sarcoma (such cases usually follow an aggressive course)*

• Fibrosarcomatous transformation is associated with a metastatic rate between 10 and 23%**


Dermatofibrosarcoma protuberans: variants

- Some tumors contain myxoid areas, slightly more commonly in the extremities, with those exhibiting >50% of myxoid area being given the designation of ‘myxoid DFSP’. Myxoid DFSP tends to lose the storiform pattern and has a random arrangement of the tumor cells in abundant myxoid stroma, though areas of conventional DFSP are encountered in up to 60% of myxoid DFSP.

- Pigmented variant of DFSP (Bednar tumor)**
- Sclerotic variant of DFSP***
- Pseudocystic variant of DFSP****

*Reimann JD, Fletcher CD. Am J Surg Pathol 2007;31:1371-1377
Giant cell fibroblastoma

- **Juvenile variant of DFSP** with predilection for **infants and children** (median age 3 years) (though giant cell fibroblastoma may also present in adults)

- The most common tumor site is the back of the thigh, the inguinal region and chest wall, slightly more common in male children

- It **coexists with conventional DFSP** in approximately 15% of cases and they share the COL1A1-PDGFB gene fusion

- Compared to classical DFSP, there is an **absence of storiform growth** (except if there is a coexisting DFSP component), cellularity is typically lower and collagen content higher; presence of **distinctive giant cells** with large and hyperchromatic nuclei **often lining pseudovascular spaces embedded in a collagenous background**

- Fibrosarcomatous change has only been reported in cases with coexistent classical DFSP

Shmookler BM, Enzinger FM, Weiss SW. Cancer 1989;64:2154-2161
Dermatofibrosarcoma protuberans: differential diagnosis

- Benign fibrous histiocytoma (especially the cellular variants) (most common problem in the differential diagnosis)
- Diffuse neurofibroma
- Myxoid spindle cell lipoma (in case of highly myxoid DFSP)
- Myxofibrosarcoma (in case of highly myxoid DFSP)
- Myxoid liposarcoma (in case of highly myxoid DFSP)
Angiomatoid fibrous histiocytoma

• Distinct neoplasm of low malignant potential arising most often in the form of a **cystic nodule in the extremities**, followed by the head and neck

• More than 80% appear in **patients <20 years of age**

• The rate of **local recurrence** is approximately **10%** and 1% of cases metastasize to the lymph nodes.

• Very rare cases with distant metastases and fatal outcome have been reported

Fanburg-Smith JC, Miettinen M. Hum Pathol 1999;30:1336-1343

Angiomatoid fibrous histiocytoma

• On cross section, they characteristically have the form of **hemorrhagic cystic mass**

• At low magnification, the tumor is typically surrounded by a **fibrous pseudocapsule with a peripheral cuff of lymphoid tissue**

• The tumor is usually composed of **oval, histiocyte-like** (occasionally spindled) **cells** intermixed with **pseudovascular cystic and hemorrhagic areas**

• The histiocyte-like cells have a pale eosinophilic cytoplasm frequently containing fine **hemosiderin pigment**, and the nuclei are usually **bland**
Angiomatoid fibrous histiocytoma

- By immunohistochemistry approximately 50% of tumors are positive for some combination of CD68, EMA, desmin and CD99
- Various muscle markers (h-caldesmon, smooth muscle actin, calponin) can also be positive
- Skeletal muscle-specific transcriptional regulators (myoD1 and myogenin) are never positive
- **Over 90%** harbour rearrangement of *EWSR1* with less than 10% having *FUS* rearrangement
- *EWSR1/CREB1* is by the most common gene fusion, followed by *EWSR1/ATF1* and *FUS/ATF1*

desmin
Angiomatoid fibrous histiocytoma: differential diagnosis

- *Metastatic melanoma or carcinoma involving a lymph node*

- *Vascular tumor* (in hemorrhagic examples)

- CD99 and desmin positivity may raise the differential diagnosis of *Ewing sarcoma* and *rhabdomyosarcoma*, respectively
Plexiform fibrohistiocytic tumor

• This rare fibrohistiocytic tumor occurs mostly in children and young adults with a median age of 20 years

• Most cases arise in the extremities, especially the upper extremity

• Plexiform fibrohistiocytic tumors recur in up to 40% of cases, but rarely produce lymph node or distant metastases, and extremely rarely cause death

Plexiform fibrohistiocytic tumor

• Plexiform fibrohistiocytic tumor usually has a **biphasic pattern** composed of **infiltrating slender fascicles of spindled cells** that surround **nodules of histiocytic cells**, often admixed with osteoclasts.

• The tumor usually involves the **dermis with frequent extension into the subcutis**.

• Rare examples involve the underlying skeletal musculature.

• The histiocyte-like nodules are often positive for **CD68**, while the fascicles of spindled cells are positive for **SMA**. The tumor cells are negative for **S100**, **HMB45**, **CD34**, **desmin** and **cytokeratin AE1/AE3**.

• **No consistent molecular abnormality** has been described.
Plexiform fibrohistiocytic tumor: differential diagnosis

• Granulomatous processes

• (lipo)fibromatosis

• Cellular neurothekeoma
Fibrohistiocytic tumors with malignant features

• Pleomorphic dermal sarcoma
Atypical fibroxanthoma (AFX)/pleomorphic dermal sarcoma (PDS)

- AFX and PDS are histologically and molecularly related tumors that occur on heavily sun-damaged skin of older patients, typically involving the head and neck
- When strictly defined, AFX has an excellent prognosis with essentially no risk of metastasis
- PDS may demonstrate cutaneous and pulmonary metastasis. While in one large series, PDS had no significant risk of tumor associated mortality*, another found tumor related death in up to 20% of patients**

Atypical fibro-xanthoma (AFX)/pleomorphic dermal sarcoma (PDS)

- AFX is typically a polypoid, sometimes ulcerated cutaneous nodule composed of round to spindled, frequently highly pleomorphic, hyperchromatic and multinucleated cells with numerous typical and atypical mitoses that tend to form an expansile dermal nodule.

- Clear cell*, granular cell**, spindled cell*** and pseudoangiomatous**** variants have been described.

- PDS is the designation for tumors sharing histologic, immunohistochemical and molecular features with AFX, but including features such as deep subcutaneous invasion, necrosis, lymphovascular or perineural invasion*****

* Requena L, Sangueza OP, Sanchez Yus E, Furio V. J Cutan Pathol 1997;24:176-182
Atypical fibroxanthoma (AFX)/pleomorphic dermal sarcoma (PDS)

- Both AFX and PDS are diagnoses of immunohistochemical exclusion!
- Immunostains for **CD10** have been touted as effective positive marker for AFX/PDS, but CD10 immunoreactivity is not specific for AFX/PDS
- By definition, the tumor cells of AFX and PDS must be negative for keratin, S100/SOX10, h-caldesmon, desmin, CD34 and ERG expression
- Immunoreactivity for **SMA** (70%) and **CD31** (48%) is described, isolated cases are described showing immunoreactivity for EMA, Melan A and p63
- Both entities have shown high incidence of **FAT1**, **NOTCH1/2**, **CDKN2A**, **TP53** and **TERT** promoter activating mutations using next-generation sequencing methods, as well as a similar profile of copy number gains and losses using comparative genomic hybridization

Melan A
Atypical fibroxanthoma (AFX)/pleomorphic dermal sarcoma (PDS): differential diagnosis

• Sarcomatoid/spindle cell squamous cell carcinoma

• Spindle cell melanoma

• Angiosarcoma

• Cutaneous leiomyosarcoma
Conclusion

• Cutaneous fibrohistiocytic neoplasms are a diverse category of tumors that resemble fibroblasts and histiocytes, but in general do not show a well-defined lineage or cell of origin.

• Careful attention to the clinical and histologic features, and judicious use of ancillary tests generally allows for the accurate diagnosis and appropriate subsequent management.