Case Report

rare tumors

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Epithelioid hemangioendothelioma of the distal lower extremity and the role of radiotherapy: A report of two cases

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Abstract

We report two cases of epithelioid hemangioendothelioma (EHE) in the distal lower extremity. Our first patient had unicentric EHE of the left os calcis initially treated with an intralesional procedure; however, later developed two recurrences which were managed with radiation therapy. Our second patient had multicentric EHE of the distal tibia and fibula managed with primary radiation therapy. Although EHE is typically treated with wide resection or an intralesional procedure, we present two cases of EHE in the distal lower extremity to discuss the therapeutic role of radiation therapy in the management of distal EHE.

Keywords

Epithelioid hemangioendothelioma, radiotherapy, sarcoma, EHE, lower extremity

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Introduction

Epithelioid hemangioendothelioma (EHE) of bone is a rare, low-to intermediate-grade vascular tumor that accounts for less than 1% of all primary bone tumors.[1] EHE of bone is typically thought to behave more aggressively than a benign hemangioma of bone, though less so than angiosarcoma.[2] Given the variability in presentation and morphological similarities of EHE to other tumors are two genetic hallmarks such as the *WWTR1-CAMTA1* and *YAP1-TFE3* fusions have proven useful.[3,4]

The majority of EHE of bone present as multicentric lesions.[1] Furthermore, more than half of EHE of bone arise in the lower extremities. For surgical treatment, wide resection or an intralesional procedure are preferred for localized disease when feasible, and appears to be a reasonable option for most EHE of bone throughout the lower extremity.[5] Chemotherapy and embolization have also been described for unresectable or multifocal and metastatic EHE of bone. Radiation has rarely been addressed in the literature for the treatment of this disease.

EHE of the distal lower extremity including the foot and ankle is often not amenable to wide surgical resection as reconstructive options in this anatomic region are prone to poor functional outcomes and failure.[6] Oftentimes, lesions in the distal lower extremity would be surgically best be treated with amputation; however, amputation is understandably a drastic approach for low grade disease. Due to the rarity of EHE and the complex treatment strategy for EHE in the distal lower extremity, we report on two separate cases of EHE of bone in this location treated with radiation therapy.

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Each patient was informed the data concerning their cases would be submitted, and they provided consent.

Case report

Case #1

A 35-year-old female presented with pain in the left foot. Plain radiographs demonstrated a lytic lesion involving the posterior aspect of her left os calcis.

Core needle biopsy and frozen section analysis revealed a proliferative spindle-cell lesion with bone formation. The final pathology of the biopsy revealed a mixture of spindle-shaped multinucleated cells embedded in collagen, lymphocytes, and eosinophils (Figure 1(a)). Immunohistochemical staining at that time was positive for CD31 and negative for S-100, CD68, and Keratin 8/18. Our multidisciplinary sarcoma team discussed the case and made a diagnosis of EHE of bone with a plan for aggressive intralesional excision, cauterization, and methacrylation, followed by postoperative radiation. Staging workup with total body bone scan was negative for metastatic disease.

A longitudinal incision was made over the left os calcis and the tumor was grossly excised. Internal burring was performed throughout the cortical margin followed by copious lavage and phenol washout. Methyl methacrylate was used to fill the cavity. Postoperative images 1 month following the procedure demonstrated the left os calcis lesion packed with radiopaque cement (Figure 2). The patient received radiation following the procedure.

Surveillance imaging revealed an asymptomatic recurrence in the left distal fibula 4 years after the index procedure. Intralesional excision with frozen section analysis confirmed recurrent EHE of bone (Figure 1(b)). Intraoperative imaging demonstrated the distal fibula lesion and stable postoperative changes in the left os calcis. She then returned 15 months later with additional site of disease in the left great toe distal phalanx and bone scintigraphy revealed a T9 vertebral body lesion. A third intralesional procedure was performed on the left toe lesion and the histology was identical to the prior EHE lesions, suggesting a diagnosis of multicentric EHE (Figure 1(c)). The toe lesion was treated with postoperative radiation while the spine lesion was treated with radiation alone.

At latest follow-up of 18 years, the patient has full function of the left lower extremity with radiographs demonstrating no evidence of recurrent or progressive disease.

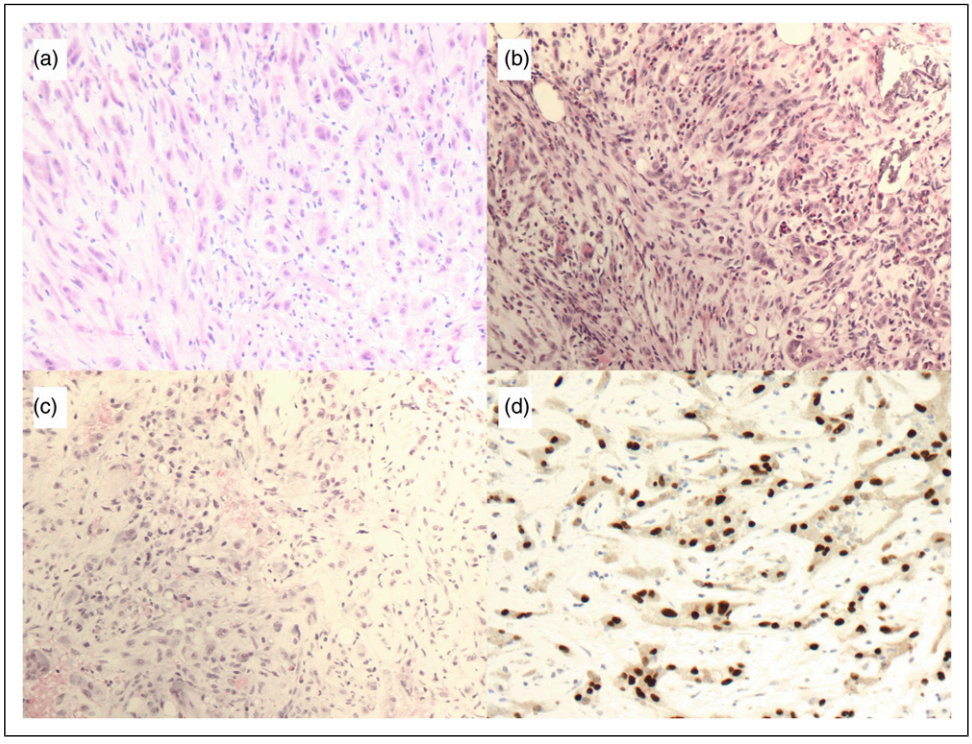

Figure 1. Intralesional excision biopsy (a) at 20 times magnification demonstrated large, eosinophilic, spindle cells in a collagenous background with lymphocytic infiltrate and some multinucleated cells. Fibular (b) and left great toe (c) intralesional biopsies demonstrating similar histology to primary EHE. Needle biopsy (d) of the lesion at 20 times magnification revealed a cord of large, elongated, eosinophilic cells forming blood vessels in a background of myxoid stroma. Intracytoplasmic lumina are present.

Case #2

A 44-year-old man was referred to the orthopedic clinic after a month-long history of left ankle pain worse at night associated with swelling. Physical examination revealed swelling about the ankle and tenderness to palpation of the medial and lateral malleoli. Ankle plantarflexion and dorsiflexion were intact and neurovascular examination was unremarkable.

Plain radiographs of the left ankle revealed an expansive meta-epiphyseal lesion involving both the distal tibia and fibula (Figure 3(a, b)). Magnetic resonance imaging (MRI) demonstrated T2 hyperintense, heterogeneous, and expansile lesions of the distal tibia and distal fibula (Figure 3(c, d)). Needle biopsy of the lesion revealed tissue with cords of large, elongated plump cells forming vessels in a background of extracellular myxoid stroma (Figure 1(d)). Immunohistochemical stains were positive for CD31, CD34, vimentin, and D2-40, and variably positive for FLI1. The tissue also stained YAP1-TFE3 positive, consistent with EHE of bone. Staging workup was negative for metastatic disease. The case was subsequently discussed at our multidisciplinary sarcoma conference and a plan was made for radiation in lieu of surgical resection as there was no reasonable option for limb salvage due to the extent of disease in distal tibia and fibula.

The patient received a cumulative 66.6 Gy over 37 fractions and tolerated radiotherapy without complications. At 1-year follow-up, the patient reports minimal pain and has resumed recreational activity while serial radiographs have demonstrated a stable bony lesion.

Discussion

Epithelioid hemangioendothelioma (EHE) of bone is a rare vascular tumor composed of epithelioid cells that demonstrate endothelial differentiation, with more than half of such cases occurring in the lower extremity.[1] Patients usually have no specific symptoms, but local pain is the most common clinical presentation.[7] In our two cases, both patients presented with pain localized in the lower extremity, with one of the patients also presenting with localized swelling.

Approximately half of patients with EHE of bone present with multicentric disease.[1] However, it is difficult to properly differentiate between the multicentric form and bone metastasis. Given the molecular characteristics of separate tumors in multicentric cases, it has been suggested that multicentricity for many of the cases are actually regional metastatic spread.[5] Our first patient had a unicentric EHE of the left os calcis that exhibited two metastatic events, both of which presented at separate bone sites (left distal fibula, left great toe and T9 vertebral body). Our second patient presented with a multicentric EHE of the bone localized in the distal tibia and fibula, which could actually have represented as regional metastatic spread.

EHE commonly stains positive for CD31, CD34, Friend leukemia integration one transcription factor (FLI-1) and negative for Desmin, EMA, and S-100.[1,4,5] One of the most characteristic histopathological hallmarks of EHE are intracytoplasmic vacuoles, reminiscent of blister-like or signet-ring cells, that may contain erythrocytes or red cell fragments.[1] When a case deviates from the typical histological presentation, EHE can look similar to epithelioid angiosarcoma, epithelioid hemangioma, or metastatic carcinoma.[1,3,8]In such cases, genetic hallmarks may aid in the diagnosis. The majority of EHE patients present with a WWTR1-CAMTA1 gene fusion, and a small subset have been found to have a YAP1-TFE3 gene fusion.[8,9] The radiological and immunohistochemical results in both of our cases did not provide any deviations from the current

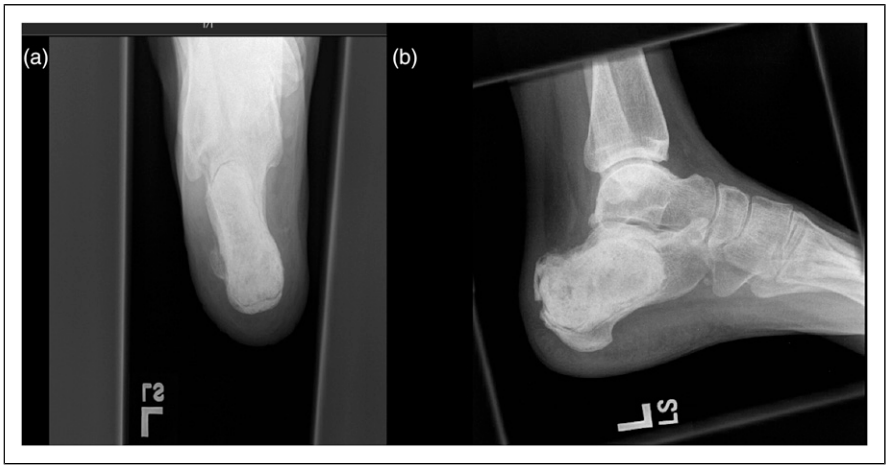

Figure 2. Harris view (a) and lateral (b) radiographs of the left calcaneus 1 month postoperatively demonstrating the calcaneal lesion status post curettage and placement of methymethacrylate cement.

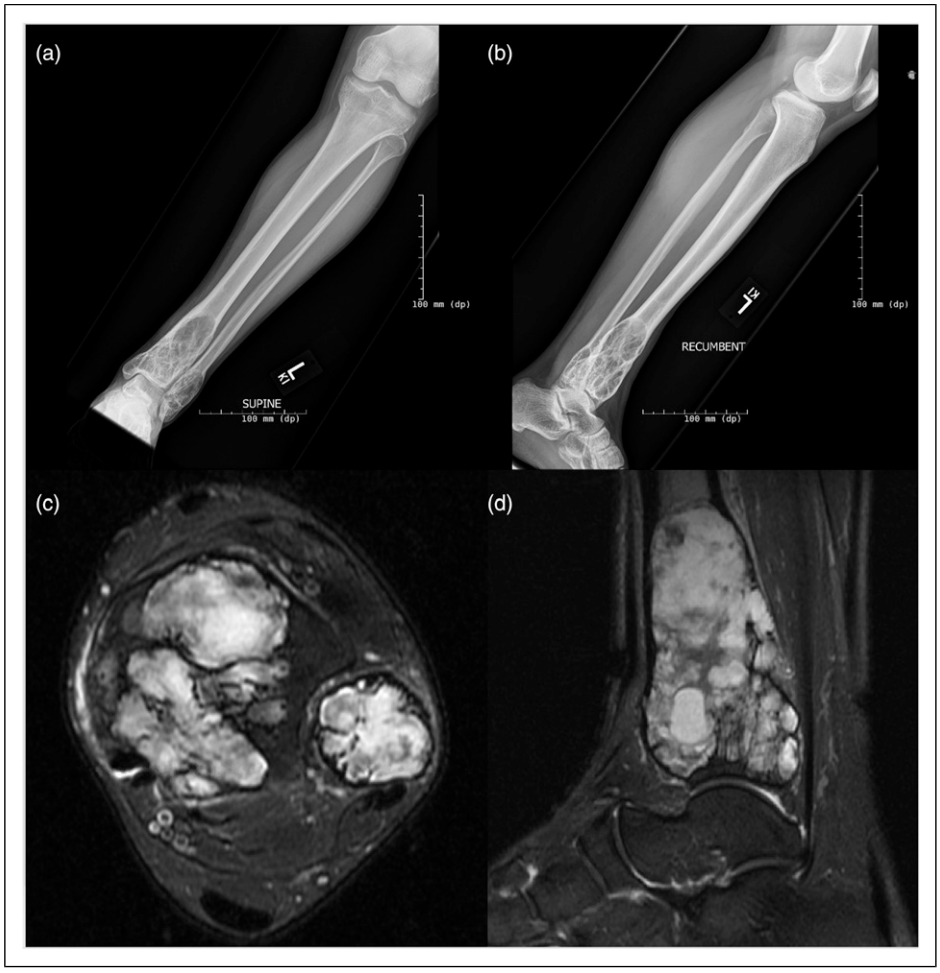

Figure 3. Anteroposterior (3a) and lateral (3b) radiographs of the left tibia and fibula demonstrating a mildly expansile meta-epiphyseal lytic lesion involving both the distal tibia and fibula. Axial (3c) and sagittal (3d) T2 magnetic resonance images of the left ankle demonstrating T2 hyperintense, heterogeneous, and expansile lesions in the distal tibia and fibula.

literature. The first case was diagnosed with a combination of histology and immunohistochemistry. The second case included the molecular characterization of the tumor, which revealed the rarer YAP1-TFE3 genetic mutation. The patient's lesion exhibited more vasoformative features than is often described for classic EHE, which supports the histological characterization of the YAP1-TFE3 mutation described in the literature.[3]

Due to the rarity of such cases, EHE of the bone currently has no standardized treatment. However, the literature that does exist supports wide resection providing favorable outcomes, at times proving to be curative with or without other treatments. It has been estimated that the overall survival of patients with EHE of bone after surgery was 92% at 10 year.[5] If surgery is not possible or if there is involvement of multiple sites, embolization, chemotherapy and/or radiation therapy (RT) have shown reasonable success in some case reports and small cohort studies.[2,5,10]Saste et al. described success in using radiation therapy in combination with chemotherapy to treat a multifocal lower extremity EHE on a young male patient.[11] Albakr et al. reviewed the current literature of spinal EHE management and describes how post-operative RT with doses ranging from 40 to 60 Gy obtained local pain control and better quality of life by at least 1-year follow-up.[12] Kleer et al. reported on a series of 40 cases EHE of bone, however was unable to conclude the efficacy of RT given the metastatic disease present in the majority of patients at the time of diagnosis.[13] Although EHE of the bone is considered radiosensitive, the role of RT as primary treatment remains to be defined. Furthermore, potential complications of RT must be considered such as impaired wound healing, fibrosis, and peripheral nerve damage.

We report on two rare cases of EHE of the bone in the lower extremity, which both exemplify the therapeutic role of RT. The first patient underwent intralesional surgery and had two recurrences. Radiation therapy was initially used postoperatively in order to reduce the risk of remission.

Primary RT was then used to treat a metastatic vertebral lesion, which would have posed a high-morbidity procedure if treated surgically. At most recent follow-up of 18 years, the patient has no recurrence or evidence of progression of their disease highlighting the efficacy of RT in this patient. For the second patient, wide resection would have precluded any adequate reconstruction options given the challenging location at the distal tibia and fibula. Primary RT yielded a good outcome after a 1-year follow-up. These two cases demonstrate the role of primary radiotherapy in the management of patients with EHE in locations where surgery is not an option or poses high morbidity. In both cases, RT was decided by our multidisciplinary sarcoma team. The necessity of RT treatment for rare tumors such as EHE should be discussed in multidisciplinary settings to weigh the risks and benefits of RT in the perioperative setting or as primary treatment.

Conclusion

These cases support the use of RT as adjuvant and primary RT for non-resectable EHE of the bone lesions. Ultimately, therapy that appropriately addresses EHE of the bone needs to be tailored to the specific case, taking into consideration the presenting symptoms, the tumor location, and the extent of the disease.

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Author contributions

LL and RG and GV researched literature. ATB and LL conceived the study. LL, GV, SCT, RB were involved in obtaining images and writing and editing. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ATB is on the Rare Tumors editorial/governing board. All other authors have no pertinent financial disclosures or pertinent conflicts of interest.

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Ethics approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the patients for their anonymized information to be published in this article.

IRB approval

Rush IRB approval was waived as a non-Human Subject Research (NHSR) form was completed for this case series.

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