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Case Report

A primary solitary vascular tumor of calcaneum: case report and review of literature ☆

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ABSTRACT

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor with metastatic potential and estimated prevalence of less than one case per million. Among the musculoskeletal system, the long bones are commonly involved with approximately half patients experiencing multicentric involvement. Clinical course of EHE is often variable and nonspecific. Poorly demarcated osteolytic lesions are most commonly seen radiologically. Diagnostic confirmation is usually obtained by biopsy and histopathological exam, including immunostaining for endothelial markers. We present a rare case of unicentric EHE involving the calcaneum. Our patient had an indolent course of disease after surgical resection and no recurrence in seven years on clinical and radiological surveillance.

Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumor with an epithelioid and histiocytoid appearance, originating from vascular endothelial or pre-endothelial cells. Among vascular tumors, it is considered a low-grade malignancy, between hemangioma and angiosarcoma. It represents less than 1% of all vascular tumors and was initially described in 1975 by Dail and Liebow as pulmonary-EHE. The most commonly involved organs include lungs, liver, and bones [1]. In the musculoskeletal system, lower extremity long bones are most commonly involved, followed by upper extremity long bones and the axial skeleton. EHE often presents as a poorly demarcated lytic lesion, although imaging features are nonspecific [2]. Clinical outcome in EHE is unpredictable. Diagnosis is confirmed by biopsy and immunostaining for endothelial markers [3]. It is often misdiagnosed and not suitably treated, which can lead to poor prognosis. We present an interesting case of solitary calcaneal EHE in a 60-years old male.

Case presentation

A 60 years-old male non-smoker presented with six months of right foot pain with no history of trauma. Patient reported significant pain with ambulation. He denied arthralgia of other

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joints or fullness or masses in the groin region. Review of systems was negative for nighttime pain, fever, chills, rashes, anorexia, and weight loss. His past medical history was unremarkable except for hamstring surgery 12 years prior. Patient worked as a carpenter; however, he was not able to work recently because of the right foot pain. He denied any outpatient medications, known drug allergies, and alcohol or recreational drug use. Family history was noncontributory. On exam, his vitals were within normal limits. Patient was not in acute distress. His distal pulses were palpable. Examination of his right foot revealed mild tenderness to palpation of the calcaneus. There were no open wounds or masses seen. There was mild fullness at the lateral aspect of the right ankle, likely due to significant varicosities. There were no palpable lymph nodes in the popliteal or groin region.

Plain radiograph of the right foot revealed a large heterogenous lytic lesion involving the calcaneum with no sclerotic border or periosteal reaction (Fig. 1). The remainder of the foot bones and ankle joint were unremarkable. Non-contrast MRI of the right ankle showed hypointense signal on T1WI and hyperintense signal on T2WI and STIR images within the lesion which measured 3.1×3.2×3.3 cm. No obvious cortical disruption or abnormal soft tissue mass was identified on MRI. There was mild adjacent marrow edema of the calcaneus. The flexor, extensor, and Achilles tendons as well as the plantar fascia were unremarkable (Fig. 2).

Patient underwent CT-guided core needle biopsy of the right calcaneum (Fig. 3). Following the procedure, patient was given a cam boot and crutches to allow non-weight bearing on the right side. Based on significant pathology findings of epithelioid hemangioendothelioma, his further diagnostic work up included PET-CT (Fig. 4) which showed hypermetabolic bilateral hilar and mediastinal adenopathy (SUV range 7.0 - 14.5). Right calcaneal lesion measured 3.9×2.6 cm with maximum SUV of 8.7. There were scattered osseous debris adjacent to the calcaneum suggestive of post-biopsy cortical disruption/fracture (Fig. 5). There were no other hypermetabolic metastatic foci seen within lungs, liver, spleen or bones. Flexible bronchoscopy with transbronchial fine needle aspiration of hypermetabolic lymph nodes revealed marked histiocytes with hyalinized fibrotic tissue and anthracotic pigment suggestive of granulomatous inflammation but no malignant cells. Considering these findings and the solitary bone lesion, patient underwent excision of the right calcaneal lesion with argon beam and filling of defect with cement/Steinman pins (Fig. 6). Patient tolerated the procedure well. Surveillance PET-CT and MRI were performed at 6 and 12-month follow up to assess for recurrent local or systemic disease (Fig. 7). At 5 year follow up, the patient had no symptoms or limitations, with no evidence of recurrence. He continues with ongoing clinic and radiographic surveillance.

Pathology: Core needle biopsy of right calcaneum revealed cords and clusters of epithelioid cells and foci of spindle cells in a myxoid matrix (Fig. 8A). Some of the epithelioid cells contained vacuoles, and rare red blood cells were noted within vacuoles (Fig. 8B). Immunohistochemical stains were performed to help further define the nature of neoplastic cells (Fig. 9). CD34 was strongly and diffusely positive and

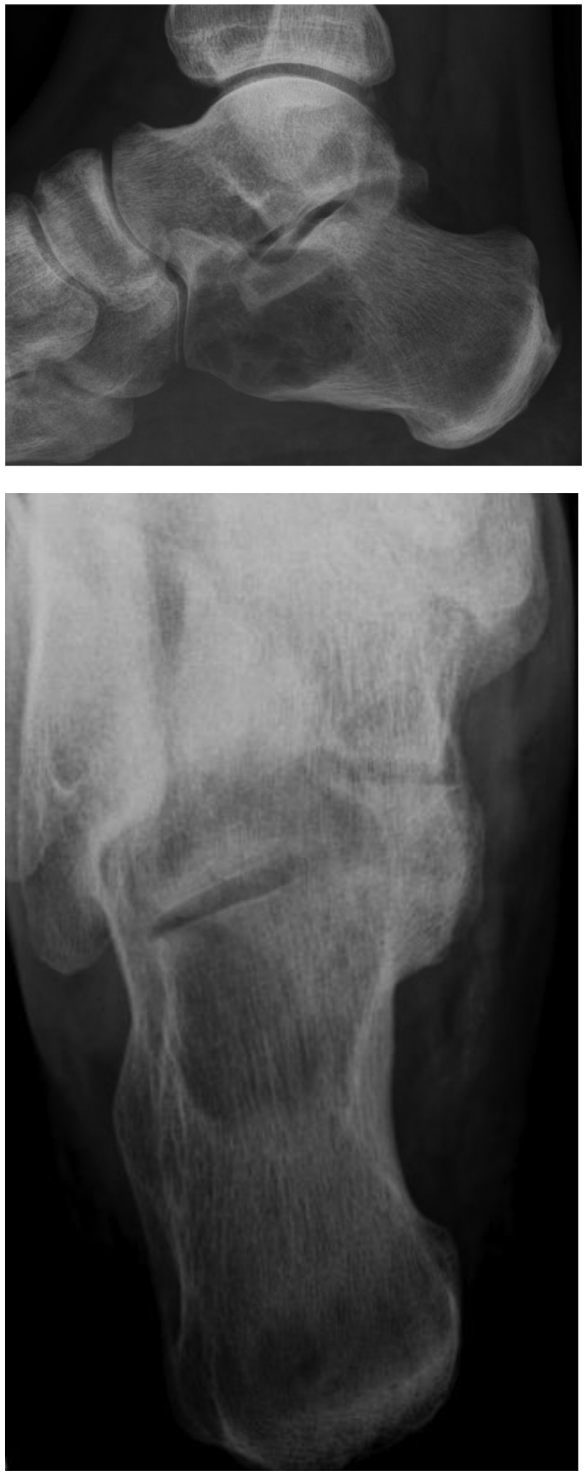


Fig. 1 – Lateral and axial x-rays of the calcaneum show a lytic lesion in the anterior calcaneum without periosteal reaction or peripheral sclerosis

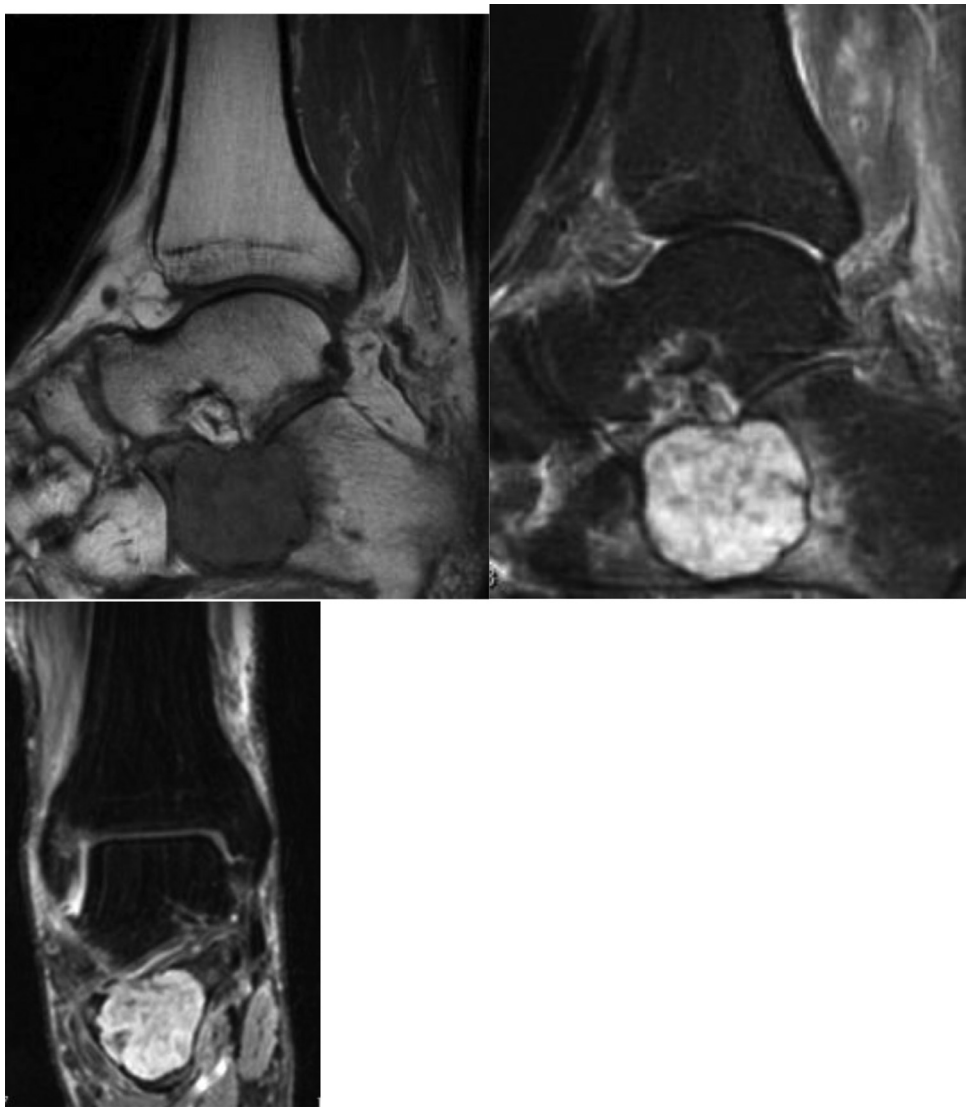


Fig. 2 – Sagittal T1W image, Sagittal T2W image and Coronal PD image of the right ankle show hypointense signal on T1WI and hyperintense signal on T2W/PD images with mild adjacent marrow edema on T2W images. No obvious soft tissue mass associated with lesion

outlined the cords and clusters of cells (Fig. 10). CD31 was weakly positive in neoplastic cells. MCK demonstrated very focal and equivocal staining. D2-40 and EMA were negative. Results were consistent with epithelioid hemangioendothelioma.

Discussion

The WHO (2002) classification describes EHE as lesions that fall into the category of locally aggressive tumors with metastatic potential [4]. Estimated prevalence of EHE is <1 in one million [5]. It frequently affects lung, liver and bone; however, it can involve head and neck, breast, lymph node, mediastinum, spine, abdomen and skin [1]. International Hemangioendothelioma, Epithelioid Hemangioendothelioma, and Related Vascular Disorders (HEARD) Support Group registry data shows that it is relatively more common in females [6]. Mean age at presentation is 43 years. (Jang JK) It has propensity to occur in the second and third decades of life [7].

Lytic lesions of bone are more commonly metastatic in origin and less commonly arise from primary bone malignancy. It was estimated that the age-adjusted incidence rate for all bone and joint malignancies is 0.9 per 100,000 persons/year [8]. EHE more frequently involves the long bones, particularly the tibia (23%), femur (18%), and humerus (13%) [2]. Around 50% of patients present with multicentric tumor. Review of the current literature found five cases of calcaneum involvement; one case was unicentric calcaneum involvement, similar to our case [9].

Radiographic and CT findings include poorly demarcated osteolytic lesions involving both the medullary cavity and cortex near the ends of the bone. Surrounding sclerosis can be

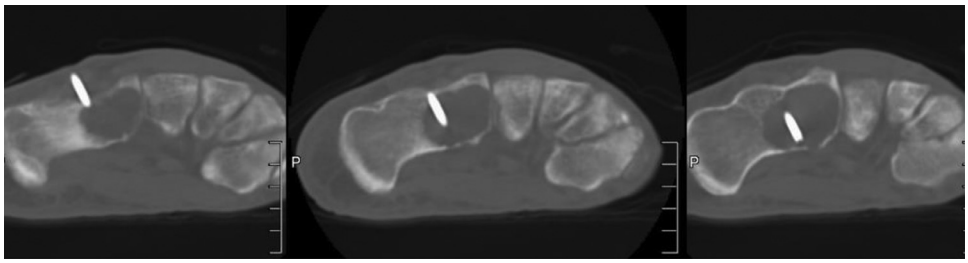


Fig. 3 – CT-guided core needle biopsy of the lesion

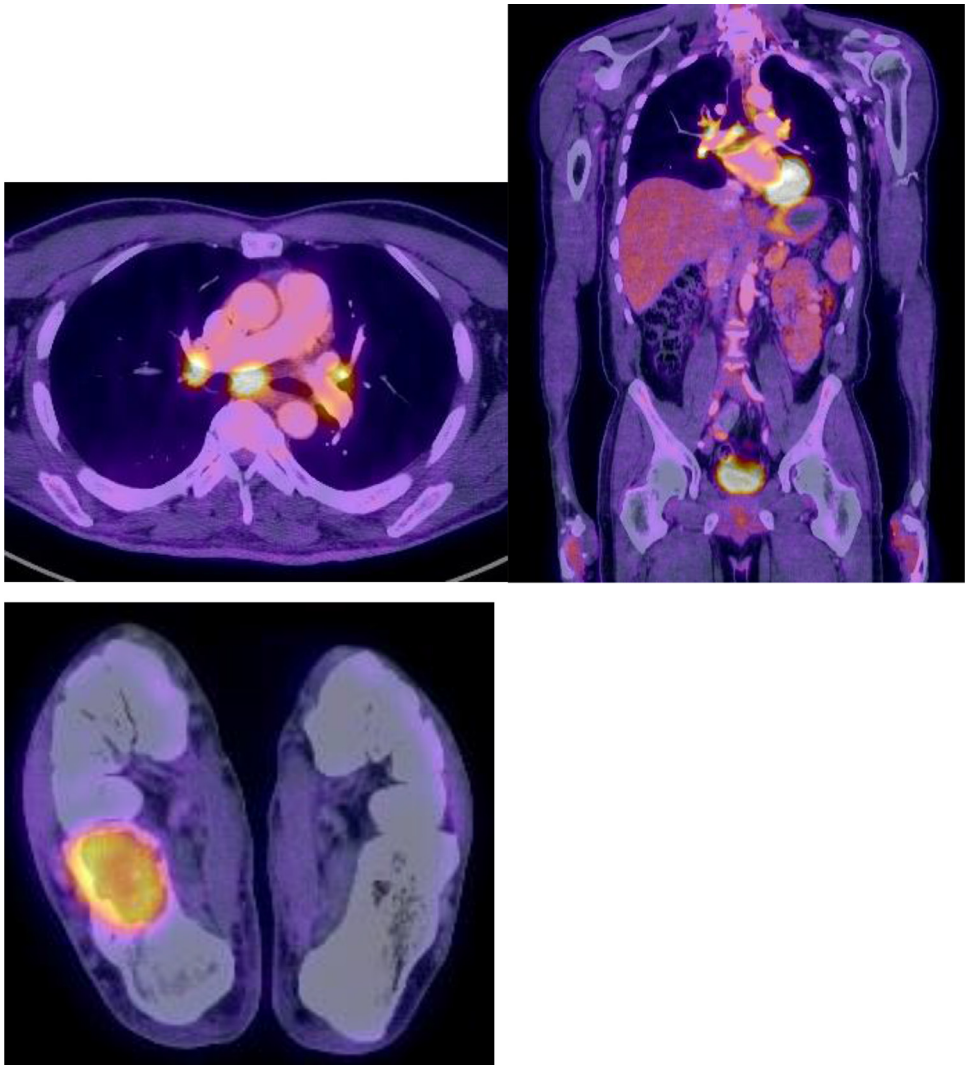
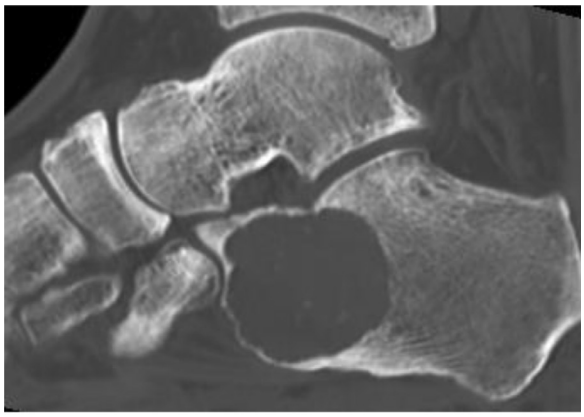


Fig. 4 – Axial and coronal PET-CT image shows hypermetabolic mediastinal lymph nodes and the hypermetabolic calcaneal lesion

seen in a few cases. Cortical disruption and extension into surrounding soft tissue can be present [2]. It may invade the adjacent joint [10]. No matrix mineralization or periosteal reaction was present, unless associated with pathological fracture. When EHE involves soft tissue, it is noted adjacent to vessels. On MRI, bone lesion appears intermediate to low signal on T1 weighted images and high signal on T2- weighted images. Presence of flow void is not typical of EHE [11]. It shows homogenous or peripheral post contrast enhancement [2]. Soft tissue extension and extension across the joint are best seen by MRI. EHE shows increased uptake on ^{99m}TC sestamibi bone scintigraphy. Disease extent can be better evaluated by bone scan, as it can be multicentric in nature. Serial bone scintigraphy has been used to monitor response in such settings [2].



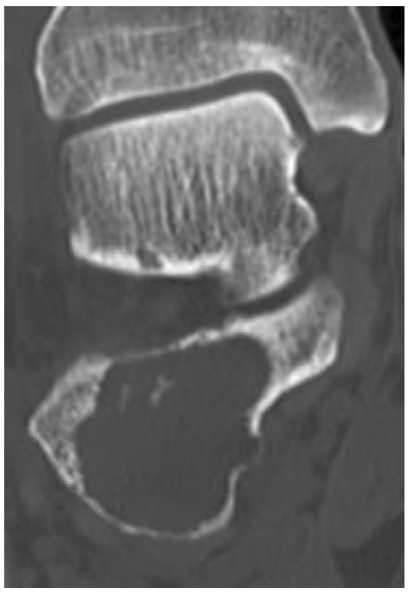


Fig. 5 – Sagittal and coronal post biopsy CT image shows scattered osseous debris with post-biopsy cortical disruption/fracture

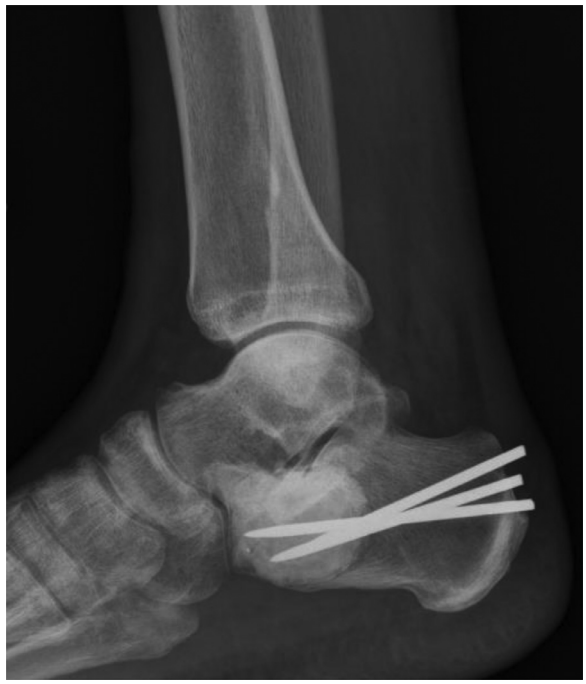


Fig. 6 – Lateral x-ray shows excision of right calcaneal lesion with argon beam and filling of defect with cement/Steinman pins

Fig. 7 – Axial PET-CT image of the ankle obtained a year after treatment on follow up scans shows no hypermetabolic lesion

Fluorine-18 FDG PET is useful to detect extraosseous metastasis. Preferred order of investigation can be MRI to look for adjacent soft tissue and joint involvement after initial radiographs. Subsequently, bone scan is preferred over the PET scan due to multicentric nature of the disease as well as to monitor the response therapy.

The differential diagnosis for a solitary EHE depends on the patient's age and bone destruction pattern. It can range from benign lesions, like intraosseous lipoma, simple bone cyst, fibrous dysplasia and to malignant lesions, such as osteogenic sarcoma, fibrosarcoma, and multiple myeloma [7]. EHE is a very rare condition, and one should consider EHE after excluding more common benign lesions found in calcaneum like lipoma and simple bone cyst. Lipoma is more often centrally located and shows central calcification on radiograph. It is hyperintense on T1 and T2 weighted MRI images. EHE would not have central calcification and is hypointense on T1 weighted MRI image. Simple bone cyst is homogenous lytic lesion and usually noted within the center of calcaneum. On MRI, cyst

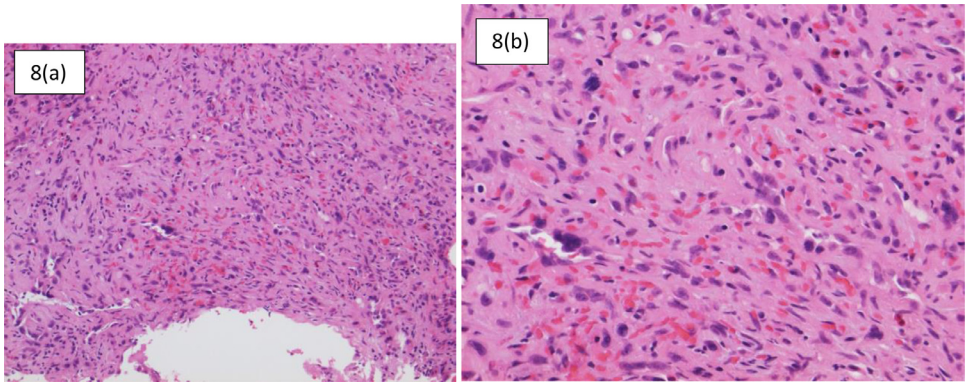


Fig. 8 – (A): Distinctive malignant vascular neoplasm characterized by predominant cords and clusters of epithelioid tumor cells and foci of spindle tumor cells within a characteristic myxoid to hyaline matrix, at 20x. (B): Malignant epithelioid cells in a myxoid background, with intracytoplasmic vacuoles at high power 40x. Rectangle; Intracytoplasmic vacuoles with epithelioid tumor cell

shows uniform hyperintensity on T2W image where as EHE shows heterogenous hyperintensity. There is no post contrast enhancement with cyst, whereas EHE is hyper enhancing lesion. EHE appears to be within the anterior aspects of calcaneum due to proximity of vascular channel. Imaging findings which raise the suspicions for EHE includes heterogenous lytic lesion located on the anterior aspect of calcaneum, cortical thinning with impending pathological fracture as in our case, extension across the joint, and multicentric disease. Because the imaging features are nonspecific, confirmation of the diagnosis is usually only possible with histopathologic examination [11].

Some of the histologic characteristics of EHE consist of endothelial cells arranged in nests and cords. Spindle-shaped tumor cells can be present as well. Some cells contain distinct intracytoplasmic vacuoles that occasionally compress the nucleus leading to a signet-ring appearance [12]. A variety of endothelial proteins may be useful to identify EHE. The Fli-1 protein is expressed by the endothelium as well as the T-cells and megakaryocytes: this nuclear protein has proven useful in identifying vascular neoplasm including EHE, showing a better combined sensitivity and specificity than the endothelial markers CD31 and CD34. CD34 is reported to be expressed by more than 90% of vascular tumors, so this marker has poor specificity as a variety of soft tissue tumors also express it. In contrast, CD31 is regarded as a relatively specific vascular tumor marker, which was identified in our histopathology examination [1].

The prognosis of EHE is variable; some demonstrate an indolent clinical course, as in our case, while others tend to metastasize [12]. The prognosis depends on multicentricity and degree of histologic differentiation and cytological atypia of the neoplastic endothelial cells. There have been no predisposing factors identified. Despite the variable nature of EHE, overall survival is high [13,14]. Metastasis has been shown to occur in up to 31% of cases and is more common in those with marked cellular atypia, increased mitotic activity, spindling and necrosis [15]. Patients with unifocal disease are best treated with surgery, while those with multifocal tumors are often treated with radiation therapy. Davis AT *et al*. reported a

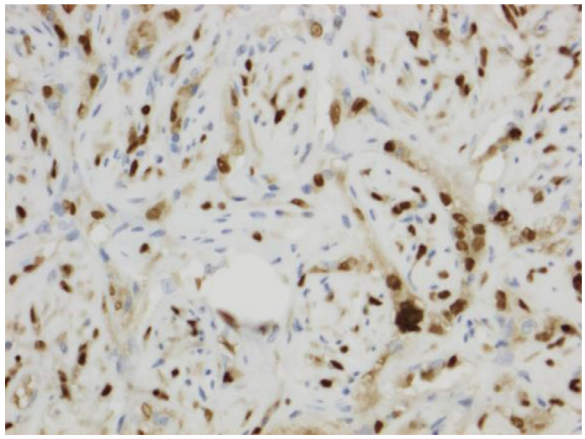


Fig. 9 – High power image 40x demonstrating strong nuclear CAMTA positivity in the tumor cells

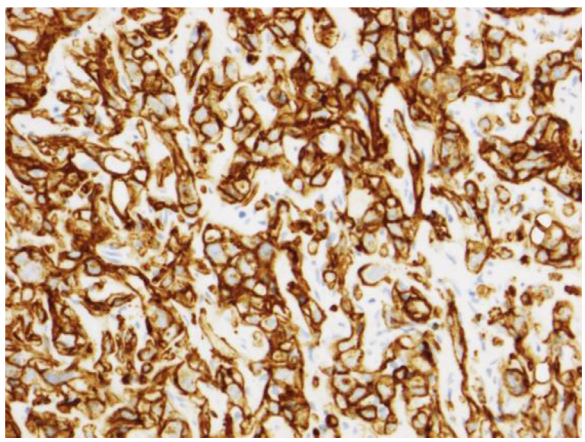


Fig. 10 – CD34 stain demonstrates strong membranous staining of the tumor cells

case of successful treatment of multifocal EHE with wide excision of all soft tissue lesions and radiofrequency ablation of the bone lesion [16]. Late recurrence may occur with EHE, and long term follow up is suggested [11].

Conclusion

EHE is an extremely rare tumor of vascular origin. The current reported literature is limited to case reports and retrospective descriptive case series to help characterize the clinical, pathological and radiographic features and to guide the management approach.

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