Atlas of Genetics and Cytogenetics
in Oncology and Haematology

OPEN ACCESS JOURNAL

INIST-CNRS

# Solid Tumour Section

## Short Communication

# Bone: Epithelioid hemangioendothelioma

**Andreas F Mavrogenis, Andrea Angelini, Costantino Errani, Pietro Ruggieri**

First Department of Orthopaedics, Athens University Medical School, ATTIKON University Hospital, Athens, Greece (AFM), Istituto Ortopedico Rizzoli, Bologna, Italy (AA, CE, PR)

Published in Atlas Database: June 2014

Online updated version : http://AtlasGeneticsOncology.org/Tumors/EpitHemangioendotBoneID5617.html
DOI: 10.4267/2042/56303



## Abstract

Review on epithelioid hemangioendothelioma with data on clinics and the genes implicated.

## Identity

**Other names**

Hemangiosarcoma
Hemangioendothelioma
Hemangioendothelial sarcoma
Epithelioid angiosarcoma
Epithelioid sarcoma-like hemangioendothelioma
Pseudomyogenic hemangioendothelioma

**Note**

Vascular tumors of bone range from benign hemangioma to highly malignant angiosarcoma. They are composed of tumor cells forming vascular spaces. In 1943, Stout defined the diagnostic criteria for malignant vascular tumors, which he named hemangioendothelioma. Since 1994, the use of the term "hemangioendothelioma" referring to vascular tumors of bone has decreased due to the need of a more accurate classification.

According to the WHO Classification of Tumors of Soft Tissue and Bone and the ISSVA classification, the term "hemangioendothelioma" connotes intermediate malignancy, except in the context of epithelioid hemangioendothelioma, which is described as a distinct entity and classified as malignant. We consider the name epithelioid hemangioendothelioma of bone for low-grade malignant endothelial vascular neoplasms of bone with tumor cells showing endothelial differentiation, and a biologic behavior between that of hemangioma and angiosarcoma.

## Clinics and pathology

**Note**

Pathogenesis unclear. Highly malignant vascular tumors of bone (angiosarcomas) may arise at sites of prior radiation.

### *Epidemiology*

Epithelioid hemangioendothelioma of bone account for less than 1% of malignant bone tumors. It may occur at any age, although approximately half of the cases tend to occur during the second and third decades of life. Males and females are approximately equally affected. The tumors show a wide skeletal distribution affecting the long tubular bones of the extremity and the axial skeleton, mainly the spine. The lower extremities are predominantly affected, with more than half of the lesions located in the tibia or femur; spinal lesions account for less than 10% of the cases. Approximately one third are multicentric within a bone or multifocal, within multiple bones with lesions randomly distributed throughout the skeleton or clustered in an anatomic region, such as a single extremity. However, the distinction between multifocal and metastatic disease is not clear. In general multifocal disease is thought to be limited to a specific anatomic region (i.e., bones of the same limb) with variable involvement of individual osseous elements. Thus it is debatable whether disease in the femur and cervical spine may be considered multifocal, as opposed to metastatic given that this tumor has capacity of metastasizing hematologically. However, when disease is located in the distal femur or patella, is easier to consider it multifocal.

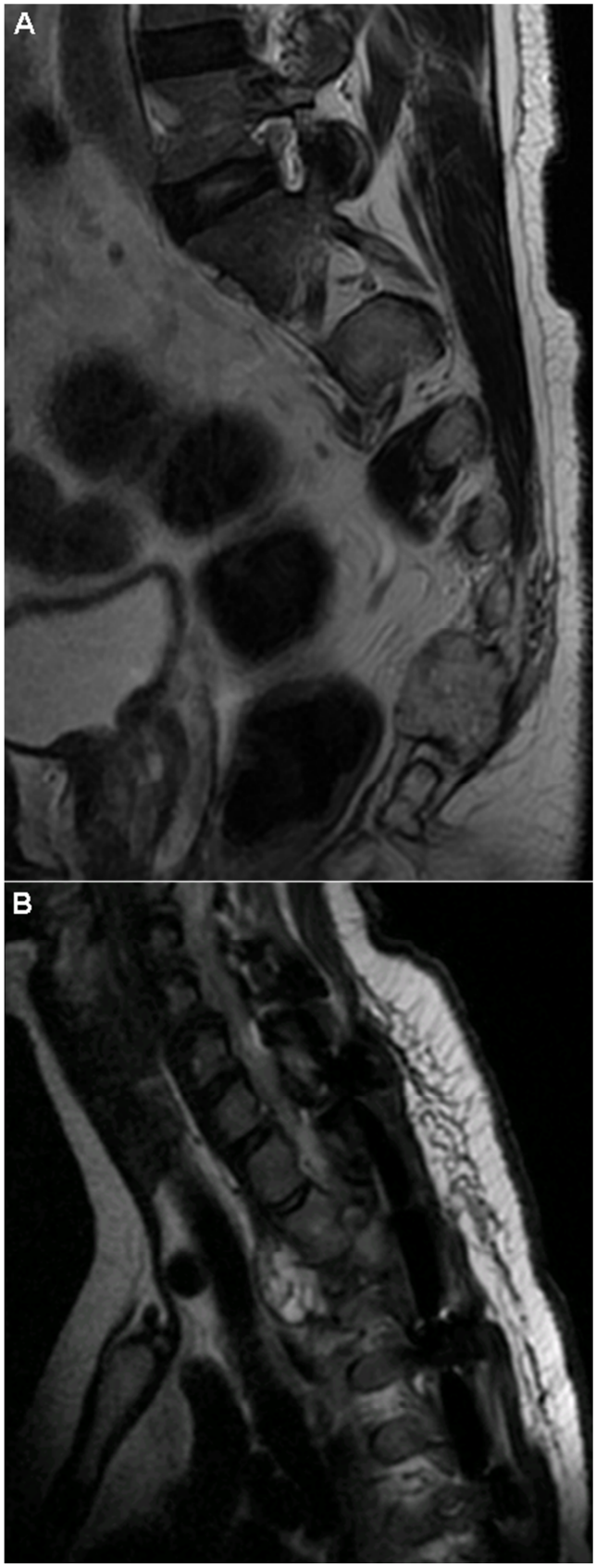


**Figure A:** Sagittal T2-weighted magnetic resonance imaging of the sacrum shows osteolysis and destruction of the coccyx with anterior soft tissue mass. Biopsy showed epithelioid hemangioendothelioma of the coccyx. **Figure B:** Sagittal T1-weighted magnetic resonance imaging of the thoracic spine of a patient with recurrent epithelioid hemangioendothelioma of the T3 vertebra.

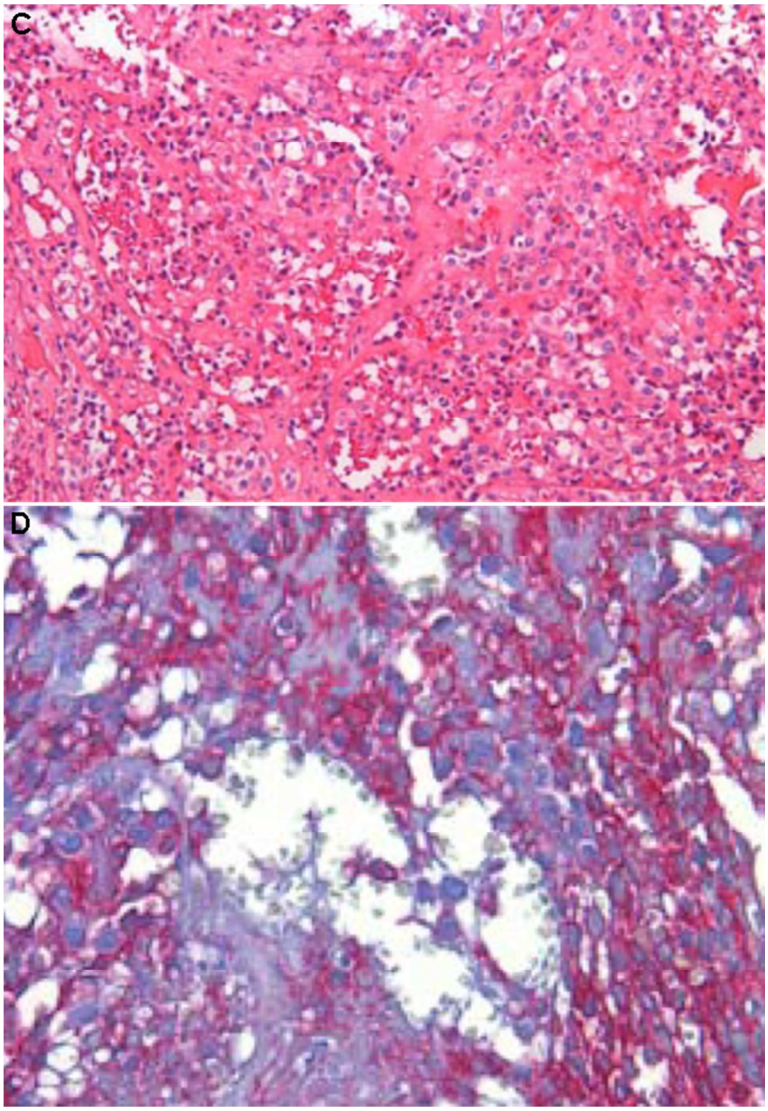


**Figure C:** Photomicrograph (stain, hematoxylin and eosin; original magnification, 10x) shows epithelioid cytomorphology with variably solid or vasoformative architecture and tumoral cells with large, pleomorphic and mildy hyperchromatic nuclei with evident nucleoli. Vascular cavities are variable and matted with neoplastic endothelial cells. **Figure D:** Photomicrograph (stain, hematoxylin and eosin; original magnification, 20x) shows blood filled cavities of different caliber rimmed by plump endothelium with epithelioid appearance. CD31 staining of the endothelium of the tumoral vessels is typically cytoplasmic.

## Clinics

Clinical symptoms include pain and possible association with a palpable tumor mass. Neurological symptoms may occur in patients with spinal involvement. Tumor growth may be rapid or slow, and infiltrative.

**Imaging**

The imaging appearance of epithelioid hemangioendothelioma of bone is non-specific.

The tumors are purely lytic, poorly marginated with varying degrees of peripheral sclerosis.

A soft tissue mass is often associated with less well differentiated tumors. Clustering of multifocal lesions in a single anatomic location suggests the diagnosis of a vascular neoplasm.

## Pathology

**Gross pathology:** Macroscopically, epithelioid hemangioendothelioma of bone tends to be firm and tan-white. The tumor can erode the cortex and extend into the soft tissue.

**Micropathology:** Microscopically, the tumor is composed of anastomosing cords, solid nests, and strands of endothelial cells that may sometimes form narrow vascular channels. The small capillary-sized tumor vessels can mimic small reactive vessels of granulation tissue. The epithelioid cells tend to have eosinophilic cytoplasm which may show vacuolization and sometimes signet ring-like appearance. The connective tissue stroma shows significant myxoid and hyalinized appearance.

The nuclei of the neoplastic cells show varying degrees of pleomorphism and anaplasia.
Although many variants of hemangioendothelioma have been reported, the striking features of growth of epithelioid hemangioendothelioma of bone are the formation of atypical endothelial cells (marked nuclear atypia, mitotic activity, spindling of cells and necrosis) arranged in cords, in greater numbers than required to line the vessels with a simple endothelial membrane, and the formation of vascular tubes with a delicate framework of reticulin fibers with a marked tendency for their lumens to anastomose. On hematoxylin and eosin stains the neoplastic epithelioid endothelial cells are embedded in a hyalinized (deep pink) or chondroid-like (light blue) matrix. No tumor should be considered an epithelioid hemangioendothelioma of bone unless these criteria are present.
**Immunophenotype:** The endothelial cells uniformly express vimentin and many cells stain with antibodies to Factor VIII, CD31, CD34, and Ulex Europaeus. Epithelioid malignancies may also express cytokeratins and EMA.
**Ultrastructure:** The endothelial cells contain Weibel-Palade bodies, but are generally difficult to find in poorly differentiated tumors. Cytoplasmic filaments are abundant.

### *Treatment*

**Surgical:** Patients with epithelioid hemangioendothelioma of bone may be cured by surgery, with or without other treatments such as chemotherapy, radiation therapy and embolization. A possible major role for wide surgery should be considered for these tumors whenever this choice does not involve high morbidity or poor functional results.
**Radiation therapy:** Adjuvant radiation therapy is advocated to decrease the risk of local recurrence. The risk for postradiation complications should be considered.
**Embolization:** As a vascular tumor the potential for intraoperative blood loss is significant. To lessen this complication, patients should have an angiographic evaluation and selective embolization when feasible.

### *Evolution*

**Outcome:** The reported local recurrence rate is up to 13%. Wide tumor resection has been related with a lower risk for local recurrence; however, a statistically significantly higher survival to local recurrence has not been shown in multivariate analysis. A median survival of 21 months, a 5-year survival of approximately 33%, and a metastatic rate of up to 31% has been reported. It is difficult to establish correctly which patient had bone metastasis and which patient had progression of the disease in the multifocal form. In the absence of a genetic analysis, patients with unifocal tumors that developed bone lesions after treatment should probably be considered as tumor progression in multifocal form.

### *Prognosis*

The histological degree of differentiation as evaluated pathologically by the histological pattern of the tumor and the cytologic atypia of the neoplastic endothelial cells, and the presence of unifocal or multifocal tumor are the most important prognostic factors.
The survival advantage for the patients with multifocal tumors may in part be related to the fact that multifocal tumors show better differentation. Conventionally, multifocal disease in a tumor with atypia would be considered a metastatic deposit, whereas when it occurs in tumors with entirely benign features it is considered a multifocal process. Additionally, tumor location in the axial skeleton and limb girdles probably precludes good prognosis because it is difficult to obtain adequate surgery, or multifocal tumors with poor outcome represent tumors with biologic behavior closer to angiosarcoma.

## Genetics

**Note**
Two epithelioid hemangioendotheliomas have shown an identical chromosomal translocation involving chromosomes 1 and 3.

## Genes involved and proteins

**Note**
Recent identification of WWTR1-CAMTA1 fusion provides a powerful diagnostic tool that can be used to distinguish an epithelioid hemangioendothelioma of bone from a hemangioendothelioma. However, genetic hallmarks of hemangioendothelioma are still under investigation.

## References

Mallory FB. THE RESULTS OF THE APPLICATION OF SPECIAL HISTOLOGICAL METHODS TO THE STUDY OF TUMORS. J Exp Med. 1908 Sep 5;10(5):575-93

Stout AP. HEMANGIO-ENDOTHELIOMA: A TUMOR OF BLOOD VESSELS FEATURING VASCULAR ENDOTHELIAL CELLS. Ann Surg. 1943 Sep;118(3):445-64

Unni KK, Ivins JC, Beabout JW, Dahlin DC. Hemangioma, hemangiopericytoma, and hemangioendothelioma (angiosarcoma) of bone. Cancer. 1971 Jun;27(6):1403-14

Rosai J, Gold J, Landy R. The histiocytoid hemangiomas. A unifying concept embracing several previously described entities of skin, soft tissue, large vessels, bone, and heart. Hum Pathol. 1979 Nov;10(6):707-30

Campanacci M, Boriani S, Giunti A. Hemangioendothelioma of bone: a study of 29 cases. Cancer. 1980 Aug 15;46(4):804-14

Wold LE, Unni KK, Beabout JW, Ivins JC, Bruckman JE, Dahlin DC. Hemangioendothelial sarcoma of bone. Am J Surg Pathol. 1982 Jan;6(1):59-70

Tsuneyoshi M, Dorfman HD, Bauer TW. Epithelioid hemangioendothelioma of bone. A clinicopathologic, ultrastructural, and immunohistochemical study. Am J Surg Pathol. 1986 Nov;10(11):754-64

Resnick D, Kyriakos M, Greenway GD.. Tumors and tumor-like lesions of the bone: Imaging and pathology of specific lesions. In: Resnick D, editor. Diagnosis of bone and joint disorders, 3rd edition. Philadelphia, PA: WB Saunders Co; 1995;3628-938.

Kleer CG, Unni KK, McLeod RA.. Epithelioid hemangioendothelioma of bone. Am J Surg Pathol. 1996 Nov;20(11):1301-11.

Mendlick MR, Nelson M, Pickering D, Johansson SL, Seemayer TA, Neff JR, Vergara G, Rosenthal H, Bridge JA.. Translocation t(1;3)(p36.3;q25) is a nonrandom aberration in epithelioid hemangioendothelioma. Am J Surg Pathol. 2001 May;25(5):684-7.

Roessner A, Boehling T.. Angiosarcoma. Pathology and genetics of tumours of soft tissue and bone. In: World Health Organization classification of tumours of soft tissue and bone. Fletcher CDM, Unni KK, Mertens F, editors. Lyon: IARC Press; 2002;322-3.

Evans HL, Raymond AK, Ayala AG.. Vascular tumors of bone: A study of 17 cases other than ordinary hemangioma, with an evaluation of the relationship of hemangioendothelioma of bone to epithelioid hemangioma, epithelioid hemangioendothelioma, and high-grade angiosarcoma. Hum Pathol. 2003 Jul;34(7):680-9.

Aflatoon K, Staals E, Bertoni F, Bacchini P, Donati D, Fabbri N, Boriani S, Frassica FJ.. Hemangioendothelioma of the spine. Clin Orthop Relat Res. 2004 Jan;(418):191-7.

Hisaoka M, Okamoto S, Aoki T, Yokoyama K, Hashimoto H.. Spinal epithelioid hemangioendothelioma with epithelioid angiosarcomatous areas. Skeletal Radiol. 2005 Nov;34(11):745-9. Epub 2005 May 5.

Gupta A, Saifuddin A, Briggs TW, Flanagan AM.. Subperiosteal hemangioendothelioma of the femur. Skeletal Radiol. 2006 Oct;35(10):793-6. Epub 2006 Jan 19.

Errani C, Zhang L, Sung YS, Hajdu M, Singer S, Maki RG, Healey JH, Antonescu CR.. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. Genes Chromosomes Cancer. 2011 Aug;50(8):644-53. doi: 10.1002/gcc.20886. Epub 2011 May 16.

Hornick JL, Fletcher CD.. Pseudomyogenic hemangioendothelioma: a distinctive, often multicentric tumor with indolent behavior. Am J Surg Pathol. 2011 Feb;35(2):190-201. doi: 10.1097/PAS.0b013e3181ff0901.

Errani C, Vanel D, Gambarotti M, Alberghini M, Picci P, Faldini C.. Vascular bone tumors: a proposal of a classification based on clinicopathological, radiographic and genetic features. Skeletal Radiol. 2012 Dec;41(12):1495-507. doi: 10.1007/s00256-012-1510-6. Epub 2012 Sep 21. (REVIEW)

Palmerini E, Maki RG, Staals EL, Alberghini M, Antonescu CR, Ferrari C, Ruggieri P, Mavrogenis A, Bertoni F, Cesari M, Paioli A, Marchesi E, Picci P, Ferrari S.. Primary Angiosarcoma of Bone: A Retrospective Analysis of 60 Patients From 2 Institutions. Am J Clin Oncol. 2013 Mar 4. [Epub ahead of print]

Angelini A, Mavrogenis AF, Gambarotti M, Merlino B, Picci P, Ruggieri P.. Surgical treatment and results of 62 patients with epithelioid hemangioendothelioma of bone. J Surg Oncol. 2014 Jun;109(8):791-7. doi: 10.1002/jso.23587. Epub 2014 Mar 18.

*This article should be referenced as such:*

Mavrogenis AF, Angelini A, Errani C, Ruggieri P. Bone: Epithelioid hemangioendothelioma. Atlas Genet Cytogenet Oncol Haematol. 2015; 19(2):150-154.