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Original Contribution

Pseudomyogenic (epithelioid sarcoma-like) hemangioendothelioma of bone: Clinicopathologic features of 5 cases

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ABSTRACT

Pseudomyogenic hemangioendothelioma (PHE) is an uncommon mesenchymal tumor of intermediate malignant potential with characteristic clinicopathologic and genetic features. Although bone involvement accompanies nearly one-fourth of reported cases of soft tissue PHEs, primary intraosseous PHE is rare. Herein, we report five cases of primary intraosseous PHEs. Male to female ratio was 4:1, with an average age of 28 years (age range, 5–44 years). Radiologically, tumors presented as lytic lesions in the proximal femur (two), diaphysis of the tibia (one), distal radius (one) and vertebrae (one). Multifocal lesions were observed in four cases. Histopathologic examination revealed plump spindle cells and prominent nucleoli. New bone formation was noted in three cases. Immunohistochemically, all tumors were positive for CD31 and negative for CD34. Pan Cytokeratin (CK) (AE1/3) was positively expressed in all, except a single tumor, in which CK7 and Cam5.2 were expressed. INI1/SMARCB1 was completely retained in all tumors. A single patient underwent surgical resection. During follow-up, two cases showed no evidence of disease within two and five years, respectively. Differential diagnosis of a PHE of bone includes osteoblastoma, epithelioid angiosarcoma, metastatic carcinoma, metastatic rhabdomyosarcoma, and epithelioid sarcoma. Caution must be exercised as pan CK (AE1/3) might not be expressed; therefore, the use of other cytokeratins, such as Cam5.2 is recommended. Awareness of such an entity in bone is the key to the diagnosis.

1. Introduction

Pseudomyogenic hemangioendothelioma (PHE), also known as epithelioid sarcoma-like hemangioendothelioma or fibroma-like variant of an epithelioid sarcoma, is an uncommon soft tissue tumor characterized with its predominance in males, extremity sites, multifocality; histological presence of plump spindle cells with eosinophilic cytoplasm, resembling rhabdomyoblasts and, to a lesser extent, epithelioid cells with rhabdoid morphology; lack of vasoformative areas; immunohistochemical expression of keratins and endothelial markers with the exception of CD34; presence of a unique translocation leading to *SERPINE1-FOSB* and a more recent *ACTB-FOSB* fusion; and an indolent clinical behavior with only rare metastases, therefore constituting a tumor of an intermediate malignant potential [1,2,4,5]. Given the multifocality, bone involvement is also seen in approximately 25% of the cases of soft tissue PHE; however, primary involvement of bone is much rarer [6].

Less than 20 cases of primary PHE of bone have been reported to date, sharing almost similar histopathologic features with the soft tissue counterpart [6-11]. Herein, we report five additional cases of primary PHE of bone with their clinical, radiological, morphological and immunophenotypic features.

2. Materials and methods

Clinical, radiological and pathological features of five cases

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Table 1
Clinicopathologic features of 5 cases.

Case	Age	Sex	Size (cm)	Location	Radiologic findings	Multi-focality	Soft tissue involvement	Morphology	Immunohistochemistry	Follow-up	Additional notes
#1	5	M	2.5	L tibia proximal and distal metaphyses, L femur distal metaphysis, L proximal fibula and distal metaphyses, L talus, calcaneus and metatarsals, L 1, 4, 5 proximal toes	Lytic lesions with contrast enhancement	Yes	Yes (fingertips, gastrocnemius, triceps sura)	Predominantly plump spindle cells	Positive for CD31, ERG, Cam5.2, CK7, FOSB. Negative for CD34, cytokeratin AE1/3, SMA, HHV8, desmin. INI1 retained.	Recent	Prebiopsy diagnosis was Mazabraud syndrome. Received chemotherapy
#2	33	M	NA	R proximal femur	Lytic lesion	No	No	Plump spindle cells, foal epithelioid reactive bone formation	Positive for CD31, cytokeratin AE1/3, Fli1. INI1 retained.	NA	
#3	33	M	3.5	R distal radius metadiaphysis	Mildly expansile lytic lesions with endosteal scalloping	Yes	No	Prominent epithelioid morphology	Positive for CD31. Low Ki67.	5 years, NED	
#4	44	F	0.5–2.1	T2–3 vertebrae	Lytic lesions involving T2 and T3 vertebral bodies	Yes	No	Spindle prominent, inflammation, merging with new bone trabeculae	Positive for INI-1, ERG, WT-1, EMA, desmin, CD31, FLI-1 (focal), and cytokeratin AE1/3 (focal). Negative for S-100, CD34, pan-keratin MNF116, low-molecular weight cytokeratin, and SOX10.	2 years, NED	Vertebrectomy. Positive for *FOSB* gene rearrangement, while *SERPINE1* gene not affected.
#5	25	M	NA	R femur diaphysis	Multifocal expansile lytic cortical lesions	Yes	No	Plump spindle cells, prominent reactive new bone formation	Positive for cytokeratin AE1/3, CD31 (focal), ERG. Negative for SMA, desmin, CD34, S100, EMA, LCA, CAMTA1, CD30.	Recent	Prebiopsy diagnosis of angiosarcoma, metastasis, hematopoietic neoplasm

NA: not available, NED: No evidence of disease.

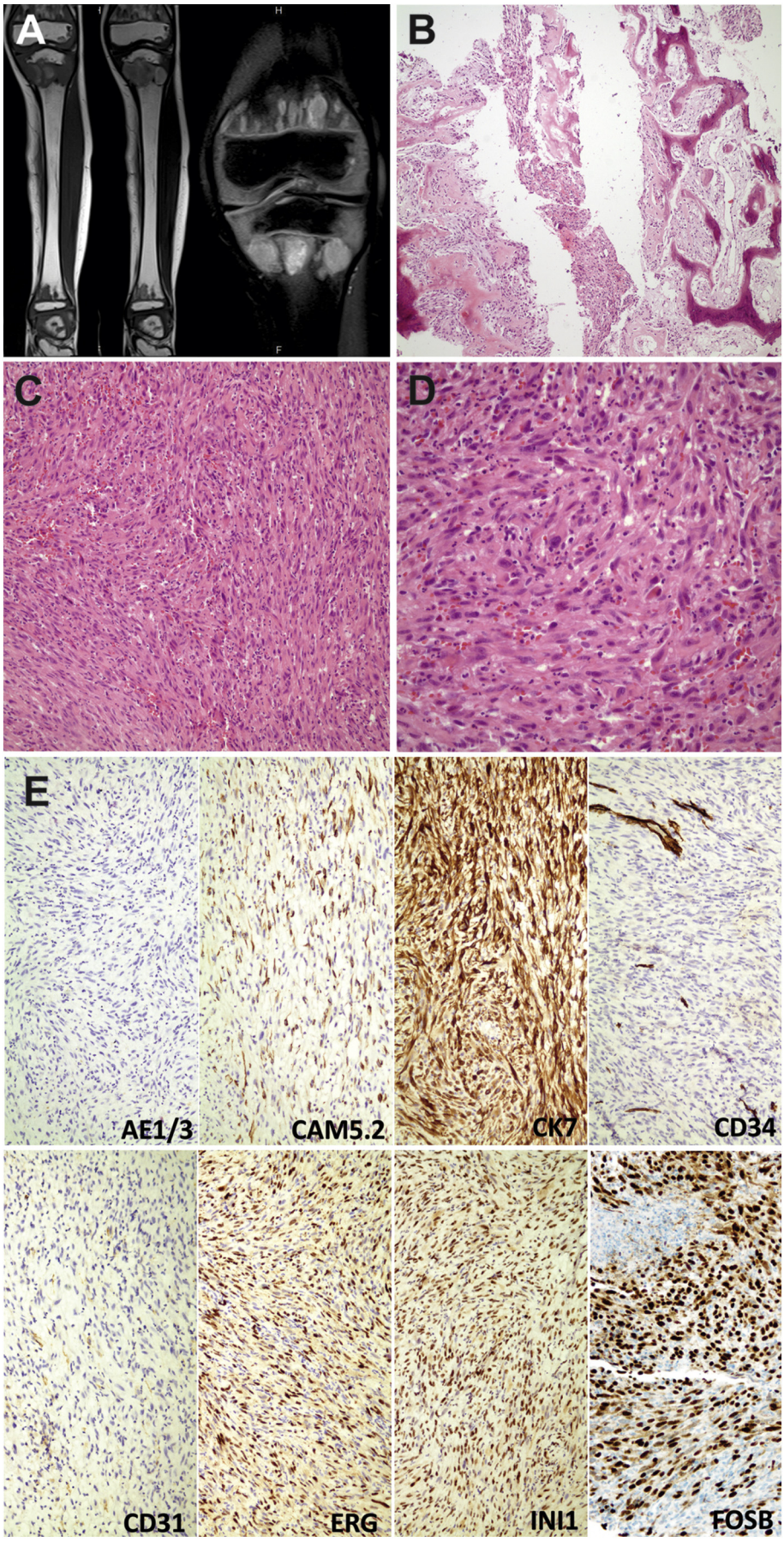

Fig. 1. A–E. Case #1: A 5-year-old boy with multifocal lesions in bones and soft tissues. A. Pre- and post-contrast T1-weighted and fat-saturated proton-density coronal MR images showed distal femoral and proximal tibial metaphyseal > epiphyseal lesions with lobulated contours. B. Spindle cell neoplasm among the woven bone. C. Fascicles of monotonous spindle cells resembling rhabdomyoblasts and accompanying mixed inflammatory cells. Note the presence of scattered atypical cells with hyperchromatic nuclei and moderate pleomorphism. D. Inconspicuous epithelioid cells with prominent nucleoli. E. Immunohistochemically, neoplastic cells are positive for Cam5.2, CK7, CD31, and ERG, while AE1/3 and CD34 are negative. INI1 is retained. FOSB showed diffuse nuclear expression.

collected from five large institutions were reviewed. Immunohistochemical results were obtained from the pathology reports. None of the patients had a prior history of cancer.

3. Results

Table 1 summarizes clinicopathologic features of five cases.

3.1. Clinical features

All cases, except Case #4, were males, with an average age of 28 years (range, 5–44 years). The pain was the most common symptom. Most lesions involved the long bones, namely proximal femur (two), diaphysis of the tibia (one) and distal radius (one). One case involved vertebrae. Multifocal lesions were observed in four cases, with less prominent soft tissue involvement in a single case (#2). Multiple bones were involved in three cases (Figs. 1A and 3A–C).

In Case #4, vertebrectomy was performed with a prior diagnosis of an osteoblastoma. The rest of the cases were treated with curettage. Two cases showed no evidence of disease within two (Case #4) and five (Case #3) years of follow-up after curettage. None of the cases showed metastatic lesion.

3.2. Radiological features

Imaging studies were available in five of six cases (except Case #2). Lesions involved metadiaphyses of long bones as well as flat bones. Bone lesions mostly involved the marrow and were predominantly lytic and mildly expansile with endosteal scalloping on plain films and computed tomography (CT) (Figs. 3A and 4A–B). One case (Case #5) displayed predominantly cortical lesions with mild expansion. Lesions were usually hypointense on T1-weighted magnetic resonance imaging (MRI) and hyperintense on fluid-sensitive MRI sequences and showed mild contrast enhancement (Figs. 1A and 3B). In Case #4, the vertebral lesion showed increased fluorodeoxyglucose uptake on positron emission tomography (PET). Index lesions on PET included a 1.5-cm lytic lesion in the T3 vertebral body with standardized uptake values of 9.0 and 10.3 (additionally, CT of the chest showed multiple sub-centimeter nodules).

3.3. Pathological features

Tumor size ranged from 0.5 cm to 3.5 cm. Tumors were usually multifocal and ill-defined with solid, cream to brown colored, heterogeneous cut-surfaces, depending on the extent of hemorrhage and osteoblastic reaction (Fig. 3C).

Microscopically, tumors were composed of intermixed spindle and epithelioid cells. Plump spindle cells were arranged in loose fascicles with little variation in their size and shapes, minimal nuclear atypia and a variable amount of cytoplasm. A few cells, with a relatively more amount of cytoplasm, showed a transition between the spindle and epithelioid morphology, simulating 'strap-like' rhabdomyoblasts (Figs. 1C–D, 2A, 3D, and 4D). Polygonal epithelioid cells were dispersed singly and in loose clusters, containing moderate to abundant deeply eosinophilic cytoplasm, enlarged nuclei, with vesicular chromatin and distinct nucleoli (Figs. 1D, 2B-C, 4E). Cells with epithelioid to rhabdoid appearance were more conspicuously seen than the spindle cell forms in one case. Tumors lacked vasoformative areas. Mitotic activity was minimal and atypical mitoses were lacking. New bone formation was noted in four cases (Figs. 1B, 3E–G, and 4C). No cases displayed a prominent osteoclastic-like giant cell component or large myxoid areas, except one case (case #5) in which a small area of myxoid degeneration was present. Necrosis was absent in all cases.

Immunohistochemically, all cases were variably positive for CD31 and negative for CD34 immunostains (Figs. 1E, 2E-F, 3J, and 4G). PanCK (AE1/3) was at least focally positive in all, except a single case (#1), in which CK7 and Cam5.2 were positively expressed (Fig. 1E). ERG was positive in three cases, while Fli1 was positive in two cases. INI1/SMARCB1 was diffusely retained in all cases. Ki67 was low in two cases. FOSB showed diffuse nuclear positivity in one studied case.

FOSB gene rearrangement was identified in undecalcified tissue; however, *SERPINE1* gene alteration was not identified in a single case (#4), tested in the laboratory of Dr. Cristina R. Antonescu, Memorial Sloan-Kettering Hospital, New York.

4. Discussion

Although certain soft tissue tumors with similar morphology were recognized about four decades ago, referred to as "fibroma-like" variant of epithelioid sarcoma, pseudomyogenic variant of epithelioid sarcoma, fibrohistiocytic/myoid variant of epithelioid sarcoma, and epithelioid sarcoma-like hemangioendothelioma, pseudomyogenic hemangioendothelioma (PHE) was finally described in the year 2011, including its clinical, morphological and immunophenotypical features [2,4]. Subsequently, in 2014, a specific gene fusion, namely *SERPINE1-FOSB*, underlying PHEs, was unraveled [5,12]. Recently, *ACTB-FOSB* has been found in nearly half of PHEs, with a solitary presentation [1]. In 2012, primary PHE of the bone without the involvement of soft tissues, a much rarer form, was reported [11]. According to the largest reported series of intraosseous PHEs, by Inyang et al. [6], comprising ten such cases, these tumors are characterized with young male predominance, involvement of the spine and long bones of distal limbs, intraosseous multifocality and similar morphologic and immunohistochemical features as their soft tissue counterparts. Although previous case reports did not suggest a gender predilection, the studies by Inyang et al. [6] and the present one, clearly show a significant male predominance (9:1 and 4:1, respectively). PHE is rare in pediatric patients. One of the cases in the present study (#1) was observed in a 5-year-old boy, constituting the youngest patient ever reported with a PHE. Invariably, these patients follow an indolent clinical course. Till date, no metastatic lesions have been reported [4-6,9].

Histopathologically, tumor cells in an intraosseous PHE, similar to its soft tissue counterpart, predominantly comprise variable number of intersecting monotonous plump spindle cells, resembling rhabdomyoblasts, along with epithelioid forms with prominent nucleoli and bright eosinophilic cytoplasm, resembling rhabdoid cells, which actually led to the earlier designation of an "epithelioid sarcoma-like" hemangioendothelioma, for these tumors [4]. Interestingly, PHE of bone displays osteogenic or osteolytic appearance on radiologic examination, leading to a diagnostic challenge in differentiating it from other primary bone tumors, such as an osteoblastoma and a giant cell tumor [6]. We observed similar features in various cases of our study; however, unlike Inyang et al. [4], we did not observe prominent areas composed of osteoclast-like giant cells in any of our cases.

The most important immunohistochemical staining for diagnosing a PHE include co-expression of keratins and vascular markers, along with the positive expression of the recently developed antibody against FOSB [5]. The neoplastic cells are typically positive for panCK (AE1/3), CD31, FLI1, and ERG, whereas negative for CD34, S100 protein, desmin, and myogenin, as observed in various cases of the present study. Among the vascular markers, CD31+/ERG (or FLI1)+/CD34- phenotype is highly indicative of a PHE of bone [4]. INI1/SMARCB1 is consistently retained, which is useful in differentiating this tumor from an epithelioid sarcoma, as noted in the present study. Previous reports stated that pan CK (AE1/3) is positive in all cases [2,4]. However, AE1/3 was negative in one of our cases (#1) and focally expressed in another (case #5). Nonetheless, CK7 and Cam5.2 were positive in the AE1/3 negative case. Therefore, in suspected cases of PHE, it is crucial to employ a wide panel of cytokeratins, including Cam5.2, especially in cases with vascular marker (CD31 and ERG) expression.

The differential diagnosis of PHE is various and mainly includes epithelioid sarcoma, rhabdomyosarcoma (metastatic rather than

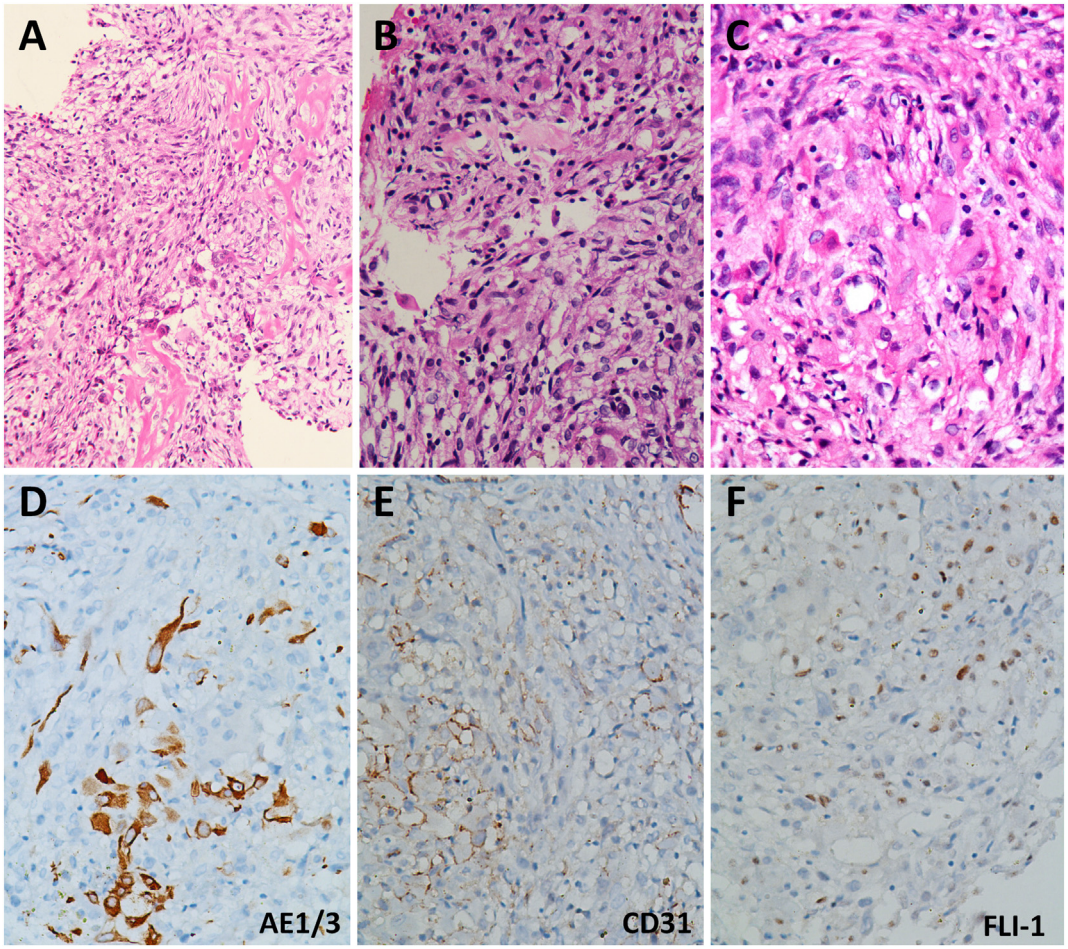

Fig. 2. A–F. Case #2: A 33-year-old man with a right proximal femoral mass. Spindle to epithelioid cells intermingled with new bone formation (A). Spindle cells with minimal pleomorphism demonstrate rhabdomyoblast-like appearance (B), whereas epithelioid cells show rhabdoid phenotype (C). Note the absence of mitotic activity. Neoplastic cells are positive for AE1/3 (D), CD31 (E), and Fli1 (F).

primary osseous), osteogenic tumors (such as osteoblastoma), metastatic carcinomas, and vascular tumors (especially epithelioid angiosarcoma and epithelioid hemangioma). All the available clinical, radiological, morphological, immunohistochemical and molecular results are useful for arriving at a conclusive diagnosis. An exaggerated reactive woven bone could invoke a radiological diagnosis of osteoblastoma, a fibro-osseous lesion or even an osteoblastic-type of metastatic carcinoma, because of multifocality. One of the cases in our study (#4) was surgically operated with a clinicoradiological diagnosis of osteoblastoma, while in another case (#1) the clinical impression was that of Mazabraud syndrome, characterized with polyostotic fibrous dysplasia and soft tissue myxomas. Although epithelioid hemangioendothelioma involving bone is admittedly rare, it may be involved in the differential diagnosis, given the fact that it shows epithelioid-to-spindle morphology with the expression of endothelial markers (and even sometimes keratin). Morphologically, presence of myxoid background and intracellular vacuoles is expected in epithelioid hemangioendothelioma, while differential immunoexpression of FOSB and CAMTA1 ultimately separate these two entities.

A conspicuous presence of fascicles of neoplastic cells with their characteristic morphology is a clue for the differentiation of PHE from bone-forming tumors, especially with relevant clinicopathological features. Primary rhabdomyosarcoma of bone is exceptionally rare, but a metastatic rhabdomyosarcoma constitutes a close differential diagnosis. Although cells of PHE resemble rhabdomyoblasts, lack of desmin, MyoD1 and myogenin are useful in ruling out this diagnosis, as in the present study. In cases, where the epithelioid component is much more prominent than the spindle cell component, metastatic carcinoma, epithelioid sarcoma, and epithelioid vascular tumors are possibilities in the differential diagnosis. In view of multifocality in case #5, a metastatic carcinoma (sarcomatoid renal cell carcinoma) was considered; however, in view lack of any lesion in the kidney on imaging and lack of PAX8 expression, this possibility was ruled out. It is noteworthy that ERG and keratins are positive in certain carcinomas especially of prostatic origin; however, relatively younger age, lack of clinical history, and positive immunoexpression of other vascular markers such as Fli1 and CD31 are useful in differentiating this tumor from metastatic carcinoma. Positive immunoexpression of CD31 and retained INI1 expression were useful in the present study in differentiating PHE from an epithelioid sarcoma, which can rarely occur in the bone. Differentiation of PHE from other vascular tumors, which show prominent epithelioid morphology, particularly epithelioid angiosarcoma, can be quite challenging since a few PHEs of bone showed subtle vasoformative areas and presented with large vein involvement [6]. Absence of prominent vasoformative foci, necrosis, and significant nuclear pleomorphism, along with fewer mitotic figures, are pointers towards a PHE, as opposed to an angiosarcoma.

Evaluation for FOSB rearrangements either *SERPINE1-FOSB* fusion as a result of t(7:19)(q22;13) balanced translocation or *ACTB-FOSB fusion*, and FOSB immunoexpression, are useful in an exact diagnosis of PHE, especially in cases with equivocal immunohistochemical staining results [1,5,12]. Epithelioid hemangiomas have some overlapping features such as multifocality, accompanying inflammatory cells, presence of epithelioid cells, and half of the cases show FOSB immunoexpression;

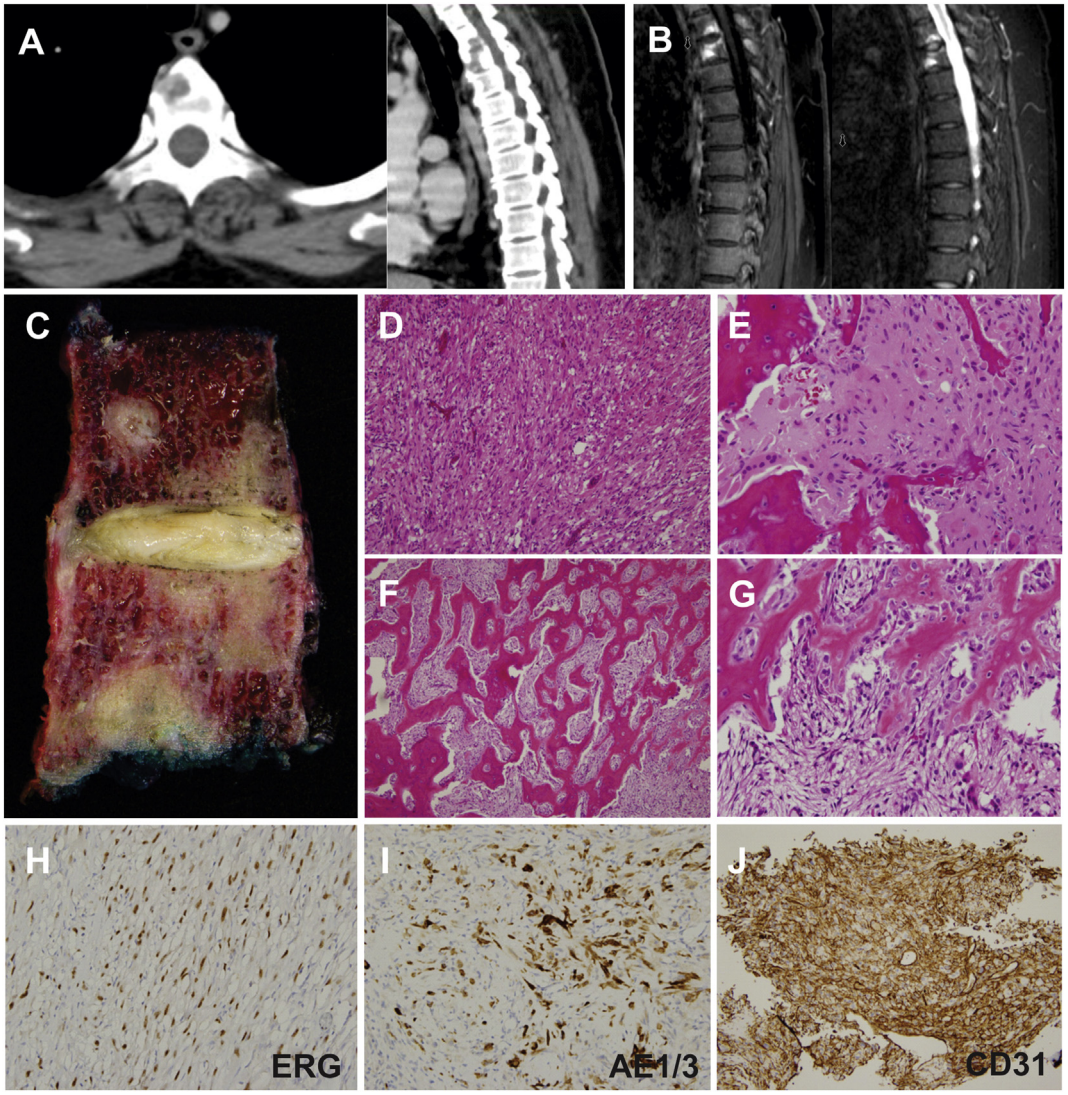

Fig. 3. A–J. Case #4: A 46-year-old woman with thoracic vertebral lesions. A. Axial CT (left) of the thoracic spine shows a lytic lesion in T3 body and sagittal reformatted CT (right) involvement of T2 and T3 bodies. B. Sagittal T1-weighted FLAIR (left) and STIR (right) MR images show the lesions in T2 and T3. C. Sagittal section of vertebral bodies of T2 and T3 connected by the intervertebral disc with three tan-white firm nodules ranging in size from 0.5 to 2.1 cm. Microscopically, tumor showing spindle cell proliferation (D), focus of epithelioid cells having an abundant amount of cytoplasm (E), woven trabeculae of bone separated by spindle cells (F), and focal osteoblastic rimming and osteoid formation (G). Immunohistochemical staining for ERG (H), AE1/3 (I), and CD31 (J).

therefore, their distinction from PHE can be challenging [4,5]. Presence of similar *FOSB* rearrangement and some morphological overlap also raise the possibility of a morphologic spectrum between epithelioid hemangioma and PHE. More recently, FOS and FOSB rearrangements are found to be ubiquitous in osteoid osteoma and osteoblastoma (89% of the cases), making the diagnostic use of *FOSB* rearrangement testing in the management of bone tumors more complicated [3].

5. Conclusion

PHE of bone is a rare neoplasm, mostly located in the long bones and vertebrae of young adults, characterized with male predominance, multifocality, exaggerated osteoblastic response, co-expression of keratin and vascular markers, and an indolent clinical course. Morphological deviations, which might complicate the diagnostic accuracy, include predominant epithelioid morphology and focal or lack expression of pan CK (AE1/3) immunostaining. Differential diagnoses in such cases are reasonably wide and awareness of PHE is the key to diagnosis. Ultimately, a high index of suspicion and awareness of PHE are prerequisites for this rare diagnosis.

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Contributions

Kemal Kosemehmetoglu: Writing, gathering patient data, study planning.

Bharat Rekhi: Gathering patient data, study planning, critical reading of the manuscript.

Paul E. Wakely, Jr.: Gathering patient data (providing clinical, pathological and prognostic data).

Vinita Pant: Gathering patient data (providing clinical, pathological and prognostic data).

Sergulen Dervisoglu: Gathering patient data (providing clinical, pathological and prognostic data).

Ustun Aydingoz: Analysis of radiological data, critical reading of the manuscript.

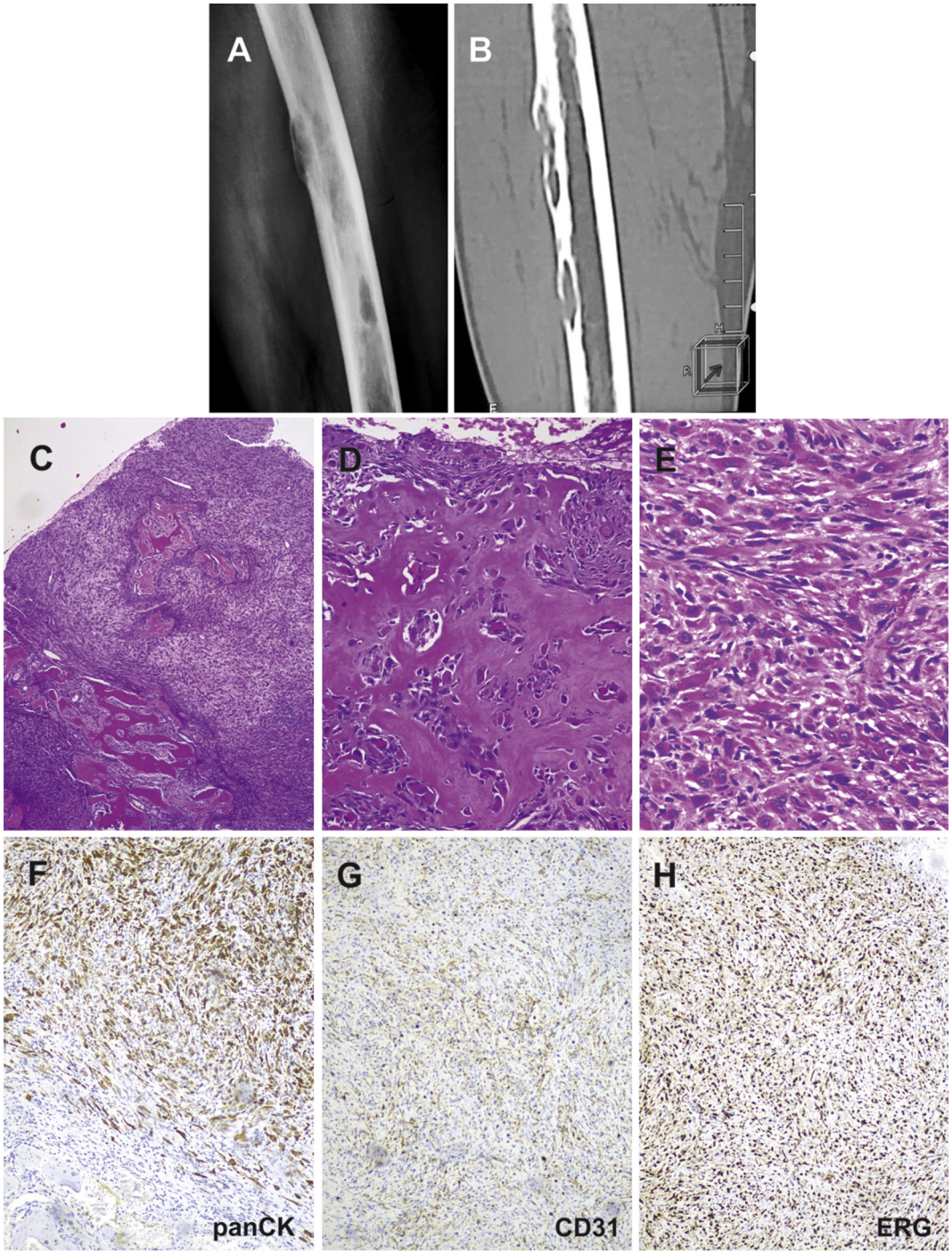

Fig. 4. A–H. Case #5: A 25-year-old man with right thigh pain. Anteroposterior plain film (A) and coronal reformatted CT (B) show multiple expansive lytic cortical lesions along the right femur diaphysis. C. Tumor with focal myxoid areas inducing woven bone formation. D. Plump spindly, 'rhabdomyoblast-like' cells with prominent eosinophilic cytoplasm. E. Spindle cells with accompanying scattered epithelioid to rhabdoid cells with prominent nucleoli. Neoplastic cells were positive for AE1/3 (F), CD31 (G), and ERG (H).

Compliance with ethical standards

In this case series, all patient's data are depersonalized in order to meet ethical standards.

Declaration of Competing Interest

None.

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