Dr. Thomas Mentzel, Friedrichshafen
MVZ Dermatopathologie Friedrichshafen / Bodensee PartG
Case 1:
M, 55 years, right thigh
hyperplasia of the epidermis, numerous vessels
admixture of round / epithelioid and plump spindled cells
Diagnosis Case 1

„epithelioid“ benign fibrous histiocytoma
middle-aged adults, 11 F, 8 M, lower limbs > everywhere
asymptomatic solitary, polypoid, red, cutaneous nodule
epidermal collarette, round cells with abundant eosinophilic cytoplasm
vesicular nuclei, small nucleolus, binucleated cells
rarely transition to more spindle-shaped cells
DD: Spitz naevus, reticulohistiocytoma

Sing Gomez C et al. Epithelioid fibrous histiocytoma of skin: clinicopathological
analysis of 20 cases of a poorly known entity. Histopathology 1994; 24: 123-129
12 M, 8 F, 7-80 years, local recurrence in 1 case
polygonal, rounded epithelioid tumour cells (> 50% of cells)
hyalinized collagen, many blood vessels
subcutaneous involvement in 2 cases
forms a spectrum with ordinary dermatofibroma

Doyle LA et al. ALK rearrangement and overexpression in epithelioid fibrous Histiocytoma. Mod Pathol 2015; 28: 904-912
- 33 epithelioid fibrous histiocytoma (29/33 ALK +, 13 ALK rearrangement)
- 41 fibrous histiocytoma (ALK -), 10 myoepithelioma (ALK -), 5 AFX (ALK -)

Dickson BC et al. Epithelioid fibrous histiocytoma: molecular characterization of ALK fusion partners in 23 cases. Mod Pathol 2018; 31: 753-762
- SQSTM1::ALK (52%), VCL::ALK (30%), DCTN1::ALK (1), PPFIBP1::ALK (1), SPECC1L::ALK (1), ETV6::ALK (1, nuclear ALK expression)

Kazakov DV et al. ALK gene fusions in epithelioid fibrous histiocytoma: a study of 14 cases, with new histopathological findings. Am J Dermatopathol 2018; 40: 805
- SQSTM1::ALK (3), VCL::ALK (3), TMP3::ALK (2), PRKAR2A::ALK (1), MLPH::ALK (1), EML4::ALK (1), no correlation to morphology!
Mansour B et al. Epithelioid fibrous histiocytoma: three diagnostically challenging cases with novel ALK gene fusions, unusual storiform growth pattern, and a prominent spindled morphology. Virchows Archiv 2022; 481: 751-757
  prominent spindle cell proliferation, storiform growth pattern
  ALK +, AP3D1::ALK, COL1A1::ALK, LRRFIP2::ALK

Kazlouskaya V et al. Spindle cell variant of epithelioid cell histiocytoma (spindle cell histiocytoma) with ALK fusions: case series and review of the literature J Cutan Pathol 2021; 48: 837-841
  3 F, 25-55 years
  exclusively spindle cell morphology, strong ALK expression
  ALK rearrangement (3), DCTN1::ALK (2)

M, 21 years, left shoulder
Conclusions Case 1

epithelioid fibrous histiocytoma represents a distinct entity

morphological differences to classic dermatofibroma
  exophytic, epithelial collarette, many vessels, perivascular growth
  no entrapment, no multinucleated giant cells

strong ALK expression, often coexpression of EMA

variable morphology

different fusion partners of ALK gene

unknown line of differentiation („ALKoma“)
Case 2: M, 47 years, left forearm, subcutis, 2.4 cm
Diagnosis Case 2

atypical angiomatoid fibrous histiocytoma
angiomatoid fibrous Histiocytoma

- Enzinger F. Angiomatoid malignant fibrous histiocytoma: a distinct fibrohistiocytic tumor of children and young adults simulating a vascular neoplasm Cancer 1979; 44: 2147
- rare neoplasm, unknown line of differentiation locally aggressive, rarely metastasizing
- children, young > elderly adults
  subcutis, extremities > trunk > head/neck
- often in the surrounding of lymph nodes
  often systemic symptoms (fever, anemia)
- well-circumscribed, indurated, nodular
  plump spindled / myoid / histiocytoid tumour cells
- syncytial growth
  pseudoangiomatous spaces
- capsule-like structures, haemosiderin deposits
  peripheral lymphocytes, plasma cells, germinal centres
- desmin + (60%), EMA + (50-60%), CD 99 +,
  CD 68 +, S-100 -, CD 34 -, ASMA -
- t(2;22)(q32.3;q12) with EWSR1::CREB1
  t(12;22)(q13;q12) with EWSR1::ATF1
  t(12;16)(q13;p11) with FUS::ATF1
Problems in the diagnosis of angiomatoid fibrous Histiocytoma

- given name (aneurysmal dermatofibroma)
- lymphnode metastasis?
- unusual anatomic locations
- unusual morphological variants
angiomatoid fibrous Histiocytoma

unusual anatomic locations:
- brain (myxoid mesenchymal intraventricular brain tumour)
  - lung, mediastinum
  - bone
  - retroperitoneum
  - intraabdominal
  - vulva
- ovary ...
angiomatoid fibrous Histiocytoma

ununusual morphological variants
- composed of small- and blue cells (CD99 + !!!)
- solid angiomatoid fibrous histiocytoma
- cystic angiomatoid fibrous histiocytoma
- pleomorphic angiomatoid fibrous histiocytoma
- spindle cell angiomatoid fibrous histiocytoma
- myxoid angiomatoid fibrous histiocytoma
- clear cell angiomatoid fibrous histiocytoma
- angiomatoid fibrous histiocytoma with rhabdomyoblast-like cells...
F, 4 years, back of the head
Myxoid variant of so-called angiomatoid "MFH": clinicopathologic characterization in a series of 21 cases
Schaefer IM, Fletcher CDM
Am J Surg Pathol 2014; 38: 816
F, 10 years, trunk, subcutis
solid variant of angiomatoid fibrous histiocytoma
F, 12 years, right forearm
solid variant of atypical angiomatoid fibrous histiocytoma
Cheah AL et al. ALK expression in angiomatoid fibrous histiocytoma: a potential diagnostic pitfall
  11 cases of angiomatoid fibrous histiocytoma
    ALK +, no ALK rearrangement
  15 cases of inflammatory myofibroblastic tumour
    67% ALK +, 9/10 ALK rearrangement
  11 cases of follicular dendritic cell sarcoma
    ALK -

van Zwam P et al. ALK expression in angiomatoid fibrous histiocytoma: confirmation of the findings of Cheah
Case 3: F, years, shoulder
Sperficial CD34+
Immunohistochemistry?
Sperficial CD34+ CD34 HPCA1 (CD34)
Sperficial CD34+ INI1

INI1
WT1 (6F-H2, N-terminus)
Diagnosis Case 3

superficial CD34-positive fibroblastic Tumor
Superficial CD34-positive fibroblastic Tumour
(Carter JM et al. Mod Pathol 2014; 27: 294)

by courtesy of Prof. Dr. A. Folpe, Rochester, USA
adult patients, 10 M, 8 F
20-76 years, 1.5 – 10 cm
extremities, dermis/subcutis
ill-defined, infiltrative
spindled tumour cells
**striking cellular pleomorphism**
no / few mitoses
tumour necrosis in 1 case
CD34 +, CK focal +, S-100 –
Desmin -, ASMA -, ERG -
locally aggressive
MTS very rare (1/13 patients
developed lymph node MTS)
Recurrent *PRDM10* gene fusion in undifferentiated pleomorphic sarcoma
- 84 undifferentiated pleomorphic soft tissue sarcomas
- 3 cases showed *PRDM10* fusions (*MED12, CITED2*)

Undifferentiated pleomorphic sarcomas with *PRDM10* fusions have a distinct gene expression profile
- upregulation of *CADM3* gene (IM CADM3 +)
- *PRDM10*-fusions represent critical driver mutations

*PRDM10*-rearranged soft tissue tumor: a clinicopathological study of 9 cases
- 9 cases, 5 M, 4 F, 20-61 years, 1/9 local recurrence
- CD34 +, PRDM10 + (nuclear), 5/6 CK + (focal)
Superficial CD34-positive fibroblastic tumor: A clinicopathologic, immunohistochemical, and molecular study of 59 cases

33 M, 26 F, 14-85 years, 1-9 cm in diameter
lower limb (73%), upper limb (8%), back (7%), trunk (3%)
local recurrence (2), lymph node metastasis (1)
spindled and pleomorphic cells
CD34 +, CADM3 + (95%), WT1 + (75%)
3/8 cases showed \textit{PRDM10} rearrangement
Conclusions: indolent rarely metastasizing tumour
SCD34FT and PRDM10-STT are related
**superficial CD34-positive fibroblastic tumor**

**Immunohistochemistry**

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Percentage Positive</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD 34</td>
<td>100% positive</td>
</tr>
<tr>
<td>AE1/3</td>
<td>70% positive (focal)</td>
</tr>
<tr>
<td>Desmin</td>
<td>35% positive (focal)</td>
</tr>
<tr>
<td>CADM3</td>
<td>95% positive (nuclear)</td>
</tr>
<tr>
<td>WT1</td>
<td>75% positive (nuclear)</td>
</tr>
</tbody>
</table>
Case 4: M, 32 years, hand
Hybridschwannoma/perineurioma
Hybridschwannoma/perineurioma

capsule

second cellular population
Diagnosis Case 4

granular cell hybrid peripheral nerve sheath Tumour (schwannoma / perineurioma)
Classification of benign peripheral nerve sheath Tumours

**Neurofibroma**: schwann cells, perineurial cell, fibroblasts (plexiform, diffuse, epithelioid, pigmented, dendritic, atypical)

**Schwannoma**: schwann cells
(cellular, ancient, plexiform, epithelioid, reticular, neuroblastoma-like)

**Perineurioma**: perineurial cells
(intra- and extraneural spindle cell, sclerosing, reticular)

**Neuroma**
(traumatic, mucosal, Morton`s, Pacinian, solitary circumscribed)
Nerve sheath tumours with hybrid features of neurofibroma and schwannoma (Feany MB et al. Histopathology 1998; 32: 405)

9 cases, 1 F, 8 M, 12 - 66 years
trunk (6), upper (2), lower (1) extremity
dermis (2), subcutis (2), subfascial (5)
plexiform growth (5), neurofibromatosis (1)
well-circumscribed, multinodular
areas of typical neurofibroma
(neurofilment positive axons)
schwannomatous nodules
(degenerative atypia (2), hyalinised vessels)
F, 61 years, back
A benign neoplasm with histopathological features of both schwannoma and retiform perineurioma: a report of six cases of a distinctive soft tissue tumor with a predilection for the fingers (Michal M et al. Virchows Arch 2004; 445: 347)

6 cases, 5 F, 1 M, 20 - 52 years
finger (4), thumb (1), thenar (1)
unencapsulated, lobular lesions
myxoid and pseudocystic changes
reticular perineurioma-like areas
- loops of elongated spindled cells, myxoid stroma, EMA +
schwannomatous areas
- compact Antoni A areas, S-100 +
by courtesy of Prof. M. Michal, Pilsen
Hybrid Schwannoma / Perineurioma
Clinicopathologic analysis of 42 distinctive benign nerve sheath tumors
(Hornick JL et al. AJSP 2009; 33: 1554)

22 F, 20 M, 2 - 85 years, 1 local recurrence
limbs (31), head / neck (6), trunk (4), colon (1)
tumour size 0.7 – 17.5 cm (mean: 3.0 cm)
skin and subcutaneous tissues (70%)
rarely deep soft tissues or visceral sites
wide age range and anatomic distribution
most often extremities
no association with neurofibromatosis
rarely recurs locally
F, 36 years, thigh, 5.6 cm
Hybrid schwannoma-perineurioma frequently harbors VGLL3 rearrangement
Dickson BC et al. Mod Pathol 2021; 34: 1116-1124

- CHD7::VGLL3 (56%)
- CHD9::VGLL3 (11%)
- MAML1::VGLL3 (11%)

Clinicopathologic and molecular study of hybrid nerve sheath tumors reveals their common association with fusions involving VGLL3

- CHD7::VGLL3 (57%)
- CHD9::VGLL3 (29%)
- CHD9::ZFHX3 (14%)

Distinct entity with molecular pathogenesis unrelated to schwannoma or perineurioma
Case 5: F, 68 years, left shoulder, known NF1
Diagnosis Case 5

low-grade malignant peripheral nerve sheath Tumour (MPNST)
Malignant Peripheral Nerve Sheath Tumour

Arise in patients with NF1, sporadically, or following radiotherapy

Diagnostic criteria:
1. origin from a nerve or a neurofibroma
2. spindle cell sarcoma in a patient with NF1
3. evidence of schwann cell differentiation by IM or EM
   (S-100 protein and SOX10 only 30-50% sensitivity)

Diagnosis in sporadic cases relies on distinctive histology and exclusion of histologic mimics
Polycomb Repressive Complexes (PRC1,2)

PRC2 recruits to chromatin and trimethylates histone H3 at lysine 27
physiologic regulation of cell fate and stem cell differentiation
deregulation – cancer development

PRC2 alterations (SUZ12 or EED mutations) in 85-90% of MPNST
homozygous mutations result in loss of H3K27me3 in > 65% of MPNST

ICH for H3K27me3 is highly specific diagnostic marker
Schaefer IM et al. Loss of H3K27 trimethylation distinguishes malignant peripheral nerve sheath tumors from histologic mimics Mod Pathol 2016; 29: 4-13
  - NF1 mutations and CDKN2A inactivation in MPNST
  - PRC2 inactivation through EED1 or SUZ12 loss
  - PRC2 inactivation leads to loss of H3K27me3
  - loss of H3K27me3 in MPNST (low-grade 29% - high-grade 83%)


Cleven AH et al. Loss of H3K27 trimethylation is a diagnostic marker for malignant peripheral nerve sheath tumors and an indicator for an inferior survival Mod Pathol 2016; 29: 582-590
Immunohistochemistry for H3K27me3 in MPNST

- low-grade MPNST: loss in 30%
- intermediate grade MPNST: loss in 60%
- high-grade MPNST: loss in 80%
- radiation induced MPNST: loss in 100%
- epithelioid MPNST: loss in 0%
F, 18 years, chest wall, known neurofibromatosis type 1
diffuse neurofibroma
diffuse Neurofibroma

H3K27me3

Wagner-Meißner corpuscles

S-100 Protein
F, 31 years, lateral neck
F, 34 years, 3 cm, mons pubis
atypical neurofibroma *versus* low-grade MPNST?
Diagnosis: 
atypical neurofibromatous Tumour
Histopathologic evaluation of atypical neurofibromatous tumors and their transformation into malignant peripheral nerve sheath tumors in patients with neurofibromatosis 1 - a consensus overview
Miettinen M et al. Hum Pathol 2017; 67: 1-10

nuclear atypia, loss of neurofibroma architecture (presence of cellular fascicles), high cellularity, mitoses (> 1/50 but <3/10 HPF)

atypical neurofibroma: only nuclear atypia (enlarged nuclei)
cellular neurofibroma: hypercellularity, retained NF architecture
atypical NFT: at least 2 of 4 features
low-grade MPNST: features of atypical NFT + 3-9 mitoses/10 HPF
high-grade MPNST: > 10 mitoses/10 HPF or 3-9 mitoses/10 HPF + tumour necrosis
Case 6: F, 65 years, left cheek
papillary haemangioma
Diagnosis Case 6

papillary Haemangioma
Papillary Haemangioma (Histopathology 2007; 51: 638)
- head / neck region
- solitary lesions, no systemic disease
- ectatic dermal vessels
- intravascular papillae
- papillae with pericytes and stromal cells
- swollen endothelial cells with hyaline globules (giant lysosomes)
- thick mantle of collagen type IV
- papillary hemangioma harbors somatic GNA11 and GNAQ mutations (Gestrich CK et al. AJSP 2024; 48: 106)

by courtesy of Dr.Suurmeijer, Netherlands
DD: glomeruloid Haemangioma
POEMS Syndrome

- Polyneuropathy
- Organomegalie
- Endocrinopathy
- Monoclonal gammopathy (M-protein)
- multiple Skin lesions
M, scrotum, related?
anastomosing Haemangangioma

• genital area, visceral organs, skin, soft tissues, children, adults
• solitary, multiple, circumscribed, infiltrative
• dilated, anastomosing vessels,
  enlarged, hobnail-like endothelial cells
• hyaline globuli, extramedullary haematopoiesis,
  lipomatous metaplasia,
  few mitoses, no endothelial multilayering
• aktivating $GNAQ$ or $GNA14$ mutations
Case 7: M, 82 years, glans penis
epithelioid KS
cellular, epithelioid vascular lesion...
Diagnosis Case 7

epithelioid Kaposi sarcoma
rare morphological Variants

• anaplastic Kaposi Sarcoma
  (aggressive clinical course, metastases)
• intravascular Kaposi Sarcoma
• lymphangioma-like Kaposi Sarcoma
• micronodular Kaposi Sarcoma
• keloidal Kaposi Sarcoma
• hyperkeratotic Kaposi Sarcoma
M, 35 years, HIV +
anaplastic Kaposi Sarcoma
Anaplastic Kaposi sarcoma: a clinicopathologic and genetic analysis
Fischer GM et al. Mod Pathol 2023; 36: Epub 2023 Apr 18.

9 anaplastic KS (8 conventional KS),
M, 51-82 years, lower extremities
angiosarcoma-like and pleomorphic spindle cell sarcoma morphology
recurrent whole chromosome gains (7,11,19,21)
gains affected genes that facilitate cyclin-dependent cell signaling
more complex genome and distinct copy number alterations
M, 30 years, right upper arm
Podoplanin (D2 40) + (Diagnosis: Lymphangioendothelioma ?)
Lymphangioendothelioma-like Kaposi Sarcoma

HHV-8
M, 42 years, HIV +
Haemangioma-like Kaposi’s sarcoma

HHV-8
Case 8: M, 58 years, penis
cellular epithelioid HE
cellular, epithelioid vascular lesion...
cellular epithelioid HE
Diagnosis Case 8

cellular, atypical, epithelioid Haemangioma
epithelioid Haemangioma

benign vascular neoplasm
head / neck > extremities > penis
10-20% multiple lesions
lobular growth
well-formed vessels
epithelioid endothelial cells
lymphocytes, eosinophils
sometimes FOSB gene fusions
intravascular, cellular, multiple eruptive variants
cellular, atypical, epithelioid Haemangioma
DD: epithelioid HE
epithelioid AS
FOS-B in vascular neoplasms
Epithelioid hemangioma (EH)

Molecular studies (FISH)
• ZFP36-FOSB fusions (20%)
• FOS gene rearrangements (1/3)

Immunohistochemistry
• FOS-B across all subtypes (>50%)

Hung et al, 2017
Multiple Eruptive Epithelioid Hemangiomas
A Subset of Cutaneous Cellular Epithelioid Hemangioma
With Expression of FOS-B

Mar Llamas-Velasco, MD,* Werner Kempf, MD,† Carlo Cota, MD,‡
Maria Teresa Fernández-Figuera, MD,§ Joyce Lee, MD,¶ Gerardo Ferrara, MD,¶
Christian Sander, MD,§ Philip E. Shapiro, MD,** Luís Requena, MD,†† and Heinz Kutzner, MD‡‡

TABLE 1. Our Patients' Lesions' Main Characteristics

<table>
<thead>
<tr>
<th>No.</th>
<th>Age (Y)</th>
<th>Sex</th>
<th>Location</th>
<th>Clinical</th>
<th>Ki67 (%)</th>
<th>HH3/FISH</th>
<th>HH3/FISH CAMTA-1</th>
<th>HH3/FOS-B</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45M</td>
<td>F</td>
<td>Left side forehead</td>
<td>Erythematous-violaceous papules. Asymptomatic. (+d) nasal and ocular symptoms. (+d) abnormal bleeding upon trauma.</td>
<td>U Y P &lt;5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>EC, Qs</td>
</tr>
<tr>
<td>2</td>
<td>50M</td>
<td>F</td>
<td>Left side forehead</td>
<td>Erythematous-violaceous papules. Asymptomatic. (+d) nasal and ocular symptoms. (+d) abnormal bleeding upon trauma.</td>
<td>M Y P &lt;5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>EC, Qs, cryosurgery</td>
</tr>
<tr>
<td>3</td>
<td>UKM</td>
<td>M</td>
<td>Left hand and arm</td>
<td>Purplish nodules. (+d) lichenoid on the fourth digit of the left hand. (+d) intense and asymptomatic. (+d) occasional bleeding and abrasions.</td>
<td>M N P 5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>EC, mitomycin once a day for 4 wk, systemic followed by radiotherapy. 0.5 mg/kg for 2 wk</td>
</tr>
<tr>
<td>4</td>
<td>38F</td>
<td>F</td>
<td>Arms, legs, and trunk</td>
<td>Erythematous-violaceous papules. Asymptomatic. (+d) occasional bleeding and abrasions.</td>
<td>M N A 5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Adrenaline, 0.06 mg/kg for 2 wk</td>
</tr>
<tr>
<td>5</td>
<td>73M</td>
<td>M</td>
<td>Face</td>
<td>Asymptomatic papules in an agminated fashion on the facial region.</td>
<td>M Y P 5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
<tr>
<td>6</td>
<td>75M</td>
<td>M</td>
<td>Head</td>
<td>Asymptomatic papules slightly pruritic.</td>
<td>U N P &gt;15</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
<tr>
<td>7</td>
<td>49M</td>
<td>M</td>
<td>Neck</td>
<td>Purple papules slightly pruritic.</td>
<td>M Y P 20</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
<tr>
<td>8</td>
<td>49M</td>
<td>M</td>
<td>Left side forehead</td>
<td>Purple papules asymptomatic.</td>
<td>U Y P</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
<tr>
<td>9</td>
<td>45M</td>
<td>M</td>
<td>Face</td>
<td>Slightly painful purplish papules. No erectile dysfunction.</td>
<td>U N P 5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
<tr>
<td>10</td>
<td>45M</td>
<td>M</td>
<td>Left side forehead</td>
<td>Asymptomatic papules.</td>
<td>U Y P 20</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
<tr>
<td>11</td>
<td>27M</td>
<td>M</td>
<td>Face</td>
<td>Persistent lesions.</td>
<td>U N P 5</td>
<td>Neg</td>
<td>Neg</td>
<td>Pos</td>
<td>Qs</td>
</tr>
</tbody>
</table>

A indicates absent; C, positive; D, disorganized; P, present; F, female; M, male; N, no; Y, yes; G, negative; NP, nuclear phosphatase; P, present; Pos, positive; Qs, quantity; U, ultrasound; V, ven.

13 patients, 34-85 years, 3-100 lesions
head/neck (5), trunk (2), extremitites (1), generalised (1)
strong expression of FOSB

(by courtesy of Dr.M. Llamas Velasco, Madrid)
Novel *GATA6-FOXO1* fusions in a subset of epithelioid hemangioma
CR Antonescu et al. Mod Pathol 2021; 34: 934-941

5 cases, 3 F, 2 M
head/neck (3), back (1), leg (1)
2 x skin, 1 intravascular
vasoformative and solid components
mild to moderate cytological atypia
FOS -, FOSB -
*GATA::FOXO1* fusions
cutaneous epithelioid Haemangioma

- no / rarely $FOSB$ rearrangement
- immunohistochemistry: $FOSB$ +
- translocations-independent phenomenon
Case 9: F, 23 years, neck
epithelioid vascular neoplasm...
A cutaneous epithelioid vascular tumor harboring a \textit{TPM3::ALK} fusion

Linos K, Chang JC, Busam K Genes Chromosomes Cancer 2024; 63:

M, 18 years, left anterior quadrant
well-circumscribed, intradermal lesion
epithelioid vascular tumour, no high-grade atypia
increased proliferative activity, no necrosis
CD31 +, ERG +, Factor VIII +, ASMA + surrounding myopericytes
in frame fusion between \textit{TPM3} exon 8 and \textit{ALK} exon 20
spectrum of epithelioid haemangioma?
epithelioid cells in vascular lesions

epithelioid Kaposi sarcoma
  clinic, plasma cells, HHV8 +
ALK + epithelioid vascular tumour
epithelioid angiomatous nodule
  well-circumscribed, CAMTA1 -, FOSB -
epithelioid haemangioma
  skin > deep soft tissue > bone
  lobular growth, eosinophils, well-formed vessels, FOSB1 +
spindle cell haemangioma
  spindled cells, cavernous spaces
  scattered epithelioid cells, IDH1/2 mutations
pseudomyogenic haemangioendothelioma
  myogenic spindled and epithelioid cells, AE1/3 +, FOSB1 +
epithelioid haemangioendothelioma
  lack of atypia, single cells, cluster and nests
  adjacent to preexisting vessels, myxohyaline stroma
  CAMTA + (TFE3 +)
epithelioid angiosarcoma
  prominent atypia, numerous mitoses, necrosis
F, 39 years, cheek, angiosarcoma?
Diagnosis: cutaneous epithelioid angiomatous nodule
Case 10: F, 54 years, left lower leg, long standing recently enlarged lesion
Diagnosis Case 10

retiform Haemangioendothelioma with malignant transformation
Case 11: F, 75 years, left thigh, 4.5 cm
Diagnosis Case 11

chondroid Lipoma*

* Meis JM, Enzinger F AJSP 1993; 17: 1103
Extraskelatal chondroma with lipoblast-like cells
Chan JK et al. Hum Pathol 1986; 17: 1285-1287

61-year-old woman, wrist
cellular lobular tumour
chondroid cells with mild nuclear atypia
univ- and multivacuolated cells with accumulation
of lipid micking lipoblasts
chondroid Lipoma

- adult patients, F > M
- slowly growing neoplasms
- subcutis / deep soft tissue
- encapsulated, lobular growth
- adipocytes, lipoblasts, small eosinophilic cells
- myxochondroid stroma
- benign clinical course
chondroid Lipoma

- vimentin +, S-100 +/-
- CD68 +/-, laminin +/-, collagen type IV +/-
- focal expression of CK in some cases
- EMA -, ASMA -, GFAP -
- t(11;16)(q13;p13) (MGC3032::MKL2 fusion)

  MKL2: myocardin-related transcription factor
  MGC3032: hypothetical protein

- **ELMI**: clefted nuclei, fat droplets, rough ER, mitochondria, knob-like cell membrane protuberances
F, 34 years, forearm, pancytokeratin
C11orf95-MKL2 is a consistent finding in chondroid lipoma: a study of 8 cases

- 4 F, 4 M, 21-81 years
- forearm (3), lower leg (2), back (1), thigh (1), head (1)
- 1 x local recurrence
- typical morphology
- 7/8 cases with C11orf95::MKL2 (PCR)
C11orf95-MKL2  ex9-ex5

MKL2

Exon8          Exon9
AspAspLeuLysValSerGluLeuLysThrGluLeuLysLeuArgGlyLeuProValSer
GATGACTTAAAGGTATCAGAACTGAAGACAGAACTGAAGTTAACGTTAAGGGGTCTGCCAGTGTCA
1201  ----------------!----------------!----------------!----------------!----------------!----------------!----------------!----------------! 1260
CTACTGAATTTCCATAGTCTTGACTTCT


C11orf95 EXON5

1 breakpoint 1159  In exon5 1799-1800

TyrGlnProArgTrpArgGlyGluTyrLeuMetAspTyrAspGlySerArgArgGlyLeu
TACCAGCCGCGTGGGCGGGCCGAGTACCTGATGAGACTACGACGGCACCCCGCGCCGGCTG
p887
1741  ----------------!----------------!----------------!----------------!----------------!----------------!----------------! 1800
ATGGTCGGCGCCACCGCCCCCCTATGGACTACCTGATGCTGCCGTCGGCCGGAC

2 breakpoint lit.1839-1840(intron exon5)

ValCysMetValCysGlyGlyAlaLeuAlaThrLeuLysValSerThrIleLysArgHis
GTGTGTAATGGTGTCGGGCGCGCTGGCCACGCTCAAGGTAGCACCATCAAGCCAC
1801  ----------------!----------------!----------------!----------------!----------------!----------------!----------------! 1860
CACACATACACACGCCCCCGCGCCGCGCGTGGCAGTTCCTCACTCGTGGTAGTTCGCGGTG

Gen: C11orf95 /Datum: 08-08-2012 /Genomisch: NC_000011.9 /mRNA: NM_001144936.1/ Eiwit: NP_001138408.1
Lipoblasts in benign lipogenic Neoplasms?

yes, no problem!

lipoblastoma / lipoblastomatosis
spindle cell lipoma / pleomorphic lipoma
chondroid lipoma
Differential diagnosis: chondroid Lipoma

extraskeletal myxoid Chondrosarcoma
no lipogenic component
uniform, eosinophilic
  round / spindled tumour cells
no cytoplasmic vacuoles
few blood vessels
prominent myxoid stroma
t(9;22)(q22;q12) >
t(9;17)(q22;q12)
F, 46 years, thigh

*EWS* break apart probe positive in 31 of 50 nuclei
Differential diagnosis: chondroid Lipoma

atypical lipomatous Tumour
no lobular growth
no / few lipoblasts
enlarged, hyperchromatic nuclei
fibrous septa with atypical cells
MDM2 + / CDK +
MDM2 / CDK4 amplification
myxoid Liposarcoma
lipoblasts, small, uniform immature cells
thin branching vessels
myxoid stroma
(Hyaluronidase sensitive)
t(12;16)(q13;p11)
  DDIT3::FUS fusion
t(12;22)(q13;q12)
  DDIT3::EWSR1 fusion

Differential diagnosis: chondroid Lipoma
Myoepithelioma
focal epithelial structures
no lipogenic cells
no eosinophilic, vacuolated cells
S-100 + (80%),
CK +/-, EMA +/-
GFAP +/-, ASMA +/-
Calponin +/-

Differential diagnosis: chondroid Lipoma
**Differential diagnosis: chondroid Lipoma**

**Hibernoma**
Macro: yellow-brown abundant eosinophilic cytoplasm with vacuoles, granular cytoplasm small nuclei no myxochondroid stroma abundant mitochondria
Case 12: M, 73 years, left shoulder, long standing, recently enlarging lesion
atypical spindle cell lipomatous tumour
atypical spindle cell lipomatous tumour
atypical spindle cell lipomatous tumour
atypical spindle cell lipomatous tumour
atypical spindle cell lipomatous tumour
Diagnosis Case 12

atypical spindle cell lipomatous Tumour
Spindle Cell Liposarcoma, A Hitherto Unrecognized Variant of Liposarcoma
Analysis of Six Cases

Angelo P. Deligenti, M.D., Thomas Moertel, M.D.,
Paul T. Newton, M.D., and Christopher D.M. Fletcher, M.D., M.R.C.Path.

Six cases of a previously undescribed variant of liposarcoma, termed spindle cell liposarcoma, are presented. This tumor displays a typical liposarcoma cell distribution with multiple recurrences, dedifferentiation, and MTS (1) histologic features. The three cases of spindle cell liposarcoma show a typical liposarcoma cell distribution with multiple small lipoblasts with mild to moderate atypia and atypical lipogenic component desmin focal (+5) CD34 focal (+2).

6 cases, 2 F, 4 M
35-82 years, 2-25 cm
shoulder (3), arm (2), back (1)
subcutis (5), intramuscular
multiple recurrences (3)
dedifferentiation, MTS (1)
spindle cells with mild to
moderate atypia + atypical
lipogenic component
desmin focal (+5), CD34 focal (+2).
„It is obvious that Dei Tos et al. are not aware of Hajdu´s description of fibroblastic liposarcoma ... 15 years ago“ (SA Hoda)

„...Steven Hajdu showed us liposarcomas with spindle cell features similar to those depicted in the recent article. In fact, he coined the term „fibroblastic liposarcoma“... I am amazed that Dei Tos et al. ignored the previous description and illustrations of spindle cell liposarcoma“ (WO Russell)
„In 1976 and again in 1979, Hajdu proposed the term fibroblastic liposarcoma... Spindle cell liposarcoma is not a new type of liposarcoma, and the article by Dei Tos et al. should serve as a confirmation and validation of Hajdu’s studies and classification of liposarcoma“ (C Urmacher)

„Such liposarcomas have been previously well illustrated and commented upon in the literature... morphologic spectrum of spindle cell liposarcoma ranging from well-differentiated cases closely resembling spindle cell lipoma ... to high-grade fibrosarcoma-like variants“ (LG Kindblom)
Figure 4-27. Fibroblastic liposarcoma. Note the complete obstruction of the space between capillary vessels by slender fibroblastic cells (proliferating). The arranged pattern of these cells resembles the storiform pattern commonly seen in fibroblastic fibrous histiocytomas (see Figure 2-20 and certain neurogenic tumors (see Figure 7-34). However, the linear or cross-link type of capillary network is distinctly that associated with liposarcomas.

Figure 4-28 and 4-29. The intimate relationship between capillary vessels and individual tumor cells is so unique that one cannot rule out possible histogenetic connection between capillaries and tumor cells (A, H & E, x100; B, H & E, x30).
Author´s Reply

„It was simply for reasons of tact that we did not quote them, since none of Dr.Hajdu´s description provide a clearly illustrated means of diagnosing these lesions. The majority of the illustrations... look remarkably like myxofibrosarcoma (myxoid MFH) of intermediate or high grade. Readers might also like to note that the existence of fibroblastic liposarcoma is not accepted in either the standard textbook of soft tissue tumors or in the recently published WHO-classification.“

(CDM Fletcher)
Nascimento AF, Fletcher CDM
Spindle cell liposarcoma/atypical lipomatous Tumor. A clinicopathologic study of 120 cases. Mod Pathol 2005; 18: 70A

locally aggressive neoplasm, may recur
no metastases, dedifferentiation very rarely
atypical lipogenic cells +
slightly atypical spindled cells

BUT

no MDM2/CDK amplification!
Well-differentiated spindle cell liposarcoma ("atypical spindle cell lipomatous tumor") does not belong to the spectrum of atypical lipomatous tumor but has a close relationship to spindle cell lipoma: clinicopathologic, immunohistochemical, and molecular analysis of six cases

Thomas Knobloch, Gabriel Pahnke, and Cornelius Kohler

Well-differentiated spindle cell liposarcoma represents a rare and heterogeneous subtype of liposarcoma that has not been reported as a variant of atypical lipomatous tumor. Moreover, well-differentiated spindle cell liposarcoma is not seen in the molecular/ pathological typing of the liposarcoma. The entity and the related tumor group, centering slightly higher than the spindle cell lipoma cell, was subjected for review. The authors studied a series of 21 well-differentiated spindle cell liposarcomas in three different settings. The results show that the tumors are more common in men than in women and are typically located in the extremities. The size of the tumors ranged from 1.5 to 10 cm. All tumors were completely excised. The histologic features of the tumors are similar to the spindle cell lipoma, but the spindle cell lipoma is more common in women and usually located in the extremities. CD34 was focally positive in all cases, whereas nuclear fascin was strongly positive in all cases. No MDM2/CDK4 amplification was detected in any of the tumors. In conclusion, the well-differentiated spindle cell liposarcoma may represent a more differentiated variant of atypical lipomatous tumor and may represent the histological grade transition of spindle cell lipoma.

2 F, 4 M, 59-85 years shoulder, trunk, thigh, lower leg, hand, paratesticular
1 out of 4 cases recurred
1.5-10 cm, subcutis (3)
deep soft tissue (3)
CD 34 focally +
Rb-1 deletion (6)
no MDM2/CDK4 amplification