

A Reappraisal of Hemangiopericytoma of Bone; Analysis of Cases Reclassified as Synovial Sarcoma and Solitary Fibrous Tumor of Bone

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Abstract: Hemangiopericytoma (HPC) was first described as a neoplasm with distinct morphologic features, presumably composed of pericytes. In soft tissue, it is accepted that most such lesions are solitary fibrous tumors (SFTs), monophasic synovial sarcomas (SSs), or myofibromatoses. It is unclear whether HPC of bone exists. We reviewed 9 primary “HPC” of bone from 4 institutions diagnosed between 1952 and 2002. Immunohistochemistry was performed for CD31, CD34, von Willebrand factor, smooth muscle actin, keratin AE1/AE3, and epithelial membrane antigen. There were 4 male and 5 female patients between 21 and 73 years. All tumors were located within bone, either sited within spine or extremities. All tumors showed thin-walled branching vessels surrounded by undifferentiated spindle or round cells. These cells showed variation in their morphologic pattern: 6 tumors showed a pattern-less architecture and varying cellularity, consistent with SFT; 3 of 5 cases examined were CD34-positive. Three tumors showed more densely packed sheets and fascicles of poorly differentiated cells, resembling SS, of which 2 showed focal staining for keratin AE1/AE3 or epithelial membrane antigen. Fluorescent in-situ hybridization confirmed the presence of SS18 rearrangement in 1 of 2 tumors examined. In conclusion, similar to their

soft-tissue counterpart, HPC-like features in bone are a non-specific growth pattern rather than a true diagnosis. We confirm the existence of 2 entities: SFT and SS of bone. Both are characterized by distinct morphology and immunohistochemical profile. SFT of bone is located within spine and has a better prognosis, whereas SS of bone is located within long bones having a poor prognosis.

Key Words: hemangiopericytoma, bone tumor, solitary fibrous tumor, synovial sarcoma, immunohistochemistry

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Hemangiopericytoma (HPC) was first described as a type of vascular tumor by Stout and Murray in 1942.²⁹ It was suggested that these lesions were derived from Zimmerman’s pericytes, so-called modified smooth muscle cells.²⁹ Histologically, this tumor was characterized by endothelial-lined tubes or endothelial sprouts surrounded by rounded or spindle-shaped cells typically supported by a meshwork of reticulin fibers.²⁹ Originally, this tumor was primarily described within soft tissue, but over the years investigators reported occasional cases occurring as solitary lesions within the bone as well.

For many years, HPC was a generally accepted histologic entity, although the diagnosis was merely based on its architectural pattern. However, Fletcher⁸ and other investigators^{13,23} showed that many soft tissue tumors could mimic a HPC-like growth pattern, including, among others, lesions such as synovial sarcoma (SS) and mesenchymal chondrosarcoma, and therefore, stated that HPC should be regarded as a nonspecific growth pattern instead of a true histologic diagnosis. This is, however, a controversial issue.⁷ Electron microscopy showed pericytic differentiation in only a minority of cases diagnosed as HPC.⁵ Basal lamina-like materials, cytoplasmic processes, cytoplasmic filaments, discrete basal lamina, and poorly formed intercellular junctions were the most frequently found features in these lesions and some soft tissue pathologists have used the presence of basement membrane at electron microscopy to distinguish HPCs from solitary fibrous tumor (SFT).⁵

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Since the era of immunohistochemistry, true pericytic differentiation could not be confirmed in the majority of the cases^{4,20,28} and on the basis of the immunohistochemical profile, a subgroup of HPCs could be reclassified as infantile myofibromatosis.^{8,18} Furthermore, the majority of so-called HPCs seemed to be indistinguishable from SFTs, a spindle-cell tumor most commonly arising in the pleura although extrapleural locations are now extensively described,¹⁹ leading to a substantial overlap between both entities.

Today, HPC is no longer recognized in the 2002 World Health Organization Classification of Soft Tissue and Bone Tumors, and as stated, so-called HPCs of soft tissue should be better classified as typically rather cellular examples of SFT.^{9,10} However, it is not clear whether HPC of the bone represents a true, separate entity or is comparable with its soft-tissue counterpart, and should be regarded as a nonspecific growth pattern and therefore reclassified as, for example, SFT of bone. We collected a series of cases diagnosed as HPC of the bone between 1952 and 2005 in 4 different bone tumor referral centers with the goal of reviewing the histology and radiology. Immunohistochemistry and fluorescent in-situ hybridization (FISH) were performed to investigate whether HPC of the bone is a distinct entity, or, similar to its soft-tissue counterpart, represents a growth pattern that can be observed in SFT, SS, or myofibromatosis arising in the bone.

MATERIALS AND METHODS

Clinicopathologic Data and Histologic Review

Sixteen tumors (from 16 patients) diagnosed as HPC of bone were collected from the archives of the departments of pathology of the Rizzoli Institute, Bologna, Italy (8 tumors), The Netherlands Committee on Bone Tumours (4 tumors), Rigshospitalet, Copenhagen, Denmark (2 tumors), and The Royal National Orthopaedic Hospital, London, UK (2 tumors). The cases were originally diagnosed between 1952 and 2005. All clinical, radiologic, and pathologic data were reviewed. All tumor samples were reviewed by 3 pathologists (J.V. M.G.B., P.C.W.H., and C.D.M.F.) who were blinded

toward any clinical data except for age, sex, and affected bone. Only cases with delicate, thin-walled branching blood vessels with a staghorn-like architecture surrounded by non-atypical, round to spindle-shaped cells with uniform, bland nuclei were included in the study. As 2 tumors did not show this true HPC-like growth pattern, they were excluded from this study. Furthermore, tumors were excluded when no tissue blocks were available (2 cases), the histologic appearance was too badly preserved due to heavy decalcification (2 cases) or a primary meningeal HPC had been documented before the bone lesion (1 case). Nine remaining cases were included in the study (Table 1). All specimens were handled according to the ethical guidelines described in “Code for Proper Secondary Use of Human Tissue in the Netherlands” of the Dutch federation of Medical Scientific Societies.

Radiology

All available radiologic data were reviewed. In one case, radiologic data was not accessible any more. In one patient only a magnetic resonance imaging scan was available and therefore the imaging was suboptimal for radiologic evaluation.

Immunohistochemistry

Formalin-fixed, paraffin-embedded tissue (FFPE) was available for all tumors and immunohistochemistry was performed for CD31, CD34, von Willebrand factor, smooth muscle actin (SMA), keratin AE1/AE3, and epithelial membrane antigen (EMA). For each antibody a positive and negative control was included. Immunohistochemical reactions were performed according to standard laboratory methods.³ The antibodies, their sources, antigen retrieval methods, and dilutions used are documented in Table 2. Immunoreactivity was evaluated as focal positive, diffuse positive, or negative.

FISH

FISH was performed on paraffin-embedded 4 μm sections of tumor tissue of all patients according to previously described standard laboratory methods.²⁷ A 10 μL Locus Specific Identifier *SS18 (SYT)* probe (Vysis, Inc, Downers Grove, IL) was used. Tissue from 2 tumors was repeatedly lost during this process; therefore, nuclei

TABLE 1. Clinical Data in 9 Cases of So-called Hemangiopericytoma of Bone

Case No.	Sex, Age (y)	Location	Therapy	Local Recurrence	Metastases	LFU (y)	Status
1	F, 21	Sacrum	Curettage	—	—	5	NED
2	M, 40	Sacrum	Resection	—	Lung and bone, after 3 y	5	NED
3	M, 50	Vertebra Th12	Resection	Yes, after 15, 17, 19, and 20 y	Lung, liver, and ST, after 21 y	22	DOD
4	M, 44	Humerus	Resection	Yes, after 4, 5, and 20 y	Lung, after 20 y	13	NED
5	F, 73	Fibula	Amputation	—	Lung, after 0.25 y	1.5	DOD
6	F, 31	Vertebra L4	Resection	—	—	4	NED
7	M, 44	Sacrum	Chemo + radiation	—	—	7	DOD
8	F, 21	Humerus	Resection	—	Lung, after 6 y	7	DOD
9	F, 55	Sacrum	Radiation	—	—	11	NED

DOD indicates death of disease; F, female; LFU (y), length of follow-up in years; M, male; NED, no evidence of disease; ST, soft tissue.

TABLE 2. Antibodies Used for Immunohistochemical Analysis

Antibody	Clone	Dilution	Antigen Retrieval	Source	Positive Control
CD31	JC70A	1:10000	Citrate	Dakocytomation	Tonsil
CD34	QBEnd/10	1:30000	—	Neomarkers	Tonsil
Cytokeratin AE1/AE3	—	1:500	Citrate	Neomarkers	Colon
Epithelial membrane antigen	E-29	1:10000	Citrate	Dako	Tonsil
Smooth muscle actin	ASM-1	1:8000	—	Progen	Colon
von Willebrand factor	—	1:8000	Citrate	Dako	Tonsil

were isolated from the FFPE material according to standard laboratory methods.¹⁷ Fluorescence signals were analyzed using a Leica DM RXA fluorescence microscope (Leica Mikroskopie & Systeme GmbH, Wetzlar, Germany) equipped with an appropriate filter set. One hundred nonoverlapping nuclei were counted.

RESULTS

Patient Data

Histology

On the basis of histology, 2 principal morphologic patterns were recognized (Fig. 1). Six tumors demonstrated a pattern-less architecture and varying cellularity (hypocellular and hypercellular areas) (Fig. 1A). These tumors consisted of monomorphic, round to spindle-shaped tumor cells (Fig. 1B). All tumor cells had uniform, bland nuclei and limited amounts of pale eosinophilic cytoplasm with indistinct cell borders. None of the 6 tumors showed nuclear overlapping. Five tumors had less than 4 mitoses per 10 high-power fields (HPF) and only 1 tumor had 5 mitoses/10 HPF. This pattern closely resembled SFT of soft tissue.¹⁰ In contrast, 3 tumors were characterized by a more fascicular arrangement of quite uniform nonpleomorphic spindle-shaped tumor cells (Figs. 1G, H). The tumor cells had a sparse amount of cytoplasm, indistinct cell borders, and showed sometimes overlapping nuclei. The mitotic activity ranged from 3 to 5 mitoses/10 HPF. Necrosis was not seen. This pattern resembled monophasic SS of soft tissue.¹⁰ The cases and their suggested diagnosis based on histomorphology are listed in Table 3. No distinctive “grungy” calcified matrix, fat, or osteoclasts were seen which would suggest phosphaturic mesenchymal tumor.¹¹

Patient Characteristics

All clinical data are summarized in Table 1. Tumors morphologically resembling SFT of bone had a wide age distribution, ranging from the third till the sixth decade (range: 21 to 55 y; median: 42 y) and an equal sex distribution (3 males and 3 females). Tumors morphologically resembling SS of bone had an age distribution ranging from the second till the eighth decade (range: 21 to 73 y; median: 44 y). There were 2 females and 1 male.

Radiologic Appearance and Localization

All patients presented with a solitary, osteolytic bone lesion with a geographic or moth-eaten pattern of bone destruction. Furthermore, in all 7 tumors, for which conventional radiology was available, cortical disruption and extension into the adjacent soft tissue was present. In all tumors, the bulk of the tumor mass was located within the bone and the majority of tumors showed only limited extension into the soft tissue, in keeping with a primary bone tumor with soft tissue extension rather than a soft tissue tumor with bone invasion (Fig. 2). In only 2 of 6 SFT-like tumors, small areas of mineralization were seen, suggestive of residual preexistent bone fragments rather than mineralization by the tumor itself, whereas 1 of 2 SS-like tumors showed focal mineralization. However, none of these radiologic criteria were characteristic for either SFT or SS-like tumors.

All SFT-like tumors were located within the spine: either the sacrum (4 tumors), the lumbar spine (1 tumor), or the dorsal spine (1 tumor). Both vertebral tumors were located within the corpus of the vertebra and showed expansion into the arch and an adjacent vertebra. All SS-like tumors were located in the extremities, especially the long tubular bones, without any predilection for diaphysis, metaphysis, or epiphysis. Clinically and radiologically, there were no signs of osteomalacia or any other metabolic bone disorder.

Patients Follow-up

In all patients, follow-up data was available, ranging from 1.5 to 22 years (median: 7 y; Table 1). All patients were treated, either with surgery: curettage (case 1) or margin-free resection/amputation (cases 2 to 6 and 8), or when inoperable with chemotherapy combined with radiotherapy (case 7) or radiotherapy only (case 9) (Table 1). Only one patient with an SFT-like tumor (case 3) and one with an SS-like tumor (case 4) developed a local recurrence after 15 and 4 years, respectively. Five patients developed metastases ranging from 0.25 to 21 years after the initial diagnosis (median: 6 y). All patients with SS-like tumors developed lung metastases, whereas only 2 patients with a tumor resembling SFT developed metastases. In one of these SFT patients (case 2), the metastases were located within the lungs and bone, whereas the other (case 3) developed metastases within the lungs, liver, and soft tissue. Only the primary tumor in case 3 had more than 4 mitoses/10 HPF.

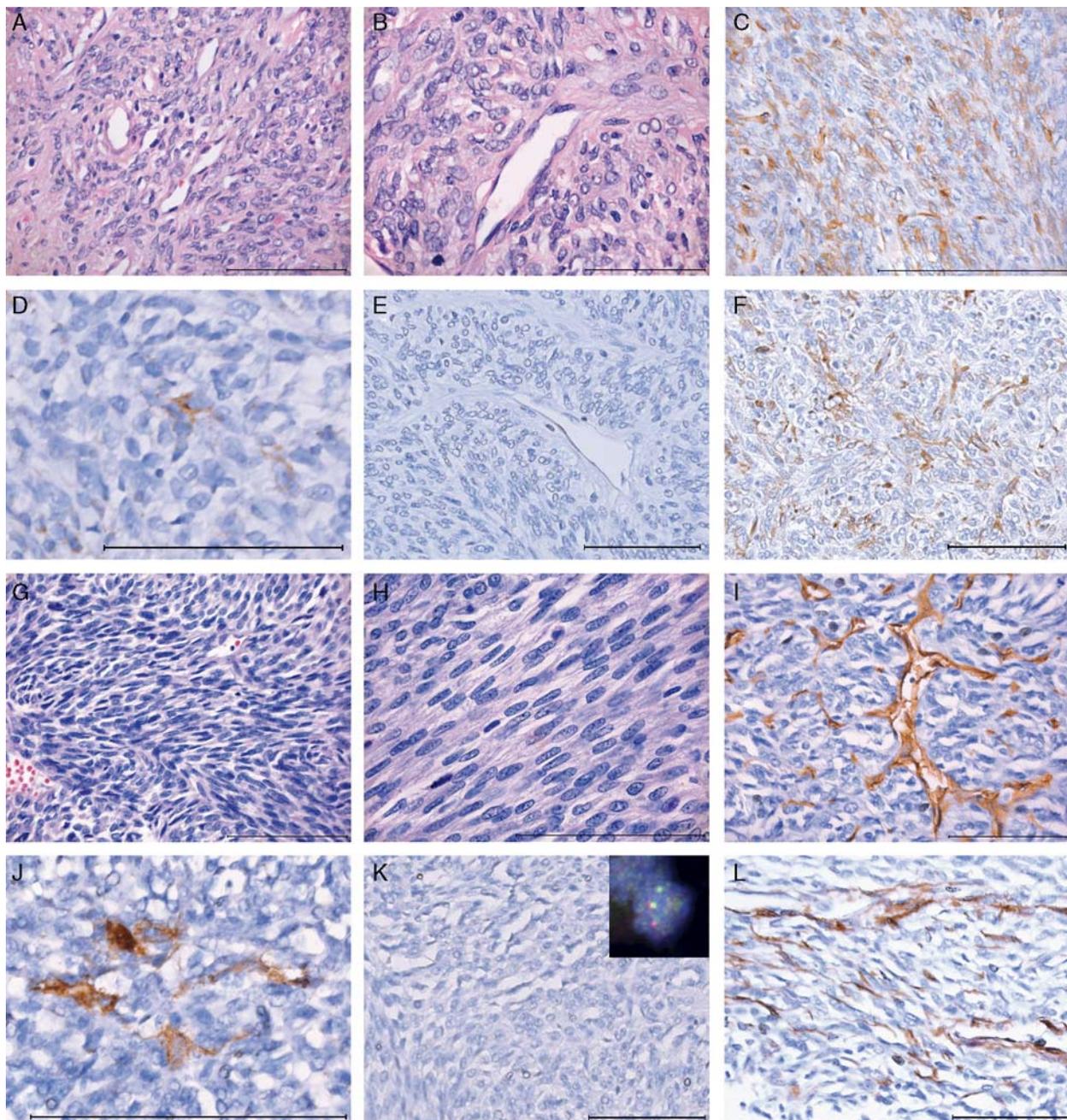


FIGURE 1. The 2 principal morphologic patterns that are recognized: solitary fibrous tumor-like tumor showing a varying cellularity and a monomorphic tumor cell population [(A, B) hematoxylin and eosin staining; scale bar: 50 μ m; case number 2] and SS-like tumor showing a fascicular arrangement of non-atypical, spindle-shaped tumor cells [(G, H) hematoxylin and eosin staining; scale bar: 50 μ m; case number 5], and their corresponding immunohistochemical profile as listed in Table 3: (C, I): CD34; (D, J): epithelial membrane antigen; (E, K): keratin AE1/AE3; (F, L): smooth muscle actin (scale bars: 50 μ m). Inset in (K): SS18-fluorescent in-situ hybridization showing a break-apart of the probes and confirming the diagnosis of SS. SS indicates synovial sarcoma.

Immunohistochemistry

Three of 5 tumors resembling SFT showed diffuse or more focal staining for CD34 (Fig. 1C). One tumor showed focal staining for SMA (Fig. 1F). Three and 2 tumors showed focal staining for EMA and keratin AE1/AE3 (Figs. 1D, E), respectively. Two tumors resembling

SS showed either focal-positive staining for EMA or keratin AE1/AE3 (Figs. 1J, K). The keratin-positive tumor showed some focal staining for CD34. The other 2 tumors were negative for CD34 (Fig. 1I). All tumors showed focal-positive staining for SMA (Fig. 1L). None of the 9 tumors showed expression of CD31 or

TABLE 3. Histologic and Immunohistochemical Data in 9 Cases of So-called Hemangiopericytoma of Bone

Case No.	Histology				Immunohistochemistry							New Diagnosis
	Cellularity	Growth Pattern	Nuclear Overlap	Mitoses (per 10 HPF)	CD31	CD34	vWF	KerAE1/3	EMA	SMA	SS18-FISH	
1	Variable	Patternless	No	3	—*	—*	—	+	—	—	—	SFT
2	Variable	Patternless	No	5	—	++	—	—	+	+	—	SFT
3	Variable	Patternless	No	1	—	++	—	+	+	—	—	SFT
4	Constant	Fascicular	Yes	3	—	+	—	+	—	+	—	SS
5	Constant	Fascicular	Yes	5	—	—	—	—	+	+	+	SS
6	Variable	Patternless	No	2	—	—	—	—	—	—	—	SFT
7	Variable	Patternless	No	1	—	+	—	—	+	—	—	SFT
8	Constant	Fascicular	Yes	4	—	—	—	—	—	+	Failed	SS
9	Variable	Patternless	No	0†	—	—	—	—	—	—	—	SFT

*Internal control negative.

†Only biopsy available.

+ indicates focal positive; —, negative; ++, diffuse positive; EMA, epithelial membrane antigen; FISH, fluorescent in-situ hybridization; HPF, high-power field; SFT, solitary fibrous tumor; SMA, smooth muscle actin; SS, synovial sarcoma; vWF, von Willebrand factor.

von Willebrand factor. Results of immunohistochemical analysis for all cases are listed in Table 2.

FISH

Only 1 tumor showed in 82 nuclei a break-apart of probes flanking the *SS18 (SYT)* gene, confirming the diagnosis of SS (Fig. 1K inset). One tumor having morphology consistent with SS failed repeatedly, probably because of decalcification effects. In 6 tumors, 1 resembling SS and 5 resembling SFT (including those showing focal positivity for keratin and EMA), an *SS18* rearrangement was not detected. Results of the FISH analysis for all cases are listed in Table 2.

DISCUSSION

Although the existence of HPC of bone has been reported, mainly in single case reports, they are extremely rare.^{31,33} The largest series consisted of 11 cases and was described by Wold and colleagues in 1982.³³ However, to date there is no consensus whether this entity truly exists. Today, it is accepted that the “so-called” HPC of soft tissue merely represents a nonspecific growth pattern, instead of a true, specific entity. Over the years, it has become clear that many tumors exhibit this growth pattern.^{8,10,13} As true pericytic differentiation could not be confirmed in the majority of the tumors, it has been stated that most of these lesions should be classified as

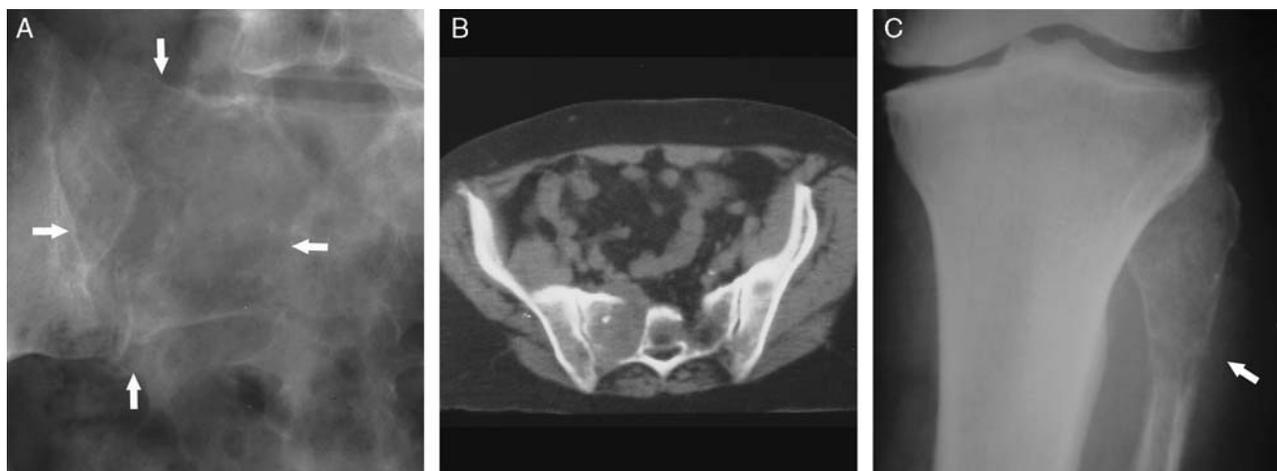


FIGURE 2. Radiologic appearance of the 2 different entities: solitary fibrous tumors of bone [(A, B) case number 9] and synovial sarcoma of bone [(C) case number 5] showing that the bulk of the tumor mass is located within the bone, corresponding with a primary bone tumor. A, Anteroposterior conventional radiograph of the sacrum showing an ill-defined osteolytic lesion (arrows) in the area of the first and second sacral vertebra with loss of delineation of the sacral foramina on the right. B, The computed tomography slice demonstrates the intraosseous origin of the tumor, the anterior cortical interruption, and the subsequent soft-tissue extension. C, Anteroposterior conventional radiograph of the knee showing an ill-defined osteolytic lesion arising in the medullary cavity of the proximal fibula. There is a permeative cortical destruction and a periosteal reaction with possible extension into the soft-tissue extension (arrow).

SFT, monophasic SS, and (infantile) myofibromatosis or myofibroblastic lesions.^{8,10,13,18} In addition, a hemangiopericytomatous vascular pattern is seen in phosphaturic mesenchymal tumor.¹¹ We therefore collected a series of so-called HPC of bone to see whether these were distinctive lesions, or that, similar to its soft-tissue counterpart, also in bone this is a nonspecific growth pattern. In addition, in neuropathology, there is a current shift from meningeal HPC toward meningeal SFT. It is well known that these tumors tend to metastasize to bone.¹⁶ Therefore, we excluded all patients with brain surgery or confirmed meningeal HPC/SFT in their medical history.

The histologic review of the 9 bone tumors with a strict hemangiopericytomatous vascular pattern suggested the existence of 2 categories: 6 tumors consistent with the morphology of SFT and 3 tumors consistent with the morphology of SS. To support or confirm these diagnoses, immunohistochemistry and SS18-FISH were performed.

Within the group of tumors reminiscent of SS, 2 of 3 tumors either showed focal keratin or EMA expression, which is more or less consistent with the literature.¹⁰ One tumor also showed focal staining for CD34. Although most SS are negative for CD34, positivity has been reported in a minority of cases, up to 7.7%, mainly of monophasic or poorly differentiated types.^{2,6,22,26} Positivity for SMA has also been described in up to 21% of the SSs.²⁶ As SMA can be present in either SS or SFT, it is not a useful marker for distinguishing between these diagnoses.

SS is characterized by a tumor-specific translocation t(X;18)(p11.2;q11.2) leading to the *SS18-SSX* fusion gene which is present in 90% to 95% of the SSs. SS18-FISH was performed and the presence of a break in the *SS18* gene confirmed the diagnosis of SS and therewith the existence of primary SS of bone. However, we could demonstrate the tumor-specific translocation in only 1 of 2 cases evaluated. Both FISH and reverse transcription-polymerase chain reaction can be used to detect the SS-specific translocation in FFPE material.^{1,30} It has been shown that FISH is slightly less sensitive compared with reverse transcription-polymerase chain reaction, which may explain the negative result in one tumor.^{1,30} Alternatively, as 5% to 10% of the SSs lack this tumor-specific translocation, we can not rule out another complex genetic aberration not detectable by the FISH-probe used. Nevertheless, the morphology and the immunohistochemical profile in this SS18-negative tumor (case 4), suggest SS. In the third case, the FISH failed repeatedly, most probably due to heavy decalcification methods or poor fixation of the specimen. This tumor (case 8) also did not show any immunoreactivity for keratin AE1/AE3 or EMA. Furthermore, this tumor was negative for CD34, although the numerous blood vessels present within the tumor were positive. Thus, although the morphology, mitotic rate, and clinical behavior were consistent with SS, immunohistochemistry and molecular diagnostics could not definitively support reclassification of this tumor.

Immunohistochemistry in the group of tumors reminiscent of SFT revealed 3 tumors with either diffuse (2 tumors) or focal (1 tumor) staining for CD34, whereas 2 tumors were CD34 negative. One tumor did not show any immunoreactivity for CD34, repeatedly, and also the internal control (blood vessels) was negative, suggesting loss of antigenicity for this marker possibly because of heavy decalcification. Although CD34 is the most useful marker to diagnose SFT,^{10,24} it is expressed by many other spindle-cell neoplasms, such as neurofibromas, gastrointestinal stromal tumors, spindle cell lipoma, and dermatofibrosarcomas protuberans.^{14,25} In addition, expression of CD34 in SFT is rather variable ranging from 80% to 95% of cases in the literature,^{10,13} which may explain the 2 CD34-negative tumors. So far, it has not been elucidated why a small percentage of SFT are CD34 negative. Although the expression of keratin and SMA is rare, these markers have been reported to be positive in about 2% to 3% of SFT, whereas EMA can be positive in up to 20% to 35% of the tumors.¹⁰ We found EMA positivity in 3 of 5 and keratin positivity in 2 of 5 bone tumors with SFT-like morphology. It may therefore be that SFT of bone is more often negative for CD34 and more often positive for EMA as compared with morphologically similar tumors arising in soft tissue. Alternatively, these cases represent other entities. However, none of the EMA-positive cases demonstrated a break in the *SS18* gene and none of the CD34-negative cases had the characteristic features of phosphaturic mesenchymal tumor.

Unfortunately, there is no specific immunohistochemical marker or a specific genetic aberration that can be used to further support the diagnosis of primary SFT of bone. Cytogenetic aberrations are uncommon in small SFTs but are more common (and also heterogeneous) in the larger ones.²¹

Despite the fact that this is a multicenter study, numbers are small and statistical analysis is not meaningful. However, our studies suggest that SS of bone tends to have a predilection for the long tubular bones. In contrast, SFT of bone is located within the spine, in particular the sacrum or lower lumbar region. It has been reported that SS metastasizes in about 40%, most often to lungs and bone.¹⁰ All 3 SSs in our series metastasized to the lungs, whereas only one SFT metastasized to lungs and bone and one SFT metastasized to lungs, liver, and soft tissue. According to the literature, SS has a 5-year survival of 36% to 76% and a 10-year survival of 20% to 63%.¹⁰ Although the number of SS cases in this study is very limited, the survival curve of our 3 patients shows a similar pattern. Two of 3 SS died 1.5 and 7 years after diagnosis (cases 5 and 8, respectively). For SFT, there is not always a consistent correlation between morphology and biologic behavior. It has been stated that 10% to 15% of the tumors behave aggressively for which increased mitotic rate (4 or more mitoses/10 HPF) was reported to be the most useful predictive factor.^{12,15,32} In our series, 2 patients with SFT died due to progressive disease.

In conclusion, comparable with their presumed soft-tissue counterpart, we believe that HPC of bone should be regarded as a nonspecific growth pattern. Metastatic disease, in particular metastasis of meningeal HPC/SFT, should be excluded. Two entities formerly classified as HPC of bone can be distinguished: primary SFT and primary SS of bone, respectively. SFT of bone is characterized by a pattern-less architecture and variable cellularity, and often shows diffuse CD34 positivity. These tumors, mostly located within the spine, tend to have a better prognosis. SS of bone is characterized by a more spindled and fascicular morphology, often with focal keratin or EMA positivity. These tumors are located within the long bones and have a poor prognosis. The latter can be confirmed by SS18-FISH, if nonaggressive decalcification methods are used.

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