Update in cutaneous soft tissue tumors of uncertain histogenesis

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Case 1

- 34 y man
- skin lesion on the back
- clinical dx: hemangioma
- excision
Dx: epithelioid fibrous histiocytoma

- **Clinical findings:**
  - 5th decade (also younger)
  - Lower extremities (60%)
  - Upper extremities, trunk, head and neck, groin

- **Pathogenesis:**
  - ALK rearrangement with ALK expression (ca 90% of the cases; Doyle et al Mod Pathol 2015)
  - Fusion partners: SQSTM1, VCL (70%)
  - Others: DCTN1, ETV6, PPFIBP1, SPECC1K, TMP3, PRKAR2A, MLPH, EML4 (Dickson et al 2018)
Dx: epithelioid fibrous histiocytoma

Macroscopy:

- Exophytic, sessil or polypoid
- Skin colored, some lesions with prominent vascularisation imitate hamangioma
- Size: 0.3 to 2.0 cm
Dx: epithelioid fibrous histiocytoma

Microscopy:
- Exophytic, collarette, confined to the superficial dermis
- Epithelioid cells with amphophilic cytoplasm
- Nuclei rounded and vesicular, prominent nucleoli
- Binucleated, trinucleated cells
- Low mitotic activity
- Teleangiectasia and myxoid changes are possible
- No collagen entrapment
- Epidermis: hyperplasia, no pigmentation
- Few secondary elements (multinucleated giant cells, hemosiderin-laden macrophages, lymphocytes, plasma cells, mast cells)
Dx: epithelioid fibrous histiocytoma

- IHC:
  - ALK (90%)  
  - EMA (65%)  
  - Factor XIIIa (focally, 70%)  
  - D2-40 (50%)  
  - SMA (focally, 25%)
Spindle cell-predominant epithelioid fibrous histiocytoma
Spindle cell-predominant epithelioid fibrous histiocytoma
Epithelioid FH – other peculiar morphological features

FIGURE 2. Cytological variations in EF H. Note cells with nuclear grooves (arrows) and numerous bi- or multinucleated cells (arrowheads) (A), cells with lobulated nuclei (arrowheads, B), and numerous mucinous cells (arrowheads, C).

FIGURE 3. EFH (case 7) with nested pattern (A, B) locally resembling a melanocytic lesion. Note plentiful cells with intranuclear protein inclusions in less cellular (C) compared with the nested area (B).

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Epithelioid FH – differential diagnoses

- **Perineurioma**: whorls, long cytoplasmic processes, EMA, CD34
- **Myoepithelioma**: different cells, expression of keratins, S100, SOX10
- **PEComa**: nested, trabecular, melanocytic markers (HMB45, Melan A), smooth muscle markers (desmin, SMA)
- **Leiomyoma**: fascicles, blunt ended nuclei, smooth muscle markers
- **Melanocytic tumors**: melanocytic markers (S100, SOX10, HMB45, Melan A)
Perineurioma
Myoepithelioma
PEComa

dermpedia
Leiomyoma
Case 2

- 39 y female
- prominent “lymph node” right groin
- excision
• **Immunohistochemistry:**
  - Desmin +
  - SMA +/–
  - ALK +
  - Negative: CD34, keratin

• **Suggested diagnosis:** inflammatory myofibroblastic tumor

• **Molecular genetic findings:**
  - FISH: ALK –, EWSR1 +
  - RT-PCR: EWSR1-CREB1
Dx: Angiomatoid fibrous histiocytoma
ALK expression, no ALK rearrangement
Cheah et al AJSP 2019, van Zwam et al AJSP 2019
Angiomatoid fibrous histiocytoma

Clinical features:

• Adolescents, young adults, also older patients
• Deep dermis/subcutis
• Extremities, trunk, head and neck
• Sometimes visceral
• Therapy: excision
• Behaves commonly benign, recurrence up to 15%, metastases up to 5%

(Thway et al Surg Pathol 2019)
Angiomatoid fibrous histiocytoma

Macroscopy:
• (multi)nodular, tan-white, hemorrhagic

Microscopy:
• Tumor nodules encapsulated
• Uniform histiocytoid or spindle cells
• Compact syncytial growth
• Small cell morphology could be confused with small blue round cell tumor/sarcoma
• Rarely: cellular atypia and increased mitotic activity (not associated with outcome)
• Blood-filled pseudovascular spaces
• Outside the capsule lymphocytic cuff (with germinal centers)

IHC: desmin, ALK, EMA (50%)

Genetics: EWSR1/FUS – CREB1/ATF1/CREM (Yoshida et al AJSP 2019)
Angiomatoid fibrous histiocytoma
Angiomatoid fibrous histiocytoma
Angiomatoid fibrous histiocytoma – pure spindle cell variant

Thway et al, Pathol Res Pract 2016
Angiomatoid fibrous histiocytoma – myxoid variant

Schaefer et al AJSP 2014
DD: Inflammatory myofibroblastic tumor
DD: Inflammatory myofibroblastic tumor
Tumors with EWSR1/FUS - CREB1/ATF1/CREM (CREB family) fusions

- Angiomatoid FH
- Clear Cell Sarcoma
- CCS-like tumor GI-tract
- Primary pulmonal sarcoma
- Intracranial primary mesenchymal tumor
- Hyalinizing clear cell carcinoma salivary gland/thymus
- Odontogenic clear cell carcinoma
- Mesothelioma in young adults
Case 3

- 48 y male
- Multiple lesions axilla with recurrence (after 1 year)
- Excision/re-excision
S100
Dx: Ossifying fibromyxoid tumor
Ossifying fibromyxoid tumor

Clinical Features:
• Adults, ca 50 y
• Lower extremity (>40%, mainly thigh), head and neck, trunk wall
• Mostly superficially located (subcutis, rarely skin)
• Grows slowly
• Therapy: excision
• Benign, recurrences, rarely metastases (malignant morphological features)
Ossifying fibromyxoid tumor

Macroscopy:
• (multi)nodular, tan-white, firm

Microscopy:
• Commonly well-defined, nodular, incomplete bone shell (lacking in 20-40%), possible satellites/infiltrative growth
• Nests, cords, sheets of uniform, round/oval cells
• Small nuclei, (light) eosinophilic cytoplasm
• Low mitotic activity
• Fibromyxoid matrix
• Atypical features: increased cellularity, nuclear atypia, increased mitotic figures (>2/50), randomly distributed bone

IHC:
• S100 (>90%), desmin (50%), exceptionally keratin
Ossifying fibromyxoid tumor

Genetics:

- Fusion genes mostly with PHF1 (ca 85% cases), irrespective of dignity
- EP400-PHF1
- PHF1-TFE3
- EPC1-PHF1
- MEAF6-PHF1
- CREBBP-BCORL1

- (Graham et al AJSP 2013, Antonescu et al GCC 2014, Mitelman et al 2019, Mitelman database)
Classical OFMT
OFMT
Ossifying fibromyxoid tumor – differential diagnoses

- Sclerosing epitheloid fibrosarcoma
- Low-grade fibromyxoid sarcoma
- Myoepithelial tumors
- Extraskeletal myxoid chondrosarcoma
Sclerosing epitheloid fibrosarcoma
Low-grade fibromyxoid sarcoma
Extraskeletal myxoid chondrosarcoma
Myoepithelial carcinoma
Case 4

- 61 y female
- Lesion dorsal aspect left foot, 2cm
- Excision, re-excision
Dx: EWSR1-SMAD3 rearranged fibroblastic tumor

- Recently characterized by Kao et al and Michal et al, AJSP 2018
- Rare
- Wide age range (1 – 68 y)
- Extremities, mainly acral
- Characteristic morphology: nodular, infiltrative growth, hypercellular fibroblastic areas merging with hyalinized areas
- Complete excision, recurrence
EWSR1-SMAD3 rearranged fibroblastic tumor
EWSR1-SMAD3 rearranged fibroblastic tumor

Diffuse strong nuclear ERG expression (40x)
Michal et al 2018 AJSP
EWSR1-SMAD3 rearranged fibroblastic tumor - differential diagnoses

- Myofibroma
- Monophasic synovial sarcoma
- Myoepithelial tumors
Myofibroma
Myofibroma
Synoviosarcoma
Myoepithelioma (syncytial), EWSR1 +
Nice – Nike – greek goddess of victory
Nice- Nike - greek goddess of victory

• Phoenicians conquered Ligurians and founded the city more than 2300 years ago