Vascular Tumours of Skin and Soft Tissues

Dr. Thomas Mentzel
MVZ Dermatopathologie Friedrichshafen / Bodensee PartG
ISSVA Classification of vascular Tumours (Melbourne 2014, update 2018)

vascular Malformations
   simple (capillary, lymphatic, venous, arteriovenous, arteriovenous fistula)
   combined of major named vessels
   associated with other anomalies

vascular Neoplasms
   benign
   locally aggressive / borderline
   (Kaposi sarcoma, haemangioendotheliomas)
   malignant
   (epithelioid HE, angiosarcoma)
Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas
M, 8 years, left thigh, biopsy capillary haemangioma?
Diagnosis: vascular malformation in Klippel-Trenaunay
Lawley LP et al.:

Expression of Wilms tumor 1 gene distinguishes vascular malformations from proliferative endothelial lesions.

Arch Dermatol 2005; 141: 1297-1300

„Defects in WT1 signaling may underlie the inability of malformation endothelial cells to undergo physiologic apoptosis and remodeling.“
WT-1 (6F-H2, N-terminus) cytoplasmic staining of endothelial cells
6F-H2, WT49, EP122 recommended by NordiQC
M, 21 years, large vascular lesion, trunk
CD10 is expressed in endothelial cells of vascular malformations
Mod Pathol 2018; 31: 578A
Vascular Malformations

- relatively frequent (0.3% of population), genetically very heterogeneous
- disturbances in vessel development in the 4th-10th week of pregnancy, manifestation often later, no regression
- proper diagnosis also of underlying genetic changes is important for treatment
  
  Rapamycin in lymphangiomatous malformations
  Alpesilib in PIK3CA associated overgrowth syndroms (Nature 2018; 558: 540-546)
**Vascular Malformations + Genetics**

*PIK3CA*-mutations: PROS-PIK3CA associated overgrowth syndrome (Alpesilib treatment)

- CLOVES syndrome (congenital lipomatous proliferation, vascular MF, epidermal naevi, scoliosis)

- Megalencephaly-capillary malformation

- Dysplastic Megalencephaly

- CLAPO syndrome (capillary MF lower lip, lymphatic MF head/neck, overgrowth)
RASA1 mutations
- CM-AVM syndrome (elongated vessels)
- Parkes-Weber syndrome (arteriovenous MF + overgrowth)

GNAQ/GNA11 mutations
- Sturge-Weber syndrome
- capillary MF + overgrowth of the extremities

IDH1/2 mutations
- Mafucci syndrome

PTEN mutations
- PTEN hamartomatous syndrome

AKT1 mutations
- Proteus syndrome
M, 50 years, multiple lesions, grow slowly, Kaposi’s sarcoma was suspected
Glomangiomatous vascular Malformation
lymphangioma / lymphangieectasia
Superficial haemosiderotic lymphovascular Malformation
(“targetoid haemosiderotic haemangioma“
 „hobnail haemangioma“)
Differential Diagnosis: capillary vascular Malformation - pyogenic Granuloma («lobular capillary haemangioma»)
Differential Diagnosis: capillary vascular malformation - cellular infantile Haemangiomata
infantile Haemangioma

commonest benign tumour of childhood (4-5%)
rapid proliferative growth phase
slow involution phase
superficial, deep, mixed
localized, segmental, multifocal
frequent head / neck region
lobular, cellular, capillary proliferation
Glut-1+ (placental differentiation, hypoxia induces angioneogenesis)
vascular markers +
complete layer of ASMA-positive myopericytes
Complications

infiltrative growth
superinfection, ulceration
PHACE (posterior fossa malformations, haemangiomas
arterial anomalies, cardiac defects,
眼 abnormalities, sternal clefting) Syndrom
involvement of visceral organs
prominent scarring, destruction
increased risk in segmental and multifocal
haemangiomas

successful treatment with Propranolol!
Cellular infantile Haemangioma: Glut-1 +

**DD: Congenital Haemangioma**

**Rapidly Involuting CH**
- Glut-1 negative
- rapid shrinking
- often thrombosis

**Non Involuting CH**
- Glut-1 negative
- persist over time
- grow proportionally with the child
- arteriolobular fistulæ

**Partially Involuting CH**
- Glut-1 negative
The histopathology of congenital haemangioma and its clinical correlations: a long-term follow-up study of 55 cases
S El Zein et al. Histopathology 2020; 77: 275

- histopathological features are similar in all three subtypes
- histopathological features are related to the time since disease onset
- RICH, NICH, and PICH are a single entity
- intralobular expression of podoplanin was related with thrombocytopenia
Differential Diagnosis

infantile HE: Glut-1 +, WT-1 +
(Propranolol sensitive)

congenital HE: Glut-1 -, WT-1 +

vascular MF: Glut-1 -, WT-1 -, CD10 +
Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomases
- Angiosarcomas
Angiomatosis

- diffuse dermal Angiomatosis
- reactive Angioendotheliomatosis
- Lymphangiomatosis (of the limbs)
- multifocal Lymphangioendotheliomatosis with thrombocytopenia
- prurigiform Angiomatosis
- bacillary Angiomatosis
- kaposiform Lymphangiomatosis

(dermis, ST, lung, mediastinum, spleen, skeleton
dilated lymphatics + haemosiderotic spindled endothelial cells
activating NRAS mutation, AJSP 2022; 46: 963)
M, 79 years, in the area of an a.v. shunt
Diffuse Dermal Angiomatosis*

Clinicopathological Findings

• elderly patients, rapid growth
• large, ulcerated, red-violet plaques
• distal to a.v. fistula, severe atherosclerosis
• may show spontaneous regression
• diffuse proliferation of narrow vessels
• newly formed dermal vessels
• CD31 + endothelial cells, ASMA + pericytes
• mitoses, spindled cells, fibrosis
• biologically benign vascular lesion

Diffuse Dermal Angiomatosis versus Reactive Angioendotheliomatosis

Related or identical?

Reactive Angioendotheliomatosis:
cryoglobulinaemia, infection
intravascular endothelial proliferation
formation of capillary tufts
no proliferation of newly formed vessels
often fibrin thrombi

Related but not identical!
Reactive Angioendotheliomatosis in Cryoglobulinaemia
Reactive Angioendotheliomatosis in Cryoglobulinaemia
M, 74 years, right testis
(by courtesy of Prof. E. Montgomery, U.S.A.)
Ergebnis der molekularpathologischen Untersuchung des GNAQ Gens
(Guanine nucleotide-binding protein Q polypeptide, OMIM-Nummer 600998)
Histologie-Nummer 18/K 3781

<table>
<thead>
<tr>
<th>Mutationsstatus</th>
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<tr>
<td>Sequenzierung von</td>
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<td>GNAQ Exon 5 (Codon 209)</td>
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Nach: "Guidelines for mutation nomenclature" der "Human Genome Variation Society" (HGVS; www_hgvs.org/)

Prof. Dr. Mentzel / Dr. Palmedo 09.01.2018
Anastomosing hemangioma of the genitourinary tract: a lesion mimicking angiosarcoma. (Montgomery E, Epstein JL AJSP 2009; 33: 1364)

Anastomosing hemangioma arising in unusual locations: a clinicopathologic study of 17 soft tissue cases showing predilection for the paraspinal region (John I, Folpe AL AJSP 2016; 40: 1084)

Recurrent GNAQ mutations in anastomosing hemangiomas. (Bean GR et al. Mod Pathol 2017; 30: 722)
anastomosing Haemangioma

- 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
- activating \textit{GNAQ} or \textit{GNA14} mutations
young female patient, since early childhood, slowly growing, indurated lesion
no prominent endothelial atypia, no mitoses
Lymphangiomatosis of the limbs (courtesy of Prof. Fletcher, Boston) AJSP 1995; 19: 125-133 (no systemic involvement, benign clinical course)
Multifocal Lymphangioendotheliomatosis With Thrombocytopenia
A Newly Recognized Clinicopathological Entity
Paula E. North, MD, PhD; Teri Kahn, MD; Maria R. Cordisco, MD; Soheil S. Dadras, MD, PhD; Michael Detmar, MD; Ilona J. Frieden, MD

Background: Severe thrombocytopenic coagulopathy may complicate platelet-trapping vascular tumors such as kaposiform hemangioendothelioma and tufted angiomata. Low-grade, chronic consumptive coagulopathy may occur with extensive venous and lymphatic malformations. We have also observed patients with rare multifocal, congenital skin and gastrointestinal (GI) tract vascular anomalies of distinctive and remarkably similar appearance, all associated with coagulopathy. We studied the clinical and histopathologic features of 3 patients demonstrating this previously uninvestigated phenomenon.

Observations: All 3 patients presented with hundreds of congenital red-brown skin plaques as large as a few centimeters, with similar lesions throughout the GI tract and severe GI tract bleeding. One patient had synovial involvement. All had significant thrombocytopenia, with prothrombin and partial thromboplatin times and fibrinogen levels near the reference range. Corticosteroids and/or interferon alfa treatment resulted in equivocal or no improvement. Skin lesions from all 3 patients were histologically distinctive and similar, including dilated, thin-walled vessels in the dermis and subcutis lined by hobnailed, proliferative endothelial cells (10%-15% immunoreactive for Ki-67), most displaying intraluminal papillary projections. Immunoreaction for the lymphatic marker LYVE-1 was uniformly present.

Conclusions: We propose the term multifocal lymphangioendotheliomatosis with thrombocytopenia to distinguish this newly recognized clinicopathological entity. These congenital lesions, like tufted angiomata and kaposiform hemangioendothelioma, show lymphatic differentiation, strengthening the association between abnormal lymphatic endothelium and coagulopathy.

Arch Dermatol. 2009;145:599-606

M ULTIFOCAL VASCULAR tumors and malformations are relatively unusual among vascular anomalies, but are characteristic of several well-defined disorders. These include so-called neonatal hemangiomatisis (benign and disseminated), I blue rubber bleb nevus syndrome, 2 glomuvenous malformations, 3,4 Maffucci syndrome, 5 hereditary hemorrhagic telangiectasia, 6,7 familial cutaneous cerebral capillary malformations, 8,9 and familial multiple macrocavernous venous malformations. 10,11 We herein describe 3 patients with an entirely different disorder, characterized by multiple discrete cutaneous and GI tract vascular anomalies associated with coagulopathy identified independently at different institutions. Medical records were reviewed, and hematoxylin-cosin-stained tissue sections were reviewed and compared by one of us (P.E.N). Biopsy specimens included skin samples of the lower back and right hip symmetry (patient 1, aged 5-6 years), a punch biopsy specimen from a left buttock lesion (patient 2, aged 6 years), and a resection specimen from the cheek (patient 3, aged 13 years 9 months). Histochemical, immunohistochemical, and immunofluorescent studies, including evaluation for expression of the lymphatic marker LYVE-1, were performed.

For immunofluorescent microscopy, paraffin-embedded sections (6 μm thickness) were deparaffinized, rehydrated, and treated with 0.01% protease XXIV (Sigma-Aldrich Corp,
• 3 patients (2 M, 1 F, 5, 6, 13 years), hundreds of congenital skin plaques
• dilated vascular structures with hobnail endothelial cells, LYVE-1 +
• GI-vascular lesions with bleeding, synovial vascular lesions (1 patient)
• significant thrombocytopenia (vascular lesions of lymphatic diff.)
• association of abnormal lymphatic endothelium and coagulopathy
• represents a vascular malformation
M, newborn, multifocal haemangiomatosis of the skin and visceral organs (spleen), disseminated intravascular coagulation, thrombocytopenia
Prurigiform angiomatosis and endothelial growth factors: a distinct reactive angioproliferation in the skin

- non-neoplastic, reactive increase of vessels
- elderly patients, M > F, buttock, intergluteal fold, erythematous / brown plaques
- epidermis hyperplasia with VEGF secretion and increase of organoid vessels
- band- or plaque-like, dermal vascular proliferation inflammatory cells, fibrosis
- mechanical injury, inflammation are triggers of angiogenesis driven by epidermal VEGF expression
- no topical treatment
F, 81 years
previous breast cancer and CLL since 6/12 nodular, ulcerated skin lesions ? angiosarcoma
numerous vessels lined by slightly atypical endothelial cells
numerous neutrophils, nuclear dust
Sequenzvergleich:

16/ K 1726 I  GCCCTCGGGCGCTCTCTACTATTAAAGGAGAAGACTTTTTGTGT  50

B. quintana  GCCCTCGGGCGCTCTCTACTATTAAAGGAGAAGACTTTTTGTGT  42

Referenzbande: Bartonella DNA-Fragment
bacillary Angiomatosis

- tumour-like vasoproliferative lesion
- Bartonella henselae (quintana)
- often in immunosuppressed patients
- skin > lymph node, spleen
- often multiple dermal nodules
- lobular vascular proliferation
  epithelioid endothelial cells, neutrophils, extracellular amorphous material
- excellent response to erythromycin
Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomases
- Angiosarcomas
„Borderline“ malignant vascular tumours
Haemangioendotheliomas
Mallory EB J Exp Med 1908; 10: 575

- spindle cell HE
- Dabska Tumour
- kaposiform HE
- retiform HE
- polymorphous HE
- composite HE
- pseudomyogenic HE
- epithelioid HE

- spindle cell haemangioma
- PILA, lymphatic tumour
- locally aggressive
- locally aggressive, rare MTS
- locally aggressive, rare MTS
- locally aggressive, rare MTS
- locally aggressive, rare MTS

malignant neoplasm
Haemangioendothelioma
Be specific!
spindle cell Haemangiomia

- children, young adults, also in elderly patients
- 10% of cases: associated abnormalities (lymphedema, Maffucci Syndrom, Klippel-Trenaunay Syndrom)
- dermis / subcutis of distal extremities
- 50% of cases: multiple lesion, mostly in one anatomic region
- no progression, no metastases
- small (< 2 cm), often painful, blue, dermal nodules
- \textit{IDH 1/2} mutations
spindle cell Haemangioma

- haemorrhagic, dermal and / or subcutaneous nodules
- well-circumscribed, unencapsulated
  1. dilated, cavernous vascular spaces
  2. bland spindle cells
     - epithelioid endothelial cells (cytoplasmic vacuoles)
     - endothelial bridges
- abnormal thick-walled vessels (vascular malformations)
- 20-30% intravascular
Podoplanin (D2-40)

WT-1
papillary intravascular Lymphangioendothelioma* (Dabska’s Tumour)

- children and young adults, locally aggressive, good prognosis, no metastases
- lymphangioma-like vascular spaces, prominent, hobnail endothelial cells, intravascular papillae (coll.core, hobnail cells)
- no surrounding actin + myopericytes, foci of lymphatic infiltrate

* Fanburg-Smith JC et al. AJSP 1999; 23: 1004
papillary intravascular Lymphangioendothelioma

courtesy of Dr. L. Requena, Madrid
M, 15 years, thigh
F, 2 years, retroperitoneum, large lesion
Podoplanin (D2-40)
kaposiform Haemangioendothelioma*

- children >> adults, retroperitoneum, extremities
- deep soft tissues >> dermal
- prognosis related to size and depth!
- locally aggressive, no metastases

Cave: Kasabach Merritt syndrome

- cellular neoplasm, lobular growth
- bland spindled cells, fibrin thrombi
- focally podoplanin +, prox-1 +, LYVE-1 +
- associated lymphangiomatous changes
- spectrum with tufted haemangioma!

* Tsang WY, Chan JKC AJSP 1991; 15: 982
Zukerberg LR et al. AJSP 1993; 17: 321
tufted Haemangioma

Pathological Findings
- infants, children >> adults
- head / neck, trunk
- slowly growing lesions
- cannon-ball distribution of cellular vascular tufts
- peripheral lymphangiomatous changes
- CD31 +, ASMA +
- Podoplanin focal +
- spectrum with kaposiform haemangioendothelioma

F, 18 months
F, 40 years, recurrent lesion right big toe
retiform Haemangioendothelioma*

- young adults, dermis, subcutis, often distal extremities
- slowly growing red-bluish plaques, nodules
- destructive growth, many R, rare metastases
- very rarely multiple lesions
- retiform vascular channels
  - hobnail endothelial cells, solid foci possible, associated lymphocytes
- CD31 +, CD34 -/+ , VEGFR +, D2-40 +

* Calonje E et al. AJSP 1994; 18: 115
M, 24, right foot
multiple small nodules
**pseudomyogenic Hemangioendothelioma:**
A distinctive, often multicentric tumor with indolent behavior
(„epithelioid sarcoma-like Hemangioendothelioma“)
(Hornick JL, Fletcher CDM AJSP 2011; 35: 190)

- 50 cases, 41 M, 9 F, 14 - 80 years
- extremities >> trunk, head / neck region
dermis / subcutis > deep soft tissue > bone
- multifocal neoplasms (2-15 neoplasms) (66%)
- fascicles, sheets of plump spindled cells,
few epithelioid cells, neutrophils
- AE1/3 +, MNF116 -, Fli-1 +, 22/47 CD 31 +,
7/49 EMA +, CD 34 -, INI1 +, S-100 -
- local recurrence (58%), MTS (2 x)
pseudomyogenic Haemangioendothelioma

- t(7;19)(q22;q13) (Cancer Genetics 2011; 204: 211)
- SERPINE1-FOSB fusion (J Pathol 2014; 232: 534)
- SERPINE1: promotor for FOSB
- FOSB: encodes a transcription factor (FOS family) a component of the activating protein 1
FOS-B in vascular neoplasms
Pseudomyogenic hemangioendothelioma (PHE)

$t(7;19)$ SERPINE1-FOSB

*ORIGINAL PAPER*

A novel SERPINE1–FOSB fusion gene results in transcriptional up-regulation of FOSB in pseudomyogenic haemangioendothelioma

Charles W. W. Walther,1,2,* Johnbosco Tseyihwa,1 Henrik Ulljesjö,1 Linda Magnusson,1 Jenny Nilsson,1 Fredrik Vult von Steyerm,1 Ingrid Øra,1 Henryk A Domanski,1 Thos Fioretos,1 Karolin H. Nord,1 Christopher DM Fletcher,6 and Fredrik Pernstens1

*RESEARCH*

Diagnostic utility of FOSB immunohistochemistry in pseudomyogenic hemangioendothelioma and its histological mimics

Shintaro Sugiya1, Hikoshi Hirano1, Noriaki Kikuchi1, Terufumi Kubo1, Hiroko Asahina1, Tomoyuki Asayama1, Makoto Emori1 and Tadashi Hasegawa1

FOSB immunohistochemistry useful marker
strong nuclear expression $>95\%$ of cases
courtesy of Prof. Fletcher, Boston, MA
polymorphous Haemangioendothelioma*

- extremely rare neoplasm
- adult patients
- lymph node > soft tissue
- retiform and solid areas
- enlarged, but uniform hobnail cells

* Chan JKC et al. AJSP 1992; 16: 335
  Nascimento AG et al. AJSP 1997; 21: 1083
F, 66 years, chest wall, 5.5 cm
Haemangioma-like + infiltrating component
epithelioid HE-like
composite Haemangioendothelioma
(Nayler SJ et al. AJSP 2000; 24: 352)

- adult patients
- mainly distal lower extremities > head / neck
- locally aggressive, 50% R, single MTS
- irregular admixture of:
  - haemangioma-like areas
  - low-grade areas (i.e. RHE-like)
  - malignant areas (i.e. EHE, AS)
- composite hemangioendothelioma with neuroendocrine marker expression: an aggressive variant (Mod Pathol 2017; 30: 1589)
Recurrent *YAP1* and *MAML2* gene rearrangements in retiform and composite hemangioendothelioma
Antonescu CR et al. AJSP 2020; 44: 1677

13 RHE, 10-55 years; 11 CHE, 7-68 years
Skin, soft tissues, extremities > head / neck
M, 37 years, CHE with neuroendocrine differentiation (pancreas, liver, lung)
5/13 RHE and 3/11 CHE *YAP1* rearrangement
5 cases showed *YAP1-MAML2* fusion
*PTBP1-MAML1* fusion in neuroendocrine CHE
Close relationship between RHE and CHE
Neuroendocrine CHE appears a distinct subset
F, 56 years, deep soft tissue, thigh
epithelioid Haemangioendothelioma

- adults, rarely in childhood
- solid > multicentric, soft tissues > skin
- arise from large vessels in 50% of cases
- ill-defined, infiltrative neoplasms
- nests, cords, trabeculae, epithelioid cells, cytoplasmic vacuoles (with erythrocytes), myxohyaline stroma
- endothelial markers +, podoplanin + in 40%, CK + in 25%
epithelioid Haemangioendothelioma

courtesy of Dr.L.Requena, Madrid
M, 9 years, painful erythematous plaque
cervical lymph node metastasis
J Cutan Pathol 2008; 35: 80
epithelioid Haemangioendothelioma

- EHE (17), epithelioid haemangioma (13), epithelioid AS (5), pseudomyogenic HE (4)
- t(1;3)(p36.3;q25), WWTR1-CAMTA1 fusion present only in cases of EHE
- WWTR1-CAMTA1 oncogenic function

- nuclear expression of CAMTA1 distinguishes EHE from histologic mimics
- rabbit polyclonal antibody (Novus Biologicals) is highly sensitive (85%) and specific
A Novel WWTR1-CAMTA1 Gene Fusion is a Consistent Abnormality in Epithelioid Hemangioendothelioma of Different Anatomic Sites

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2Department of Orthopaedic Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
3Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY, USA
4Department of Medicine/Pediatrics, Mount Sinai School of Medicine, New York, NY, USA

Abstract

The classification of epithelioid vascular tumors remains challenging, as there is considerable morphologic overlap between tumor subtypes, across the spectrum from benign to malignant categories. A t(12;22) (p13;q12) translocation was reported in two cases of epithelioid hemangioendotheliomas (EHE), however, no follow-up studies have been performed to identify the gene fusion or to assess its prevalence in a larger cohort of patients. We undertook a systematic molecular analysis of 17 EHE, characterized by classic morphologic and immunophenotypic features, from various anatomic locations and with different malignant potential. For comparison we analyzed 13 epithelioid hemangiofibromas, five epithelioid angiosarcomas and four epithelioid sarcoma-like EHE. A fluorescence in situ hybridization (FISH) positional cloning strategy, spanning the cytogenetically defined regions on chromosomes 1p13.3 and 3q25, confirmed rearrangements in two candidate genes from these loci in all EHE cases tested. None of the other benign or malignant epithelioid vascular tumors examined demonstrated these abnormalities. Subsequent RT-PCR confirmed in three EHE the WWTR1-CAMTA1 fusion product. CAMTA1 and WWTR1 have been previously shown to play important roles in oncogenesis. Our results demonstrate the presence of a WWTR1-CAMTA1 fusion in all EHE tested from bone, soft tissue and visceral location (liver, lung) in keeping with a unique and specific pathological entity. Thus, FISH or RT-PCR analysis for the presence of WWTR1-CAMTA1 fusion may serve as a useful molecular diagnostic tool in challenging diagnoses.

INTRODUCTION

Epithelioid vascular tumors encompass a wide histologic spectrum, including epithelioid hemangiofibroma (EHF), a benign tumor, epithelioid hemangioendothelioma (EHE), a low grade malignant tumor; and epithelioid angiosarcoma (EAS), a high grade malignant tumor (Wenger and Woold, 2000; O’Connell et al., 2001; Fletcher et al., 2002). Although some of
Novel *YAP1-TFE3* fusion defines a distinct subset of epithelioid hemangioendothelioma (Antonescu CR et al. Genes Chromosomes & Cancer 2013; 52: 775-784)

- t(11;X)(q13;p11) with *YAP1-TFE3* fusion
- *YAP1-TFE3* oncogenic function
- young patients
- well-formed vasoformative vascular structures, more solid growth
- abundant pale eosinophilic cytoplasm
- strong nuclear TFE3 expression, TFE3 immunohistochemistry is not specific
Novel YAP1-TFE3 Fusion Defines a Distinct Subset of Epithelioid Hemangiendothelioma

Cristina R Antonescu1, Francois Le Loarer7, Juan-Miguel Mosquera2, Andrea Bosen2,3, Lei Zhang1, Chun-Liang Chen1, Hai-Hao Chen1, Naveen Pathani, Thomas Kraus2, Brendan C Dickson1, Ilan Weinreb4, Mark A Rubin4, Meera Hamilton5, and Christopher DM Fletcher6
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Abstract

Conventional epithelioid hemangiendothelioma (EHE) have a distinctive morphologic appearance and are characterized by a recurrent t(1;17) translocation, resulting in a NTRK1-CAMTA1 fusion gene. We have recently encountered a fusion-negative subset characterized by a somewhat different morphology, including focally well-formed vasoformative features, which was further investigated for recurrent genomic abnormalities. Based on a case showing strong TFE3 immunoreactivity, FISH analysis for TFE3 gene rearrangement was applied to the index case as well as to 9 additional cases, selected through negative NTRK1-CAMTA1 screening. A control group, including 18 epithelioid hemangioendothelomas, 9 pseudomyxoma peritoneal, and 3 epithelioid angiosarcomas, was also tested. TFE3 gene rearrangement was identified in 10 patients, with equal gender distribution and a mean age of 38 years old. The lesions were located in somatic soft tissue in 6 cases, lung in 3 and one in bone. One case with available frozen tissue was tested by RNA sequencing and FusionSeq data analysis to detect novel fusions. A YAP1-TFE3 fusion was thus detected, which was further validated by FISH and RT-PCR. YAP1 gene rearrangements were

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TFE3  break-apart probe
F, 43 years, occipital region
Archer expanded sarcoma fusionplex analysis: 
YAP1::TFE3 fusion 

Diagnosis: 
epithelioid EHE with 
YAP1::TFE3 fusion
Prognostic stratification of clinical and molecular epithelioid hemangioendothelioma subsets
E Rosenbaum et al. Mod Pathol 2020; 33: 591-602

- 93 translocation positive cases
- 83 patients with \textit{WWTR1-CAMTA1} gene fusion
- 10 patients with \textit{YAP1-TFE3} gene fusion
- \textit{WWTR1-CAMTA1} fusion: 59% 5-year survival
  \textit{YAP1-TFE3} fusion: 86% 5-year survival
- multifocality, pleural involvement, lymph node and distant metastases are adverse prognostic factors
- more than half of the analysed cases showed additional genetic changes
epithelioid Haemangioendothelioma

many recurrences
20-30% MTS
10-20% DOD

ture malignant vascular neoplasm (better prognosis in dermal EHE)

size > 3 cm,
> 3 mitoses/50 hpf

5-year survival 59%

62 cases, CAMTA1 subtype (59), TFE3 subtype (2)
22 cases atypical histology (>2 mitoses/mm², high nuclear grade, necrosis)
DOD (11 cases, 18%), 5-year survival 78.8%
> 3 cm, histological atypia = shorter survival
3-tiered risk assessment system
low-risk (5-ys. 100%), intermediate risk (5-ys. 81.8%), high-risk (5-ys. 16.9%)
4 cases synaptophysin + = high-risk lesions, aggressive clinical course
Vascular Tumours of Skin and Soft Tissues

- vascular Malformations
- Angiomatoses
- Haemangioendotheliomas
- Angiosarcomas
Angiosarcoma

Cutaneous Angiosarcoma
- lymphedematous angiosarcoma
- postirradiation angiosarcoma
- (idiopathic) actinic angiosarcoma

Angiosarcoma of Soft Tissues
Lymphedematous Angiosarcoma (congenital chronic lymphedema)

by courtesy of Dr. L. Requena, Madrid
Lymphedematous Angiosarcoma (Stewart Treves Syndrome)

by courtesy of Dr. L. Requena, Madrid
Postirradiation Angiosarcoma
Vascular Proliferations after Radiotherapy

BLAP

Atypical vascular Proliferation

Angiosarcoma

* Brenn T, Fletcher CDM AJSP 2005; 29: 983
Mattoch IW at al. JAAD 2007; 57: 126
Benign lymphangiomatous Papule

by courtesy of Dr. L. Requena, Madrid
Benign lymphangiomatous Papule

1.5 years after Radiotherapy

Diaz-Cascajo C et al. Histopathology 1999; 35: 19
Requena L et al. AJSP 2002; 26: 328
Benign lymphangiomatous Papule

Podoplanin (D2-40)
Atypical vascular proliferation after RT
(Fineberg S, Rosen PP AJCP 1994; 102: 757)

Clinicopathological Findings

• brown to erythematous papules / nodules
• single or multiple, circumscribed lesions
• anastomosing vessels, endothelial cells with hyperchromatic nuclei, no prominent nucleoli
• chronic inflammation
• no significant atypia, no mitoses
• no papillary endothelial proliferation
• no „blood lakes“, no infiltration of subcutis
Table 1. Histopathological features that help distinguish atypical vascular lesions from angiosarcoma (from Fineberg and Rosen\textsuperscript{25})

<table>
<thead>
<tr>
<th>Histopathological feature</th>
<th>AVL</th>
<th>AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infiltration into subcutis</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Papillary endothelial hyperplasia</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Prominent nucleoli</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Mitotic figures</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>Significant cytological atypia</td>
<td>−</td>
<td>+++</td>
</tr>
<tr>
<td>‘Blood lakes’</td>
<td>−</td>
<td>++</td>
</tr>
<tr>
<td>Dissection of dermal collagen</td>
<td>±</td>
<td>+++</td>
</tr>
<tr>
<td>Anastomotic vessels</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Hyperchromatic endothelial cells</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Chronic inflammation</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Relative circumscription</td>
<td>+++</td>
<td>−</td>
</tr>
<tr>
<td>Projections of stroma into lumen</td>
<td>+++</td>
<td>−</td>
</tr>
</tbody>
</table>

AVL, atypical vascular lesion; AS, angiosarcoma.
atypical vascular proliferation with progression to well-differentiated angiosarcoma
(by courtesy of Prof. Dr. Metze, Münster, Germany)
hyperchromatic endothelial cells

multiple lesions 11 years after radiotherapy AVP with transition into well-diff. AS
Mentzel T, Schildhaus HU, Palmedo G, Büttner R, Kutzner H. Postradiation cutaneous angiosarcoma after treatment of breast carcinoma is characterized by MYC amplification in contrast to atypical vascular lesions after radiotherapy and control cases: clinicopathological, immunohistochemical and molecular analysis of 66 cases. Mod Pathol 2012;25(1):75-85


F, 63 years, BLAP

c-myc amplification
F, 65 years, AVL, NSR at 36/12

CD 31
F, 65 years

c-myc amplification

c-myc
Problematic issue: Incidence of postradiation Angiosarcoma

Marchal C et al. Int J ROBP 1999; 44: 113
9 AS in 18115 patients = 0.049%

estimated incidence is 0.16%

estimated rate 0.05% - 1.11%

Hornick JL Practical Soft Tissue Pathology
reported risk varies from 0.09% to 0.3%
Breast carcinoma in Denmark 1995-2014

- Nr. of breast cancer patients in Denmark
- Breast conserving surgery

AS of the breast in DK, the year of AS diagnosis

- Secundary AS
- Primary AS
1995-2006: 13,150 patients received radiotherapy. 35 patients developed AS within follow-up period. Incidence of RT-induced AS 0.266%. 9 patients developed other sarcomas. Incidence of RT-induced sarcomas 0.319%.

Katalin Kiss et al. Mod Pathol 2017; 132A: 517
Conclusions

• all cutaneous vascular lesions after radiotherapy should be excised completely
• presence / absence of c-myc amplification / expression represents an additional finding in order to establish the correct dignity in RT-associated vascular lesions
• c-myc stainings may be used for mapping
• raises the possibility of new potential therapeutic options (MYC / FLT4 amplification) i.e. Sorafenib
• extended follow-up studies are necessary
M, 76 years (by courtesy of Dr. L. Requena, Madrid)
Cutaneous actinic Angiosarcoma

- irregular red plaques, nodular lesions, resemble inflammatory lesions, cut. lymphomas
- infiltrating, anastomosing vessels, atypical endothelial cells, mitoses, epithelioid morphology only rarely, prominent lymphocytic infiltrate
- CD31 +, CD34 -/+, D2-40+/-, Lyfe-1 +/-
- locally aggressive, many recurrences, late metastases, 5-years survival 15-30%
- adjuvant therapy: i.e. Paclitaxel, Thalidomide

(Eur J Cancer 2008; 30: 639; Cancer 2005; 104: 361)
Primary cutaneous epithelioid angiosarcoma: a clinicopathologic study of 13 cases of a rare neoplasm occurring outside the setting of conventional angiosarcomas and with predilection for the limbs

Suchak R et al. AJSP 2011; 35: 60

- 13 cases, $x = 66$ years, extremities (10)
- solitary (10), multicentric (3)
- dermis, infiltration of subcutis
- confluent areas of epithelioid tumour cells
- atypia, mitoses, necrosis (40%)
- CD 31 +, Fli-1 +, CK in 2/3 +
- 6/11 MTS, 6/11 DOD
F, 88 years
abdominal wall
Conclusions: cutaneous Angiosarcoma

• varying clinical presentation mimicking an inflammatory disorder, cut. lymphoma
• often prominent inflammation
• clinically very aggressive neoplasms
• morphological grading has no prognostic influence (AJSP 2008; 32: 1896)
• rare epithelioid angiosarcoma has a worse prognosis (AJSP 2011; 35: 60)

!!! Think on cutaneous angiosarcoma !!!
Angiosarcoma of Soft Tissues

- very rare (< 1 % of all sarcomas)
- elderly patients, M > F,
  lower > upper extremities, trunk > head
- rarely intraabdominal, retroperitoneal
- rarely multicentric
- very rarely in preexisting haemangiomias
- very rarely in nerve sheath tumours
- local recurrences in 20-30%
- metastases in 50%
- 5-year survival 20-30%
- aggressive surgery
epithelioid Angiosarcoma
M, 74 years, BCC was suspected, biopsy
Signet ring cell Angiosarcoma

Salviato T et al. AJDP 2013; 35: 671
- two cases, F, 68 years, M, 85 years
- parietal, retroauricular skin
- CD 31+, CD 34 +, Podoplanin +

Wood et al. Histopathology 2015; 66: 856
(2 x signet ring AS, 2 x foamy cell AS,
1 x granular cell cell AS)
M, 68 years, large tumour, face
foam cell angiosarcoma (by courtesy of Dr. Th. Brenn, Calgary)
Angiosarcoma in a pre-existing schwannoma
F, 73 years, neck
(Mentzel T, Katenkamp D
Histopathology 1999; 35: 114)
Histopathologic grading in angiosarcoma

WHO-classification 2019: grade does not correlate with prognosis

Primary angiosarcoma of the breast: clinico-pathologic analysis of 49 cases, suggesting that grade is not prognostic

Nascimento AF et al. AJSP 2008; 32: 1896
Histopathologic grading is of prognostic significance in primary angiosarcoma of breast: proposal of a simplified 2-tier grading system

Kuba MG et al. AJSP 2023; 47: 307-317

low-grade: no / < 10% of solid foci
< 10 mitoses/mm²
no tumour necrosis

high-grade: > 10% of solid foci
> 10 mitoses/mm²
tumour necrosis
low-grade angiosarcoma of the breast
5-year survival: 74%

high-grade angiosarcoma of the breast
5-year survival: 38%

*PIK3CA* and *KDR* alterations were identified in angiosarcomas of the breast with worse prognosis
Array-CGH analysis identifies two distinct subgroups of primary angiosarcoma
SLJ Verbeke et al. Genes Chromosomes Cancer 2015; 54: 72

- bone (13) and soft tissue (5) neoplasms
- array-CGH, FISH analysis and IM have been performed
- group 1: complex genetic profile
  (disrupted Rb pathway in 55%, lack of CDKN2A expression)
- group 2: few genetic aberrations only
  (*MYC* amplification, *FLT4* coamplification,
  high level amplification of 2q, 17q)
- no genetic differences between bone and soft tissue AS
Consistent *MYC* and *FLT4* gene amplification in radiation-induced angiosarcoma but not in other radiation-associated atypical vascular lesions
T Guo et al. Genes Chromosomes Cancer 2011; 50: 25-33

*KDR* activating mutations in human angiosarcomas are sensitive to specific kinase inhibitors

Recurrent CIC gene abnormalities in angiosarcomas: A molecular study of 120 cases with concurrent investigation of PLCG1, KDR, MYC, and FLT4 gene alterations (120 cases)

Targeted massively parallel sequencing of angiosarcomas reveals frequent activation of the mitogen activated protein kinase pathway
R Murali et al. Oncotarget 2015; 6: 36041
DNA methylation profiling identifies distinct clusters in angiosarcoma
Weidema ME et al. Clin Cancer Res 2020; 26: 93

36 primary angiosarcomas
6 visceral AS, 5 soft tissue AS, 14 radiation-induced AS, 11 UV-induced AS
DNA methylation revealed two main clusters (A,B) and four subclusters
A1: UV-induced AS
A2: radiation-induced AS
B: visceral and soft tissue AS
Cluster A: increased chromosomal instability better overall survival compared with cluster B
Conclusions: Vascular tumours of skin and soft tissues

- recognition of vascular malformations
- angiomasoses are a heterogeneous group
- haemangioendotheliomas are a heterogeneous group of vascular neoplasms
- AVL after RT should be handled cautiously
- angiosarcomas may mimic inflammation / cutaneous lymphoma / pseudolymphoma
- broad morphological spectrum of AS
- AS are heterogeneous genetically
SMILE!!!!
it confuses people