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No conflict of interest to disclose.

Case History

- 41 year-old man who underwent a right chest wall mass en-bloc resection for a lesion involving the 3rd rib. The tumor was diagnosed as a low grade malignant tumor at the outside hospital, and appeared completely excised.
- The patient presented 4 years later at our institution for a local recurrence in the soft tissue chest wall bed, for which a re-excision was performed.
- Frozen tissue for molecular characterization was made available at the time.
Low Power: Nodular Growth Pattern

High Power: solid growth in a hemorrhagic background

Epithelioid cells with dense eosinophilic cytoplasm

Intra-cytoplasmic empty vacuoles (so-called 'blister cells')

Overt vasoformation – dilated lumens

Overt vasoformation – small vessels

Plump endothelial cells with eccentric, bulging nuclei - 'tombstone pattern'

Periphery of the lesion
Epithelioid Vascular Neoplasm

? Atypical histologic features

Present

• Solid growth
• Increased cellularity
• Mild nuclear pleomorphism
• Mitotic Activity

Absent

• Necrosis
• Marked Pleomorphism
• Atypical mitoses

Differential Diagnosis

• Epithelioid Hemangioma

• Epithelioid Hemangioendothelioma
  – Lacks well-formed channels
  – Molecular: WWTR1-CAMTA1

• Epithelioid Angiosarcoma
  – High nuclear grade, macronucleoli, necrosis

RNA Sequencing Discovery

RT-PCR Experimental Validation – both transcripts

FISH

RNA Sequencing Discovery

RT-PCR Experimental Validation – both transcripts

FISH
**Diagnosis:**

*Epithelioid Hemangioma of Bone with FOS-LMNA Fusion*

**Epithelioid Hemangioma (EH)**

- **Definition**
  - Benign vasoformative tumor composed of epithelioid/histiocytoid endothelial cells

- **Morphologic spectrum** - wide
  - Solid growth, mature vessels, blister cells
  - Variable inflammatory infiltrate (lymphocytes, eosinophils)

- **Clinical Features**
  - Wide age range (peak 3rd-5th decade)
  - Location: head & neck, soft tissue & bone of extremities, penis

**Epithelioid Hemangioma – Pathologic Features**

- Vasoformation – lined by hobnailed epithelioid cells, ‘tombstone pattern’

**Epithelioid Hemangioma – Pathologic Features**

- Well-formed, ‘mature’ vessels
- Lobular growth pattern
Epithelioid Hemangioma – Worrisome Histologic Features

- Solid growth pattern
- Nuclear enlargement
- Mild nuclear pleomorphism
- Scattered mitotic figures

Angiolympoid Hyperplasia with Eosinophilia

- Synonymous to Epithelioid Hemangioma

Angiolympoid Hyperplasia with Eosinophilia (ALHE)

- Mostly skin/H&N
- Mixed lymph and eos inflammatory infiltrate
- Vascular damage 'blow-out pattern'
- Fibro-intimal hyperplasia
- Angiocentric capillary proliferation

Genetics of Epithelioid Hemangioma

- FOS gene rearrangements in 30% of EH
  – with different gene partners (LMNA, Vimentin)
  (Huang SC, AJSP 2015; van IJzendoorn DG, Genes Chromosome Cancer 2015)

- ZFP36-FOSB fusions in 20% of EH
  – showing atypical histology
  (Antonescu CR, Genes Chromosome Cancer 2014)
Epithelioid Hemangioma with FOS Gene Rearrangements: 17/58 (29%)

- Mean age: 43 years (range 15-67)
- Male gender (12 M/5 F)
- Location:
  - Extremities: 71%
  - Trunk: 18%
  - Head and neck: 6%
  - Penis: 6%


Epithelioid Hemangioma with FOS Gene Rearrangements

- Tissue Planes:
  - Bone: 59%
  - Soft tissue: 35%
  - Cutaneous: 6% (penile)
- Histologic variants:
  - Cellular variant: 71%
  - Typical variant: 29%
  - ALHE: 0%


FOS-rearranged Typical EH

- Radiographic findings were suggestive of fibrous dysplasia
- Low power lobulated pattern
- Well-formed vascular spaces

FOS-positive Cellular EH

- Intra-vascular growth
- Spindling
- Solid growth

23/M, 9th rib
FOS-rearranged EH with unusual histologic features

FOS gene fusion partner

- **LMNA** was only found in the index case and not found in any other FOS rearranged EH
- Review of the literature for other epithelioid vascular tumors involving the **FOS gene locus at 14q24**
  - A previous intra-osseous EHE reported as 46, XX, -6, t(10;14)(p13;q24) karyotype
  
  He M et al, Cancer Genet Cytogenet 2006

No FOS gene rearrangements in Angiolympoid Hyperplasia with Eosinophilia

FISH positional cloning identified **VIM** (vimentin) gene as FOS partner

- t(10;14)(p13;q24)

VIM Break-apart FISH assay

He M et al, Cancer Genet Cytogenet 2006
**FOS-VIM positive Bone Epithelioid Hemangioma**

- 56/F
- multifocal, foot
- cellular variant
- NED 9 years

**Epithelioid Hemangioma with FOSB gene alterations (ZFP36-FOSB fusions)**

EH with atypical Histologic Features
Index Case Proximal Tibia – 52/M

- ZFP36-FO SB positive Epithelioid Hemangioma
  - N=9/46 (20%)
  - 8M/1F; mean age 37 yrs (11-51)
  - Location:
    - Penis, n=4
    - bone, soft tissue
  - Atypical histologic features:
    - Mild to moderate pleomorphism
    - Necrosis (n=3)
  - No recurrences to date (FU limited)

A. RNAseq Discovery:

C. RNAseq Expression:

Break-apart Assay

51/M

ZFP36-FO SB positive – 4/6 Penile Epithelioid Hemangioma

Antonescu CR, Genes Chromosome Cancer 2014
**Epithelioid Hemangioma of Bone Controversy**

- Multifocal presentation/destructive growth
- Aggressive radiographic appearance
- Rare lymph node involvement
- Limited eosinophilic infiltrate
- Worrisome histologic features

**FOS & FOSB Gene Rearrangements in EH of Bone in 75-85%**

- Distinct from the genetic abnormalities seen in Epithelioid Hemangioendothelioma
- **FOS gene rearrangements:**
  - 70% (5/7) van Iizendoorn DG, Genes Chromosome Cancer 2015
- **FOSB gene rearrangements:**
  - Both with necrosis
  - Calcaneus (multifocal: foot ankle)
**FOS gene family**

- FBJ murine osteosarcoma viral oncogene homolog
- Fos family: FOS, FOSB, FOSL1, and FOSL2.
  - No FOSL1 or FOSL2 gene rearrangement in other EHS
- Encode leucine zipper proteins that can dimerize with proteins of the JUN family, thereby forming the transcription factor complex AP-1.
- Implicated as regulators of cell proliferation, differentiation, and transformation

*Maroncin, Proc Natl Acad Sci U S A. 1999*

**The other vascular tumor with FOSB gene rearrangements**

- Epithelioid Sarcoma-like Hemangioendothelioma
- Pseudomyogenic Hemangioendothelioma

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**Epithelioid Sarcoma-like Hemangioendothelioma**

- resemble Epithelioid Sarcoma more than EHE morphologically
- express epithelial and vascular markers such as CD31, Fli1
- young adults, limbs, multifocal, rare locoregional metastases

*Billings et al; Am J Surg Pathol 2003*

**Pseudomyogenic Hemangioendothelioma**

- rhabdomyoblast-like appearance - brightly eosinophilic cytoplasm
- Young males, multifocal, high local recurrence
- Diffuse positivity for AE1:AE3 and Fli1, variable for CD31

*Hornick et al. Amer J Surg Pathol 2011*
Pseudomyogenic Hemangioendothelioma

FISH analysis showing FOSB and SERPINE1 Gene Rearrangements

FOS gene family abnormalities in vascular tumors

- *FOS* rearrangements in 30% of EH (up to 70% in bone EH)
- *ZFP36-FOSB* in 20% of EH (+/- atypical histologic features; higher in penile site)
- *SERPINE1-FOSB* – predominant gene fusion in pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma

Differential Diagnosis – Epithelioid Vascular Tumors

- Epithelioid Hemangioma (benign)
- Pseudomyogenic Hemangioendothelioma (a.k.a. Epithelioid sarcoma-like Hemangioendothelioma) (rarely metastasizing category)
- Epithelioid Hemangioendothelioma (malignant)
- Epithelioid Angiosarcoma (malignant)
Epithelioid Hemangioendothelioma

- Angiocentric malignant vascular tumor
- Superficial or deep ST limbs
- Painful
- 3rd decade of life, slight female predominance

Epithelioid Hemangioendothelioma - Pathology

- Epithelioid endothelial cells arranged in cords, nests

Epithelioid Hemangioendothelioma - Pathology

- Immature intra-cytoplasmic lumina – 'blisters cells'

Epithelioid Hemangioendothelioma - Pathology

- A distinctive stroma of sulphated acid-rich matrix: myxochondroid, hyaline, myxoid
Epithelioid Hemangioendothelioma - Pathology

Growth Pattern:
- cords, single-file
- solid
- diffuse infiltrative (not-lobular)

No mature vascular channel formation!

Unusual EHE Subset with 'alveolar pattern'

EHE Subset with TFE3 gene rearrangements

- WWTR1-CAMTA1 negative
- IHC: strong TFE3 expression as well as endothelial markers (but negative for CK and HMB45)
- FISH: TFE3 gene rearrangements
EHE Subset with TFE3 gene rearrangements

ERG
TFE3

35/M, H&N soft tissue, multiple LR and loco-reg mets, NED 22 yrs FU

EHE Subset with TFE3 gene rearrangements

56yM, T2 vertebra

Multifocal Pulmonary Involvement
Rhomboid crystals

EHE Subset with TFE3 gene rearrangements

YAP1

Recurrent YAP1-TFE3 Fusion in a subset of EHE

Antonescu CR, Genes Chr Cancer 2013
**YAP1-TFE3 Fusion Positive EHE (n=10)**

- Young adults, mean 30 yrs-old
- Location: ST, bone, lung
- Epithelioid cells with abundant eosinophilic cytoplasm
- Well-formed vascular spaces (pseudo-alveolar)
- Indolent clinical course, despite high propensity for metastases
- Screened by TFE3 IHC/FISH
- To be determined if YAP1-TFE3 positive EHE will be classified under EHE or a separate entity

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**High Grade Epithelioid Angiosarcoma**

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**Differential Diagnosis of Epithelioid Vascular Tumors**

**Conclusions**

- FOS and FOSB gene rearrangements are present in more than half of EH, especially in cellular and atypical variants.
  - FISH analysis can be used in challenging cases to distinguish from EHE and epithelioid AS
- Dysregulation of the FOS family of transcription factors through chromosomal translocation is a key event in the tumorigenesis of EH.
- The lack of FOS gene abnormalities in the ALHE variant suggest a different pathogenesis
Conclusions

- **EH of bone** harbor *FOS* and *FOSB* gene rearrangements in 75-85% of cases, distinct from the genetics of EHE
  - Molecular findings finally confirm that EH in the bone is a stand-alone pathologic entity

- Despite some atypical histologic features, locally aggressive behavior or occasional multifocal growth – the accumulating clinical evidence is in keeping with a BENIGN neoplasm

Morphologic Spectrum - Index case

Epithelioid Hemangioma with ZFP36-FOSB Gene Fusions

Antonescu CR, Genes Chromosome Cancer 2014
**Differential Diagnosis**

- **Epithelioid hemangioendothelioma (EHE)**
  - Angiocentric, cords of epithelioid endothelial cells in myxohyaline stroma
  - *WWTR1-CAMTA1*, *YAP1-TFE3* fusions

- **Epithelioid angiosarcoma (AS)**
  - Solid proliferation or inter-anastomotic channels of highly pleomorphic epithelioid endothelial cells
  - *KDR*, *PTPRB*, *PLCG1*, mutations or *MYC/FLT4* gene amplification