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Review Article

Primary vascular tumors of bone: a spectrum of entities?

Sofie L. J. Verbeke[1,2], Judith V. M. G. Bovée[1]

[1]Department of Pathology, Leiden University Medical Center, Leiden, The Netherlands; [2]Department of Pathology, Antwerp University Hospital, Edegem, Belgium

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Abstract: Vascular tumors of bone are a heterogeneous group. Numerous terms have been introduced as well as different classification systems. None of the classification schemes have been accepted due to lack of consistent terminology, accepted histologic criteria, and limited correlation with clinical outcome. It is acknowledged that vascular tumors of bone originate from endothelial cells, resulting in variable expression of endothelial markers. None of these markers are useful to discriminate between benign and malignant lesions. Although radiologic appearance is not specific, radiologic multifocality should trigger to include a vascular neoplasm in the differential diagnosis. This review gives an overview of current literature by describing all different histologic subtypes in correspondence with clinical, radiologic and genetic data. We propose the classification of vascular tumors of bone according to the three-tiered World Health Organization classification scheme for soft tissue tumors dividing entities into a benign, intermediate and malignant category. Hemangioma is the most often and commonly recognized benign lesion. Epithelioid hemangioma has been better defined over the past few years. Based on its locally aggressive behavior and occurrence of lymph node metastases, classification within the intermediate category could be considered. Angiosarcoma is the only accepted term for high-grade malignant vascular tumor of bone and so far, epithelioid hemangioendothelioma is the only accepted low-grade malignant vascular tumor of bone. It is still unclear whether other low-grade malignant vascular tumors of bone (e.g. hemangioendothelioma) truly exist. Unfortunately, molecular / genetic studies of vascular tumors of bone which might support the proposed classification are very sparse.

Keywords: vascular tumor of bone, hemangioma, epithelioid hemangioma, epithelioid hemangioendothelioma, angiosarcoma, bone tumor

Introduction

Today, vascular tumors of bone consist of a wide variety of different clinicopathologic entities, ranging from benign lesions on one hand and frankly malignant tumors at the other hand. Since the first report on malignant vascular tumors of bone in 1921 by Wells [1], various entities have been described and many different terms have been proposed. Over the years, terms such as angiosarcoma, hemangiosarcoma and hemangioendothelioma have been used sometimes as synonyms or to stress different histologic entities, confusing numerous medical experts [2-6]. Also the classification of vascular tumors of bone is highly controversial, especially considering the lack of consistent terminology, accepted histological criteria, and the limited correlation with clinical outcome. As a consequence, so far none of the suggested classification schemes have been generally accepted [7, 3, 4, 6]. Wenger and Wold acknowledged the confusing terminology and proposed in 2000 a new classification system for benign and malignant vascular tumors and stated that these lesions should be regarded as a spectrum [6, 8]. However, this is still controversial since a spectrum implicates the possibility of progression of a benign lesion towards a malignancy over time and only single case reports have described this phenomenon [9-16].

Since 1942, it is generally accepted that vascular tumors of bone originate from endothelial cells [17]. The exact mechanism or possible genetic aberrations resulting in tumorigenesis still remains unknown. In this review we want to give an overview and update of the current classification of vascular tumors of bone (**Table 1**) by describing all different histologic subtypes in

Table 1. Proposed classification of vascular tumors of bone

Benign vascular tumors of bone
Hemangioma
Cavernous
Capillary
(Hem)angiomatosis
Non-aggressive, regional
Non-aggressive, disseminated (cystic angiomatosis)
Aggressive or massive osteolysis or Gorham Stout's Disease
Intermediate (locally aggressive, rarely metastasizing) vascular tumors of bone
Epithelioid hemangioma
Malignant vascular tumors of bone
Epithelioid hemangioendothelioma
Angiosarcoma
Primary
Irradiation-induced
Bone infarction associated

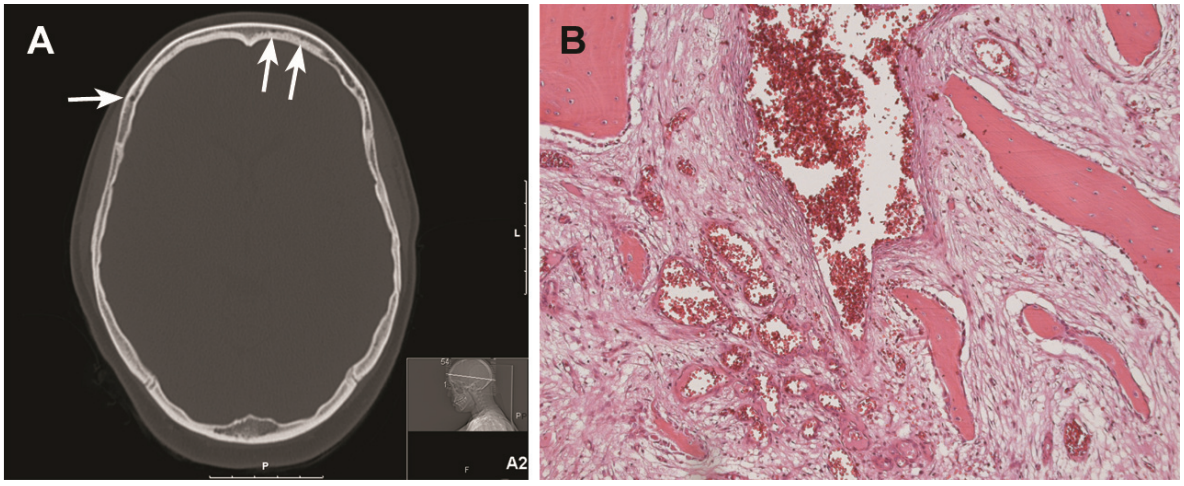

Figure 1. Hemangioma of bone. **A.** Radiology: conventional X-ray of the scalp showing multiple small well-demarcated osteolytic lesions (arrows); **B.** Histology: multiple vascular spaces lined by non atypical endothelial cells filled with erythrocytes (haematoxylin-eosin staining, 20x).

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correspondence with clinical, radiologic and when available genetic or biologic data. Vascular tumors, for which a primary bone origin is extremely rare, are not discussed within this review. Since molecular studies on vascular tumors of bone are sparse, their value in the classification of these lesions is limited.

Radiographic imaging

Because of the heterogeneity of vascular tumors of bone, imaging is not very specific. However, some radiographic alterations can indicate the probability of a benign or malignant osseous vascular tumor (**Figure 1, 2, 4** and **5**). By conventional radiographs, the majority of the hemangiomas show a well demarcated, lucent lesion with frequent coarse trabeculations [8, 18, 19]. Although cortical expansion can be seen in hemangiomas, cortical disruption and invasion into the surrounding soft tissue is most often characteristic of malignancy. Moreover, malignant vascular tumors of bone are most often characterized by an ill-defined, osteolytic lesion with cortical disruption and endosteal scalloping. Up to one third of the malignant vascular tumors of bone presents with synchronic multiple osseous lesions which can be either contiguous (adjacent bones affected) or disseminated [20]. Although the radiographic fea-

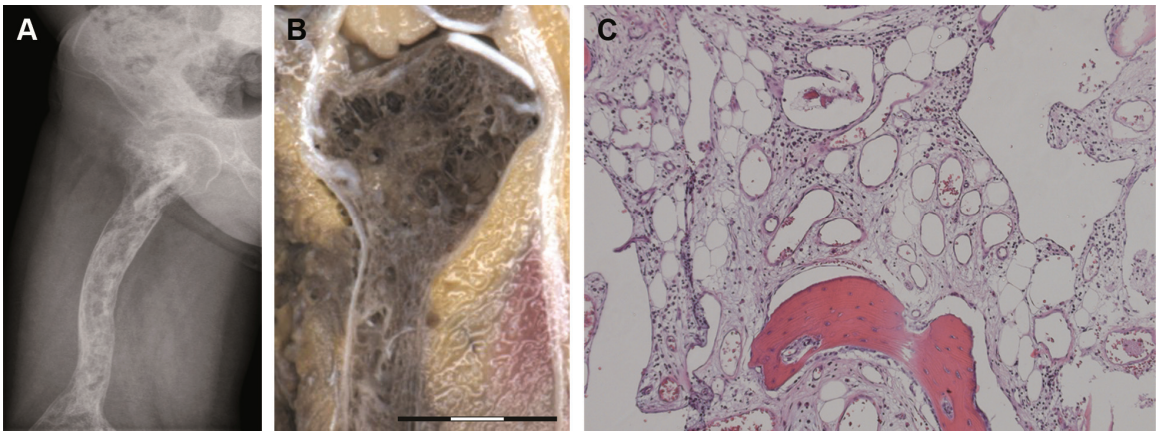

Figure 2. Angiomatosis of bone. (Gorham- Stout disease, vanishing bone disease): **A.** Radiology: conventional X-ray of the femur showing bone deformation with multiple osteolytic lesions; **B.** Gross examination of an amputation specimen showing multiple cystic lesions within the bone marrow of the femur (scale in centimeters); **C.** Histology: demonstrating the morphology of a hemangioma consistent of multiple vascular spaces lined by non atypical endothelial cells filled with erythrocytes (haematoxilin-eosin staining, 20x).

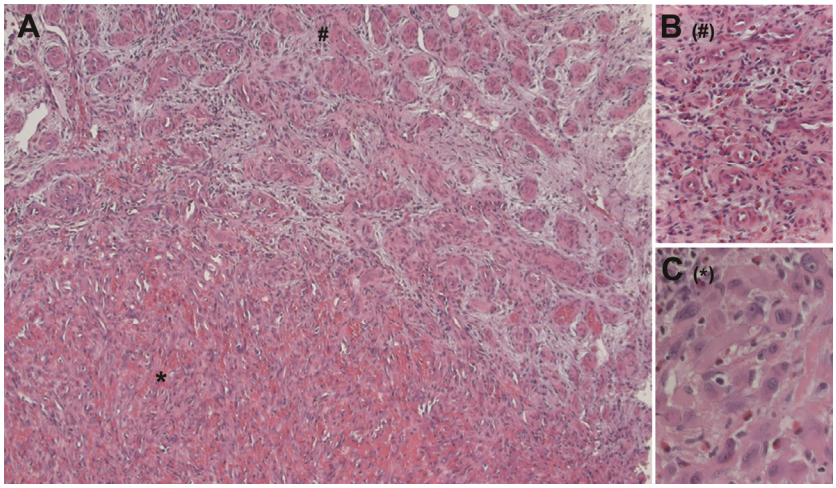

Figure 3. Epithelioid hemangioma of bone**. A.** Histologic overview of an epithelioid hemangioma of bone composed of two distinct areas (marked with * and #) haematoxilin-eosin staining, 10x): **B (*).** the peripheral area with numerous small arteriolar-like vessels and an infiltrate consistent of numerous eosinofilic granulocytes (haematoxylin-eosin staining, 40x) and **C (#).** the cellular central area with large, polyhedral, epithelioid cells with a more solid growth pattern intermixed with eosinofilic granulocytes (HE staining, 40x).

tures of malignant vascular tumors of bone are non-specific, multifocal lesions in one anatomic region should trigger the radiologist to include a vascular neoplasm in the differential diagnosis [20, 21].

Immunohistochemistry

It is generally accepted that vascular tumors, both of soft tissue and bone, originate from endothelial cells resulting in a variable expression of endothelial markers such as CD31, CD34, Fli-1 and von Willebrand Factor (Factor VIII) [22, 23, 24]. Although it has been reported that CD31 and von Willebrand Factor are the best diagnostic markers for malignant vascular tumors of bone, the use of a panel of endothelial markers is essential to confirm the diagnosis because a minority of the malignant tumors only express CD34 [25]. Based on the expression of the endothelial markers it is impossible to discriminate between benign and malignant vascular tumors. Vascular tumors variably express D2 -40 (31%) [25], a presumed lymph-endothelial marker, and its expression in angiosarcoma is associated with a worse prognosis, suggesting lymphangiosarcoma of bone may exist [26, 25]. Cytokeratin (69%) [25] and/ or epithelial membrane antigen (4-35%) [27, 28], are also expressed, in particular but not exclusively in neo-

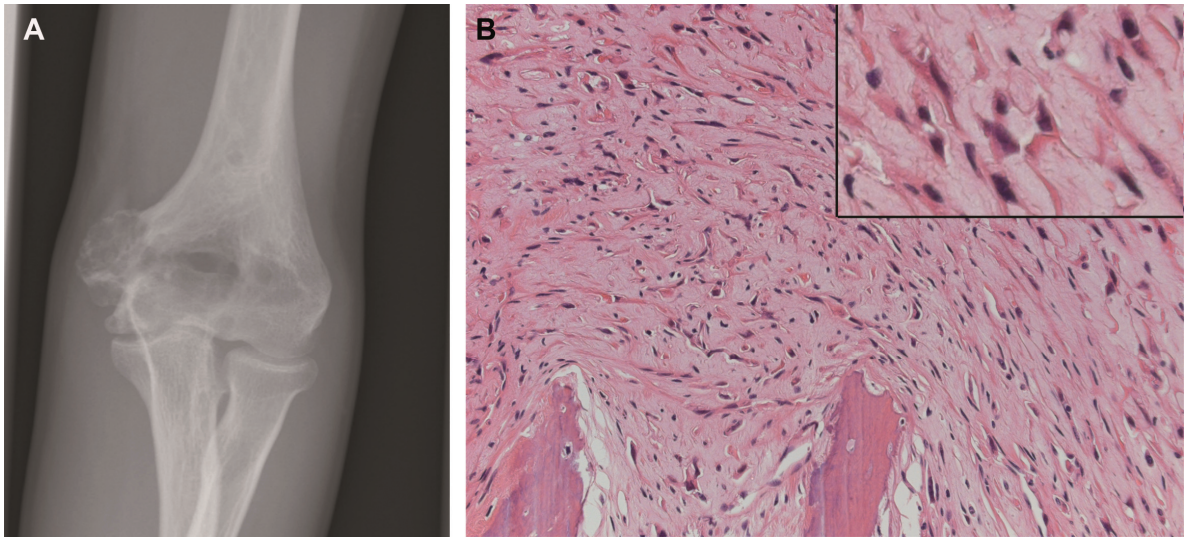

Figure 4. Epithelioid hemangioendothelioma of bone. **A.** Radiology: conventional X-ray of the distal humerus showing an excentric osteolytic lesion (arrow); **B.** Histology: characteristic strands and cords of epithelioid endothelial cells surrounded by a hyalinized stroma (haematoxilin-eosin staining, 20x) with inset: showing the nuclear detail and presence of cytoplasmic vacuoles (haematoxilin-eosin staining, 63x).

plasms with an epithelioid morphology [20, 25]. Since these lesions have a tendency to occur multifocal (contiguous or disseminated), the epithelioid morphology and keratin positivity may easily lead to an erroneous diagnosis of metastatic carcinoma.

Benign vascular tumors of bone

Hemangioma

Hemangioma of bone (**Figure 1, Table 2**) is the most common benign vascular tumor of bone [8]. Its etiology is still unknown. Moreover, it is still unclear whether these lesions are true neoplasms or should be regarded as hamartomas [18, 29]. Despite the lack of appropriate data regarding the incidence or prevalence of hemangioma, autopsy reports have demonstrated that vertebral hemangioma occurs in approximately 10% of adults [18]. Hemangiomas occur in both men and women, with a wide age range and are mostly located in skull and vertebra [8, 18]. Although these lesions can cause various signs and symptoms the majority of patients present with an asymptomatic and incidental radiographic finding [8, 18]. Several different histologic subtypes are described, such as cavernous, capillary and sclerotic hemangioma [18]. Malignant transformation is only described in a few cases [9-15]. In general, hemangiomas have a very good prognosis and a low recurrence rate.

Angiomatosis

Skeletal angiomatosis (**Figure 2, Table 2**) is a rare disorder and is defined as multiple cystic bone lesions with or without soft tissue involvement. Soft tissue involvement is present in 60-70%, and in general the spleen is affected [30]. Clinical presentation is dependent on localization, the size and the number of lesions and can vary from an incidental finding to local pain, swelling and/ or pathological fracture [31, 32, 33, 34]. These lesions are classified based on their clinical behavior (aggressive or nonaggressive) and pattern of skeletal involvement (regional or disseminated) [35, 20, 31]. Regional involvement is defined as corrosion of one or more bones of one anatomic region, whereas disseminated involvement is characterized by multifocal disease with typically involvement of the trunk bones [35]. Gorham's Disease, also known as massive osteolysis or disappearing bone disease, is an aggressive form of regional skeletal angiomatosis. Although the etiology still remains unknown, half of the cases are associated with trauma [36, 37]. This disease results in progressive destruction of one bone and sometimes also adjacent bones. It is merely a clinicoradiologic diagnosis, since the

Table 2. Overview of epidemiologic, clinical and histologic characteristics of the different subtypes of vascular tumors of bone

	Hemangioma	Angiomatosis	Epithelioid hemangioma	Epithelioid hemangioendothelioma	Angiosarcoma
M vs F ratio	2:3	males>females	1.4:1	males>females	males>females
Age range (d)	1th-8th	1th-7th	1th-8th	1th-8th	2nd-8th decade
Peak age (d)	4th-5th	within first 3 decades of life	4th	2nd	6th-8th decade
Location	skull, vertebrae	shoulder, hip	long tubular bones	long tubular bones of extremities	long tubular bones of extremities, spine
Multifocality (%)	5-18%	100%	18%	50-64%	33%
Histology					
Growth pattern	vascular spaces	vascular spaces	lobular growth pattern periphery: arteriolar-like vessels central: epithelioid cells	strands/ cords of solid nests epithelioid endothelial cells Intracytoplasmatic vacuoles myxoid/ hyalinized stroma	heterogeneous: vasoformative to solid macronulceolus <5 eosinophils/ 10 HPF
Atypia	no	no	no	variable degree	yes
Mitoses/ 10 HPF	no	no	<5	no or little	≥3
Atypical mitoses	never	never	never	no or little	yes
Survival	100%	dependent on visceral involvement	100%	dependent on visceral involvement	33% 5-year survival
Recurrence rate	low	n.k.	8%	n.k.	n.k.
Metastatic rate	0%	0%	2%	n.k.	high
Treatement	conservative	dependent on the extent	curettage, marginal en bloc resection	en bloc resection	dependent on tumor stage, multimodality treatment

d = decades; n.k. = not known.

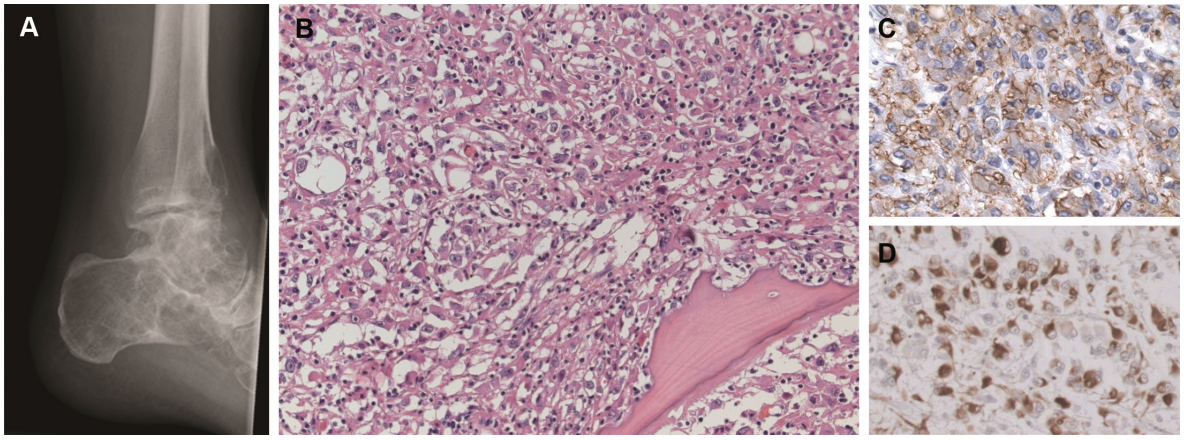

Figure 5. Angiosarcoma of bone. **A.** Radiology: conventional X-ray of the foot with multiple not sharply demarcated osteolytic lesions; **B.** Histology: epithelioid angiosarcoma of bone with a solid growth pattern, consisting of atypical endothelial cells with an epithelioid morphology (haematoxilin-eosin staining, 20x); **C.** CD31 shows a diffuse positive staining of the tumor cells (20x); **D.** Cytokeratin AE1/AE3 shows a positive staining in a part of the tumor cells (20x).

histology is reminiscent of hemangioma [35, 20]. Malignant transformation to angiosarcoma is highly unusual, but has been described [16]. In extraordinary cases, angiomatosis is associated with syndromes such as von Hippel-Lindau syndrome, Maffucci's syndrome, Klippel-Trenaunay syndrome, Kasabach Merritt syndrome, Parkers-Weber syndrome and Osler-Weber-Rendu disease [38, 35]. In the majority of these syndromes the etiology and pathogenic mechanisms are unknown. However, von Hippel -Lindau syndrome and Osler-Weber-Rendu disease are caused by genetic aberrations in the VHL gene and HHT genes, respectively [39, 40]. Prognosis of angiomatosis is dependent on the extent and localization of the disease [41, 38, 35]. Extended visceral involvement bears a more aggressive course, especially due to massive hemorrhaging [41, 38, 35].

Benign or intermediate?

Epithelioid hemangioma

Currently, epithelioid hemangioma (**Figure 3, Table 2**) (previously known as angiolymphoid hyperplasia with eosinophilia or histiocytoid hemangioma) is a recently described and accepted clinicopathologic entity in bone [7, 42]. The majority of epithelioid hemangiomas present as solitary lesions. Rarely, local cortical destruction and extension into the surrounding soft tissue have been reported. Also, small foci of necrosis can be present. The precise classification of this newly described entity is still controversial. Some authors such as Wenger and Wold have considered this a benign lesion [8]. Although Nielsen and colleagues have demonstrated that epithelioid hemangioma is a locally aggressive, rarely metastasizing tumor, they argue about the true malignant potential of this neoplasm [42]. In the 2002 World Heath Organisation Classification of Soft Tissue and Bone, all soft tissue tumors are categorized into a four-tiered classification system: benign, intermediate locally aggressive, intermediate rarely metastasizing and malignant. The intermediate category is defined by an infiltrative and locally destructive growth pattern, often recurring and occasionally (< 2%) metastasizing [20]. If these criteria are applied to epithelioid hemangioma of bone, recurring in 11% and metastasizing in 2.7% [42], this entity fits best within this intermediate category, in between hemangioma (benign) and angiosarcoma (malignant) of bone [20]. Curettage or limited local surgery (marginal en bloc resection) is considered to be an adequate therapy and has an excellent prognosis [42]. Although an allergic reaction, trauma, and an auto-immune process have been implicated as possible causes in the soft tissue counterpart [43, 44], no data regarding genetic alterations or pathophysiologic mechanisms have been reported so far for bone.

Malignant vascular tumors of bone

Epithelioid Hemangioendothelioma

Epithelioid hemangioedothelioma of bone

(**Figure 4, Table 2**) is, similar to its soft tissue counterpart, considered a low grade malignant vascular tumor. All bones can be affected, however approximately 50% of these tumors occur in the long tubular bones of the extremities [4, 45, 6]. Multifocality is more frequently seen - in about 50 to 64% - as compared to angiosarcoma of bone and it is unclear whether this is a synchronous involvement or is caused by metastatic spread [20, 4, 6]. Pain is the most common clinical presentation, however non-specific [6, 20, 36]. Gross examination can vary from a soft, red nodular mass to a firm tan-white mass [36, 4, 20]. So far, no genetic alterations are described within epithelioid hemangioendothelioma of bone. However, in two cases of epithelioid hemangioendothelioma of soft tissue (one arising in the liver and one arising in the soft tissue of an extremity) an identical translocation involving chromosomes 1 and 3 [t (1; 3) (p 36.3; q 25)] have been described, suggesting a tumor-specific translocation [46, 47, 36]. Literature about the behavior and prognosis of this entity is somewhat conflicting [4]. It seems that tumors with a visceral involvement behave worse [48, 49, 45, 6].

Angiosarcoma

Today, angiosarcoma (**Figure 5, Table 2**) is the most accepted term for high-grade vascular malignancy in bone [20]. These tumors are rare and account for less than 1% of malignant bone tumors. The majority of these tumors arising in bone are primary, however, a very small percentage is either radiation induced or associated with bone infarction. Although there is no specific clinical presentation, the majority of the patients present with a chronic dull pain and/or tumor mass [20, 29]. The latter is more often seen in patients with a solitary lesion [29]. About one third of the tumors are multifocal. It is still unclear whether this is due to synchronous involvement of different bones by multiple separate foci or is caused by metastatic spread [7, 29, 42]. At the histologic level, angiosarcoma of bone represents a heterogeneous group of lesions, ranging from well-differentiated tumors with a clear vasoformative growth pattern to poorly differentiated tumors with a more solid growth pattern sometimes even mimicking metastatic carcinoma [20, 25]. Due to the heterogeneity of these tumors and the overlap in nomenclature over the past years, there is no full agreement regarding exact histologic criteria defining these tumors, although there is some consensus about the presence of nuclear atypia and mitoses [3, 4, 6]. We recently reported that primary angiosarcoma of bone exhibiting more than 3 mitoses per 10 HPF, with a prominent nucleolus and fewer than five eosinophilic granulocytes per 10 HPF have a more aggressive course and worse outcome, indicating that these histologic criteria have prognostic value [25]. Recently, a novel t(1;14) (p21;q24) translocation has been described in an angiosarcoma of bone [50]. This is the first cytogenetic aberration reported in angiosarcoma of bone. However, small series have shown the involvement of tumor-suppressor genes such as p53 and p16, mainly in angiosarcoma of soft tissue, suggesting a possible role in tumorigenesis in a subset of angiosarcomas. P53 gene mutations are most commonly found in angiosarcoma of the liver associated with toxic vinyl chloride exposure [51, 52, 53] and angiosarcoma of the scalp [54, 55]. However, it was sporadically reported in angiosarcoma of the breast, extremities, heart, lung, liver (not toxic induced) and also in one angiosarcoma of bone [54, 56, 55, 52, 57]. Moreover, the involvement of c-MYC, K-RAS and KDR (VEGFR2) has been recently described [58, 56, 59, 60, 53]. Whereas high levels of c-MYC amplification are found in angiosarcoma secondary to irradiation or chronic lymphedema [59], KDR mutations are present in primary angiosarcoma of the breast [58], suggesting that angiosarcoma (of soft tissue) can be separated in different subtypes each with tumor-specific alterations and as a consequence different therapeutic targets. It is still unclear whether primary angiosarcoma of bone is a true separate entity or is similar to primary angiosarcoma of deep soft tissues. It is generally accepted that angiosarcomas have an aggressive course with a one and 5-year survival rate of 55% and 33%, respectively [25].

Controversial/ Disputable entities: do they exist?

Hemangioendothelioma

The existence of hemangioendothelioma of bone as a true, separate entity has been highly controversial in the literature [42,61]. Some authors and investigators believe that there is a subgroup of vascular tumors of bone representing a low-grade malignancy, preferably called

hemangioendothelioma [6, 3, 5, 62, 35]. However, the absence of apparent histologic criteria and restricted correlation with clinical outcome have hampered the general acceptance of this entity. Nielsen and colleagues have demonstrated that over the years many authors have reported vascular tumors of bone labeled as hemangioendothelioma, which demonstrate histological features that are identical to epithelioid hemangiomas [42]. To date, it is therefore unclear whether a low-grade angiosarcoma other than epithelioid hemangioendothelioma truly exists.

Hemangiopericytoma

This tumor was first described by Stout and Murray in 1942 as a vascular soft tissue neoplasm, composed of a proliferation of endothelial sprouts and tubules surrounded by rounded or spindle-shaped cells typically supported by a meshwork of reticulin fibers [63]. Occasional solitary bone lesions have been reported ever since. In the early nineties it became clear that many different tumor types could mimic a hemangiopericytoma-like growth pattern. Therefore, it was stated by several authors that this is most likely a non-specific histological growth pattern, rather than a true diagnosis [64, 65, 66].Today, the 2002 WHO Classification of Soft tissue and Bone Tumors does not recognize this entity any longer [67] and in soft tissue it is accepted that most of these lesions can be classified as solitary fibrous tumors, monophasic synovial sarcomas or myofibromatoses [64, 65, 67, 68]. Also in bone it has recently been demonstrated that these tumors are most probably solitary fibrous tumors or synovial sarcoma of bone [25]. Positive immunohistochemical reaction for epithelial membrane antigen and/ or cytokeratin as well as the detection of the tumor -specific translocation t (X; 18) (p 11.2; q 11.2) is helpful for the diagnosis of synovial sarcoma of bone, whereas diffuse CD34 reactivity is seen in the majority of solitary fibrous tumors of bone [25]. Although heterogeneous cytogenetic aberrations have been reported for larger solitary fibrous tumors of soft tissue [69], this has not been confirmed in solitary fibrous tumors of bone.

Conclusion

Vascular tumors of bone consist of a heterogeneous group of entities, which over the past decade have been better delineated, especially regarding the entity epithelioid hemangioma. Based on its locally aggressive behavior as well as the occurrence of lymph node metastases (in 2%) classification within the intermediate category, in between hemangioma (benign) and angiosarcoma (malignant), could be considered (**Table 1**). Epithelioid hemangioendothelioma is a separate entity morphologically identical to its soft tissue counterpart and is the only accepted low-grade malignant vascular tumor of bone. It is still debatable whether other low-grade malignant vascular tumors of bone exist. Therefore, it is recommended to avoid the term hemangioendothelioma of bone because it could confuse clinicians and radiologists. Unfortunately no molecular genetic data are available to support the proposed classification. Future molecular studies might reveal whether there is indeed a continuum between hemangioma and angiosarcoma i.e. according to a multistep genetic progression model as is also known for instance for chondrosarcoma [70], liposarcoma [71], or colorectal cancer [72]. Also, molecular studies may shed light on whether angiosarcoma of bone is comparable to angiosarcoma of deep soft tissue or whether it represents a separate entity within the heterogeneous group of angiosarcomas.

Address correspondence to: J.V.M.G. Bovée, Leiden University Medical Center, Department of Pathology, L1Q, P.O. Box 9600, 2300 RC Leiden, the Netherlands Tel: ++31 71 5266617 Fax: ++31 71 5266952 E-mail: j.v.m.g.bovee@lumc.nl

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