Angiosarcoma

36

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Abstract

Angiosarcoma is a high-grade malignant neoplasia characterized by cells with endothelial differentiation. It is rare in bone, usually seen in adult patients, affecting bones of the extremities, especially the femur, followed by the pelvis and axial skeleton. Most cases are unifocal but can be multifocal. It is usually painful. Its cells express endothelial markers, its epithelioid variant also expressing epithelial markers. Angiosarcoma is a very aggressive neoplasia, and its eventual multifocality makes it difficult or impossible to control; the prognosis is dismal in most cases.

Definition

- A high-grade malignant neoplasia with endothelial differentiation, rare in bone

Synonyms

- Hemangiosarcoma

Etiology

- Unknown.
- Some cases were associated to exposure to radiation, to bone infarcts, and to metallic implants.
- Multipotential bone marrow-derived hematopoietic stem cells or early endothelial progenitor cells expressing CD117, CD34, and CD45 are involved in angiosarcoma formation.

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Epidemiology

- Less than 1 % of primary bone tumors
- Usually seen in adult patients from the second to the eighth decade
- Rare in children

Sites of Involvement

- Bones of the extremities, especially the proximal femur, account for more than 70 % of cases. The pelvis and axial skeleton follow in frequency.
- Most cases are unifocal (around 70 %); the rest are multifocal affecting the same bone or multiple, contiguous bones and may also be widespread in the skeleton.

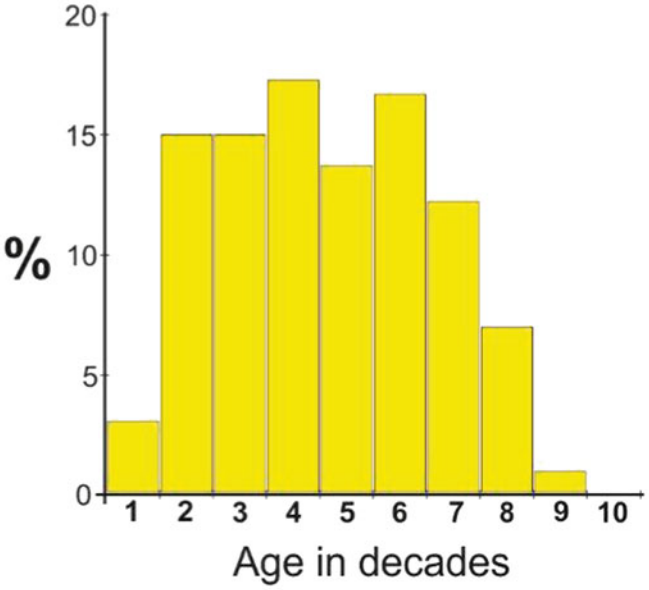
Clinical Symptoms and Signs

- Pain is usually the first symptom.
- A local mass may be present.

E. Santini-Araujo et al. (eds.), *Tumors and Tumor-Like Lesions of Bone: For Surgical Pathologists, Orthopedic Surgeons and Radiologists*, DOI 10.1007/978-1-4471-6578-1_36,

Angiosarcoma

Sex	%
Male:	59
Female:	41



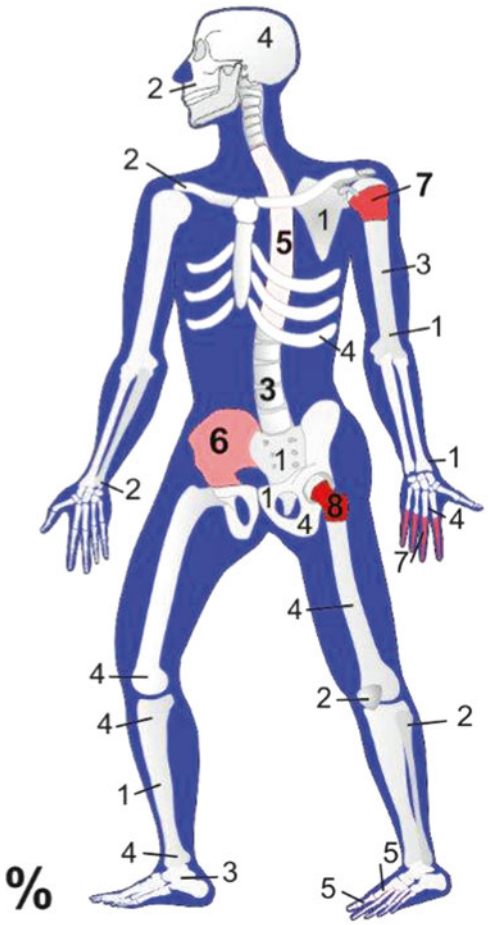


Image Diagnosis

- Radiographically, angiosarcoma usually is a completely lytic, uni- or multilocular lesion, with medullar and cortical permeation. Less commonly, it may be sclerotic or mixed, lytic and sclerotic. It usually has infiltrative margins, but these can be well defined and with no peripheral sclerosis. Periosteal reaction is absent. Invasion of the neighboring soft parts may also be seen.
- CT and MRI demonstrate more clearly the multifocal aspect of the bone or bones affected. Secondary aneurysmal bone cyst may be seen in a few cases. Reactive changes may be seen. MRI, characteristically, demonstrates low signal intensity on T1-weighted images and heterogeneously intermediate to high signal intensity on T2-weighted images.
- The imaging finding of multiple lesions by itself should be sufficient to include angiosarcoma as a diagnostic possibility.

Image Differential Diagnosis

- **Metastatic carcinoma, multiple myeloma, and lymphoma** may be difficult to differentiate by image methods alone. See also epithelioid hemangioendothelioma.

Pathology

Gross Features

- It is useful to radiograph the specimen in order to locate possible multiple foci as well as resection margins related to the lesions before sectioning.
- The cut surface shows a large or multiple hemorrhagic lesions, friable, with cortex permeation.

Histopathological Features

- Angiosarcoma is histologically classified in three grades according to cytological atypia.
- Microscopically, the tumor is composed of sheets of atypical epithelioid cells with eosinophilic cytoplasm where one or more vacuoles may be seen ("blister cells"). The occasional finding of erythrocytes or its fragments in these vacuoles is characteristic of the endothelial origin of the tumor cells. In a minority of cases, cells may be spindled. The nuclei are large, vesicular, and with prominent nucleoli. Atypical and numerous mitotic figures are common.
- Another tissue pattern that may be found, especially in well-differentiated tumors, is vasoformative, with the atypical endothelial cells lining irregular vascular spaces.
- Inflammatory infiltrate, hemorrhage, hemosiderin deposits, and necrotic areas are usually seen, and the tumoral infiltration by erythrocytes and neutrophils is considered suggestive of endothelial tumors.

Pathology Differential Diagnosis

- **Epithelioid hemangioendothelioma or epithelioid hemangioma** – These tumors do not present the numerous atypical cells and atypical mitosis usually seen in an angiosarcoma.
- **Metastatic carcinoma** – As angiosarcoma may stain with epithelial markers, this differential must be considered in a biopsy sample. Endothelial markers are needed to establish the correct diagnosis. Desmoplastic stromal reaction is more common in metastatic carcinoma than in angiosarcoma.
- **Metastatic melanoma** – Negative for endothelial markers and positive for melan-A, HMB45, and S100.

Ancillary Methods

- Angiosarcomas express endothelial markers as CD31, CD34, von Willebrand factor, FLI1, and ERG. Epithelioid cells of epithelioid angiosarcoma usually express epithelial markers. A few cells may be positive for SMA. Lymphangiogenic marker D2-40 may be positive in a few cases.

Genetics

- Translocation t(1;14)(p21;q24) was described in one case.
- In nearly 55 % of the angiosarcomas of the bone, the retinoblastoma (Rb) pathway was affected, suggesting that this pathway is involved in tumorigenesis of angiosarcoma. The loss of CDKN2A expression was associated with a significantly worse prognosis. No overexpression of TP53 or MDM2 was found. Angiosarcoma of the bone showed highly active TGF-β signaling with immunoreactivity for phospho-Smad2 and PAI-1. PIK3CA hotspot mutations were absent. The PI3K/Akt pathway is activated in both angiosarcomas of the bone and soft tissue, however, with a different cause; contrary to its soft tissue counterpart, PTEN expression is decreased in angiosarcoma of the bone.

Prognosis

- Angiosarcoma is a very aggressive neoplasia, and its eventual multifocality makes it difficult or impossible to control.
- One- and five-year survival rates average 55 % and 33 %, respectively.
- Pathologic characteristics of worse prognosis are:
  - Tumors larger than 10 cm
  - Presence of macronucleolus
  - Three of more mitoses per 10 HPF
  - Fewer than five eosinophilic granulocytes per 10 HPF
  - D2-40 positivity by immunohistochemistry
  - Loss of CDKN2A expression

Treatment

- Early diagnosis and surgical resection may offer the best hope of cure, but in the large majority, especially in advanced cases, the prognosis is dismal.
- Radiation for close surgical margins or worrisome pathologic features can result in long-term survival.
- The effectiveness of adjuvant chemotherapy is unknown, but there can be dramatic responses in a minority of patients.

Images

See Figs. 36.1, 36.2, 36.3, 36.4, 36.5, 36.6, 36.7, 36.8, and 36.9 for illustrations of angiosarcomas.

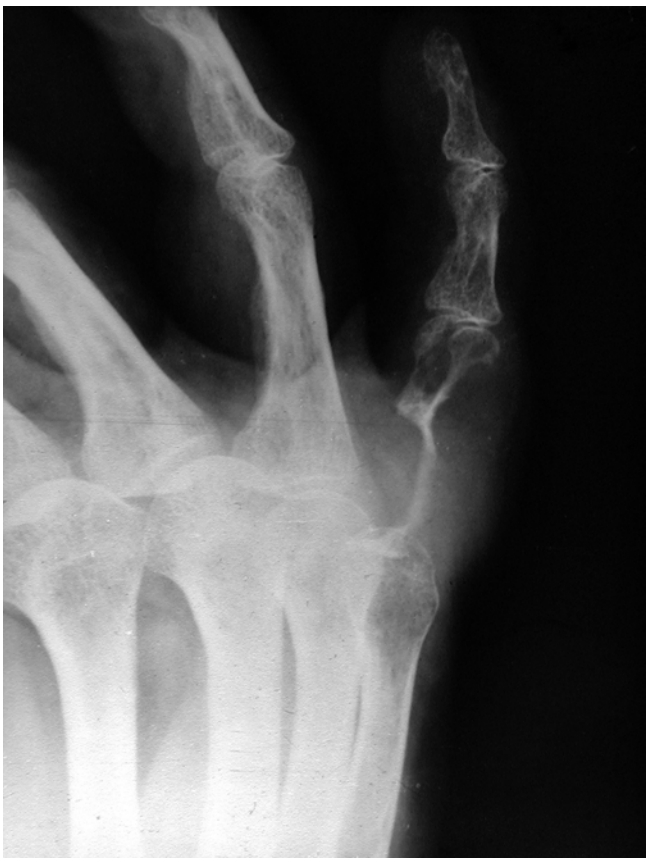


Fig. 36.1 Radiograph showing angiosarcoma involving multiple regional bones of the hand

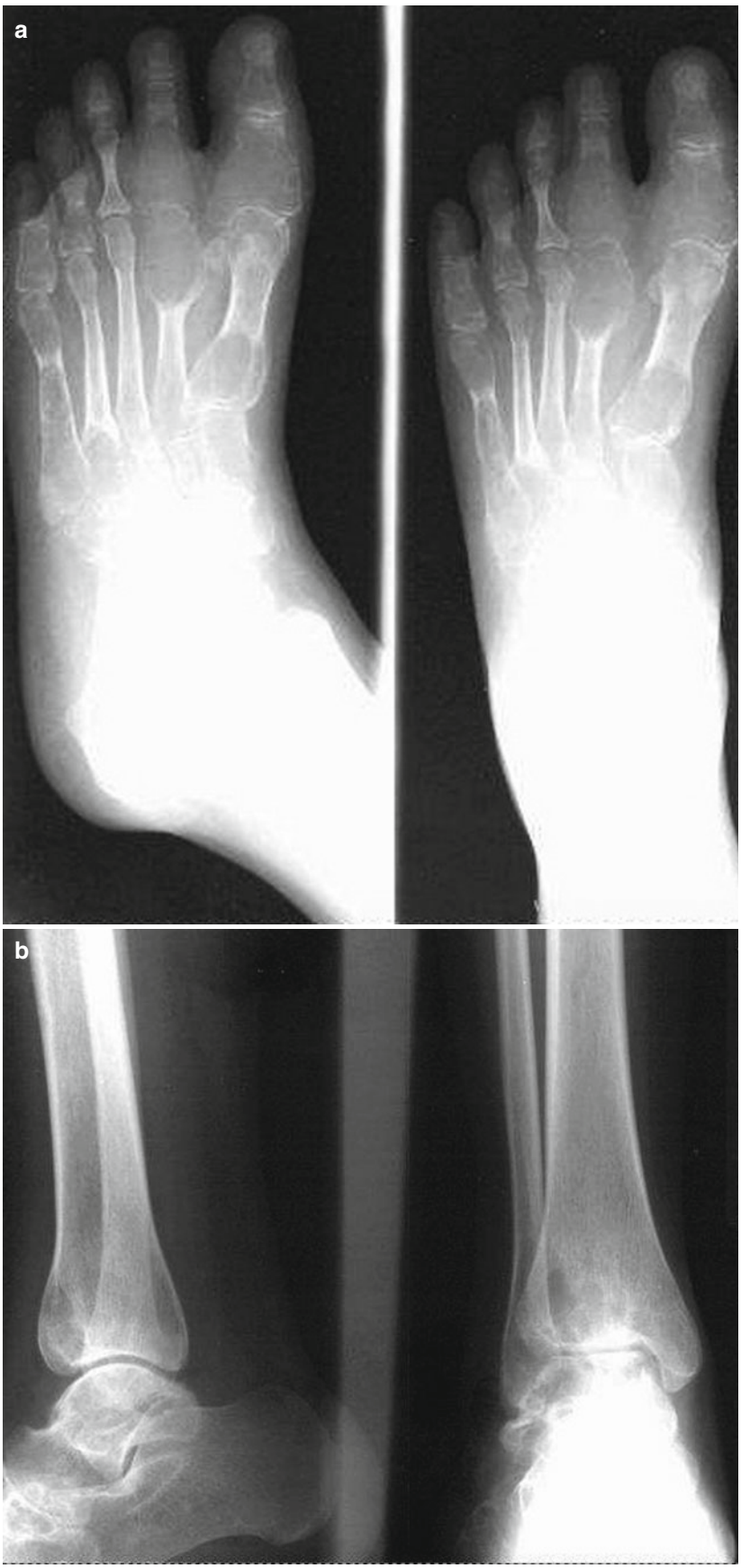


Fig. 36.2 (**a**) Radiograph showing another example of angiosarcoma involving multiple regional bones of the foot. (**b**) The tibia was also involved in this case

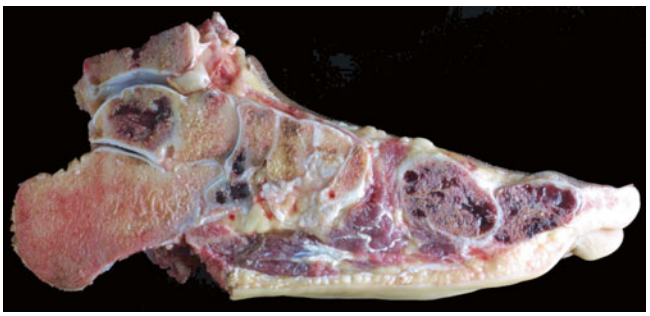


Fig. 36.3 The same case as the previous figure. Macrophotography shows involvement of multiple bones of the foot by a spongy brown tissue with small cyst-like or large vascular spaces filled by blood

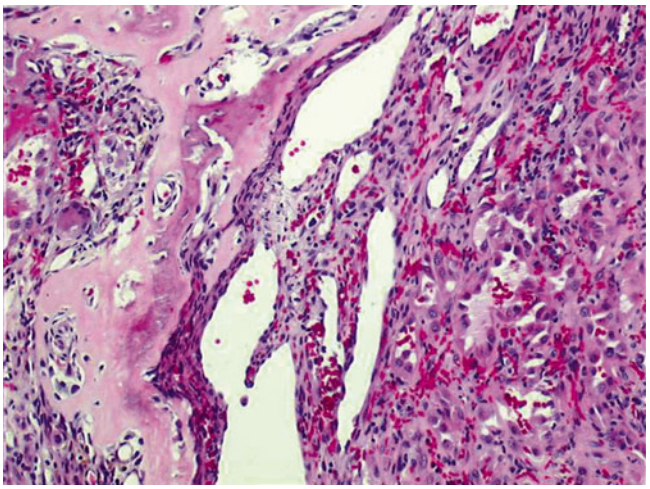


Fig. 36.4 Microphotography showing bone involvement by a richly vascular tissue. Dilated neoplastic vessels at the periphery of a tumoral nodule

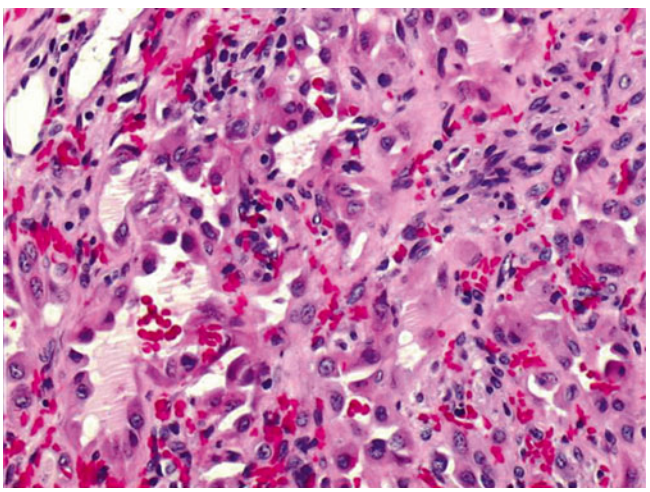


Fig. 36.5 Microphotography of the same field as the previous figure. Well-differentiated angiosarcoma, in this field constituted by small vascular channels lined by epithelioid endothelial cells with moderate atypia

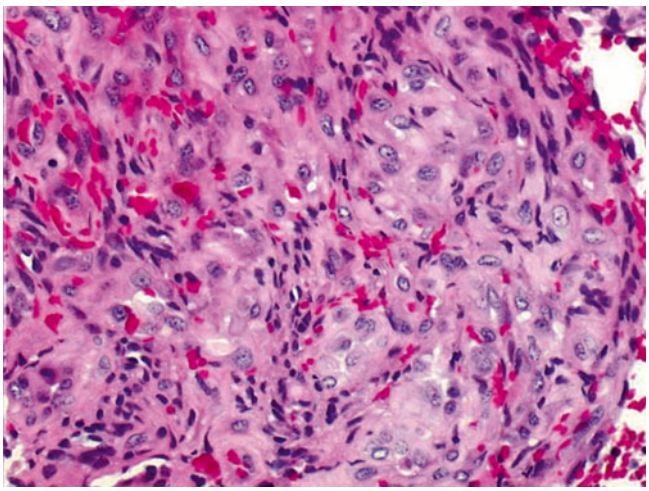


Fig. 36.6 Another field of the same case as the previous figure. Solid proliferation of moderate differentiated epithelioid cells

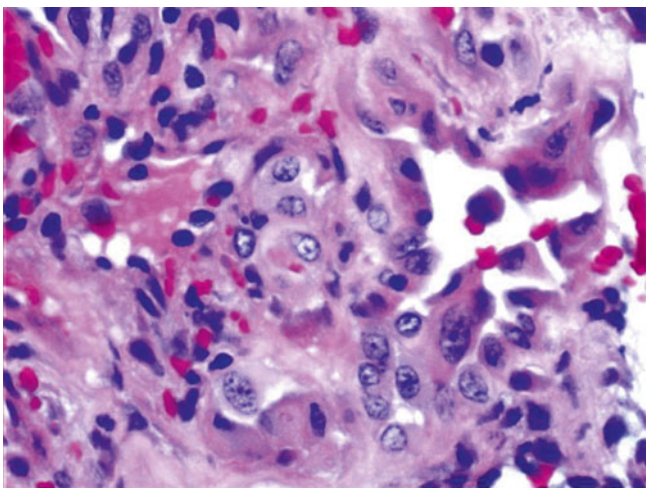


Fig. 36.7 Higher-power view of the previous case highlighting the epithelioid morphology of the cells as well as moderate atypia

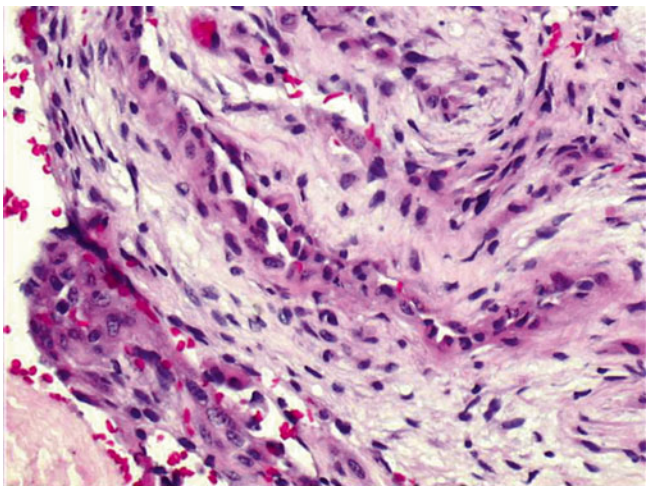


Fig. 36.8 Irregular vascular channels lined by moderately atypical endothelial cells in a loose, somewhat myxoid, stroma

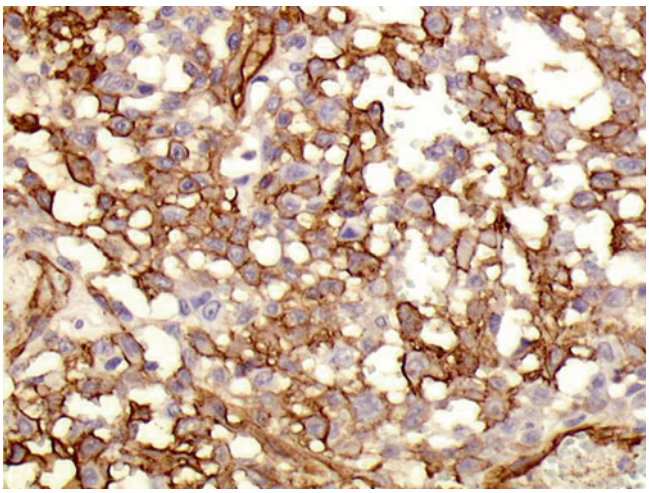


Fig. 36.9 Immunohistochemistry demonstrated positivity for CD34

Recommended Reading

Abdelwahab IF, Klein MJ, Hermann G, et al. Angiosarcomas associated with bone infarcts. Skeletal Radiol. 1998;27:546–51.

Abraham JA, Hornicek FJ, Kaufman AM, Harmon DC, Springfield DS, Raskin KA, Mankin HJ, Kirsch DG, Rosenberg AE, Nielsen GP, Desphpande V, Suit HD, DeLaney TF, Yoon SS. Treatment and outcome of 82 patients with angiosarcoma. Ann Surg Oncol. 2007;14(6):1953–67.

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;41(12):1495–507.

Fletcher CDM, Bridge JA, Hogendoorn PCW, Mertens F, editors. WHO classification of tumors of soft tissue and bone. 4th ed. Lyon: IARC Press; 2013.

Hart JL, Edgar MA, Gardner JM. Vascular tumors of bone. Semin Diagn Pathol. 2014;31:30–8.

Liu L, Kakiuchi-Kiyota S, Arnold LL, Johansson SL, Wert D, Cohen SM. Pathogenesis of human hemangiosarcomas and hemangiomas. Hum Pathol. 2013;44(10):2302–11.

McDonald DJ, Enneking WF, Sundaram M. Metal-associated angiosarcoma of bone: report of two cases and review of the literature. Clin Orthop Relat Res. 2002;(396):206–14.

Mittal S, Goswami C, Kanoria N, Bhattacharya A. Post-irradiation angiosarcoma of bone. J Cancer Res Ther. 2007;3(2):96–9.

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. 2014;37(6):528–34.

Verbeke SL, Bertoni F, Bacchini P, Sciot R, Fletcher CD, Kroon HM, Hogendoorn PC, Bovée JV. Distinct histological features characterize primary angiosarcoma of bone. Histopathology. 2011;58(2):254–64.

Verbeke SL, Bertoni F, Bacchini P, Oosting J, Sciot R, Krenács T, Bovée JV. Active TGF-β signaling and decreased expression of PTEN separates angiosarcoma of bone from its soft tissue counterpart. Mod Pathol. 2013;26(9):1211–21.