Virchows Arch (2009) 454:161–179
DOI 10.1007/s00428-008-0709-3

ORIGINAL ARTICLE

Vascular lesions of bone in children, adolescents, and young adults. A clinicopathologic reappraisal and application of the ISSVA classification

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Received: 11 February 2008 / Revised: 10 November 2008 / Accepted: 19 November 2008 / Published online: 24 December 2008

Abstract Vascular lesions of bone are rare and their terminology is not standardized. Herein, we report 77 patients with such lesions in order to characterize their morphologic spectrum and the applicability of the International Society for the Study of Vascular Anomalies (ISSVA) classification. In this system, malformations are structural anomalies distinguishable from tumors, which are proliferative. The radiologic images/reports and pathologic materials from all patients were reviewed. All lesions were either restricted to bone or had minimal contiguous soft tissue involvement with the exception of some multifocal lymphatic lesions that extensively affected soft tissue and/or viscera. We found that certain lesions of bone often regarded as tumors should be classified as malformations. Malformations (n=46) were more common than tumors (n=31); lymphatic and venous malformations were equally frequent. In the tumor category, hemangioendothelioma and epithelioid hemangioma were the most common. We also describe new vascular entities that arise in or involve bone. Utilizing the ISSVA approach, the diverse and often contradictory terminology of vascular lesions of bone can be largely eliminated. Standardized nomenclature is critical for scientific communication and patient management, and we hereby recommend the ISSVA classification be applied to vascular lesions of bone, just as for skin, soft tissue, and viscera.

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Keywords Bone · Vascular malformation · Vascular tumor · Hemangioma · Lymphatic · Pathology · Pediatric · Kaposiform · Hemangioendothelioma · Lymphangiomatosis

Introduction

Primary vascular lesions of bone are rare in surgical pathology [1, 2]. Their uncommon occurrence is exemplified by the Mayo Clinic experience with 11,087 bony lesions of which only 201 (1.8%) were vascular and, of these, only 32 (14.5%) occurred during the first two decades of life [3]. However, the most common vascular lesion of bone, the vertebral "hemangioma," was incidentally found in 10.7% of individuals in a careful study of the spine at autopsy [4]. The histopathology of vascular lesions of bone in young individuals has not been as thoroughly described and categorized as it has been in adults.

Vascular lesions, in general, have been notoriously difficult for pathologists to diagnose and classify because of the large number of entities and their variants, the frequently overlapping clinical and histopathologic features, and, until recently, the lack of markers distinguishing blood vascular from lymphatic endothelium. This problem has been compounded by imprecise terminology with various names referring to the same lesion or, conversely, a particular term denoting different entities. For example, "hemangioma" has often been used in a generic and indiscriminate manner resulting in the inclusion of lesions with different biology under one rubric. In this regard, we have encountered patients with malformative lesions that had been previously diagnosed at other institutions as "hemangioma" or "lymphangioma" or some other designations ending in "oma" and regarded as being neoplastic lesions, and therefore treated inappropriately with anti-angiogenic agents, sometimes resulting in morbidity and rarely fatality. Our experience is that precise terminology of vascular lesions is essential for their proper treatment.

For these reasons, the International Society for the Study of Vascular Anomalies (ISSVA), an organization comprised of specialists in various disciplines interested in vascular anomalies, approved a classification of vascular lesions that distinguishes malformations from tumors and provides an easily understood and concise nomenclature [5]. This classification has proven invaluable in improving scientific communication and the management of patients with vascular anomalies involving skin, soft tissue, viscera, and bone. The ISSVA nomenclature has not been widely applied to the categorization of osseous vascular lesions. A brief introduction to this concept was recently published by us in the German literature [6].

We present, herein, our experience with osseous vascular lesions applying the ISSVA classification, from two institutions—the Bone Tumor Reference Center at the University Hospital in Basel, Switzerland, serving as a registry for osseous tumors in Switzerland and major parts of Germany and Austria, and the Vascular Anomalies Center and Department of Pathology at Children's Hospital Boston that regularly evaluates a large number of patients with vascular lesions, particularly those that are difficult to diagnose or manage. This work is primarily a histopathological study of vascular lesions of bone and the application of the ISSVA classification system. Treatment and follow-up are beyond the scope of this study. The natural history of the classical entities we describe is well documented in the literature.

Materials and methods

All vascular lesions of bone were retrieved from the files of the Basel Bone Tumor Reference Center (from 1978 to 2007) and the Department of Pathology at Children's Hospital Boston (from 1975 to 2006) that included patients evaluated at its Vascular Anomalies Center. The lesions selected for the study were either restricted to bone or had minimal contiguous soft tissue involvement, with the exception of some multifocal lymphatic malformations (LMs) and kaposiform lymphangiomatosis that also extensively affected soft tissue and/or viscera. All patients had biopsy or resection of the osseous lesion except for four with multifocal lymphatic and one with arteriovenous malformation (AVM) who had only the soft tissue component biopsied.

This study includes only patients 25 years or younger since termination of skeletal maturation with closure of all epiphyseal growth plates and apophyses occurs by this age [7, 8]. Patients with predominantly soft tissue lesions and only minor cortical bony involvement, such as those that can occur with venous or lymphatic malformations, kaposiform hemangioendothelioma, Klippel-Trenaunay syndrome, and PTEN-associated vascular anomaly were excluded from the study.

A total of 77 patients (44 from Children's Hospital Boston and 33 from the Basel Bone Tumor Reference Center) constitute this report. The clinical and imaging data as well as the pathological material including reports, slides, and photographs were reviewed. Immunohistochemistry was performed in 33 selected cases, largely determined by the availability of paraffin blocks. These cases included eight venous malformations, four lymphatic malformations, four epithelioid hemangiomas, seven epithelioid hemangioendotheliomas, three kaposiform hemangioendotheliomas, four kaposiform lymphangiomatoses, five angiosarcomas, and three unclassifiable tumors. Antibodies utilized were those against CD31 (DAKOCytomation, Glostrup, Denmark), CD34 (DAKOCytomation, Glostrup, Denmark), and factor-VIII-related antigen (Medite, Nunningen, Switzerland) for identifying hemovascular endothelium,

D2-40 (DAKOCytomation, Glostrup, Denmark) and LYVE-1 (Reliatech, Braunschweig, Germany) for lymphatic endothelium, smooth muscle actin (DAKOCytomation, Zug, Switzerland) and caldesmon (DAKOCytomation, Zug, Switzerland) for smooth muscle, GLUT-1 (NeoMarkers, Fremont, CA, USA) for infantile hemangioma, CD68 (DAKOCytomation, Zug, Switzerland) for histiocytes, MIB1 (DAKOCytomation, Zug, Switzerland) for cellular proliferation, and WT1 (used in seven venous malformations, two epithelioid hemangiomas, two hemangioendotheliomas, one angiosarcoma; DAKOCytomation, Zug, Switzerland) a transcription factor expressed in endothelium of hemangiomas and absent in malformations [9].

This study was approved by the Children's Hospital Boston Committee on Clinical Investigation and the Basel Ethics Committee.

Results

We used the ISSVA classification [5] (Table 1) to categorize 77 vascular lesions of bone as shown in Table 2. The age of the patients ranged from 3 months to 25 years (median 15 years, average 13.1 years). The sex ratio was nearly equal with 41 males and 36 females.

To help differentiate between malformations and tumors, the following were taken into consideration: clinical history, imaging, histopathology, and proliferative activity including immunohistochemistry applying a proliferation marker. Malformations often presented at or shortly after birth, did not usually show disproportionate expansion in relation to child's growth, and morphologically were lined by flattened endothelium without mitoses and had a negligible proliferative index.

Forty-six lesions were classified as malformations and 31 as tumors. Lymphatic and venous malformations were equally common (22 of each type). Lymphatic malformations were localized (monostotic) in nine patients and multifocal (polyostotic) in 13. Only three venous malformations were multifocal (polyostotic). In the tumor category, there were seven epithelioid hemangiomas, eight hemangioendotheliomas (seven epithelioid and one NOS), three kaposiform hemangioendotheliomas (*vide infra*), four provisionally designated as kaposiform lymphangiomatoses, five angiosarcomas, and three were unclassifiable.

Malformations

Venous malformations

VMs were most often located in craniofacial bones, followed by vertebra, appendicular skeleton, and pelvis. The radiographic features varied according to the skeletal region. The cranial lesions typically showed expansion of the bone with extensive sunburst-like new bone formation (Fig. 1). In contrast, those in the vertebral body, for example, usually showed preservation of bony contours, osteolysis, and coarse vertical striations. In the long bones, there was minor expansion and osteolysis with peripheral sclerosis.

Histopathology showed thin-walled, irregularly round or elongated, sometimes focally anastomosing channels, ranging from approximately 20 μm to 4 mm in diameter and lined by flat or occasionally slightly plump endothelium (Fig. 2). In some lesions, there was a minor small vessel component (vessel diameter around 20 μm). No atypia or mitoses were present. The stroma was loosely collagenous and usually scant, but areas with back-to-back channels were sometimes present, and some lesions had solid foci with slit-like lumens. Pericytes were present, but smooth muscle investiture was absent except in occasional large channels. The channels contained blood and occasionally organizing thrombi or were empty. Organizing thrombi with Masson papillary endothelial hyperplasia were occasionally observed. In most calvarial lesions, bone formation was prominent, in contrast to vertebral VM, where bone resorption predominated. Endothelial positivity was strong for

Table 1 Classification of vascular anomalies according to the International Society for the Study of Vascular Anomalies (ISSVA)

Vascular anomalies
Tumors
Hemangioma[a]
Infantile hemangioma
Epithelioid hemangioma
Spindle cell hemangioma
Other
Hemangioendothelioma
Hemangioendothelioma NOS
Epithelioid hemangioendothelioma
Angiosarcoma
Other tumors
Malformations
Simple
Capillary
Lymphatic
Venous
Arterial
Combined
Arteriovenous malformation
Capillary–venous malformation
Capillary–lymphatic–venous malformation
Lymphatic–venous malformation
Capillary–arteriovenous malformation
Capillary–lymphatic–arteriovenous malformation

Modified from Enjolras and Mulliken [5]

[a] "Hemangioma" refers to a benign neoplastic endothelial proliferation; the term should include an appropriate qualifier, e.g., "infantile," "spindle cell," "epithelioid"

Table 2 Classification of 77 vascular lesions of bone

Malformation	Number of patients	Age range	Sex	Sites (*n*=frequency of involvement)	Localized (L), multifocal (M)	Extraosseous involvement (skin, soft tissue, viscera)
Venous	22 *n*=4: calvaria, mandible *n*=3: maxilla *n*=2: pelvis, tibia, phalanx *n*=1: humerus, metacarpal, femur	4–24 years, mean 16.0 years	11M,11F	*n*=7: vertebra *n*=1: tongue, skin	L 15, M 6	*n*=2: cheek muscle
Lymphatic	22	3 months–24 y, mean 9.9 years	15M, 7F	*n*=9: rib, vertebra *n*=7: femur *n*=5: calvaria *n*=4: clavicle, humerus, pelvis *n*=3: sternum *n*=2: mandible, scapula, tibia *n*=1: cranial base, maxilla, radius, sacrum, fibula	L 9, M 7 Gorham 6	*n*=3: skin, chest wall, pleura, spleen *n*=2: soft tissue (periocular, mediastinum, retroperitoneum) *n*=1: soft tissue (forehead, tongue, shoulder, axilla, subclavicular, suprasternal, thoracic duct, diaphragm, mesentery, peritoneum, arm, buttock, thigh), liver, pancreas
Arteriovenous	3	2–15 years, mean 9.3 years	3F	*n*=1: maxilla, mandible, humerus, ulna, radius, carpus	2 L, 1 M	*n*=1: soft tissue upper limb
Tumor						
Epithelioid hemangioma	7	8–23 years, mean 15.7. years	3 M, 4 F	*n*=3: phalanx, tibia *n*=2: mandible, metatarsal *n*=1: cranial base, orbit, navicular, cuboid, cuneiform, tarsus (NOS)	L 3, M 4	*n*=1: soft tissue (infratemporal fossa, cheek/buccal mucosa, foot)
Hemangioendothelioma	8	7–19 years, mean 14.9 years	M 3, F 5	*n*=3: calvaria, clavicle *n*=1: vertebra, ulna, tibia, fibula *n*=1: sternum, scapula, pelvis, radius, navicular, cuneiform, metatarsal	L 4, M 5,	*n*=3: lung *n*=1: soft tissue finger, liver
Kaposiform hemangioendothelioma	3	3–15 years, mean 8.4 years	M1, F2	*n*=1: humerus, ulna, femur, tibia	L 2, M 1	*n*=1: soft tissue (thigh, upper limb)
Kaposiform lymphangiomatosis[a]	4	3–14 years, mean 8 years	M 3, F 1	*n*=3: vertebra *n*=2: pelvis *n*=1: skull, mandible, clavicle, scapula, rib, humerus, radius, ulna, carpus, femur, tibia	L 1, M 3	*n*=3: spleen *n*=2: mediastinum *n*=1: soft tissue neck, skin, thyroid, esophagus, lung, retroperitoneum
Angiosarcoma	5	3–25 years, mean 15 years	M 3, F 2	*n*=2: humerus, ulna, tibia *n*=1: mastoid, vertebra, radius, ulna, femur	L 1, M 4	*n*=1 soft tissue thigh, lung, liver
Unclassified	3	Birth–18 years, mean 9.7 years	M 2, F 1	*n*=1: maxilla, mandible, tibia	L 2, M 1	*n*=1: liver

[a] This is a designation for a proposed entity that requires further investigation to be validated.

CD34 and moderate to strong for CD31 and FVIII whereas immunoreactivity for GLUT1 or D2-40 was consistently absent. Smooth muscle actin immunoreactivity was present in pericytes and smooth muscle. Immunoreactivity for WT1 was either absent or present in rare endothelial cells. The MIB1 proliferative index was low (far less than 1%).

Lymphatic malformations

LMs affected most commonly the craniofacial bones, followed by the appendicular skeleton (Table 2). Radiographs demonstrated confluent geographic osteolysis with faint marginal sclerosis (Figs. 3 and 4). Histopathology showed elongated, anastomosing tubular, and stag-horned or grape-like thin-walled vessels, generally ranging from approximately 20 μm to 2 mm in caliber without an obvious smooth muscle coat and lined usually by flattened endothelial cells. Rarely, the lesions appeared as solitary spaces up to 2 cm in diameter. Lumina were empty or contained lacy proteinaceous material, lymphocytes, or a few macrophages, some containing hemosiderin. The lining cells expressed D2-40, but reactivity in the larger channels tended to be focal and faint. A discontinuous thin periendothelial layer of pericyte-like cells was immunoreactive for smooth muscle actin. There was no discernible endothelial labeling for MIB1.

Multifocal LMs affected one or more skeletal regions with variable involvement of individual osseous elements. The bones of the spine, thorax, and shoulder girdle were most often involved, followed by femur and pelvis (Table 2). Radiographs showed poorly circumscribed confluent osteolysis of cortical and cancellous bone with moderately coarse striations and focal minor expansion. Massive bone loss (Gorham-Stout disease) was seen in six patients with subtotal or total destruction of individual or contiguous skeletal elements. Both cortex and medulla were affected with loss of bony contours and slight sclerosis of residual cancellous bone resulting in a coarsely striated trabeculated pattern. Remaining skeletal elements showed tapering ends. Soft tissue and visceral involvement were almost always present (Table 2). Histopathology was similar to the localized form, but the lesions tended to be more permeative with smaller channels and a more prominent anastomotic pattern. Areas of massive osteolysis showed prominent osteoclast-mediated bony resorption and fibrous replacement. Endothelial cells were either negative or showed rare immunopositivity for MIB1.

Arteriovenous malformations

One arteriovenous malformation (AVM) involved the maxilla, another the mandible, and the third affected multiple bones of an upper extremity (Table 2). Radiographs showed multiple osteolytic foci with cortical thinning and disruption, minimal perilesional sclerosis, variable bone expansion, and coarse trabeculation of residual bone. Angiographically, the lesions were fast-flow with large tortuous arteries entering convoluted vascular aggregates and early venous filling. Histopathologically, AVM consisted of an assortment of variably sized arteries and veins and some vessels of indeterminate morphology separated by loose stroma (Fig. 5). Some channels showed thick muscular walls and/or intimal myofibroblastic proliferation. Focal organizing thrombi were observed. Adjacent bone showed osteoclast-mediated osteolysis and minimal sclerosis.

Tumors

Epithelioid hemangioma

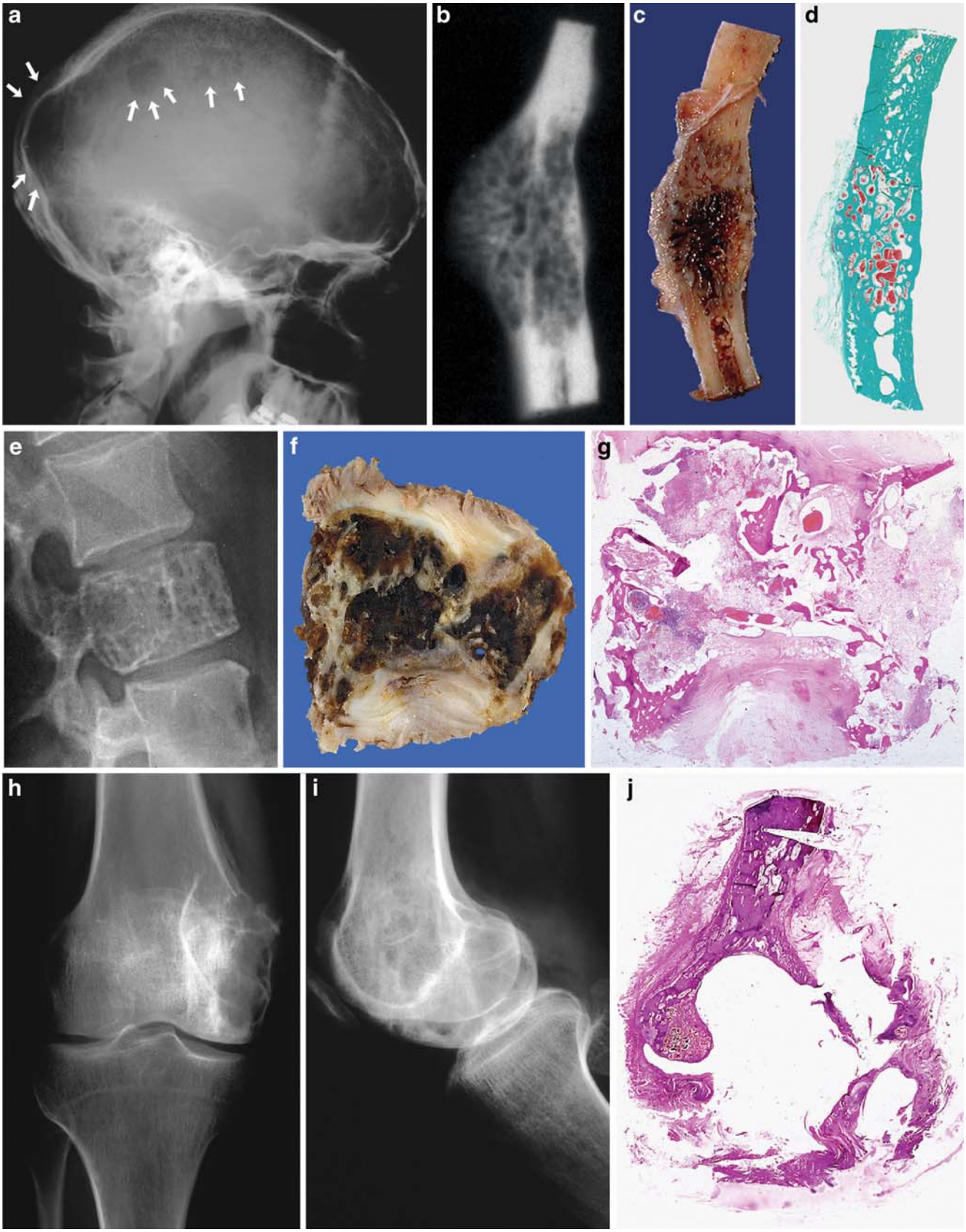
The predominant site for epithelioid hemangioma was the distal lower extremity followed by the craniofacial skeleton (Table 2). Radiographs showed solitary or multifocal excentric geographic osteolysis with minimal marginal sclerosis, cortical erosion, and expansion (Fig. 6). Three lesions extended into adjacent soft tissue. Histopathology typically showed lobular architecture; solid sheets and cords were also present (Fig. 7). Small or inconspicuous lumens were lined by large epithelioid cells resulting in a cobblestoned or brick-like appearance. The cells had abundant eosinophilic to amphophilic cytoplasm with an occasional large vacuole. The nuclei were small without significant pleomorphism. Mitoses were inconspicuous and necrosis was absent. The intervening loose to moderately dense fibrous stroma contained occasional eosinophils. Basophilic cartilage-like matrix and stromal hyalinization were not observed.

Four tumors also had a spindled cell component, which comprised up to half of the tumor, and were regarded as epithelioid and spindle cell hemangioma, a variant of epithelioid hemangioma (Andrew Rosenberg, personal communication). Spindled cells were bland and monomorphous with moderately prominent nucleoli and occasional mitoses. Small foci of necrosis were accompanied by hemosiderin and neutrophils.

The surrounding medullary and cortical bone showed moderate osteoclastic resorption and minimal new bone. Immunohistochemistry revealed expression of CD31, CD34, and factor VIII in tumoral endothelium but not GLUT1, D2-40, caldesmon, or CD68. WT1 was strongly positive in lesional endothelial cells. MIB1 was positive in approximately 3% of lesional cells. Endothelial aggregates and channels were surrounded by smooth-muscle-actin-positive cells.

Hemangioendothelioma

Multiple skeletal elements and/or viscera were involved in more than half of the patients (Table 2). Radiographically,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◀ **Fig. 1** Venous malformation. **a** Cranial geographic osteolysis on lateral plain film (*arrows*; 17-year-old male). **b–d** Specimen radiograph, gross and whole mount section showing spongy appearance and expansion of the skull. Large abnormal channels contain blood (same patient as in **a**). **e–g** Coarsely trabeculated osteolytic lesion of the third lumbar vertebra (22-year-old female). The hemisected vertebral body and whole mount section show central collapse, loss of bone and abnormal channels of varying size. The vertebra was removed because of compression fracture following sclerotherapy. **h–j** Multiple lucent areas with coarse trabeculations involving distal femur on radiographs and spongy appearance with massive channels on whole mount section (22-year-old male)

they typically exhibited partly permeative osteolysis with variable peripheral sclerosis, cortical destruction, and periosteal new bone.

Seven tumors had characteristics typical of epithelioid hemangioendothelioma with densely cellular sheets lacking a lobular architecture or obvious lumen formation (Fig. 8). The tumor cells were epithelioid with abundant eosinophilic or amphophilic cytoplasm, often with a solitary vacuole which sometimes contained erythrocytes. Nuclei were moderately pleomorphic with prominent nucleoli and mitoses were few without atypical forms. Focal necrosis was present. Tumor cells were dispersed in a pale or myxoid matrix that was focally calcified when adjacent to residual bone. Perilesional bone showed active osteoclastic resorption and seams of woven bone. WT1 immunoreactivity was strongly and diffusely positive and MIB1 proliferative index up to 50%.

One hemangioendothelioma consisted of small monotonous mildly pleomorphic epithelioid cells with prominent lumen formation but also with solid zones. Cytoplasmic vacuoles were absent and areas of pale myxoid/chondroid

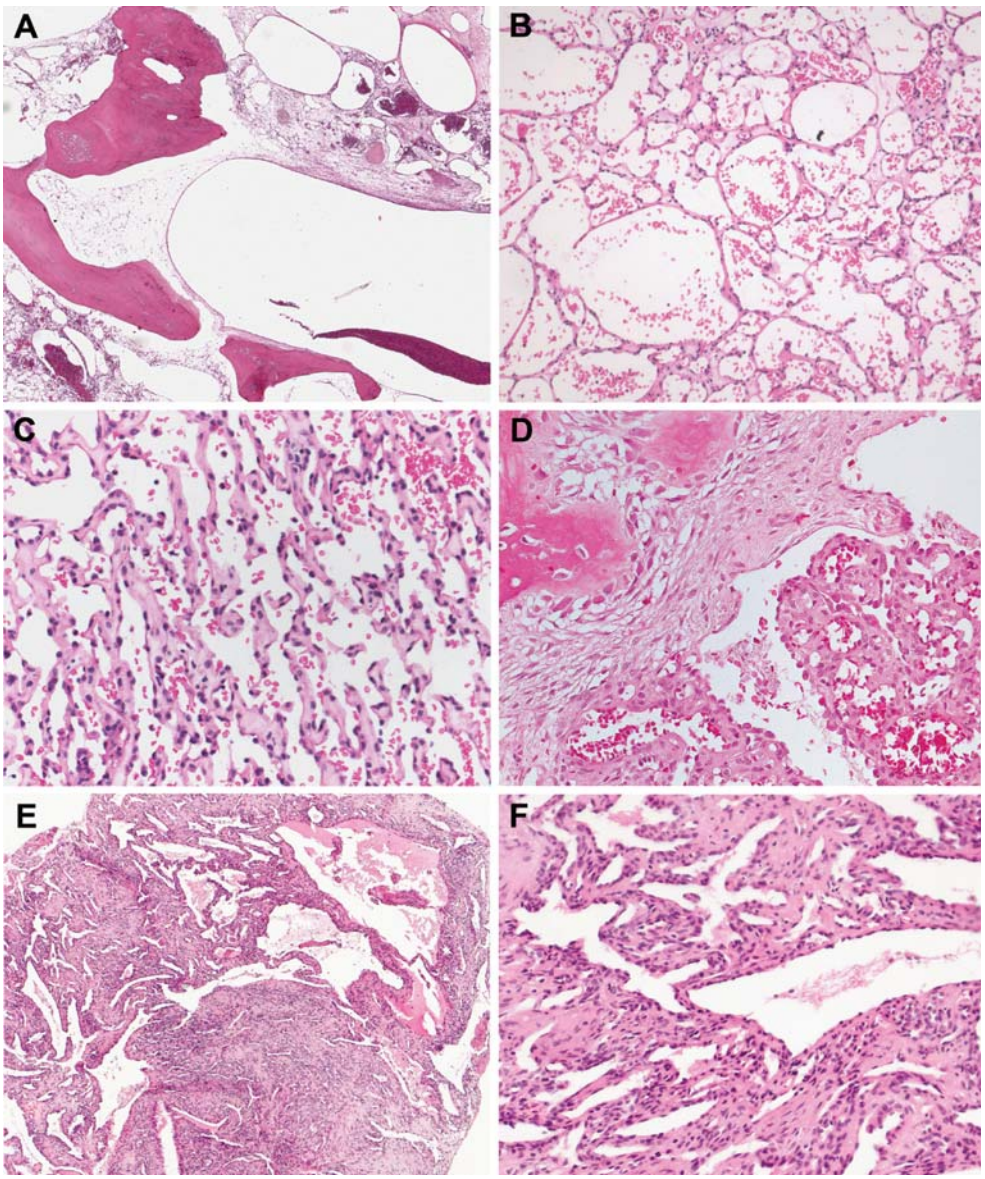


Fig. 2 Venous malformation. **a** Mostly large thin-walled channels, some containing blood (22-year-old female). **b** Back-to-back, small-to-large, irregularly round channels have flat endothelium and are devoid of muscle (same patient as in **a**). **c** Anastomosing elongated channels have bland endothelium (same patient as in **a**). **d** Focus of small round channels with a more prominent endothelium protrudes into large channel (13-year-old female). **e–f** Interspersed with large channels are more solid areas with stromal collagen (4-year-old male)

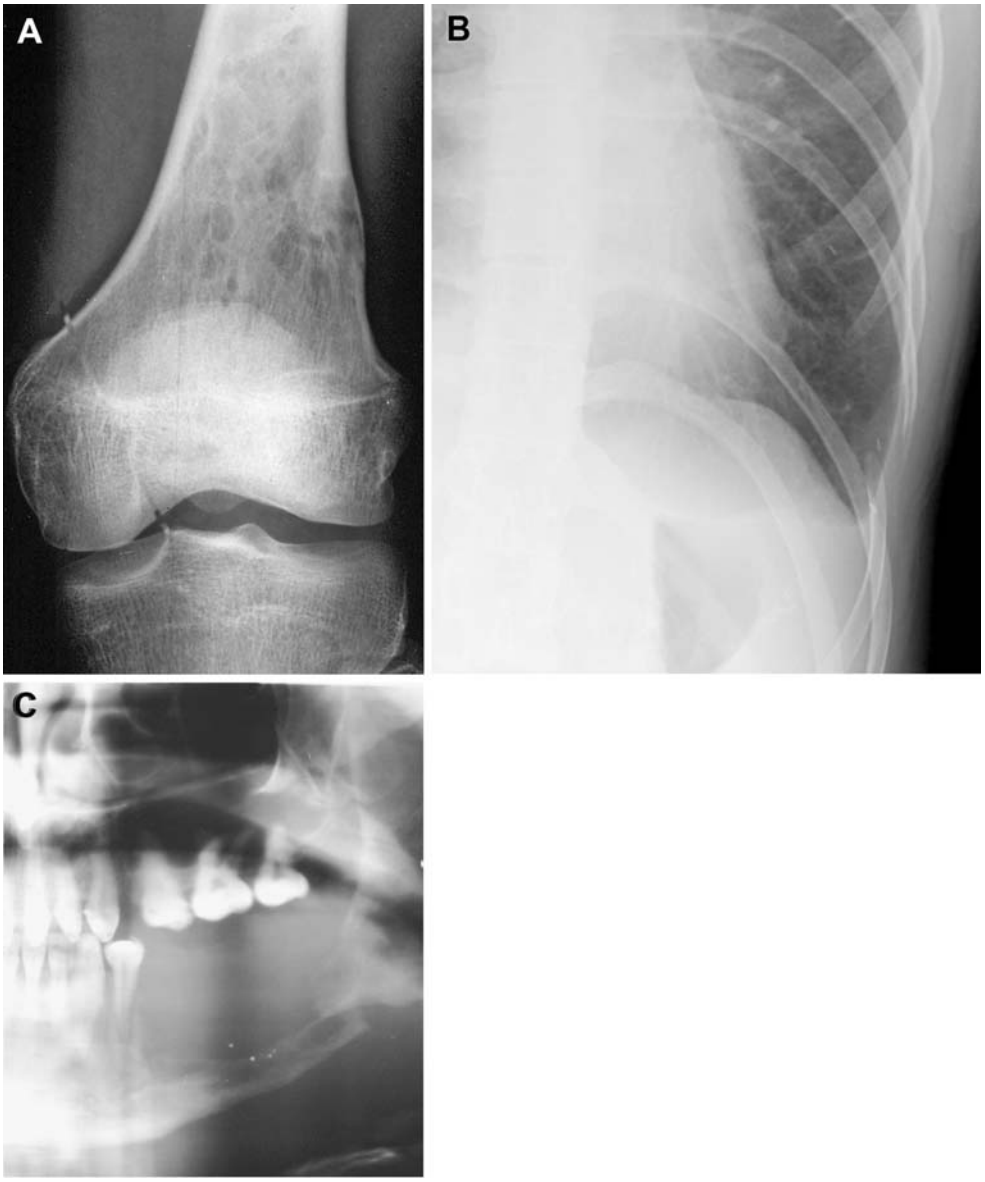


Fig. 3 Lymphatic malformation. **a** Frontal plain film of the knee shows multiple coalescing radiolucent foci in the metaphysis of the distal femur. There is incomplete sclerosis of the margins and cortical thinning and elevation (18-year-old male). **b** Lymphatic malformation with massive osteolysis of left ninth rib (Gorham-Stout disease; 16-year-old female). **c** Large mandibular osteolytic lesion without marginal sclerosis; there is loss of alveolar bone and teeth (24-year-old male)

matrix were minimal. The biopsy was small and although epithelioid hemangioendothelioma was a distinct possibility, because of the lack of some of the typical features, we chose to designate this lesion hemangioendothelioma NOS.

Kaposiform hemangioendothelioma

These tumors showed a histopathologic resemblance to kaposiform hemangioendothelioma of soft tissue (Fig. 9). They were in the humerus, ulna, femur, and tibia and radiographically showed irregular osteolysis with minor soft tissue extension in two patients. One patient had involvement of two bones. Histopathology showed ill-defined coalescing nodules of spindled moderately plump cells forming strands and fascicles with slit-like lumina containing erythrocytes. Foci of round cells with larger nuclei and clear cytoplasm were also seen. Cytoplasmic hemosiderin and cytoplasmic hyaline globules were present and one lesion had microthrombi. Dilated lymphatic channels were not conspicuous. Immunohistochemistry showed the lesional cells to be positive for CD31 and CD34, focally positive for D2-40, and negative for GLUT1.

Kaposiform lymphangiomatosis (provisional term)

These lesions were multifocal and involved soft tissue, viscera, and bone in all patients. The affected bones were rib, clavicle, scapula, vertebra, sacrum, ilium, femur, radius, ulna, and those of the wrist. Radiographs showed osteolysis as in multifocal LM. Histopathologically, the soft tissue and visceral lesions were that of multifocal LM, but were also accompanied by isolated areas that mimicked kaposiform

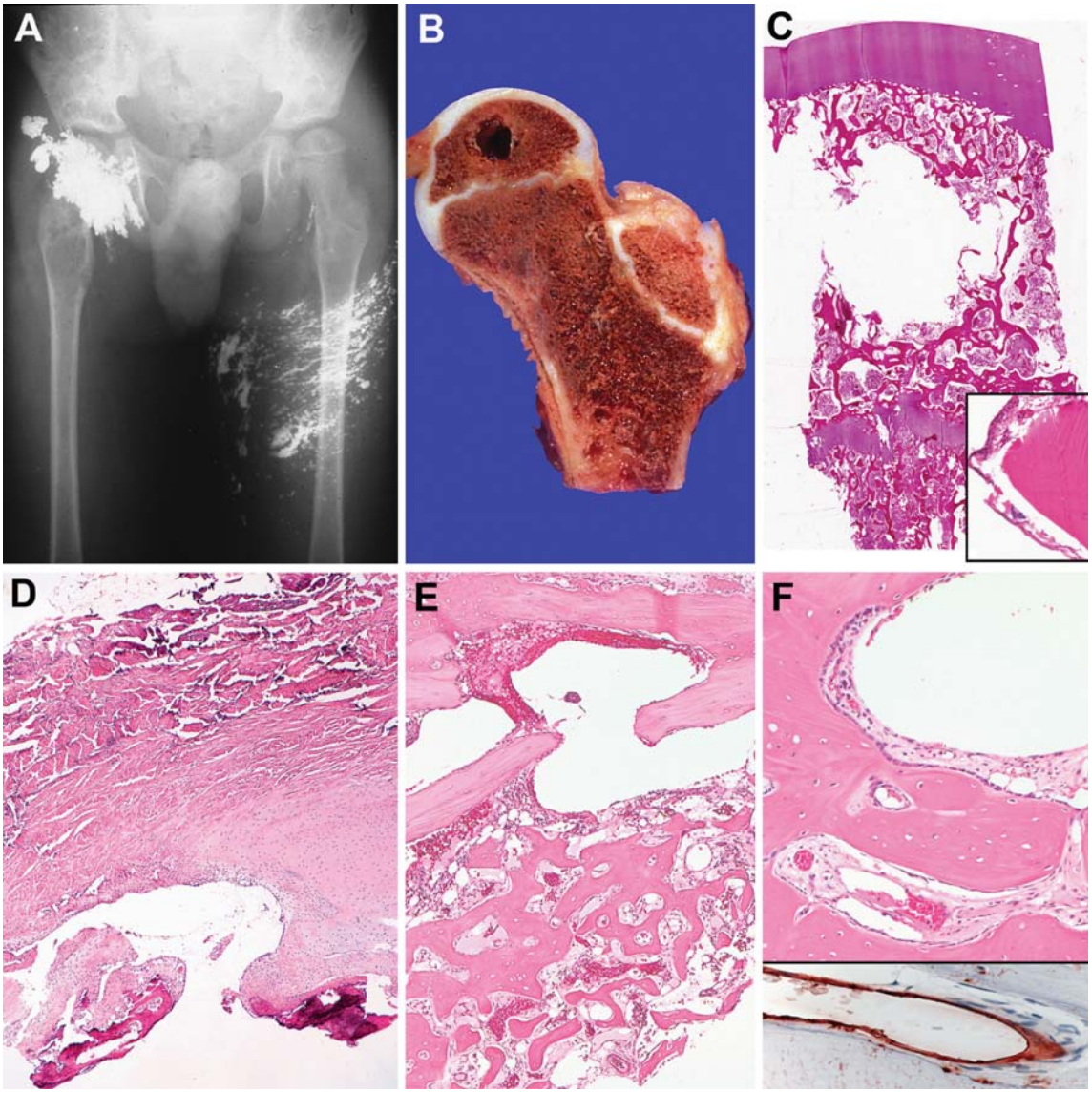


Fig. 4 Lymphatic malformation. **a** Multiple geographic osteolyses of pelvic bones, femoral metaphyses and left femoral head. Lymphangiogram shows ectatic channels in skin and soft tissue (11-year-old male). **b** Hemisectioned proximal femur at autopsy shows single epiphyseal cavity and multiple spaces in the metaphysis and diaphysis (*arrows*; same patient as in **a**). **c** Whole mount section of femoral head of same specimen depicted in **b** shows a large irregular space rimmed by trabecular bone and lined by a flat endothelium (*inset*; same patient as in **b**). **d** Cortical resorption and extension of thin-walled channels into periosteum. Contiguous soft tissue also shows lymphatic malformation (4-year-old male). **e**–**f** Anastomosing network of lymphatic channels permeating medulla and cortex. Extensive reactive medullary bone is present (17-year-old female). **g** Lymphatic channels have thin walls and flattened endothelium immunoreactive to D2-40 (*inset*; 18-year-old male)

hemangioendothelioma with densely cellular small sheets of irregularly ovoid to spindled cells with slit-like lumina containing erythrocytes. These areas had minimal or absent nuclear pleomorphism and rare mitoses, and the cytoplasm was frequently hemosiderotic. The biopsied skeletal lesions had the histopathology of multifocal LM, but in three patients the kaposiform component was also present (Fig. 10). The lesional cells were immunopositive for CD31 and CD34 and focally for D2-40. The surrounding bone showed osteoclastic resorption.

Angiosarcoma

These tumors were localized (monostotic) in three patients and multifocal (polyostotic) in two. The affected bones were mastoid, humerus, radius, ulna, femur, and tibia. Multicentric tumor involving a single skeletal element was present in two patients, one with monostotic (tibia) and another with polyostotic disease (radius). Radiographs showed areas of irregular osteolysis involving cortex and medulla, absent perilesional sclerosis, and minimal periosteal reaction.

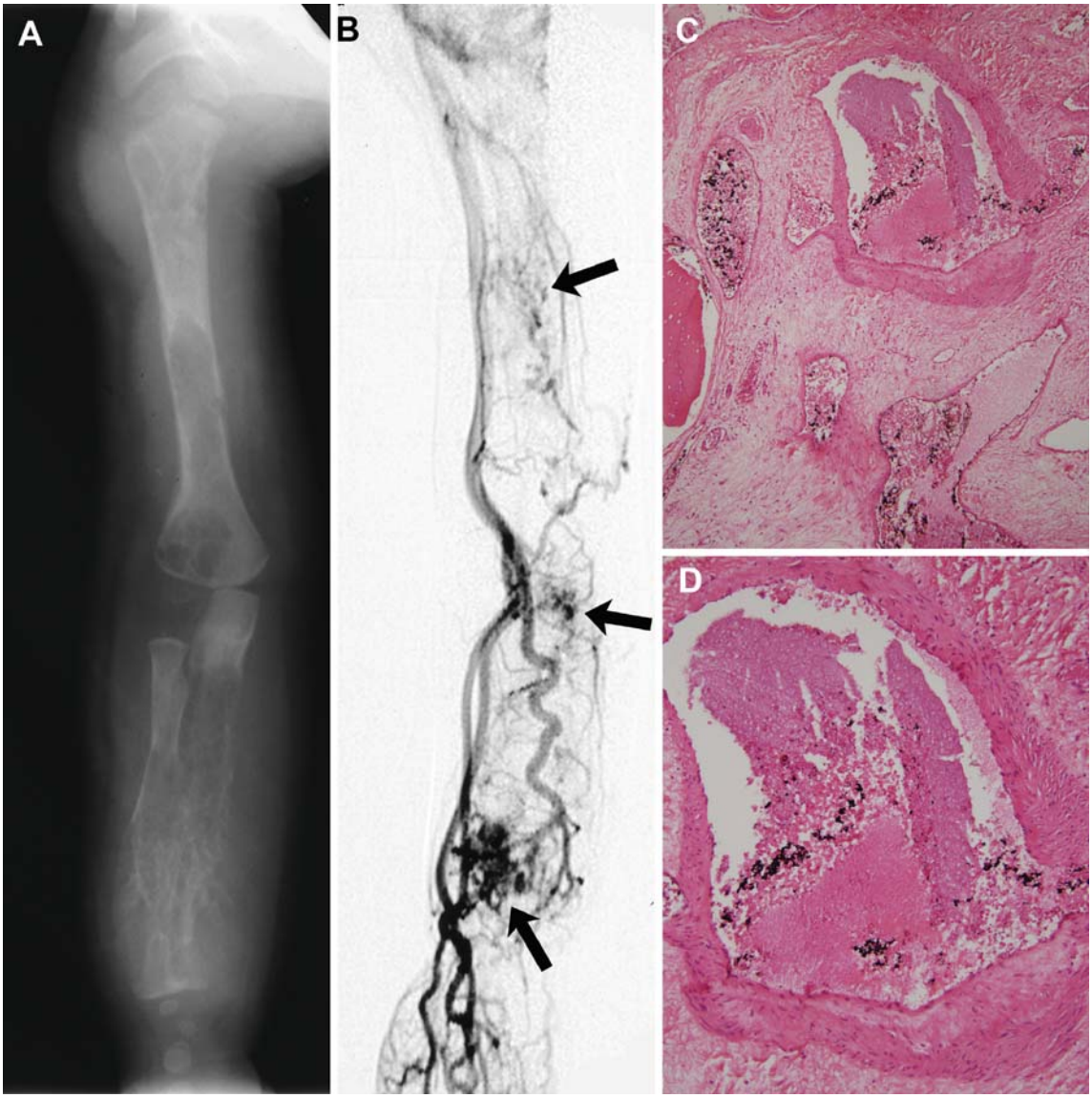


Fig. 5 Arteriovenous malformation. **a** Extensive lytic changes in humerus, ulna, and radius with cortical thinning and disruption and minimal reactive bone (1-year-old female). **b** Venous phase of an arteriographic study demonstrates filling of ectatic and tortuous veins communicating with the osseous malformations (*arrows*; same patient as in **a**). **c**–**d** Arteriovenous malformation involving maxilla with thin-walled venous structures and a large vessel of indeterminate type with irregular muscular wall and intimal hyperplasia (6-year-old female; in this patient, the maxillectomy specimen was extensively involved, but because of a dominant soft tissue component, she was excluded from the study)

Histopathology varied among the tumors as well as within individual tumors (Fig. 11). Tumor cells were arranged in cords, strands, and sheets with infiltrative margins. Vasoformation was variable and cytoplasmic vacuoles were rare. The channels were generally small, round, elongated, or irregular with complex anastomotic patterns. Significant cellular atypia with nuclear pleomorphism, hyperchromasia, and mitoses were present in all lesions. In two cases, there was a prominent epithelioid component with cells having abundant eosinophilic cytoplasm and large nucleoli. Cellular spindled cell areas were observed in one tumor. The surrounding bone showed osteoclastic resorption with minimal new bone; there was invasion of the soft tissue in all. WT1 was strongly and diffusely expressed in tumor cells and MIB1 proliferative index was high.

Unclassifiable

Three vascular tumors had unusual histopathologic features and could not be classified. A large congenital tumor of the maxilla had variably sized and shaped thin-walled vascular channels lined by bland flat-to-cuboidal endothelium within

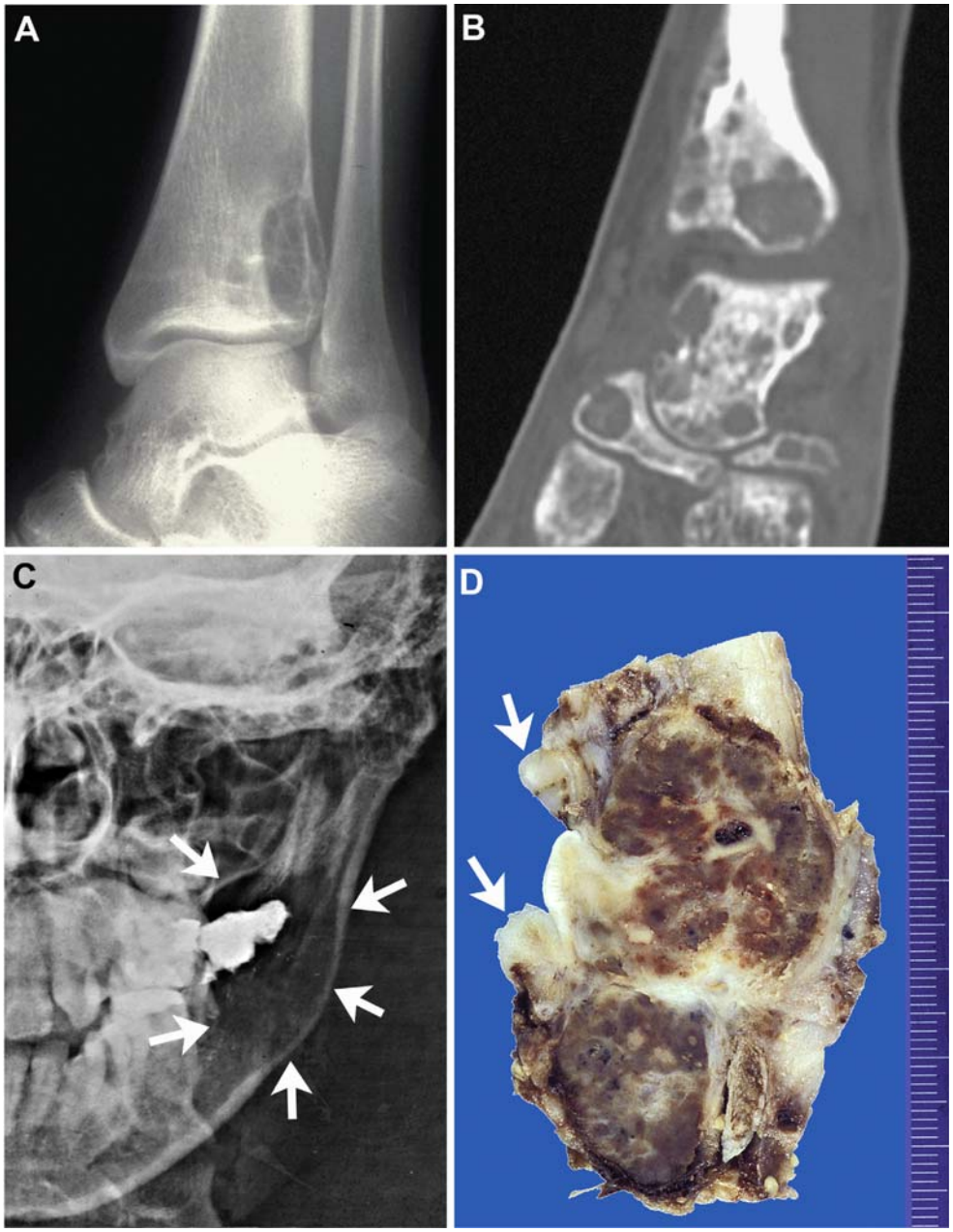


Fig. 6 Epithelioid hemangioma. **a** Excentric, well-defined lucencies in distal tibia with thinning of cortex (17-year-old female). **b** CT shows multifocal osteolyses and rarefaction of distal tibia and tarsal bones with focal cortical loss (17-year-old male). **c** Expansile osteolytic lesion of the angulus and ramus mandibulae (16-year-old female). **d** Partial mandibulectomy, hemisectioned specimen after fixation from patient depicted in **c**, shows dark-brown solid tumor destroying bone and extending into adjacent soft tissue. Two teeth are displaced (*arrows*)

a densely fibrous stroma. A morphologically similar small mass was identified within the liver. They had some resemblance to polymorphous hemangioendothelioma of soft tissue [10]. A mandibular lesion in an 18-year-old consisted of clusters of large thin-walled vascular structures with grape-like and glomeruloid tufts and an endothelium that was focally hobnailed. The tumor had some similarities to non-involuting congenital hemangioma [11]. A tibial tumor in an 11-year-old was comprised of an irregular network of small vessels with plump and focally epithelioid endothelium and bore some resemblance to epithelioid hemangioma; however, cytoplasmic vacuoles were not present and a loose fibrous stroma was prominent.

Discussion

The nomenclature of vascular anomalies has been confusing, hindering communication and contributing to errors in diagnosis, treatment, and research. Therefore, in 1996, the ISSVA issued a multidisciplinary consensus on a binary classification of vascular lesions: *tumors* that arise by endothelial proliferation and *malformations* that are structural abnormalities exhibiting slow (normal) endothelial turnover [5]. They stated that the suffix "oma" should refer only to neoplastic growths. Therefore, terms such as "lymphangioma," "venous hemangioma," or "arteriovenous hemangioma" are inappropriate since these are malforma-

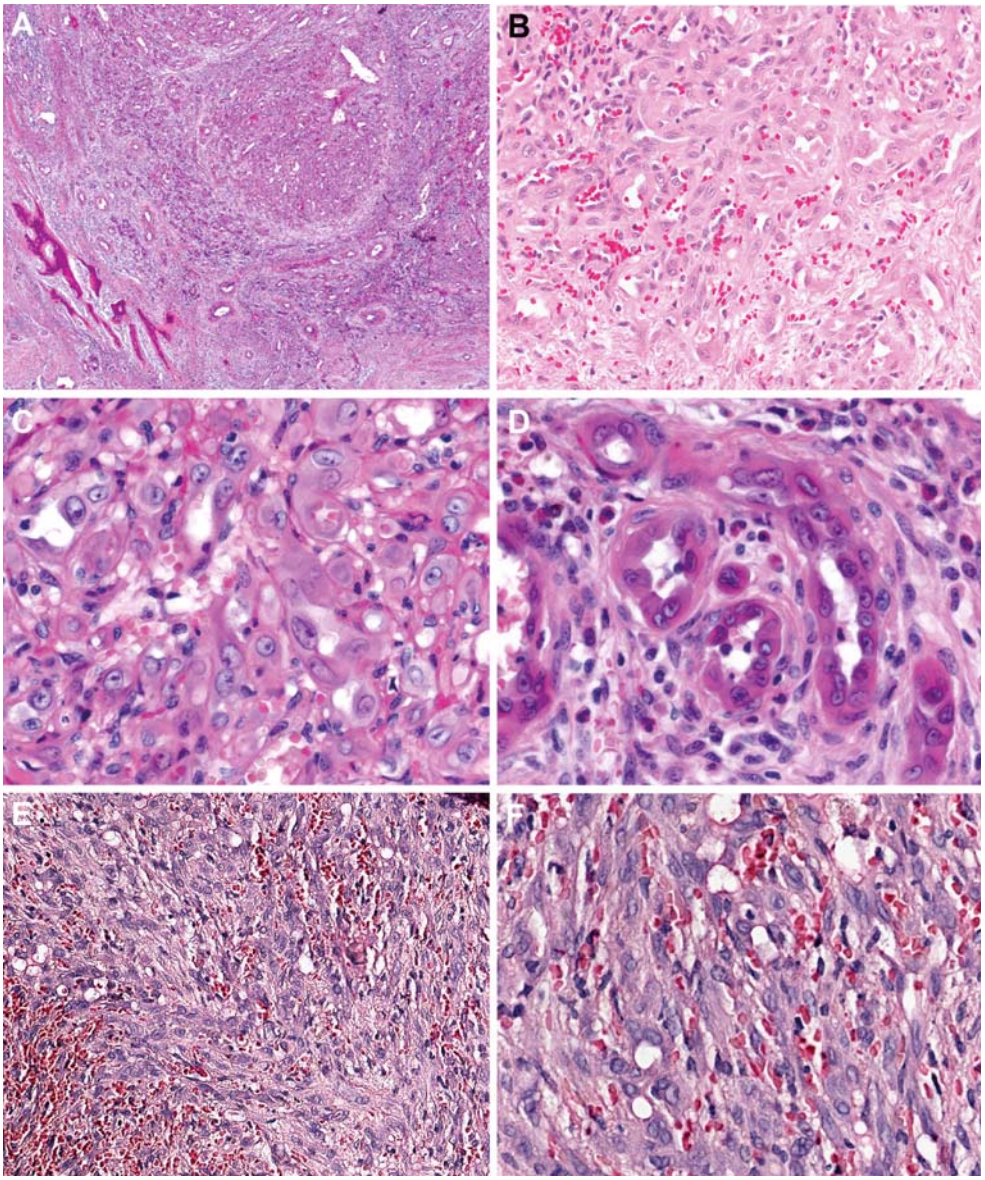


Fig. 7 Epithelioid hemangioma. **a** Nodular masses of tumor have destroyed cortex and extend into soft tissue (16-year-old female). **b** Vascular channels lined by large epithelioid cells with eosinophilic cytoplasm (16-year-old female). **c** Epithelioid cells have large rounded nuclei with minor variation in size and shape, open chromatin, and small distinct nucleoli. The eosinophilic cytoplasm has occasional vacuoles (same patient as in **a**). **d** Well-formed vascular channels in a background containing lymphocytes and eosinophils (same patient as in **a**). **e**–**f** Spindled cell component with numerous interspersed red blood cells, nascent canalization, occasional cytoplasmic vacuoles, and absence of hemosiderin (same patient as in **a**)

tions that do not exhibit disproportionate growth in relation to the child. Furthermore, they indicated that the term "hemangioma" has been used indiscriminately to designate various tumors and malformations. It was recommended that hemangioma refer only to a benign lesion that arises by endothelial proliferation and that it should be accompanied by the appropriate qualifier, e.g., "infantile," "spindle cell," and "epithelioid,"

Besides ISSVA, others are in agreement with our concept that certain lesions often regarded as tumors are in fact malformations. For example, in the *WHO Classification of Tumours of Soft Tissue and Bone* [12] the following statements are made: "The clinical evolution and clinicopathological features (of 'venous haemangioma') suggest that these lesions represent vascular malformations"; "Arteriovenous haemangioma (AVH) is a non-neoplastic vascular lesion…"; "Early or even congenital appearance in life and lesional architecture (of 'lymphangioma') are in favour of developmental malformations, with genetic abnormalities playing an additional role"; and finally, "angiomatosis probably represents congenital malformations (rather than neoplasms) which make their appearance during childhood". Consequently, none of the lesions that we consider malformative are regarded by the WHO as tumors.

We were able to apply the ISSVA nomenclature to the categorization of osseous vascular lesions in our study. All bony vascular lesions, except the unclassifiable ones, had histopathologic features that are similar to their counterparts in skin, soft tissue, and viscera. Therefore, just as in extraskeletal sites, it was possible to classify the bony lesions as malformations or tumors. Table 3 depicts the

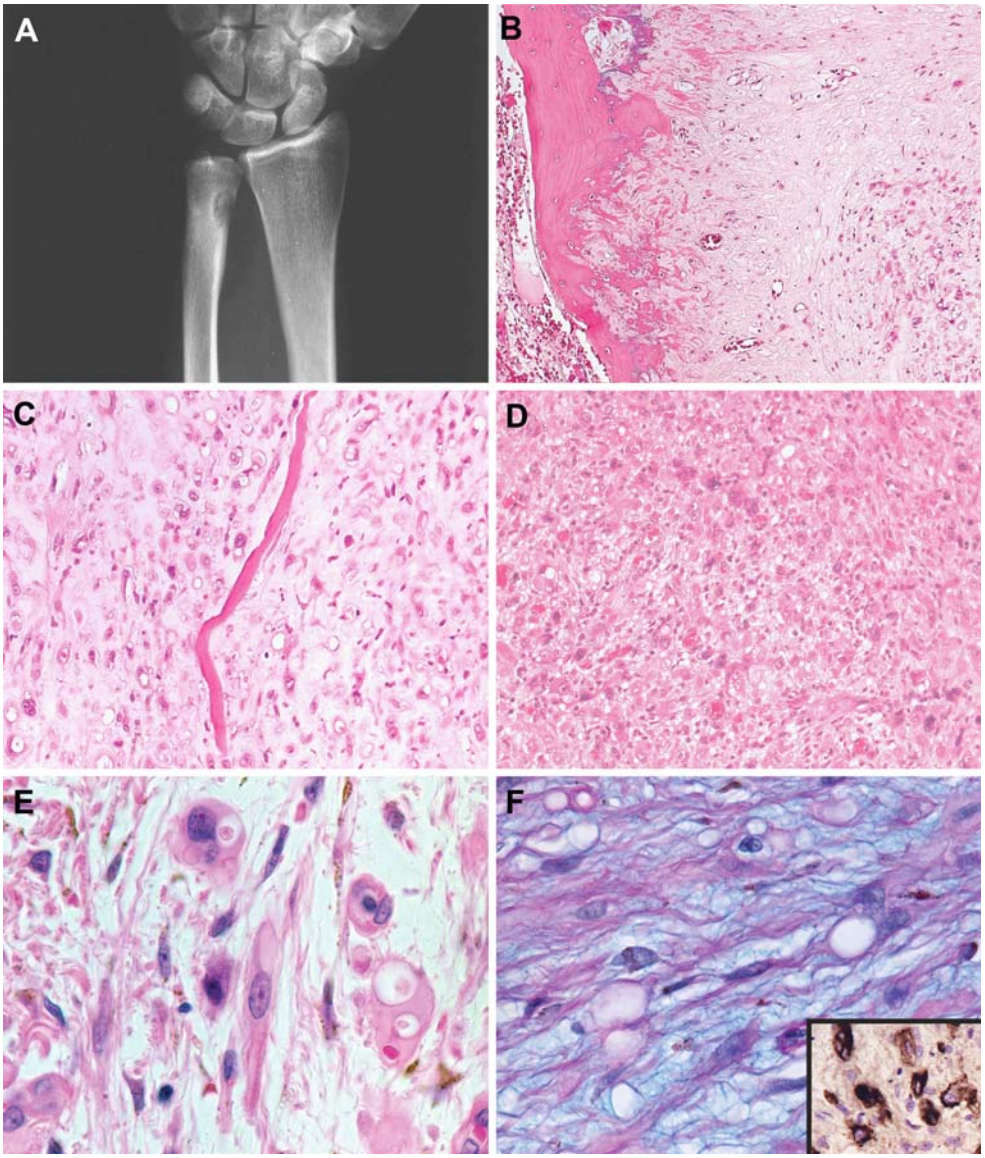


Fig. 8 Epithelioid hemangioendothelioma. **a** Well-circumscribed excentric osteolysis of the distal ulna with cortical destruction (19-year-old female). **b** Tumor cells are dispersed in ample extracellular matrix. Cortical destruction is present (10-year-old female). **c** Mostly single epithelioid and spindled tumor cells with variable nuclear pleomorphism and cytoplasmic vacuoles are immersed in pale extracellular matrix. A thinned bony trabecula is surrounded by tumor (same patient as in **b**). **d** Cellular area with focal anaplasia. Nascent canalization is present (same patient as in **b**. **e** Cytoplasmic vacuoles containing erythrocytes and other hematogenous cells (same patient as in **a**). **f** Mucopolysaccharide-rich matrix is stained with alcian blue (19-year-old female). Tumor cells are immunoreactive for factor-VIII-related antigen (*inset*; same patient as in A)

equivalent terminology for the various entities listed in the WHO classification of vascular tumors of bone [12] and those in the ISSVA schema as applied to our series.

Localized osseous VM in the literature is generally called "hemangioma of bone," whereas multiple VM is variously termed "hemangiomatosis" or "angiomatosis" when regional and "cystic angiomatosis" when generalized [2, 13]. These designations with the suffixes "oma" or "omatosis" imply neoplasia; however, the clinical and histopathological features are more those of a vascular malformation. Clinically, in soft tissue and visceral VM, there is usually no disproportionate growth, except some expansion during puberty or over time, a phenomenon attributed to hormonal or rheologic factors, respectively [14]. Also, in osseous VM, there is no disproportionate growth except occasionally in some lesions, particularly calvarial. Histopathologically, the lesions are composed mostly of large, thin-walled channels lined by flattened cells without mitoses, indicating a relatively inert endothelium. As in extraskeletal VM, there can be foci of small channels, cuboidal endothelium, or organizing thrombi, which mimic a proliferative lesion. Evidence of proliferative activity reflected by MIB1 expression has been observed in some cutaneous, soft tissue, and cerebral vascular malformations [15–17]. We have also found evidence of proliferative activity in some venous malformations, but the proliferative index was low. Several explanations for this finding are possible including growth of the lesion (commensurate with that of the child), slow expansion because of rheologic mechanisms facilitated by the diminished muscle in the malformed veins (LaPlace's law), and reparative changes due to organizing thrombi or hemorrhage, which may be subtle or resolved and therefore not always evident in the sections. Furthermore,

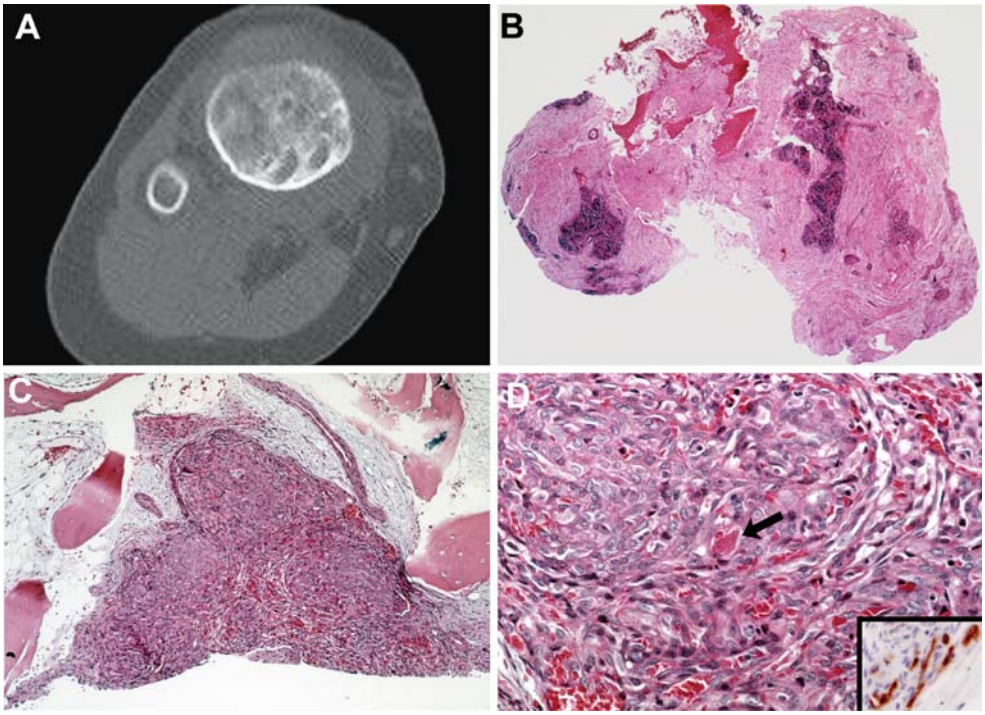


Fig. 9 Kaposiform hemangioendothelioma. **a** Axial CT image of proximal tibia demonstrates confluent heterogeneous osteolysis, cortical thinning and destruction, and faint reactive sclerosis (7-year-old female). **b** Irregular islands of tumor with sclerotic stroma infiltrating and destroying bone (7-year-old female). **c** Coalescent nodules of tumor with spindling at their periphery (same patient as in **b**). **d** Nodule of plump tumor cells with peripheral spindling, variable canalization and thrombus (*arrow*; same patient as in **c**). Some channels are immunoreactive for D2-40 (*inset*; 7-year-old female)

WT1 immunoreactivity, which is observed in tumors but not in malformations, in our study, was absent or rare in the VMs [9].

The concept of so-called vertebral "hemangioma" as a malformation was proposed by Jaffe nearly 50 years ago; he observed that "these asymptomatic vertebral vascular lesions probably represent, for the most part, mere focal varicosities rather than true hemangiomas" [18]. In addition to the WHO, others have also stated that most or all "hemangiomas of bone" are developmental or hamartoma-

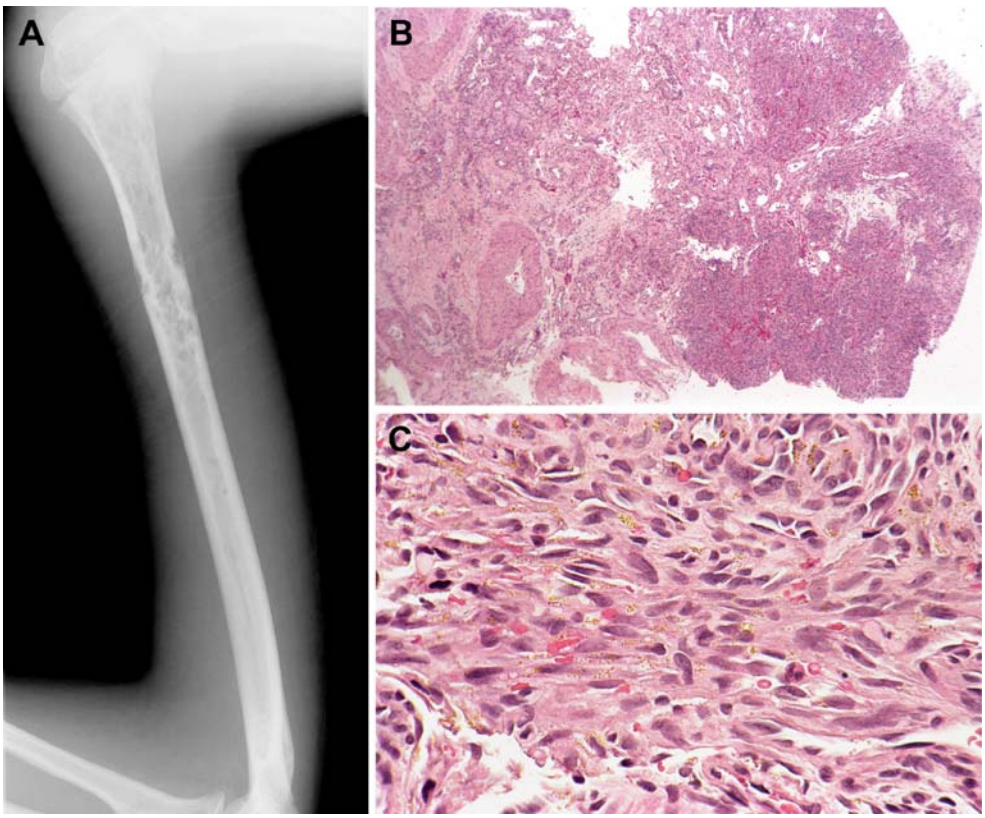


Fig. 10 Kaposiform lymphangiomatosis (provisional term). **a** Multiple confluent lucencies of cortex and medulla of proximal humeral metadiaphysis (14-year-old male). **b** Biopsy of fifth metacarpal lesion showing coalescent cellular nodules and aggregates of abnormal vessels (same patient as in **a**). **c** Hemosiderotic spindled cells with interspersed erythrocytes (same patient as in **a**)

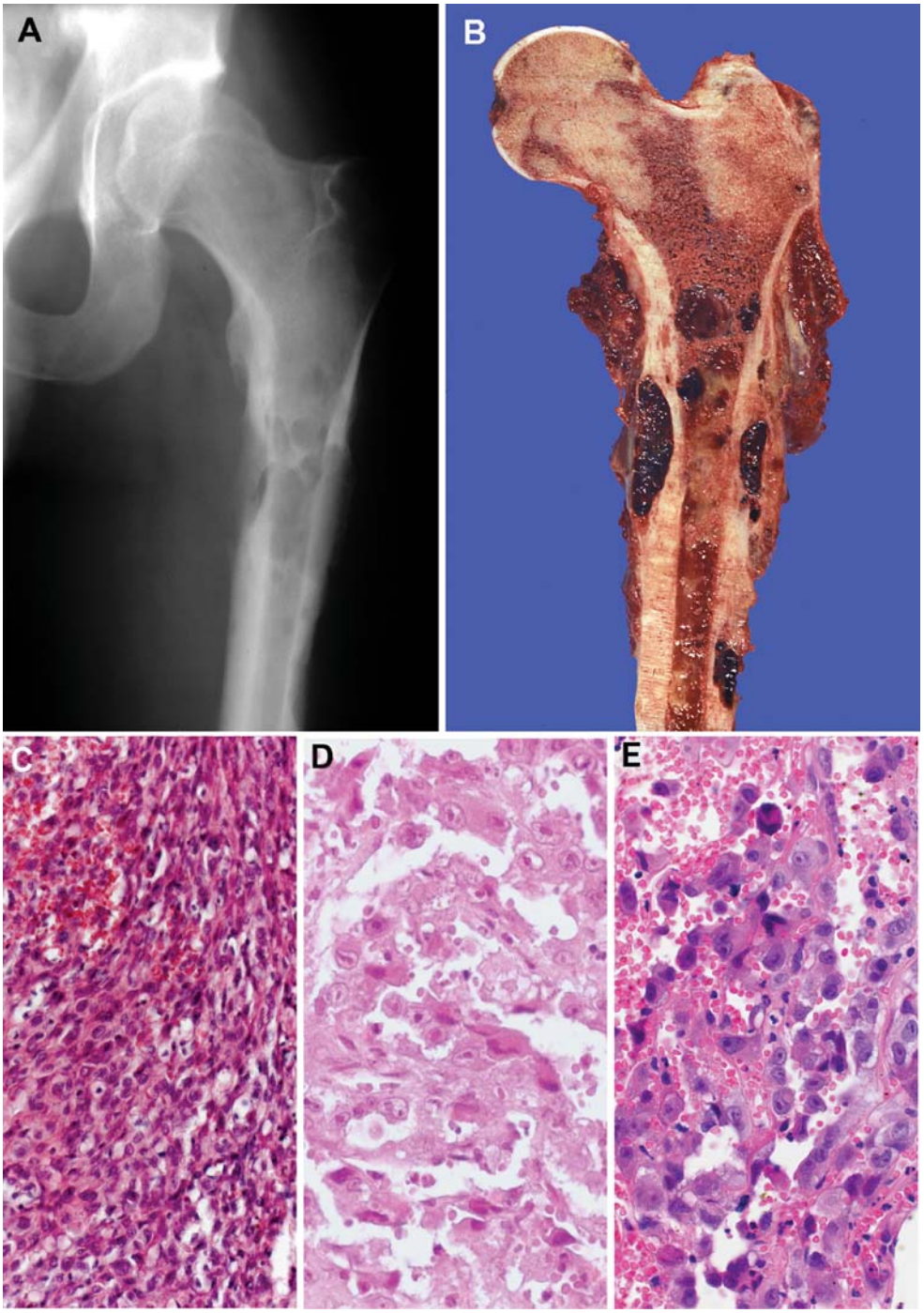
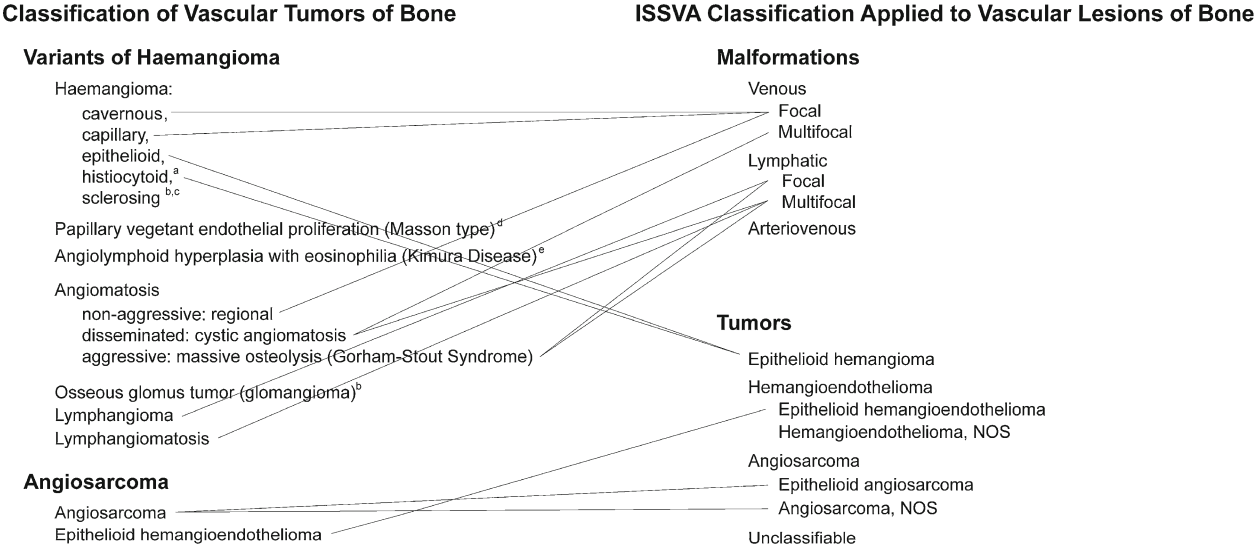


Fig. 11 Angiosarcoma. **a** Plain film of the proximal femur demonstrates osteolytic areas in the metadiaphysis with cortical destruction and lack of sclerosis (25-year-old male). **b** Hemisected femur shows multiple dark-red–brown osteolytic foci in the diaphyseal cortex and medulla. Periosteal elevation is present laterally and there is extensive soft tissue infiltration (the pale yellow areas in the femoral head, metaphysis, and greater trochanter are fatty marrow; same patient as in **a**). **c** Soft tissue component showing highly cellular area of spindled endothelial cells with moderate nuclear pleomorphism and slit-like lumina containing red blood cells (same patient as in **a**). **d** Epithelioid angiosarcoma. Moderately anaplastic tumor cells have abundant pink cytoplasm and prominent eosinophilic nucleoli (25-year-old male). **e** Discohesive growth of epithelioid anaplastic cells forming irregular channels (same patient as in **d**)

tous rather than true neoplasms [2, 3, 13, 19, 20]. With the increasing appreciation that these lesions are malformative rather than neoplastic, sclerotherapy is growing in popularity, thereby avoiding the morbidity of an operation, antiangiogenic therapy, or radiation.[21–25]. In one study, the authors describe their experience in treating a series of vascular malformations of the mandible and advocate that terms such as "intraosseous central or peripheral angioma" and "tumoral angioma" should not be used so as to avoid tumor therapies such as radiation [23].

Localized VMs were more common than multiple VMs. No patient had cutaneous involvement as has been reported in patients with multiple mucocutaneous VMs and Maffucci, or blue rubber bleb nevus syndromes [26, 27]. The majority of VMs, particularly those in the vertebrae, are discovered incidentally, have characteristic imaging, and do not require biopsy. Histopathologically, VM often suggests a differential diagnosis that includes, in particular, LM. LMs generally have thinner walls without pericytes or smooth muscle and their lumens may be empty or contain a

Table 3 Comparison of the WHO classification with the ISSVA classification (as applied to our series)



NOS not otherwise specified

[a] Currently considered synonymous with epithelioid hemangioma

[b] Not encountered in our series

[c] Sclerosing hemangioma is not discussed in standard textbooks describing vascular tumors of bone

[d] Currently considered a secondary process in organizing thrombi or hematomas

[e] Angiolymphoid hyperplasia with eosinophilia is currently considered a synonym for epithelioid hemangioma and unrelated to Kimura disease

proteinaceous lacy network, macrophages, and lymphocytes. Luminal blood may be present but is usually related to surgical trauma. Immunoreactivity of the endothelial cells for D2-40 is characteristic of LM and discriminates between these two lesions. The somewhat polymorphic appearance of VM and its small vessel component may mimic a neoplasm, but the proliferative index is low except in areas of organizing thrombi. Some venous malformations have organizing thrombi or organizing hemorrhage further mimicking a neoplastic proliferation. In small biopsies, AVM may also mimic VM when only dilated venous channels are seen and channels of indeterminate type or with thick muscular walls and/or intimal myofibroblastic proliferation have not been sampled. While some aspects of VM may suggest infantile hemangioma, diagnostic features are absent, including Glut-1 immunoreactivity [28]. It is intriguing that, to the best of our knowledge, infantile hemangioma, the most common vascular tumor in children, has not been convincingly shown to originate in bone. A congenital cranial hemangioma that regressed with time has been reported but the histopathology was not illustrated [29].

Mutations in the genes for *TIE1* and *TIE2*, *Glomulin*, and *KRIT1* have been described in various extraskeletal VMs [30]. It is unknown if the molecular mechanisms underlying osseous VMs are similar.

In the literature, LM is most often designated "lymphangioma" when localized and "lymphangiomatosis" or "cystic angiomatosis" when multifocal. These terms with the suffixes "oma" or "omatosis" imply neoplasia. We believe that LMs are malformations; there is no disproportionate growth except if they are expanded by lymph, become infected, or bleed. The diagnosis of osseous LM is usually possible by imaging, as with VM. In contrast to VM, multifocal lesions were more common than localized lesions. In multifocal LM, extraskeletal extensive involvement of skin, soft tissue, and viscera is almost always present.

The most common histopathological mimicker of LM is VM. Although there are histopathological differences (*vide supra*), the distinction is greatly facilitated by endothelial immunopositivity for D2-40 and LYVE-1 in LM [31]. Although, in our experience, decalcification impairs LYVE-1 immunoreactivity, that of D2-40 is preserved. The histopathology of multifocal LM is similar to that of localized LM, except that, in the former, there is a tendency for the channels to be smaller, more numerous, and to have more complex anastomoses.

LM can be associated with chromosomal abnormalities such as Down, Turner, and Noonan syndromes and mutations in *FLT4*, *FOXC2*, and *SOX18* have been reported in various types of congenital lymphedema [32]. Nevertheless, genetic alterations in primary osseous lymphatic malformations have not been described.

The terms massive osteolysis, disappearing bone disease, phantom bone disease, or Gorham-Stout disease refer to a gradual and often complete resorption of one or multiple skeletal elements with the vertebrae, scapulae, clavicles,

ribs, proximal humeri, ilia, and proximal femora being the sites of predilection [33–35]. Gorham and colleagues [34, 35] used the term "angiomatosis" (or "hemangiomatosis") of blood vessels and rarely of lymphatic vessels to describe the histopathology. It has been stated that "the vascular changes in Gorham disease represent hemangiomas, lymphangiomas, or a combination" [2]. Our experience is that massive osteolysis is associated only with LM.

Although the pathogenesis of Gorham-Stout disease is not entirely elucidated, it is thought that the monocyte-derived precursors of osteoclasts play a crucial role [36]. Circulating osteoclastic precursors with increased sensitivity to interleukin (IL)-6, IL-1β, and tumor necrosis factor alpha and elevated serum levels of IL-6 have been reported [37].

AVM was the least common malformation encountered in our series and, as in the literature, the craniofacial bones were most commonly affected. The involvement of the skeletal element(s) is usually extensive and there may be an adjacent soft tissue component. Hypertrophy of the skeletal element(s) may ensue. Lesional change in size associated with microvascular proliferation, attributed to rheologic factors, may occur, particularly in areas with substantial shunting [15]. The molecular basis for AVMs is an area of active investigation. Mutations in the *RASA1* gene cause the capillary malformation–arteriovenous malformation phenotype, but primary osseous involvement in this condition has not been reported [30]. The lesions in hereditary hemorrhagic telangiectasia caused by mutations in activin and endoglin may include large AVMs of lung, liver, and brain but not bone.

In the tumor category, benign neoplasms outnumbered malignant ones. The most commonly encountered benign tumor was epithelioid hemangioma. This tumor has been delineated from other epithelioid vascular tumors such as epithelioid hemangioendothelioma and epithelioid angiosarcoma [38]. Nevertheless, some investigators have questioned the ability to distinguish epithelioid hemangioma from epithelioid hemangioendothelioma [39]. Although epithelioid hemangioendothelioma is often multicentric or polyostotic, in our series, 25% of epithelioid hemangiomas were similarly so, indicating that these features do not necessarily imply malignancy. The histopathology of epithelioid hemangioma is usually characteristic, but, when solid growth predominates and/or nuclear pleomorphism is present, epithelioid hemangioendothelioma and epithelioid angiosarcoma should be considered in the differential diagnosis. Cytologic atypia in epithelioid hemangioma, if present, is minor and solid growth is always accompanied by more typical areas. The stromal hyalinization or basophilic chondroid ground substance characteristic of epithelioid hemangioendothelioma and necrosis are not present [40]. Absence of significant cellular atypia and frequent mitoses, including abnormal forms, helps to exclude epithelioid angiosarcoma.

Epithelioid and spindle cell hemangioma, originally delineated as a separate entity [41], is now regarded as a variant of epithelioid hemangioma (Andrew Rosenberg, personal communication). Our experience with four patients is in accordance with published data that this lesion is benign and a variant of epithelioid hemangioma.

The term hemangioendothelioma has been applied to tumors of indeterminate behavior, with the prototype being epithelioid hemangioendothelioma. Currently, in the WHO soft tissue section, it is stated that "the behaviour of epithelioid hemangioendothelioma is intermediate between haemangiomas and conventional (high grade) angiosarcomas…" whereas, in the bone section, it is classified as an angiosarcoma [12]. With one exception, epithelioid hemangioendothelioma was the only type of hemangioendothelioma encountered in our series. It has a tendency to be multicentric within an individual osseous element or multifocal (polyostotic), particularly in the same skeletal region. Synchronous involvement of paired bones is common, further confounding the issue of multifocality versus metastasis. Visceral involvement, particularly hepatic and/or pulmonary, may also be present, as noted in our study. Radiographically, they are lytic lesions which may include cortical destruction and extension into soft tissue and joints, but the features are not specific. We observed a hemangioendothelioma that was difficult to characterize, which we designated hemangioendothelioma NOS. The major differential diagnosis is epithelioid hemangioma and epithelioid angiosarcoma. The histopathological features helpful in distinguishing it from epithelioid hemangioma are described above. Epithelioid angiosarcoma has more nuclear pleomorphism, hyperchromasia, and a higher mitotic rate.

The molecular pathogenesis of epithelioid hemangioendothelioma is gradually being unraveled. A t(1;3)(p36.3; q25) translocation has been reported in two epithelioid hemangioendotheliomas [42]. Overexpression of TP53, murine double minute protein, and vascular endothelial growth factor and decrease of caveolin 1 have been observed in one patient with a progressive tumor [43].

Pediatric angiosarcoma of bone has only rarely been reported [44]. It is typically a localized lesion, but, in our series, more than half of the lesions were multicentric within an individual osseous element and/or multifocal (polyostotic). Radiographically, they are destructive lytic lesions with poorly defined borders and may extend into soft tissue. The diagnosis can be challenging given the great variability in their histopathology. The malignant nature of the tumor is usually evident with disorganized architecture, marked cytologic atypia, and frequent mitoses. While vasoformation is usually present, immunopositivity for endothelial markers is helpful or sometimes essential to reach a diagnosis. Angiosarcoma often expresses immuno-

phenotypic markers associated with both blood vascular and lymphatic endothelium [45].

The prognosis of pediatric angiosarcoma is poor, as it is in adults. Our limited follow-up does not permit a definitive statement in this regard: only one patient, who had an intermediate-grade angiosarcoma treated with chemotherapy and radical resection, is a long-term survivor.

Kaposiform lymphangiomatosis has been recently described in an abstract as a provisional entity that mostly affects older children and frequently involves bone, retroperitoneum, mediastinum, lungs, and spleen [46]. Recurrent pleural effusions, progressive multifocal osteolytic lesions, and minor thrombocytopenia dominate the clinical course. Mediastinal, pleural, pericardial, or abdominal hemorrhage can occur and be fatal. Imaging shows a multifocal LM (lymphangiomatosis). The histopathology is also that of multifocal LM with a minor component of small sheets of closely apposed spindled cells with poorly formed or slit-like lumina containing erythrocytes and occasional microthrombi, prominent cytoplasmic and interstitial hemosiderosis, and focal cytoplasmic eosinophilic globules. Kaposiform lymphangiomatosis has a superficial similarity to kaposiform hemangioendothelioma. However, unlike kaposiform hemangioendothelioma, kaposiform lymphangiomatosis is not a single mass; the dominant component is a multifocal LM; the kaposiform component is minimal, is intimately admixed with the lymphatic component, and generally lacks solid growth, lobular architecture, glomeruloid structures, and intersecting fascicles [46]. Additionally, in contrast to kaposiform hemangioendothelioma, older children or adolescents are affected; thrombocytopenia is absent or minor, and a diffuse splenic sinusoidal involvement is characteristic.

Our understanding of kaposiform lymphangiomatosis is incomplete, but the lesion could be provisionally viewed as either an "*ab initio*" disorder or as a multifocal LM that has undergone focal transformation to low-grade neoplasia. It should be emphasized that this is simply a provisional descriptive term for a lesion that needs to be further investigated.

Kaposiform hemangioendothelioma arising in bone has not been reported, although it can secondarily involve bone [47]. A 39-year-old woman with a recently diagnosed cutaneous KHE had a long history of osteolytic lesions in the humerus and radius, but the original diagnosis of the osseous lesions was not stated and the pathology slides were not retrievable for review [48]. Three tumors in our series had histopathologic features similar to kaposiform hemangioendothelioma. Unlike the typical child with kaposiform hemangioendothelioma, these patients were older and only one had thrombocytopenia, albeit minor. Histopathologically, the lobularity in these tumors was minimal and there were no vicinal dilated or malformed lymphatics. It is possible that these morphologic differences are related to the particular milieu of the site of origin. The lesions had features that prompted one to consider spindle cell hemangioma, epithelioid and spindle cell hemangioma, Kaposi sarcoma, and kaposiform lymphangiomatosis in the differential diagnosis. Nevertheless, the clinical findings and the constellation of the histopathological features, including focal immunopositivity for D2-40, are those that characterize kaposiform hemangioendothelioma. Additional studies of similar tumors should help resolve whether these lesions are *bona fide* kaposiform hemangioendothelioma.

Although most osseous lesions in this study were similar to their extraskeletal counterparts, there remained a small heterogeneous group which could not be classified. Some may be known entities with a modified appearance because of the site of origin, while others may be lesions yet to be described.

In summation, a multidisciplinary approach to diagnosis and management of vascular anomalies of bone is crucial, as it is in all bony lesions. Particularly important is radiologic imaging, and, in most malformations, it is characteristic if interpreted by radiologists with experience in this area. Biopsy is usually not required. If there is uncertainty about the nature of the lesion, biopsy might be necessary. Malformations outnumbered tumors with LM and VM being the most common. In the tumor category, hemangioendothelioma and epithelioid hemangioma were the most frequent. We describe kaposiform hemangioendothelioma which has not been reported arising in bone, and expand upon our experience with a lesion that we provisionally termed kaposiform lymphangiomatosis. We also conclude that the standardization of the nomenclature of vascular lesions of bone could be achieved by employing the ISSVA system and its use will facilitate scientific communication and patient management.

Acknowledgments We are indebted to the technical staff of the Department of Pathology of Children's Hospital Boston and the Institute of Pathology, University Hospital Basel for performance of immunohistochemistry and coordinators of the Vascular Anomalies Center of the Children's Hospital Boston. We thank Thomas Schuerch and Jan Schwegler for scanning radiographs and whole mount sections and for help with the digital imaging. Above all, we are grateful to Petra Huber of the Basel Bone Tumor Reference Center for her invaluable assistance in retrieval of slides, clinical charts, and radiographic documentation.
We declare that we have no conflict of interest

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