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RESEARCH ARTICLE

WILEY

Epithelioid hemangioma of bone harboring *FOS* and *FOSB* gene rearrangements: A clinicopathologic and molecular study

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Abstract

The diagnosis of epithelioid hemangioma (EH) remains challenging due to its rarity, worrisome histologic features, and locally aggressive clinical and radiographic presentation. Especially in the bone, EH can be misdiagnosed as a malignant vascular neoplasm due its lytic, often destructive or multifocal growth, as well as atypical morphology. The discovery of recurrent *FOS* and *FOSB* gene fusions in the pathogenesis of most EH has strengthened its stand-alone classification, distinct from other malignant epithelioid vascular lesions, such as epithelioid hemangioendothelioma or angiosarcoma. In this study we investigate a group of molecularly confirmed skeletal EH by the presence of *FOS* or *FOSB* gene rearrangements to better define its clinical and pathologic characteristics within a homogenous molecular subset. The cohort included 38 patients (25 males, 13 females), with a mean age at diagnosis of 38 years (range, 4–75). Regional, multifocal presentation was noted in 10 cases. Only six cases were correctly recognized as EH by the referring institutions, while most were misdiagnosed as other vascular tumors. Of the 17 patients with follow-up data available, five patients (29%) developed local recurrence after marginal en bloc excision ($n = 3$) or curettage ($n = 2$). Local recurrence-free survival rates were 84% at 3 years and 38% at 5 years. No metastasis or disease-related death was identified. Imaging studies exhibited no specific features, showing cortical bone destruction and soft-tissue extension in 14 (38%) cases. *FOS* gene rearrangements were detected in 28 (74%) of cases, while *FOSB* rearrangements in 10 (26%) cases. Our results highlight the significant challenges encountered in establishing a correct diagnosis exclusive of the molecular testing, mainly due to its overlap to other malignant epithelioid vascular tumors. Skeletal EH emerges as a genetically defined locally aggressive vascular neoplasm, with a high rate of local recurrence, but lacking the propensity for distant spread.

KEYWORDS

epithelioid hemangioma, *FOS*, *FOSB*, fusions

1 | INTRODUCTION

Epithelioid hemangioma (EH) is an uncommon but distinctive vascular neoplasm displaying well-formed vascular channels lined by prominent epithelioid endothelial cells.^{1–3} EHs are ubiquitously located and have

been described at various anatomic sites including skin, soft-tissue, bone, and viscera.^{1–3} The morphologic spectrum of EH exhibits a wide range of appearances, including cellular/solid proliferation, atypical cytomorphology, prominent inflammatory infiltrate, and intravascular growth.^{4–8} The genetic hallmark of EH includes the presence of *FOS*

or *FOSB* gene rearrangements.^{9,10} Although the pathogenesis of EH has long been controversial, with some early reports suggesting that in particular skeletal EH represents a variant of epithelioid hemangioendothelioma (EHE), thus having metastatic potential,^{11,12} it is now widely recognized that EH is a benign, locally aggressive neoplasm.¹³

Our group previously have identified *FOS* and *FOSB* gene rearrangements, including *FOS*-*LMNA* and *FOS*-*VIM* in 29% of EH⁹ and *ZFP36*-*FOSB* or *WWTR1*-*FOSB* fusion genes in a small subset of EH.¹⁰ Despite these molecular advances, the diagnosis of skeletal EH remains challenging, with most referred cases in our practice being misclassified, often as malignant vascular tumors, that is, epithelioid angiosarcoma. To avoid these pitfalls, the current study focuses its investigation on a group of molecularly confirmed cases of EH presenting in the bone in order to assess their clinicopathologic features, imaging characteristics and potential correlations with the *FOS*/*FOSB* fusions.

2 | MATERIAL AND METHODS

2.1 | Patients selection and data collection

The Pathology Department and the personal consultation files of the senior author (CRA) were searched for diagnosis of EH arising in the bone during a 15-year period (2005-2019), which had molecular results or material available for genetic workup. A total of 38 molecularly confirmed skeletal EH were identified. The study was approved by the Institutional Review Board.

Hematoxylin and eosin-stained slides and immunohistochemical stains were rereviewed. The tumors were assessed for growth pattern, cytomorphology, cellular pleomorphism, nuclear features including nuclear contour, chromatin pattern and presence of nucleoli, mitotic activity, necrosis, and type of extracellular stroma. The endothelial differentiation was confirmed by CD31 and ERG immunohistochemistry using standard protocols.

Retrospective chart review was conducted to collect clinical information, such as greatest tumor diameter, tumor location, stage at diagnosis (primary vs distant metastasis at diagnosis), modality of initial therapy, local recurrence or metastasis, vital status at last follow-up, and survival time.

2.2 | Fluorescence in situ hybridization

Fluorescence in situ hybridization (FISH) for break-apart assay was applied on formalin-fixed and paraffin-embedded 4 μ m sections as previously described.¹⁴ Custom probes using bacterial artificial chromosomes (BACs) covering and flanking the *FOS*, *FOSB*, *VIM*, *LMNA*, *ZNF36*, and *WWTR1* genes were utilized. The BAC clones were selected according to the UCSC genome browser (<http://genome.ucsc.edu>) and obtained from the BACPAC sources of Children's Hospital of Oakland Research Institute (CHORI) (Oakland, CA) ([\[bacpac.chori.org\]\(http://bacpac.chori.org\)\). DNA from individual BACs was isolated in line with manufacturer's instructions, labeled with different fluorochromes in a nick translation reaction, denatured, and hybridized to pretreated slides. These slides were then incubated, washed, and mounted with DAPI. Two hundred tumor nuclei were evaluated using a Zeiss fluorescence microscope \(Zeiss Axioplan, Oberkochen, Germany\), controlled by the Isis 5 software \(Metasystems, Newton, MA\). A cutoff of >20% nuclei showing a break-apart signal was considered to be positive for rearrangement. Nuclei with incomplete set of signals were omitted from the score.](http://</p></div><div data-bbox=)

2.3 | Statistical analysis

Kaplan-Meier curves were used to estimate local recurrence-free survival (LRFS). LRFS was defined as the time from the definitive surgery to local recurrence and were censored at the date of the latest follow-up or death. Variables were compared between groups using chi-squared tests or Mann-Whitney *U* test. Statistical analyses was performed using SPSS version 21 (IBM, Armonk, US), with significance set at two-tailed *P* < .05.

3 | RESULTS

3.1 | Clinical findings

The clinical features of EH of bone are summarized in Table 1. The study cohort consisted of 25 men and 13 women, with a mean age at diagnosis of 38 years (range 4-75). The most common sites affected were the extremities (54%), with 11 cases in the lower limb (including 8 in the foot) and 9 in the upper limb. Other anatomic sites included spine (7, 19%), skull (4, 11%), rib (3, 8%), and pelvis (3, 8%). Among the 33 patients with available data, 9 (27%) presented with regional multifocal tumors (Table 1). A detailed description of the patients symptoms at presentation was available in 20 patients, which included pain in 18 (90%), numbness in one (5%), and incidental finding with no symptoms in one (5%). The tumor greatest dimension obtained from either imaging studies at presentation or gross descriptions had a mean of 5.5 cm (range 1.5-9.7).

Follow-up data was available in 19 of 38 (50%) patients with duration ranging from 1 to 178 months (mean 38 months). All patients presented with localized disease at diagnosis. Surgery was the main therapy applied, being performed in all except two patients. Two asymptomatic patients were managed conservatively with observation. Of the 17 patients treated with surgery, the initial surgical procedures included: marginal en bloc resection in 7 patients (41%), curettage and bone graft/cement augmentation in 9 (53%), and Chopart amputation for multiple metatarsal bone involvement in one (6%). No adjuvants, such as cryosurgery or Argon beam laser coagulator, were used. Among the five patients (29%) who developed local recurrence, three were initially managed with a marginal en bloc resection and two with a curettage procedure. LRFS rates were 84%

TABLE 1 Clinicopathological features of patients with epithelioid hemangioma

Case	Age	Sex	Gene fusion	Site	Multifocal	Surgery	Local recurrence
1	45	M	<i>FOS-LMNA</i>	Rib	No	Yes (en bloc resection)	Yes
2	56	F	<i>FOS-VIM</i>	Foot (first, second, fourth metatarsal bone)	Yes	Yes (Chopart amputation)	No
3	31	M	<i>FOS</i> rearrangement	Foot (first proximal phalanx)	No	Yes (en bloc resection)	No
4	23	M	<i>FOS</i> rearrangement	Rib	No	Yes (en bloc resection)	No
5	41	M	<i>FOS</i> rearrangement	Spine (L5)	No	Yes (curettage)	No
6	52	M	<i>ZFP36-FOSB</i>	Tibia	No	Yes (curettage)	No
7	8	M	<i>WWTR1-FOSB</i>	Foot (Calcaneus, Talus), Distal tibia and fibula	Yes	NA	NA
8	44	M	<i>ZFP36-FOSB</i>	Pelvis (Ilium)	NA	NA	NA
9	38	F	<i>FOS-VIM</i>	Foot (Cuboid)	NA	NA	NA
10	46	F	<i>FOS</i> rearrangement	Foot (Metatarsal bone)	NA	NA	NA
11	18	M	<i>FOS</i> rearrangement	Distal radius	No	Yes (curettage)	Yes
12	15	M	<i>FOS</i> rearrangement	Proximal humerus	No	NA	NA
13	15	M	<i>FOS</i> rearrangement	Foot (Phalanx)	NA	NA	NA
14	24	M	<i>ZFP36-FOSB</i>	Spine (T9)	No	Yes (curettage)	No
15	25	F	<i>FOSB</i> rearrangement	Foot (Phalanx)	NA	NA	NA
16	45	M	<i>FOSB</i> rearrangement	Scapula	No	NA	NA
17	45	F	<i>FOSB</i> rearrangement	Spine (T2 and T3)	Yes	NA	NA
18	31	M	<i>FOS</i> rearrangement	Pelvis (Ischium)	No	Yes (en bloc resection)	Yes
19	55	F	<i>FOS</i> rearrangement	Spine (T5)	No	NA	NA
20	23	F	<i>FOS</i> rearrangement	Skull	Yes	Yes (en bloc resection)	No
21	26	M	<i>ZFP36-FOSB</i>	Skull	No	NA	NA
22	48	F	<i>FOS-VIM</i>	Spine (T7)	No	Yes (en bloc resection)	No
23	62	M	<i>FOS</i> rearrangement	Femur, Tibia, Fibula, lymph node	Yes	No (only follow-up)	NA
24	11	F	<i>FOS</i> rearrangement	Foot (Talus)	No	Yes (curettage)	No
25	58	M	<i>FOS</i> rearrangement	Femur	No	Yes (curettage)	No
26	15	M	<i>FOS</i> rearrangement	Distal radius	No	Yes (curettage)	No
27	54	M	<i>FOS</i> rearrangement	Humerus, Scapula	Yes	NA	NA
28	43	M	<i>FOS</i> rearrangement	Hand (Index and middle phalanx)	Yes	NA	NA
29	71	F	<i>FOS</i> rearrangement	Radius	No	Yes (en bloc resection)	Yes
30	34	M	<i>FOS</i> rearrangement	Humerus, Scapula	Yes	Yes (curettage)	Yes
31	47	F	<i>ZFP36-FOSB</i>	Sacrum	No	NA	NA
32	74	M	<i>FOS</i> rearrangement	Spine (L5)	No	No (only follow-up)	No
33	34	M	<i>ZFP36-FOSB</i>	Scapula	No	NA	NA
34	4	M	<i>FOS</i> rearrangement	Skull	Yes	NA	NA
35	75	F	<i>FOS</i> rearrangement	Skull	No	Yes (en bloc resection)	NA
36	19	F	<i>FOS</i> rearrangement	Spine (T3, T4)	No	Yes (en bloc resection)	NA
37	61	M	<i>FOS</i> rearrangement	Tibia	No	Yes (curettage)	No
38	30	M	<i>FOS</i> rearrangement	Pelvis (Acetabulum)	No	NA	NA

at 3 years and 38% at 5 years (Figure 1). The local recurrence did not correlate with the type of surgical procedure applied given the number of our cases, marginal en bloc resection (43%, 3 of 7) versus

curettage (22%, 2 of 9, $P = .596$, chi-squared test), nor with the gene fusion type, *FOS* gene rearrangement (33%, 5 of 15) versus *FOSB* rearrangement (0%, 0 of 2, $P = .99$, chi-squared test). Subsequent to

local recurrence, three patients underwent marginal reexcision of tumor, resulting in no recurrence. One patient received sorafenib after local recurrence, which showed stable disease for 3 months, with no increase in tumor size for 12 months after discontinuing sorafenib therapy. One patient received preoperative denosumab therapy before re-excision the local recurrence. At last follow-up, 14 (74%) patients had no evidence of disease and 5 (26%) were alive with disease. No distant metastasis or disease-related death was identified.

3.2 | Radiologic findings

Plain radiographs, CT and/or MRI were available in 15 patients. Of 13 cases with plain radiographs or CT available, a zone of transition between tumor and normal bone was well-defined in eight patients or partially ill-defined in five. All 13 cases were characterized by osteolytic lesions, with cortical destruction and soft-tissue extension found in five cases (38%, Figure 2A,B). The proportion of tumors with locally aggressive features (ie, cortical destruction and soft-tissue extension) was not significantly different between *FOS* (36%, 4 of 11) and *FOSB* gene rearrangements (50%, 1 of 2, $P = .715$, chi-squared test). All tumors located in long bones ($n = 4$) had the epicenter within the metaphysis, with extension towards the epiphysis or diaphysis (Figure 2C). All four tumors originating in the spine showed pedicle involvement (Figure 2A,D). Expansion and ballooning of underlying bone was identified in four cases (27% of 15) (Figure 2D,E). Most tumors (85%, 11 of 13) showed low to intermediate signal intensity on T1 weighted MRI image (Figure 2F) and high intensity on T2 weighted MRI images (Figure 2G). Multifocal involvement was also seen in two cases (Figure 2H,I). Tumor lobularity was detected in 11 (73% of 15) cases (Figure 2B-D, F, and H). No periosteal reaction, calcification, and mineralization were noted.

FIGURE 1 Kaplan-Meier curve showing local recurrence-free survival

3.3 | Pathologic findings

The morphologic findings of all cases were reviewed. Tumors were composed of variable proportions of solid areas and vasoformative components. Most cases showed a combination of both patterns, either intermixed or in sharp demarcation. The presence of a predominant solid component with increased cellularity represented the most common pitfall in misinterpreting the lesions as malignant vascular tumors. Regardless of the architectural pattern, the constituent cells showed a relatively monomorphic epithelioid cytomorphology, with dense, glassy eosinophilic cytoplasm and often enlarged round nuclei with open or fine chromatin. The vasoformative areas were composed of either capillary-sized vessels with pinpoint lumina, or dilated vascular channels with the characteristic tombstone pattern, with hobnailed nuclei protruding into the vascular lumen (Figures 3 and 4). Especially in larger samples, such as curettings or resection material, the vasoformative component displayed a lobular growth pattern at the periphery, in keeping with a benign vascular lesion. The lobular growth was less obvious in core biopsies. The cytologic atypia ranged from mild to moderate (Figures 3 and 4), while the mitotic activity was often low (1-2 MF/10 HPFs) to occasional cases with intermediate mitotic counts (3-5 MF/10 HPFs). None of the cases showed marked nuclear pleomorphism or a brisk mitotic activity (>10 MF/10 HPFs). Certain microscopic features appeared to correlate with the fusion type, although some of the differences noted might also be attributed to the sampling error. Necrosis was present in five cases, all associated with *FOSB* fusions (Figure 4). In fact, half of *FOSB*-positive EH displayed necrosis, which is a highly unusual feature for benign hemangiomas and represented a major pitfall in triggering misdiagnoses. An abundant eosinophilic infiltrate was also more often associated with *FOSB* fusions, seen in 4 of the 10 cases, while being noted in only 2 cases of *FOS*-positive tumors (Figure 3). In contrast, *FOS* positive tumors showed abundant hemorrhagic background and displayed in a subset of cases a spindle cell phenotype in addition to the epithelioid cell component (Figure 3). Some of these cases were reminiscent to and diagnosed as "hemorrhagic epithelioid and spindle cell hemangioma,"¹⁵ an entity that was initially thought to represent a unique vascular tumor of bone, but subsequently reclassified as a histologic variant of EH. Moreover, three *FOS*-rearranged EH were associated with exuberant new bone formation, represented by woven bone trabeculae lined by prominent epithelioid osteoblastic cells and scattered osteoclast-type giant cells (Figure 3), simulating a bone forming tumor.

Due to its diverse morphologic spectrum, the diagnosis of EH remains challenging. Of 23 cases with an initial diagnosis at an outside hospital, only six cases (26%) were correctly recognized and diagnosed as EH. Among the remaining, five cases were initially misinterpreted as EHE ($n = 2$), pseudomyogenic hemangioendothelioma ($n = 1$), angiosarcoma ($n = 1$), or giant cell tumor ($n = 1$). In 4 additional cases a distinction between EH and EHE diagnosis could not be made. Two cases were diagnosed as vascular neoplasms, not otherwise specified.

FIGURE 2 Imaging studies of bone epithelioid hemangioma (EH) illustrating destructive appearance with emphasis on diagnostic pitfalls. A, X-ray of a destructive thoracic spine lesion with left pedicle involvement; B, MRI showing spinal cord compression through soft-tissue extension of tumor. C, X-ray showing a lobulated, lytic lesion in the distal radius, with well-defined borders; D, X-ray showing a thoracic spine destructive lesion with ballooning and cortical bone thickening; E, CT showing a first metatarsal osteolytic lesion with ballooning and cortical bone destruction, which on F, MRI T1 and G, MRI T2 weighted image display a low to intermediate signal tumor; H, I, MRI image showing multifocal skull tumors

3.4 | Molecular findings

FISH analysis revealed *FOS* gene rearrangements in 28 (74%) cases and *FOSB* rearrangements in 10 (26%) cases (Table 1). However, a gene partner was identified only in a small subset of cases with *FOS* fusions, three cases harboring *VIM* gene rearrangements and one case *LMNA* gene break-apart. For the *FOSB* fusion subset, a gene partner was identified in 70% of cases, with six cases being positive for *ZNF36* rearrangement, while one case showed an *WWTR1* gene break-apart.

The median age of patients with *FOS* gene rearrangements was not significantly different from those with *FOSB* abnormalities (40 vs 39 years, $P = .660$, Mann-Whitney U test). There was also no correlation between fusion type and tumor location. Moreover, the proportion of patients with multifocal presentation was not significantly different between patients harboring *FOS* gene rearrangements (28%,

7 of 25) and those harboring *FOSB* rearrangement (25%, 2 of 8, $P = .868$, chi-squared test).

4 | DISCUSSION

Our study investigates the largest cohort of molecularly confirmed EH of bone with *FOS* or *FOSB* rearrangements to date. This analysis confirms that skeletal EH is a locally aggressive neoplasm associated with a high local recurrence rate, regional multifocal presentation, but lacks distant metastatic potential or tumor-related deaths. Imaging studies showed diverse radiographic features, often non-specific, which can be associated with either benign or malignant bone lesions, and thus non-contributory in the differential diagnosis of vascular neoplasms. Moreover, due to variegated morphologic features, the pathologic diagnosis of EH remains quite challenging, being

FIGURE 3 Morphologic spectrum of skeletal epithelioid hemangioma (EH) harboring *FOS* gene fusions. A, Whole mount view of a markedly destructive EH showing a predominant hemorrhagic appearance and very thin rim of residual bone noted at the periphery (19/F, T3-T4 lesion). B, High power of this lesion showed a mixture of spindle and epithelioid cells, forming ill-defined vascular spaces, obscured by abundant hemorrhage. C, Another example of bone EH associated with hemorrhagic stroma and predominantly spindle cells, showing only focal vasoformative areas lined by epithelioid cells (4/M, occipital lesion); D, Dilated vascular channels lined by plump epithelioid cells with densely eosinophilic cytoplasm and enlarged round nuclei with open chromatin and small nucleoli (64/M, humerus/coracoid, multifocal lesions). E, Rare *FOS*-positive EH showing abundant stromal eosinophilic infiltrate (61/M, tibia). F, EH associated with an exuberant reactive new bone formation showing foci of woven bone lined by prominent osteoblasts and scattered osteoclast-type giant cells (30/M, acetabulum) [Color figure can be viewed at wileyonlinelibrary.com]

underrecognized among practicing pathologists, without molecular confirmation.

Most findings in the current series, such as male predilection, young age at diagnosis, common primary tumor location within extremity, and proportion of patients with multifocal disease were consistent with a previous study.² The local recurrence rate of 29%, however, was higher than those of previous reports (8-24%),^{2,3} which may be attributed to longer follow-up duration or referral bias related to our quaternary institution. In most patients, recurrent tumors were controlled by additional surgery. Moreover, no patients developed distant metastases or disease-related death, supporting a conservative surgical approach. Based on these results, the preferred surgical approach for skeletal EH is either by curettage or marginal en bloc resection. Medical treatments such as sorafenib or denosumab were applied in isolated cases with recurrent disease, with one patient showing stable disease subsequent to sorafenib therapy. Sorafenib, a multi-kinase inhibitor, has shown efficacy in progressive EHE,^{16,17} but not previously reported in the setting of recurrent or advanced EH. While only surgical treatment provided cure, these medical managements may have benefit in patients with recurrent or multifocal diseases.

Imaging studies of EH are often non-specific and do not contribute in the radiographic distinction of other vascular lesions. The presence of locally aggressive findings, such as cortical destruction with adjacent large soft-tissue mass, frequently suggest a malignant process. Occasionally, the radiographic well-defined border or ballooning, suggest a benign process. Additionally, the presence of regional multifocal involvement may be the only clue indicating a diagnosis of vascular tumor,¹⁸ however, it cannot distinguish from other epithelioid vascular lesions, such as EHE, pseudomyogenic hemangioendothelioma, and so on.

Although overall there were more similarities than differences between the two molecular subsets, some interesting correlations were noted between histologic features and fusion type. Areas of necrosis were present in half of the *FOSB* fusion-positive EH, while being absent on all *FOS*-positive cases. Moreover, EH associated with *FOS* gene rearrangements showed more often abundant hemorrhagic background, areas of spindling and reactive new bone formation. Overall, due to its diverse morphologic spectrum, which includes alternating well-formed vascular channels arranged in a lobular growth, and cellular solid sheets of epithelioid cells with enlarged nuclei with mild to moderate atypia and mitotic activity, the diagnosis of EH

FIGURE 4 Histologic features of epithelioid hemangioma (EH) of bone showing *FOSB* gene rearrangements. A and B, EH of bone showing a predominant solid growth pattern composed of packed epithelioid cells with densely eosinophilic cytoplasm and scattered small-sized vascular channels interspersed. B, Higher power depicts abrupt transition to areas of necrosis (34/M, scapula). C and D, High power view of a cellular EH with plump epithelioid and ovoid endothelial cells with pale eosinophilic cytoplasm and enlarged ovoid nuclei with fine chromatin and mild to moderate atypia. D, Large areas of necrosis were also noted (8/M, calcaneus, *WWTR1-FOSB* fusion) [Color figure can be viewed at wileyonlinelibrary.com]

remains challenging, with only a quarter of cases being correctly diagnosed at the original institution. The most common misdiagnosis was with other malignant epithelioid vascular tumors, in particular with EHE and epithelioid angiosarcoma.

Approximately 90% of EHE harbor *WWTR1-CAMTA1* fusion,¹⁹ whereas a smaller subset is driven by a *YAP1-TFE3* fusion.²⁰ In a recent study, classic EHE with *WWTR1-CAMTA1* fusion was associated with an older age at diagnosis and a worse overall survival compared to the less common *YAP1-TFE3* variant.²¹ Of the 93 patients studied, only a small subset (10 cases) showed bone involvement, with seven of them occurring in patients with multifocal disease involving lung or liver.²¹ Morphologically, classic EHE with *WWTR1-CAMTA1* fusion is composed of epithelioid endothelial cells arranged in single files, cords, and sheets, lacking well-formed vascular channels, in a hyalinized or myxochondroid stroma. In contrast, the less common subset of *YAP1-TFE3*-positive EHE is characterized by well-formed vascular channels, reminiscent to EH, but with higher degree of nuclear pleomorphism. In challenging cases, molecular studies can readily distinguish between EHE and EH, by applying targeted NGS or FISH for *CAMTA1* and *TFE3* gene abnormalities.

In a previous series of 10 patients with epithelioid angiosarcoma of bone, the mean age at diagnosis was 62 years (26–83 years), with femur being the most common primary site and six showing multifocal involvement.²² The clinical behavior in that series was dismal, with two-thirds of patients succumbing of disease. Microscopically, osseous angiosarcoma displays significant nuclear pleomorphism, hyperchromasia, prominent nucleoli, with an associated high mitotic activity and necrosis. The lesions often show at least focal vasoformative features, solid components, in a hemorrhagic background. At the molecular level, angiosarcomas exhibit a more heterogeneous genetic profile, which depending on the anatomic location or clinical presentation may harbor recurrent *KDR*, *PTPRB* or *PLCG1* mutations and/or *MYC* amplification.^{23–26} However, in the context of angiosarcoma of bone there are no reliable molecular diagnostic tests that can be applied. In this setting, FISH testing for *FOS* or *FOSB* gene rearrangements remains of critical value in the distinction between an EH with cellular/ atypical histologic features from an angiosarcoma, although a subset of EH remains negative for these fusions.

One additional vascular neoplasm that can be confused with is pseudomyogenic hemangioendothelioma (PHE), also known as

epithelioid sarcoma-like hemangioendothelioma.^{27,28} In a study of 15 patients with PHE, 10 were located in the bone, having a mean age of 32 years (17–48),²⁹ 8 of them being multifocal, often including different tissue planes within one anatomic region, such as subcutis, skeletal muscle, and bone. None of the patients in that series showed metastasis or disease-related deaths. Histologically, PHE have a multinodular and infiltrative growth within the subcutaneous fat or skeletal muscle, lacking the lobular architecture and vasoformative features typically seen in EH. Microscopically, tumors are composed of a mixture of spindle and epithelioid cells in variable proportions, often with low level of cytologic atypia, embedded in a sclerotic stroma, rather than hemorrhage. The genetic hallmark of PHE are *FOSB* related gene fusions, with equal distribution between *SERPINE1-FOSB* and *ACTB-FOSB* fusion.²⁹ Thus FISH for *FOSB* alone may not be able to distinguish PHE from EH in difficult cases, and diagnostic confirmation would rely on targeted RNA sequencing to determine the fusion gene partner.

The *FOS* gene, known as FBJ murine osteosarcoma viral oncogene homolog, belongs to the *Fos* gene family including *FOSB*, *FOSL1*, and *FOSL2*.^{30,31} The *FOS* gene encodes a transcription factor that can dimerize with members of the Jun family (c-Jun, JunB, and JunD), constituting the major components of the activating protein-1 (AP-1) complex, thereby regulating cell proliferation, tumor invasion, distant metastasis, and angiogenesis.^{32,33} In EH, the fusion results in the truncation of the *FOS* gene,³⁴ which is likely to affect regulation of transcript degradation,^{35,36} and protect *FOS* from protein degradation.^{37–39}

The *FOSB* transcription factor consists of an N-terminal *FOS* homology domain, a DNA binding bZIP (basic leucine zipper) domain and a C-terminal proline-rich transactivation domain.³⁴ The bZIP domain and the C-terminal transactivation domain are typically conserved in the *FOSB* fusion oncoprotein.¹⁰ *FOSB* mRNA expression is significantly increased in EH with *ZFP36-FOSB* or *WWTR1-FOSB* fusions and in PHE with *SERPINE1-FOSB*, compared to other tumors, likely through a promoter swapping mechanism.^{10,40} Moreover, *FOS* and *FOSB* gene rearrangements have been also implicated in the pathogenesis of most osteoblastomas, another benign bone tumor, with similar mechanisms involving truncation of the *FOS* gene and promoter swapping upregulating *FOSB* gene being proposed.⁴¹

In conclusion, this is the largest study to date investigating the clinical and pathologic features of a molecularly confirmed cohort of EH of bone. Our results stress the diagnostic challenges encountered in establishing a correct diagnosis outside the molecular testing, mainly due to its resemblance to other epithelioid vascular tumors. FISH/NGS molecular methods to determine *FOS* or *FOSB* gene abnormalities are critical in reaching the correct diagnosis. Skeletal EH emerges as a locally aggressive bone neoplasm with a high rate of local recurrence but lacking distant metastatic potential.

CONFLICT OF INTEREST

The authors declare no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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