

Vascular Tumors of Bone

The Evolvement of a Classification Based on Molecular Developments



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KEYWORDS

- Epithelioid hemangioma • Epithelioid hemangioendothelioma • Vascular tumor • Angiosarcoma
- Pseudomyogenic hemangioendothelioma

Key points

- Vascular tumors with primary bone localization include hemangioma, epithelioid hemangioma, pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma, epithelioid hemangioendothelioma, and angiosarcoma.
- A panel of vascular markers should be used to confirm endothelial differentiation (including ERG, CD31, and CD34).
- Epithelioid hemangioendothelioma is characterized by WWTR1-CAMTA1 fusions, whereas epithelioid hemangioma and pseudomyogenic hemangioendothelioma carry alterations within the FOS family (FOS and FOSB). Molecular analysis or immunohistochemistry for CAMTA1 or FOSB can help in the differential diagnosis.
- Angiosarcoma of bone is highly aggressive, often epithelioid, and without recurrent genetic alterations.

ABSTRACT

The classification of vascular tumors of bone has been under debate over time. Vascular tumors in bone are rare, display highly overlapping morphology, and, therefore, are considered difficult by pathologists. Compared with their soft tissue counterparts, they are more often multifocal and sometimes behave more aggressively. Over the past decade, with the advent of next-generation sequencing, recurrent molecular alterations have been found in some of the entities. The integration of morphology and molecular changes has led to a better characterization of these separate entities.

OVERVIEW

The common denominator of vascular tumors consists of their endothelial differentiation, with a variable capability of forming mature or immature

vessels. Literature on the cell of origin for vascular tumors (other than infantile hemangioma) is scarce and points to an endothelial precursor cell or a hematopoietic precursor cell along its path of endothelial differentiation, for canine and murine hemangioma/angiosarcoma.^{1,2} The definition of these cells in mice and humans, however, is controversial.^{3,4}

The classification of vascular tumors of bone has been a matter of discussion over time.^{5–7} With the rapid elucidation of molecular changes in tumors using next-generation sequencing, however, which also included vascular tumors of bone, the classification has evolved and morphology and molecular changes were integrated to better define the separate entities⁸ that are sometimes extremely difficult to distinguish based on morphology alone. Like in soft tissue, the entity of hemangiopericytoma of bone is no longer recognized, because these lesions are rare presentations of synovial sarcoma, solitary fibrous tumor, and myofibroma primary of bone.⁹ Moreover, although in the past there has

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Table 1
Summary of prognosis and treatment of vascular bone tumors

Classification	Entity	Prognosis	Treatment
Benign	Hemangioma	100% survival, 0% metastasis	Treat symptoms
Intermediate	Epithelioid hemangioma	100% survival, 2% metastases, 9% local recurrence	Curettage or marginal excision
	Pseudomyogenic hemangioendothelioma	Limited follow-up, stable or progressive osseous disease	
Malignant	Epithelioid hemangioendothelioma	85% survival, 25% metastases	Wide resection
	Angiosarcoma	30% survival	Wide resection, consider systemic therapy

been ample discussion about hemangioendothelioma of bone as a separate entity,¹⁰ it is now generally accepted that the previously reported cases represent epithelioid hemangioma of bone,^{8,9,11} and with the elucidation of specific genetic alterations in epithelioid hemangioma of bone^{12,13} this discussion may be definitively resolved in the future.

Now that the different vascular tumors have been better characterized, their distinct behavior in bone compared with when they are located in the soft tissues is becoming obvious. Vascular tumors of bone are more frequently multifocal, affecting multiple bones.⁶ Also, although histologically and genetically similar, epithelioid hemangioma in soft tissue is considered benign, whereas in bone it behaves as a locally aggressive, rarely metastasizing lesion and is, therefore, considered of the intermediate category.⁸ In addition, atypical epithelioid hemangioma has a preference for bone and penile location.¹⁴ Moreover, after the morphologic and molecular characterization of pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma,^{15,16} cases are reported that are exclusively located in bone, with unique histologic findings.¹⁷

This article discusses the most common vascular tumors of bone. These tumor entities range from the benign hemangioma of bone, with a good prognosis and no metastasis in all patients, to the intermediate epithelioid hemangioma (including the atypical variant) and the pseudomyogenic hemangioendothelioma whose survival is excellent but with some metastasis and recurrences. Epithelioid hemangioendothelioma is considered low-grade malignant, with 85% survival and 25% metastases. Angiosarcoma is high-grade malignant with a very poor survival of only 30% over 5 years (Table 1). This review covers the classic presentations of these tumor entities, including the diagnostic pitfalls and immunohistochemistry and discusses the recent developments regarding the genetics and tumorigenesis of these vascular tumors of bone (Table 2).

IMMUNOHISTOCHEMISTRY

In all vascular tumors, endothelial differentiation can be highlighted using a panel of immunohistochemical markers, including CD31, CD34, and ERG. ERG positivity can be highly specific for endothelial differentiation, although this is dependent on the clone used: antibodies against the N-terminal part of the protein are more specific compared with antibodies directed against the C-terminal part, which can also be positive in a variety of other mesenchymal tumors.¹⁸ Moreover, approximately 50% of the prostate carcinomas harbor translocations involving ERG and thereby can be positive.¹⁹ FLI1 and von Willebrand factor (VWF), or factor VIII, can also be used. Smooth muscle actin can highlight the pericytes, whereas D2-40 (podoplanin) and Prox1 can demonstrate lymphatic differentiation. A notorious pitfall that pathologists should be aware of, especially in bone where vascular tumors are often epithelioid (93%–100%^{20,21}), is the expression of keratin in a significant percentage of vascular tumors.^{20,22,23}

HEMANGIOMA

DEFINITION, EPIDEMIOLOGY, AND CLINICAL FEATURES

Hemangiomas are common lesions that rarely ever reach a pathologist. Reported by Mirra and colleagues,²⁴ these tumors are found in approximately 10% of all autopsies and they are often seen by radiologists. They are usually asymptomatic. The vertebral bodies and the skull are most commonly affected (Fig. 1).²⁵ Kaleem and colleagues²⁶ analyzed all reported cases of hemangioma affecting the extremities in English literature through 2000 (n = 104) and found a mean age of 32 years and a slight preference for women (60%). When affecting the long bones, the diaphysis or metadiaphysis is the most common

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