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Case Report

Multifocal lower limb hemangioendothelioma in a young female: a case report and review of the literature

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Abstract: A 26-year-old female presented with pain and swelling of distal thigh and distal leg. She was diagnosed with multifocal epitheloid hemangioendothelioma (EHE) and was successfully treated with wide resection of femoral and tibial lesions followed by their reconstruction using vascularised fibular graft and local bone grafting. One year into follow-up, the patient remained asymptomatic with full Range Of Motion (ROM) and full weight bearing walking. This case illustrates a unique multifocal presentation of hemangioendothelioma and early surgical intervention leading to complete recovery, highlighting the importance of early diagnosis and intervention to help improve prognosis and quality of life of the patient.

Keywords: Hemangioendothelioma, vascular neoplasms, vascularised fibular graft, bone grafting

Introduction

Epithelioid haemangioendothelioma (EHE) is a rare malignant vascular tumour that develops from vascular endothelial or pre-endothelial cells [1-3]. It was initially described in 1975 by Dail and Liebow as a bronchoalveolar cell carcinoma of the lung [4]. Subsequently, it was named "epithelioid haemangioendothelioma" in 1982 Sarcoma by Weiss and Enzinger due to its overlapping features between a haemangioma and an angiosarcoma [5]. It has many primary sites such as subcutaneous fat, bone, retroperitoneum, lymph nodes, ovary, prostate, eyelid, and pleura. It is one of the rarest vascular tumour with an incidence of 0.038/100000/year and a prevalence of <1/1,000,000, representing <1% of primary malignant vascular tumours of the bone [1-3, 6]. Very rarely haemangioendothelioma has been reported at multiple sites in the same limb. A treatment algorithm is still not clear for haemangioendothelioma involving the skeletal system. An attempt is being made to review the literature and come out with a systemic approach for such patients and a rare presentation of the same lower limb multiple haemangioendotheliomas has been reported. Informed consent was given from the patient.

Case

A 26 year old female, daily wager by profession, came to the Orthopaedics Outpatient Department (OPD) in a tertiary care centre with complaints of pain in the left lower extremity ongoing for a year. The pain was localized to the distal thigh and distal leg left side. It was insidious in onset, gradually progressive, deep boring in character, non-radiating, increased on activity or long standing and was relieved on rest and medication. On primary clinical evaluation, she had a mild tender bony hard swelling present on the distal anterolateral aspect of the left thigh and left distal leg. On initial x-ray evaluation, she was found to have a mixed lytic-sclerotic lesion present at the distal metadiaphyseal junction of left femur and a lytic lesion present on the anterolateral aspect of distal tibia with sharp zone of transition (**Figure 1**).

Probable differentials were made that included non-ossifying fibroma, fibrous dysplasia, enchondroma, lymphoma, osteosarcoma, vascular tumors of bone and metastatic lesions.

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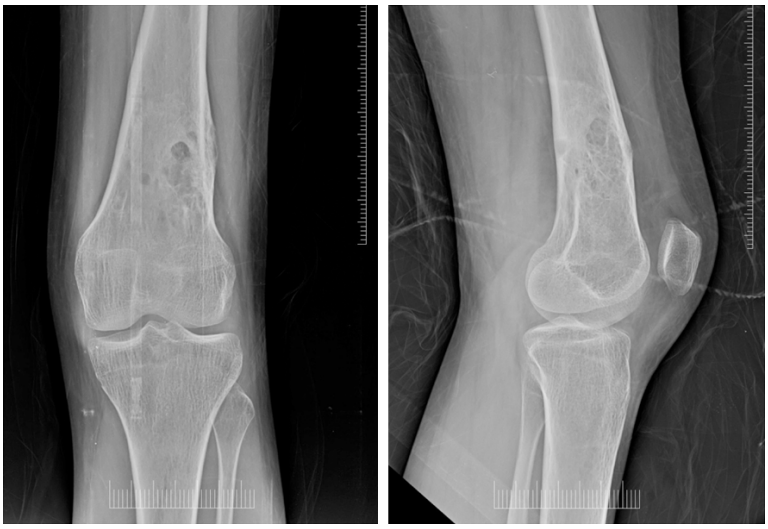

Figure 1. X rays of Knee showing distal femoral lesion.

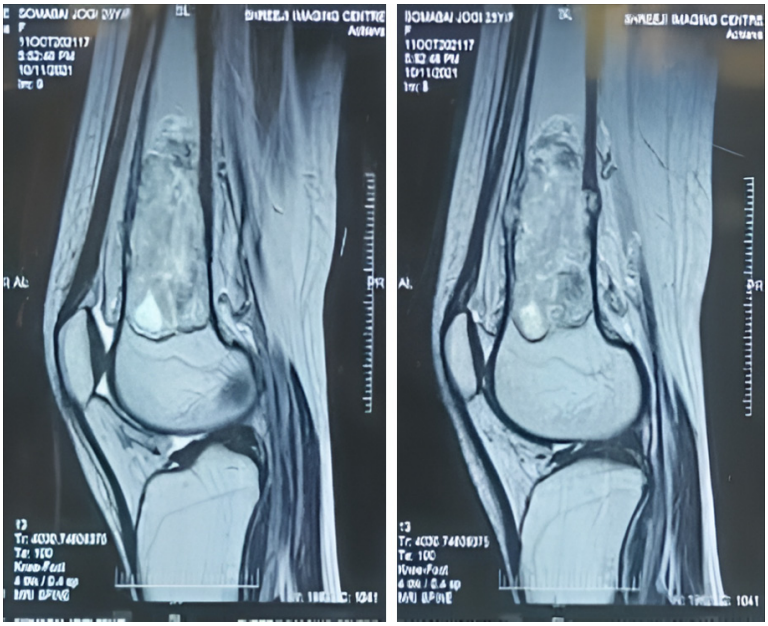

Figure 2. T2 saggital MR images showing hyperintense lesion.

Routine blood investigations were inconclusive.

Magnetic Resonance Imaging (MRI) evaluation suggested a heterogenous altered marrow signal intensity intramedullary lesion in the distal metadiaphyseal region of the distal femur which appeared hypointense on T1WI and hyperintense on T2WI with moderate heterogeneous post contrast enhancement along with a sharp zone of transition and associated cortical involvement. There was sparing of periosseous soft tissue, neurovascular bundles as well as articular surface (**Figures 2**, **3**).

On bone scan using Techetium 99m-Methyl Diphosphonate (Tc99m-MDP), there was focal increased radiotracer uptake that was noted in the distal end of the left femur and distal end of the left tibia without any significant scintigraphic evidence of skeletal lesion elsewhere.

Based on the above findings, vascular bony tumour was suspected with differentials included, hemangioma, hemangioendothelioma and angiosarcoma. To confirm our diagnosis a biopsy was performed.

Core needle biopsy showed multiple vasoformative structures lined by plump endothelium with hobnailing, hyperchromatic nuclei and inconspicuous nucleoli. The intervening stroma was bland. The vascular structures were highlighted by CD-31 but not by CD-34. Overall suggestive of Hemangioendothelioma (**Figures 4-7**).

She was operated on after confirmation of diagnosis with wide resection of the femoral and tibial lesions followed by reconstruction of the femur with vascularised fibular graft and local bone grafting for the distal tibia. A 9-hole Distal femoral locking plate and one unicortical screw were used to stabilize femur and tibia respectively.

The resected femoral and tibial tissues were sent for histopathological and microbiological evaluation which further gave confirmation of lesion being haemangioendothelioma.

She was given a slab post operatively which was removed after 6 weeks and gradual weight bearing was started. Follow up was done at 3

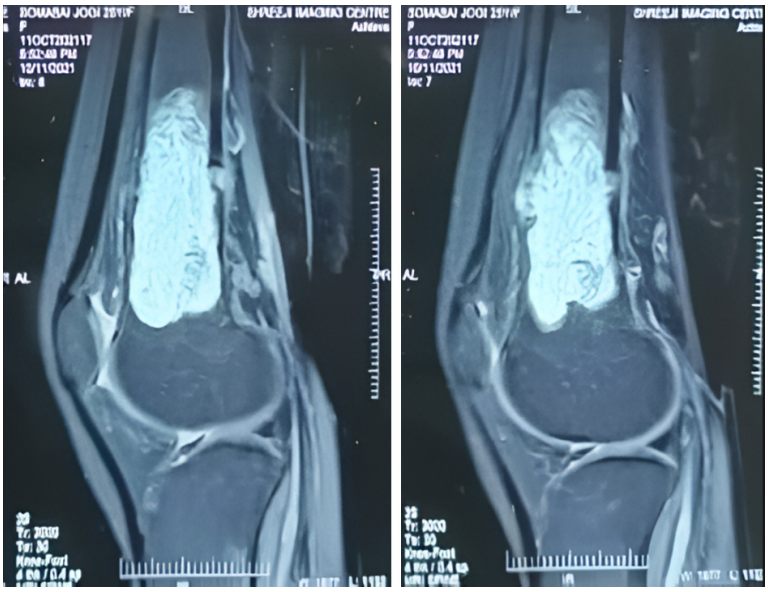

Figure 3. Fat suppressed sagittal MR images.

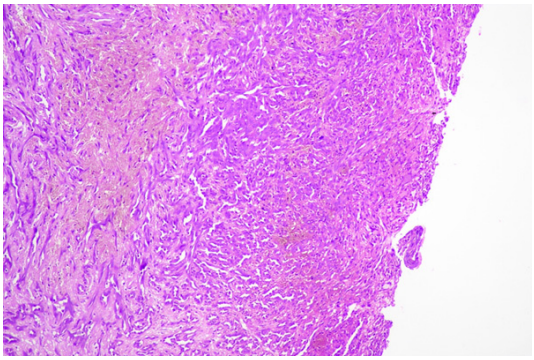

Figure 4. Section from femur shows retiform pattern and fascicles of vasoformative tumour cells. The capillaries are lined by plump, epithelioid cells. Adjacent area of hemorrhage noted (H&E; 100×).

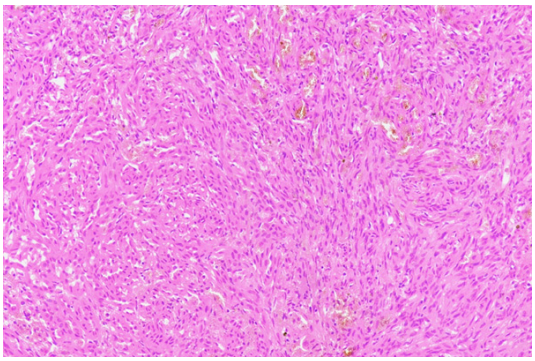

Figure 5. Section from tibia shows dominantly spindled morphology with kapsoiform-like areas. The cells which are bland, fine chromatin. No mitosis, necrosis or atypia identified (H&E; 100×).

months, 6 months and 1 year and the results showed signs of union of the graft with the parent bone and she was able to walk, full weight bearing and perform full knee ROM without difficulty. Thus far, no metastatic disease has been identified; however, she will continue to have routine screening with Computed Tomography of the chest, abdomen, and pelvis.

Discussion and review of literature

EHE can present in numerous primary sites such as subcutaneous fat, bone, retroperitoneum, lymph nodes, ovary, prostate, eyelid, and pleura. It is one of the rarest vascular tumours with an incidence of 0.038/100000/year and a prevalence of <1/1,000,000, representing <1% of primary malignant vascular tumours of the bone [1, 2, 6]. It has a slight predominance in women. The incidence peaks in the fourth to fifth decade. Presentation can be anywhere, unifocal or multifocal or with systemic metastases. Greater than 50% of patients present with metastatic disease, mostly involving the lung, liver and bone [6-8].

The World Health Organization (WHO) classification of vascular tumours of bone describes EHE as an intermediate grade tumour, separating its classification from the other primary vascular bone tumours: haemangioma (benign), epithelioid haemangioma (locally aggressive), and angiosarcoma (malignant) [9].

Due to the heterogeneity of vascular tumors of the bone, imaging is not very specific. However, some radiographic alterations can indicate the probability of a benign or malignant osseous vascular tumor. The majority of the hemangiomas show a well demarcated, lucent lesion with frequent coarse trabeculations. Although cortical expansion can be seen in hemangiomas, cortical disruption and invasion into the surrounding soft tissue is most often characteristic of malignancy. Malignant vascular tumors of bone are most often characterized by an ill-defined, osteolytic lesion with cortical disrup-

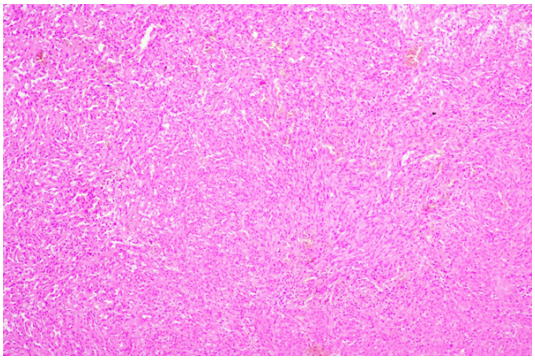

Figure 6. Indicating overlapping retiform and fascilar areas. There is mild to moderate nuclear pleomorphism. Immunostain for Pancytokeratin, S100, Desmin and myogenin was negative.

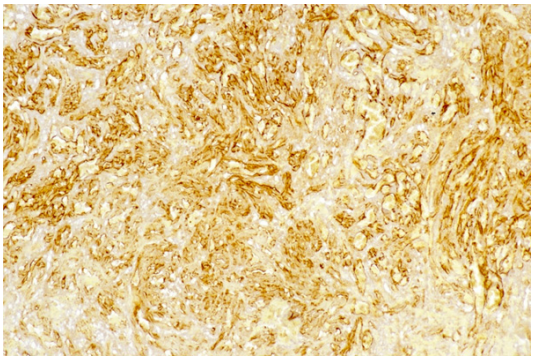

Figure 7. CD31 is diffusely positive highlighting its nature of vascular origin.

tion and endosteal scalloping and up to one third of the malignant vascular tumors of bone presents with synchronic multiple osseous lesions which can be either contiguous (adjacent bones affected) or disseminated as shown in our case.

The variable expressions of endothelial markers such as CD31, CD34, Fli-1 and von Willebrand Factor (Factor VIII) help us in differentiating the types of vascular bone tumor. Although it has been reported that CD31 and von Willebrand Factor are the best diagnostic markers for malignant vascular tumors of bone, the use of a panel of endothelial markers is essential to confirm the diagnosis because a minority of the malignant tumors only express CD34. Based on the expression of the endothelial markers it is impossible to discriminate between benign and malignant vascular tumors. Vascular tumors variably express D2-40 (31%), a presumed lymph-endothelial marker, and its expression in angiosarcoma is associated with a worse prognosis, suggesting lymphangiosarcoma of bone may exist. Cytokeratin (69%) and/or epithelial membrane antigen (4-35%), are also expressed, in particular but not exclusively in neoplasms with an epithelioid morphology. Since these lesions have a tendency to occur multifocal (contiguous or disseminated), the epithelioid morphology and keratin positivity may easily lead to an erroneous diagnosis of metastatic carcinoma [7-13].

It is usually found to be asymptomatic so it is mostly found as an incidental finding. When symptomatic, it presents with pain, palpable mass, weight loss and venous obstruction, in decreasing incidence [14, 15, 17].

Only prognostic factors are the extent of disease at presentation (tumour size or the evidence of metastatic disease) and the presence of systemic signs and symptoms [16].

It can range from a low grade malignancy to high grade sarcoma with high chances of systemic involvement. Being resistant to chemotherapeutic drugs used in sarcomas, no antitumour drug is currently approved for its treatment. Thus there is no clear cut guideline for management of haemangioendothelioma which leads to suboptimal management of haemangioendothelioma patients [14-19].

For symptomatic cases, surgery is considered as the treatment of choice especially for unifocal lesions. The local recurrence rate is 13% thus it is better complemented with radiation therapy. Post-operative RT with doses ranging from 40 to 60 Gy has been shown to offer excellent local control at 2 years in skeletal EHE. Single fraction high-dose intensity-modulated RT may be indicated in solitary bony lesions. However, given the risk of radiation-induced sarcomas, radiation therapy should be reserved for those lesions that are not amenable to wide surgical excision or when lesions are in difficult locations to surgically excise. Chemotherapy and embolization may also serve the same purpose. For bony EHE, resection should aim at R0 margins with en bloc resection of the bone of origin and of the involved soft tissues [6, 18-21].

For patients who are asymptomatic or have metastatic disease that is not amenable to

Table 1. Literature review of multicentric epithelioid hemangioendothelioma with lower extremity involvement

Authors	Year	Number of cases	Age	Sex	Number of lesions	Bones involved
Mc Namara *et al* [17]	1993	1	61	Male	4	Distal femur, tibia, third metatarsal bone, fifth metatarsal bone
Boutin *et al* [18]	1996	1	24	Male	10	Proximal and distal phalanges of the great toe, first metatarsal, medial cuneiform, tarsal navicular, C2 and C3 vertebral body, clavicle, scapulae, ilium
Kilpatrick *et al* [19]	1998	1	39	Male	2	Left Tibia
Rosenthal *et al* [20]	2001	1	21	Female	4	Fourth metatarsal, fifth metatarsal, proximal fifth phalanx, left tibia
Charfi *et al* [21]	2005	1	54	Male	2	Left femur
Kabukcouglu *et al* [22]	2006	1	48	Female	2	First metatarsal bone, left tibia
Kerry *et al* [23]	2012	1	25	Male	5	D5-D9 vertebrae
Bisbinas *et al* [24]	2014	1	41	Male	6	Distal tibia, Distal fibula, Talus, Calcaneum, Navicular, Medial Cuneiform
Kumar *et al* [25]	2015	1	43	Male	2	Distal Tibia, Talus
Kelahan *et al* [26]	2015	1	32	Male	4	L4-L5 and S1-S2 vertebrae
Zhang *et al* [27]	2015	1	20	Male	3	Distal femur, Proximal tibia and Proximal humerus
Rao *et al* [28]	2015	1	78	Male	3	Bilateral Pelvic bone and right femur
Fairfax *et al* [29]	2019	1	24	Female	2	1st and 2nd Metacarpal
Yao *et al* [30]	2019	1	49	Female	6	B—ilateral Ribs, Lumbar Vertebrae, Ilium, Pubis, Proximal Femur
Savvidou *et al* [31]	2022	1	38	Male	3	Distal Tibia, Distal Fibula, Talus

complete resection with acceptable morbidity, active surveillance is the upfront preferred approach [6, 18-21].

Review of literature has been summarized in **Table 1**.

Follow up protocol

No data to indicate the optimal length and frequency for follow-up of EHE patients treated with complete surgical resection. Currently, routine follow-up schedules differ across institutions. An MRI of the primary tumour site and a whole-body CT scan can be suggested every 6 months for the first 4 to 5 years after diagnosis. Thereafter, if no disease progression is observed, MRI and whole-body CT scans could be done yearly [16-19].

Conclusion

Epithelioid hemangioendothelioma (EHE) is a rare malignant vascular tumour. There is no common consensus regarding its management, but it is usually surgically removed in symptomatic patients supported by radiotherapy and angioembolization. A multispeciality approach to its management is required for early diagnosis and proper management.

Disclosure of conflict of interest

None.

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