Clinical Case Report

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Epithelioid hemangioendothelioma of the bone

A case report with findings of bone scintigraphy

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Abstract

Introduction: Epithelioid hemangioendothelioma (EHE) of the bone is a very rare malignant vascular neoplasm, with biologic behavior between that of locally aggressive epithelioid hemangioma and malignant epithelioid angiosarcoma. We report a case of a patient with EHE who underwent bone scintigraphy, try to identify the characteristics of it, to highlight the clinical importance of whole-body bone scintigraphy and single-photon emission computed tomography/computed tomography (SPECT/ CT) in the diagnosis and treatment of EHE.

Patient concerns: A 67-year-old man with no history of trauma who reported pain in both lower limbs for 6 months, which had been worsening over the last 20 days. Anteroposterior and lateral radiographs of both lower limbs revealed numerous osteolytic lesions in the tibia and fibula bilaterally. ^{99m}Tc-methylene diphosphonate (MDP) bone scintigraphy demonstrated increased tracer uptake in the pelvic and bilateral lower limb bones. SPECT/CT bone imaging showed numerous osteolytic lesions cluster in the same anatomic region, with high tracer uptake in lesion margins.

Diagnosis: EHE of the bone.

Interventions: Two months after the diagnosis was confirmed, the patient was rehospitalized. Nonopioid analgesic use had not provided pain relief. Magnetic resonance imaging (MRI) of both thighs showed the bone cortex was destroyed with numerous irregular lesions, and soft-tissue was involved. A second bone scintigraphy did not show any new lesions. He was administrated with recombination human endostatin injection 15 mg ivgtt qd for 14 days, combined with apatinib mesylate tablets 500 mg po qd for 18 days.

Outcomes: He was discharged voluntarily and died 2 months later.

Conclusion: EHE of the bone is a very rare malignant vascular neoplasm with no specific radiographic imaging features. Whole-body bone scintigraphy, especially SPECT/CT bone imaging, significantly reduces ambiguous diagnoses and is recommended before treatment.

Abbreviations: EHE = epithelioid hemangioendothelioma, MDP = methylene diphosphonate, MRI = magnetic resonance imaging, SPECT/CT = single-photon emission computed tomography/computed tomography.

Keywords: bone, bone scintigraphy, case report, epithelioid hemangioendothelioma, vascular neoplasm

1. Introduction

Epithelioid hemangioendothelioma (EHE) is a rare intermediate-grade malignant vascular neoplasm.[1] It can arise in many other organs and tissues, such as soft tissue, lungs, liver, bone, and so forth.[2,3] EHE occurring in the bone is extremely rare. It accounts for about 1% of primary bone neoplasms.[1] As the radiographic imaging features of EHE are nonspecific, diagnosing EHE of the bone on the basis of radiological findings is very difficult. It is usually misdiagnosed as a metastatic tumor, multiple myeloma, or brown tumor. Whole-body bone scintigraphy is often used to detect metastatic tumors. For EHE of the bone, whole-body bone scintigraphy can detect silent lesions earlier with its advantage of high sensitivity,[4,5] and show the distribution of multiple lesions. With further single-photon emission computed tomography/computed tomography (SPECT/ CT) bone imaging, bone scintigraphy can significantly reduce ambiguous diagnoses. Some reports on the bone scintigraphy findings of EHE are available; however, few have investigated the characteristics of EHE as observed on SPECT/ CT. Herein, we report a case of a patient with EHE who underwent SPECT/ CT bone imaging. And we try to identify the characteristics of EHE of the bone in the imaging, to highlight the clinical importance of whole-body bone scintigraphy in the diagnosis and treatment of EHE.

2. Patient information

A 67-year-old man was admitted because of bilateral lower limb pain for 6 months, which had been worsening for 20 days. He had no history of trauma. He had been smoking for about 40 years and drinking alcohol for about 20 years. His past medical history was unremarkable.

3. Clinical findings

The patient reported difficulty in walking. Physical examination revealed moderate tenderness in both lower limbs, but no swelling of the soft tissue was observed.

Editor: N/A.

Informed written consent was obtained from the patient for publication of this case report and accompanying images.

The authors have no conflicts of interest to disclose.

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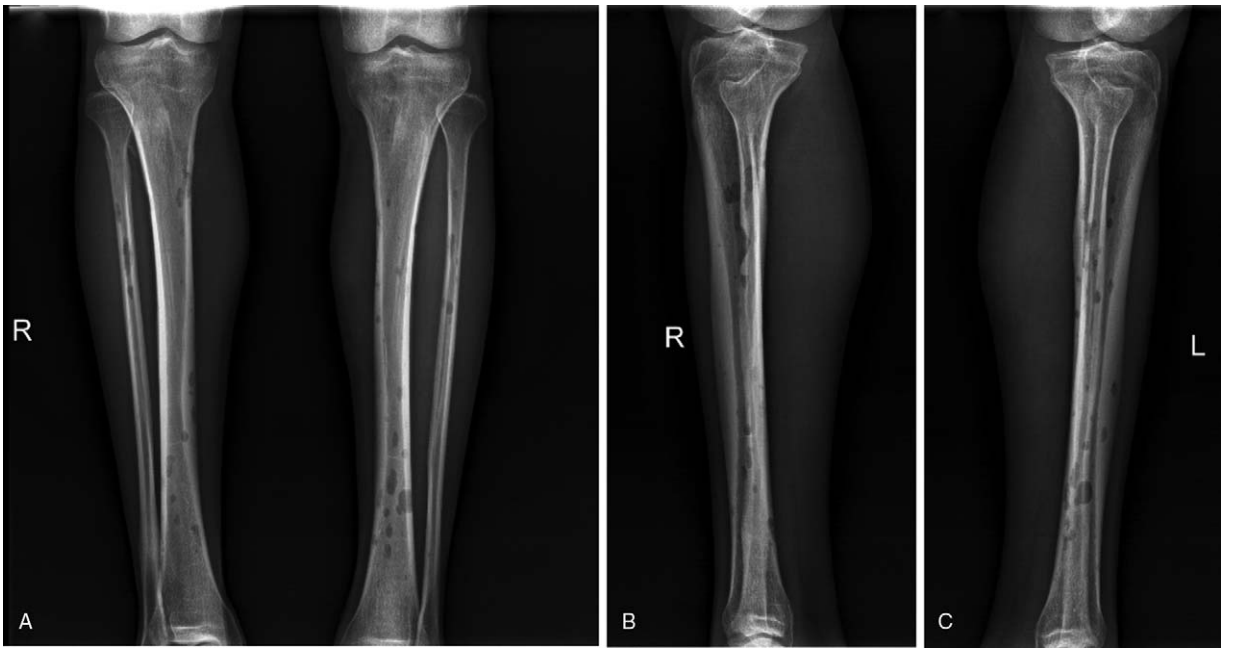

Figure 1. Anteroposterior and lateral radiographs of both lower limbs showed bubble-like osteolytic lesions with slight sclerotic margins in the bilateral tibia and fibula. Periosteal reaction and matrix calcifications were absent (A–C).

4. Diagnostic assessment

Anteroposterior and lateral radiographs of both lower limbs showed bubble-like osteolytic lesions with slight sclerotic margins in the bilateral tibia and fibula. Periosteal reaction and matrix calcifications were absent (Fig. 1A–C). On the basis of the initial radiological findings, metastatic tumor, multiple myeloma, and brown tumor were suspected. However, the CA199, CA125, CEA, and AFP levels of the blood were within the normal ranges. CT of the head and abdomen, plain radiographs of the chest, and high-frequency color Doppler for thyroid did not reveal any primary tumors. Routine blood indexes were nearly within the normal ranges. Monoclonal paraprotein was absent in the serum, and clonal plasma cells were not detected in the marrow. The blood level of calcium was slightly high (2.62 mmol/L; reference range: 2.15–2.55 mmol/L). The phosphate level was within the normal limits, and the parathyroid hormone level was low (9.62 pg/mL; range: 15–88 pg/mL). ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MDP) bone scintigraphy was performed to detect other silent lesions, and revealed increased tracer uptake in the pelvic and bilateral lower limb bones (Fig. 2A). Single-photon emission

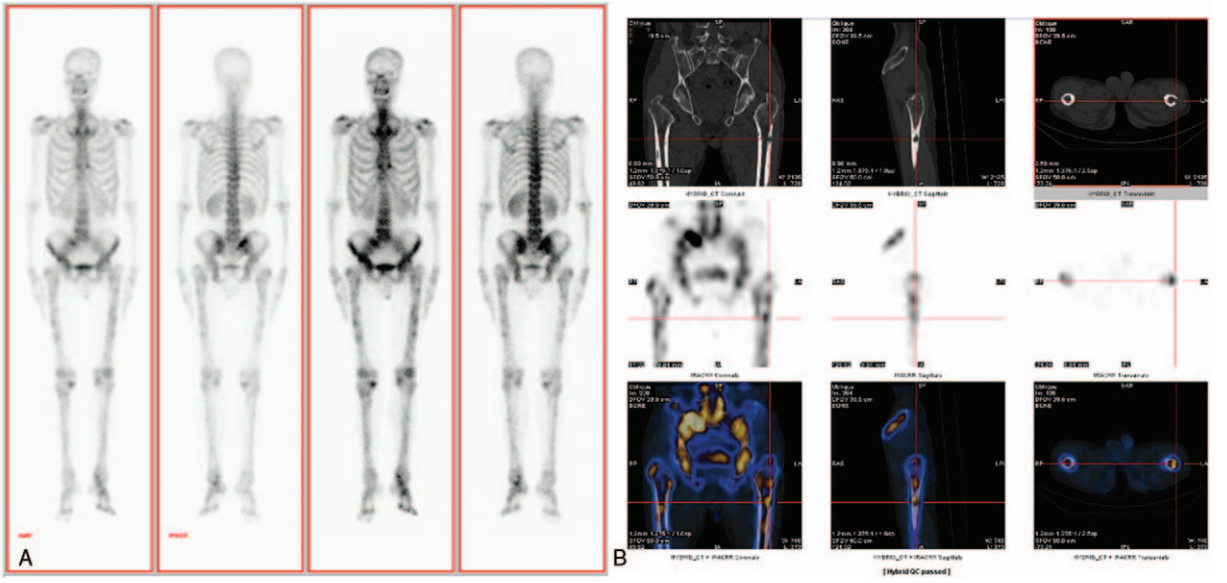

Figure 2. ^{9m}Tc-MDP bone scintigraphy revealed increased tracer uptake in the pelvic and bilateral lower limb bones (A). SPECT/CT of the area extending from the lumbar spine to the upper two-thirds of the femur showed osteolytic lesions involving the lumbar spine, sacrum, pelvis, cortex, and medullary cavity of the femur, and high uptake around the lytic lesions (B).

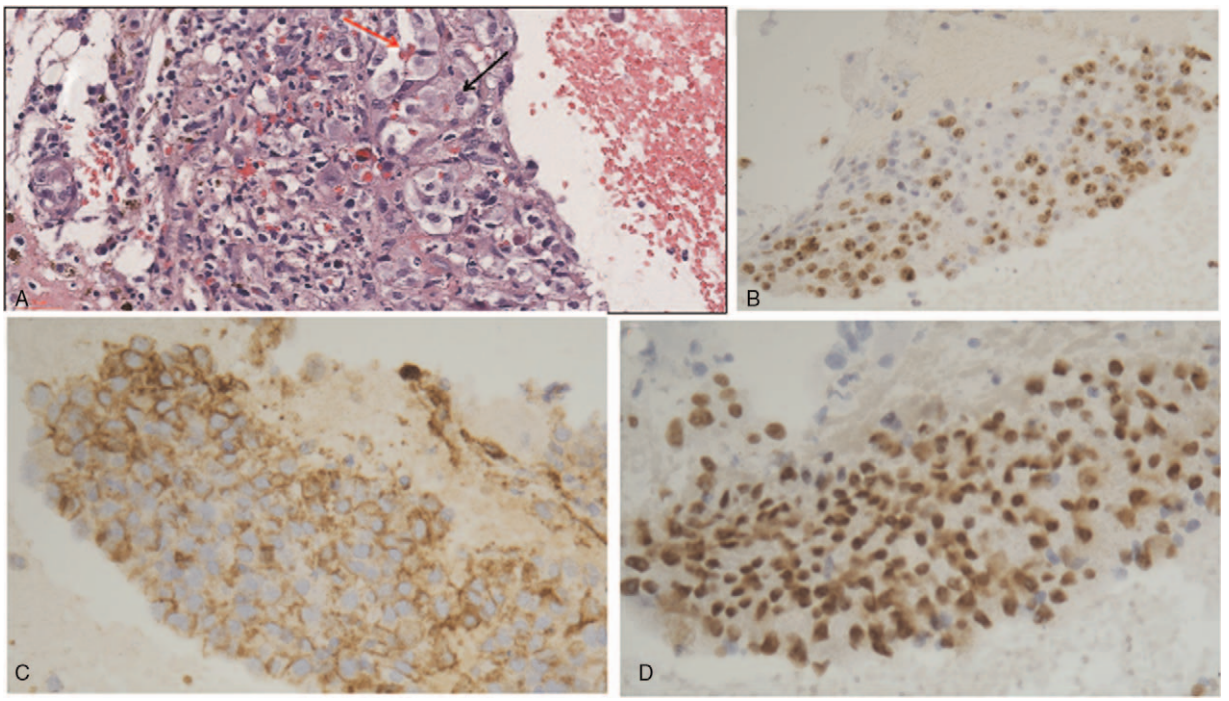

Figure 3. Right ilium biopsy revealed that the lesion consisted of a blood clot and epithelioid neoplastic cells with a pink-bright cytoplasm and vesicular nuclei (A, dark arrow). The neoplastic cells had an infiltrative growth pattern with mild atypia and were arranged in nests and cords. A primary vascular cavity formed by the tumor cells was observed (red arrow). Immunohistochemical analysis revealed 60% positivity for Ki67 (B), as well as positivity for endothelial markers CD31 (C) and ERG (D).

computed tomography/computed tomography (SPECT/CT) of the area extending from the lumbar spine to the upper two-thirds of the femur showed osteolytic lesions involving the lumbar spine, sacrum, pelvis, cortex, and medullary cavity of the femur, and high uptake around the lytic lesions (Fig. 2B). The maximum diameter of the lesion was 1.7 cm.

5. Therapeutic intervention

A biopsy of the right ilium was performed. The lesion consisted of a blood clot and epithelioid neoplastic cells with a pink-bright cytoplasm and vesicular nuclei (Fig. 3A, dark arrow). The neoplastic cells had an infiltrative growth pattern with mild atypia and were arranged in nests and cords. A primary vascular cavity formed by the tumor cells was observed (red arrow). Immunohistochemical analysis revealed 60% positivity for Ki67 (Fig. 3B), as well as positivity for endothelial markers CD31 (Fig. 3C) and ERG (Fig. 3D). The patient was diagnosed with EHE of the bone.

6. Follow-up and outcomes

Two months after the diagnosis was confirmed, the patient was rehospitalized. Nonopioid analgesic use had not provided pain relief. Magnetic resonance imaging (MRI) of both thighs was performed. Coronal images of the both thighs showed irregular lesions with intermediate intensity on T1-weighted imaging (Fig. 4A) and a high- and low-signal intensity rim (dark arrow) on

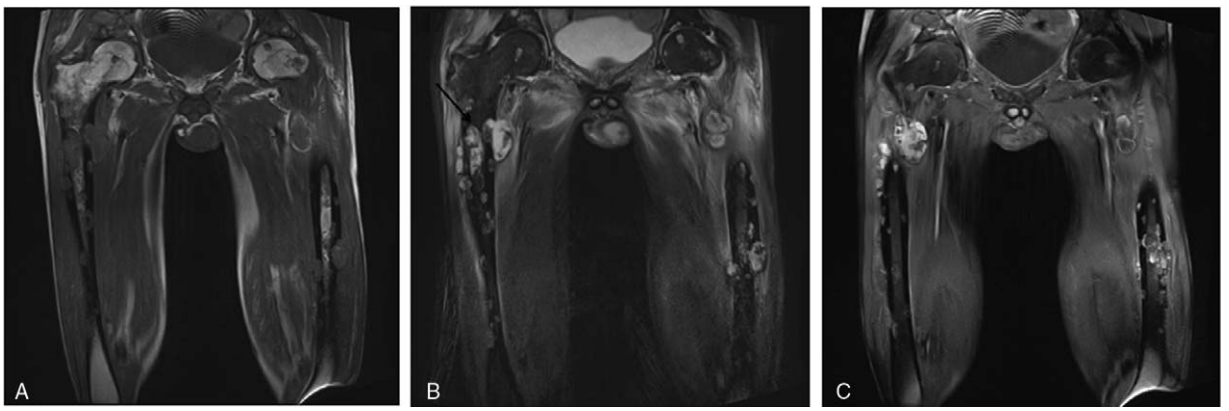

Figure 4. MRI of bilateral thighs showed irregular lesions with intermediate intensity on T1-weighted imaging (A) and a high- and low-signal intensity rim (dark arrow) on fat-suppression T2-weighted imaging (B). Annular enhancement was observed on enhanced scanning (C). The bone cortex was destroyed, with soft-tissue involvement.

fat-suppression T2-weighted imaging (Fig. 4B). Annular enhancement was observed on enhanced scanning (Fig. 4C). The bone cortex was destroyed, with soft-tissue involvement. A second bone scintigraphy did not show any new lesions. After administration of recombination human endostatin injection 15 mg ivgtt qd for 14 days, combined with apatinib mesylate tablets 500 mg po qd for 18 days, he was discharged voluntarily and died after 2 months.

7. Discussion

EHE is a very rare malignant vascular neoplasm, with biologic behavior between that of locally aggressive epithelioid hemangioma and malignant epithelioid angiosarcoma.[1] It can arise in many other organs and tissues, such as soft tissue, lungs, liver, bone, and so forth.[2,3] The neoplasm may occur at any age, but it has a propensity to occur in the second and third decades of life; however, no differences between sexes have been noted.[6] EHE occurring in the bone is extremely rare. It accounts for about 1% of primary bone neoplasms.[1] Long tubular bones are the most commonly affected, followed by the spine.[7] Around 50% of patients present with multicentric tumors.[8] The pathogenesis of EHE is still uncertain. However, recent cytogenetic studies have revealed that gene mutations participate in the tumorigenesis.[1,3,9] The CAMTA1-WWTR1 fusion gene resulted from a t (1:3)(p36.23;q25.1) translocation, a characteristic of EHE, proving that multifocal disease resulted from metastasis rather than from concurrent multiple neoplastic proliferations.[10] EHE of the bone does not have specific radiographic imaging features. It usually appears as osteolytic lesions with varying degrees of sclerotic margins on radiography and CT. Periosteal reaction and matrix calcifications are uncommon.[11,12] Most show low to intermediate intensity on T1-weighted images and high intensity on T2-weighted images on MRI imaging. Strong homogeneous enhancement or peripheral enhancement can be observed on enhanced T1-weighted images.[4,5,12] Cortical destruction and soft tissue invasion may happen in some cases.[11] Bone scintigraphy usually shows increasing tracer uptake.[4,11,13,14] But all these studies performed by SPECT, not fused by CT, so cannot show the high uptake lesions exactly. In the only case[15] that showed the characteristic of EHE on the SPECT/CT bone imaging, the increased tracer uptake was described inside the lesions. However, we found the high uptakes in most lesion margins, and defect inside lesions, that might relate to the highly active bone dissolution inside the lesions. As the advantage of high sensitivity, whole-body bone scintigraphy can help detect silent lesions earlier.[4,5] EHE of bone is usually misdiagnosed as a metastatic tumor, multiple myeloma, or brown tumor. However, clustering of multiple lesions in the same anatomic region aids in the diagnosis of a vascular tumor. Whole-body scintigraphy has the advantage to show the distributional characteristics of multiple lesions through 1 scan. And with further SPECT/CT bone imaging, body scintigraphy can not only significantly reduce ambiguous diagnoses but can also help identify lesions that are easier to biopsy.

Microscopically, the tumor cells consist of spindle-shaped or epithelioid neoplastic cells with a pink-bright cytoplasm and vesicular nuclei.[12] The neoplastic cells usually have an infiltrative growth pattern with mild atypia and are arranged in nests and cords. Primary vascular lumens formed by the tumor cells may be identified.[11,16] Fibrosis, myxoid, and hyaline degeneration can be observed in the tumor stroma.[11] Vimentin, endothelial markers CD31, CD34 and ERG, newer vascular markers Fli-1, and factor VIII-related antigen are positive on immunohistochemistry.[17] EHE is usually misdiagnosed as epithelioid hemangioma and epithelioid angiosarcoma based on the histopathological characteristics. However, CAMTA1-WWTR1 fusion protein, the product of CAMTA1-WWTR1 fusion gene, was found to differentiate EHE from epithelioid hemangioma and epithelioid angiosarcoma.[16,18]

Due to its rarity, there is limited clinical date to guide therapy choices. Wide surgical resection is recommended for limited lesions, while cytotoxic chemotherapy, radiotherapy, and targeted therapies are needed for metastatic disease.[4,16] A thorough skeletal examination is necessary before treatment, as resectable and unresectable lesions require different treatments. Whole-body bone scintigraphy is recommended to detect other silent lesions.[4] The biological behavior of EHE is diverse greatly between indolent and aggressively malignant.[16] Although it is difficult to assess the prognosis, a recent study in a cohort of 42 EHE cases suggested that tumor size >3 cm was the independent factor affecting survival.[2] Other factors included the presence of symptoms when diagnosis, high Ki-67 index, and mitotic activity implied poor prognosis.[2,19]

EHE of bone is rare. This study aims to improve the understanding of the characteristics of EHE of bone and to highlight the clinical importance of whole-body bone scintigraphy in the diagnosis and treatment of EHE. The key findings of the features of EHE on the SPECT/CT bone imaging in this study are multiple osteolytic lesions cluster in the same anatomic region, with high tracer uptake in lesion margins. But these findings may not be representative due to the single case and the limitation of the current reported literature. Whole-body bone scintigraphy is recommended before treatment of EHE of bone.

Author contributions

Data curation: Zhiyi Lin.
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Resources: Wenxin Chen.
Supervision: Wenxin Chen.
Writing – original draft: Yijin Xu.
Writing – review & editing: Yijin Xu, Wenxin Chen.

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