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A trimodality approach in the management of metastatic low-grade epithelioid hemangioendothelioma of the bone

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CASE REPORT

A trimodality approach in the management of metastatic low-grade epithelioid hemangioendothelioma of the bone

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SUMMARY

A 29-year-old man presented with a 2-week history of severe pain in the left foot with no preceding history of trauma. A left foot radiograph demonstrated a cortical lucency in the mid-distal shaft of the third metatarsal bone. MRI of the left foot showed an expansile lesion in the same location. A staging bone scan showed a focal uptake in the known lucency in the left third metatarsal and in the proximal left femur. A subsequent left hip radiograph demonstrated a lucency in the intertrochanteric region. CT scan of the chest, abdomen and pelvis was unremarkable. A biopsy of the left third metatarsal expansile lesion performed during an incision and curettage procedure revealed an epithelioid haemangioma (EHE) of the bone. MRI of the left hip performed in response to the findings on the bone scan showed metastatic disease in the left intertrochanteric region. A prophylactic left hip fixation surgery with an interlocking intramedullary femoral nail was therefore undertaken to avoid a pathological fracture of the left hip from the metastatic disease. Simultaneously, a left hip biopsy was performed, which also revealed an EHE. The patient underwent external beam radiation to the left femoral head and neck. This was followed by fractionated radiosurgery to the left third metatarsal. Once the left foot wound had healed, the patient subsequently received four cycles of doxorubicin and ifosfamide. A restaging positron emission tomography CT carried out after completion of therapy showed no metabolic evidence of residual primary tumour or metastasis. More than 2 years after completing his trimodality therapy, the patient remains fully functional and symptom free.

BACKGROUND

Primary vascular tumours of the bone represent a heterogeneous group of neoplasms with a wide spectrum of behaviours, ranging from benign to malignant. Malignant vascular tumours are very rare, representing less than 1% of primary malignant bone tumours. Over the years, there has been significant controversy surrounding the naming and classification of such tumours. In an effort to simplify and clarify the various vascular tumours, the WHO classification comprises four main groups: haemangioma (benign), epithelioid haemangioma (EHE) (locally aggressive), EHE (intermediate grade) and angiosarcoma (malignant).[1 2]

EHE of the bone is an uncommon subtype of these vascular tumours; it closely resembles an epithelial tumour, and may sometimes be mistaken for a metastatic carcinoma. EHE affects only about one person per million, worldwide, with nearly 20 cases diagnosed in the USA each year. Its treatment can be challenging as there is currently no standard therapy. Most of the experience is derived from small case series and isolated case reports. We present a case of EHE of the bone with classic histological and immunophenotypic features, low-grade cytomorphology and multifocal malignant behaviour managed with a trimodality approach including surgical excision followed by adjuvant radiotherapy and chemotherapy.

CASE PRESENTATION

A 29-year-old man presented with a 2-week history of severe pain in the left foot made worse by ambulation. It began spontaneously without preceding trauma. The dorsal left mid-foot was tender to palpation, especially over the shaft of the third metatarsal bone. The patient also complained of a vague left hip pain. The remainder of his medical, social and family history was unremarkable.

INVESTIGATIONS

Left foot radiographs demonstrated an ill-defined cortical lucency in the mid-distal shaft of the third metatarsal (figure 1).

A follow-up MRI of the left foot showed a pathological fracture extending through a 4.3×1.5×1.3 cm expansile lesion within the mid-distal shaft of the left third metatarsal with surrounding soft tissue and bone marrow oedema (figures 2 and 3).

Staging work up with a bone scan showed a focal uptake in the known lucency in the left third metatarsal and in the proximal left femur (figure 4).

Left hip radiograph demonstrated a luceny in the intertrochanteric region (figure 5).

CT scan of the chest, abdomen and pelvis showed no evidence of visceral metastasis. An incisional biopsy with curettage of the primary lytic lesion in the left third metatarsal shaft was then undertaken. This confirmed a low-grade EHE of the bone. H&E staining of the left third metatarsal biopsy revealed that the tumour in the metatarsal was associated with organising haemorrhage and bone spicules in the pathologic fracture. The tumour was not overtly malignant, with barely any mitoses or necrosis (figure 6).

The tumour was described by the pathologist as having the typical immunophenotypic features of this disease, including CD31 vascular marker

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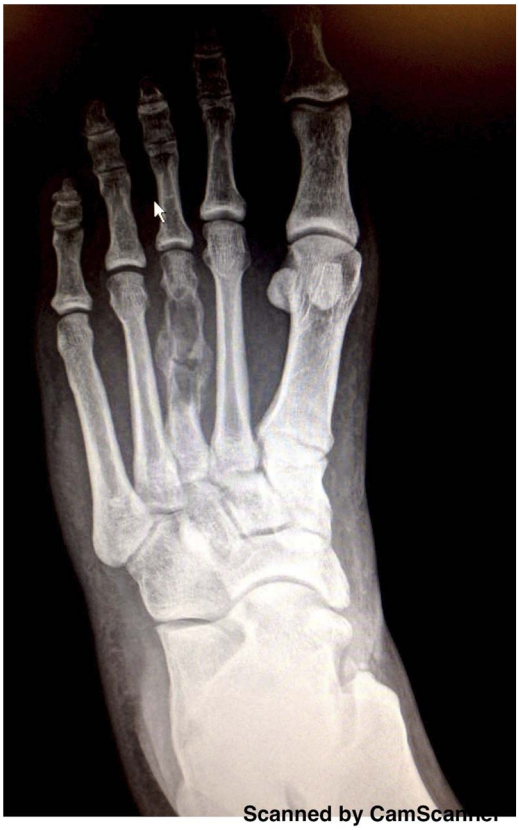

Figure 1 Left foot radiographs showing a cortical lucency in the mid-distal shaft of the third metatarsal bone.

positivity on sheets of hobnail type cells lining vascular spaces. Immunostains for S100, keratins and CD1a were negative (figure 7).

MRI of the left hip performed in response to the findings on the bone scan showed multiple foci of signal abnormality within the left femoral head and neck measuring up to 1.2 cm, worrisome for metastatic disease in the left intertrochanteric region (figure 8). The MRI of the left hip was carried out, despite the CT scan of chest, abdomen and pelvis not being suggestive of metastatic disease, to follow the radiological paradigm that a CT scan is not as sensitive as an MRI in detecting and delineating the extent of a suspected hip metastasis, which held true in our case. An MRI also serves as a more useful guide for surgeons in preoperative planning and to increase the yield of a biopsy specimen.

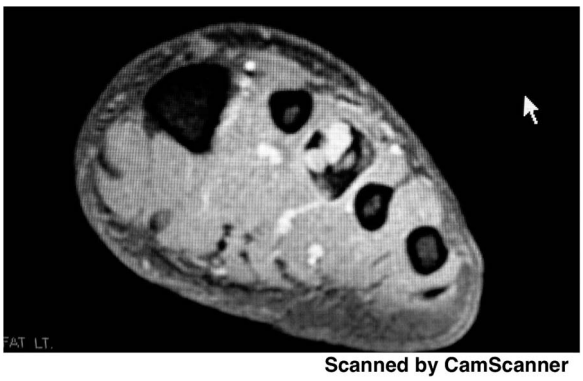

Figure 2 Left foot MRI showing an expansile lesion within the mid-distal shaft of the left third metatarsal.

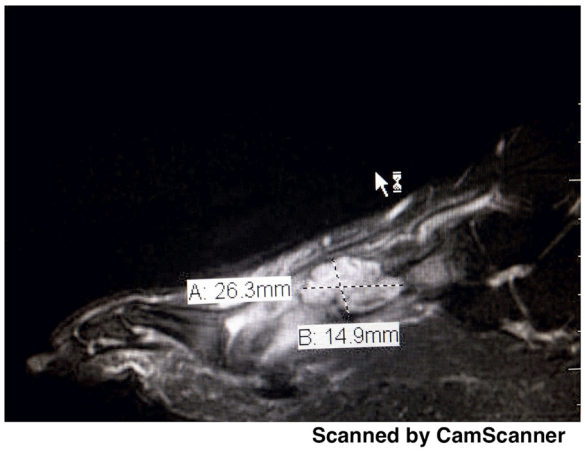

Figure 3 Left foot MRI showing an expansile lesion within the mid-distal shaft of the left third metatarsal.

A prophylactic left hip fixation surgery with an interlocking intramedullary femoral nail was therefore undertaken to avoid a pathological fracture of the left hip from metastatic disease.

Simultaneously, left hip bony reamings were obtained for pathological examination. H&E staining of this left hip biopsy showed that the tumour cells in the soft tissues and skeletal muscles of the hip were epithelioid with minimal atypia or mitoses, confirming a diagnosis of EHE (figure 9).

Postoperative positron emission tomography (PET-CT) showed moderate to intense fluorodeoxyglucose (FDG) activity in the region of the left femoral neck and intertrochanteric region, suspicious for metastasis at the level of the recently placed left femoral intertrochanteric screws. Mild FDG activity within the left foot corresponding to known tumour involvement and resultant pathological fracture of the third metatarsal were also noted (figure 10A, B left to right upper row). Multiple foci of FDG activity within the soft tissues of the left thigh and leg, the largest of which was located within the left quadriceps femoris muscle, suggested metastatic disease. The patient underwent a CT-guided biopsy of the FDG avid area in the left biceps femoris muscle, which yielded only a haematoma from postoperative bleeding, without evidence of malignancy.

We would like to bring to the reader's attention here, that additional vital information to our staging work up would have been obtained by getting a pretreatment PET CT. However, the PET CT was performed postoperatively due to delays in insurance approvals despite timely submission of PET CT requests with the necessary supporting clinical documentation from our end. We did not want to delay treatment until such approvals went through. We did perform the PET CT once insurance approvals went through postoperatively. We did this despite knowing that we would have postoperative artefacts in the left foot and left hip, because our purpose for this postoperative PET CT was not as much to focus on the known disease sites but rather to exclude other sites of critical but asymptomatic multicentric disease such as spinal or intracranial disease that may have existed, needing attention.

Postoperative radiographs of the left hip (figure 11) and left foot (figure 12) showed an uncomplicated and unchanged appearance of the left femoral intramedullary nail and fracture union at the left third metatarsal shaft, respectively.

A second restaging PET CT, carried out 15 months after therapy was completed, showed no evidence of residual tumour in the left foot or left hip and no new disease elsewhere (figure 10C, D left to right lower row).

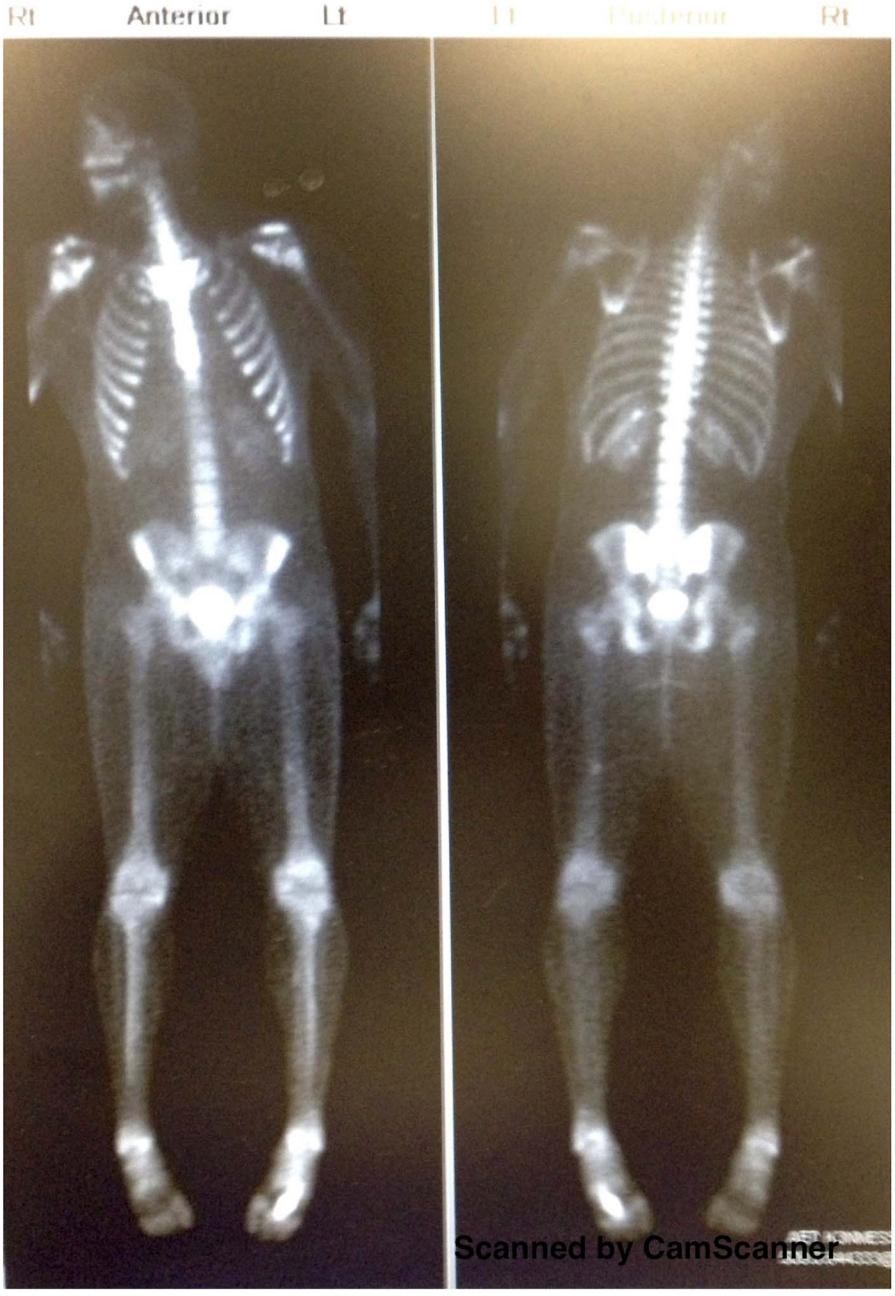

Figure 4 Bone scan showing focal uptake in left third metatarsal and proximal left femur.

DIFFERENTIAL DIAGNOSIS

- Metastatic carcinoma
- Chondromyxoid fibroma
- Epithelioid haemangioma
- Epithelioid angiosarcoma

TREATMENT

Our patient, given his multifocal disease, was treated with a trimodality approach employing wide surgical excision followed by adjuvant radiotherapy and chemotherapy.

An incisional biopsy with curettage of the primary lytic lesion in the left third metatarsal shaft was carried out first. The foot was immobilised in a cast and kept non weight bearing, which resulted in a complete union at the fracture site. The surgeons did not deem a surgical fixation necessary. The risk/benefit ratio favoured a conservative approach with immobilisation and partial weight bearing.

A prophylactic left hip fixation with dynamic hip screws and an interlocking intramedullary femoral nail was then undertaken to avoid a pathological fracture of the left hip from metastatic disease. During this procedure, bony reamings were obtained for pathological examination.

The patient underwent external beam radiation, 50 Gy in 20 fractions, with a daily dose of 2.5 Gy to the left femoral head and neck. The left third metatarsal primary site was treated by fractionated radiosurgery with a total dose of 32 Gy, prescribed to the 90% isodose line. The metastatic site of the left femoral head was treated first and the initial primary site of left third metatarsal harbouring the pathological fracture was addressed later. The two sites (femur and metatarsal) were not addressed concurrently, so as to allow the left foot wound to heal completely before subjecting it to radiation. Additionally, given the presence of a left foot plaster cast, radiating the left hip first made more clinical sense. The left hip metastasis, being much

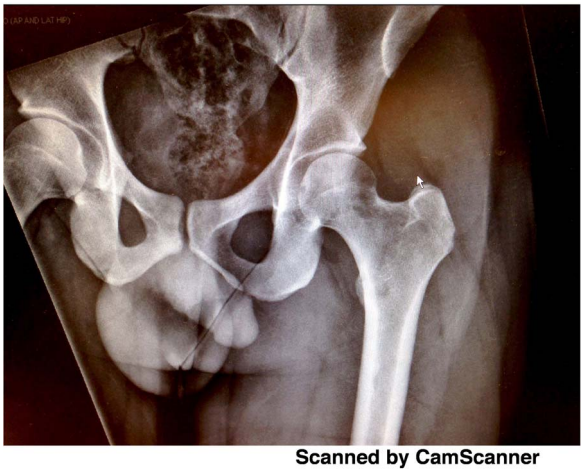

Figure 5 Left hip radiograph showing a lucency in the intertrochanteric region.

larger in size, with a potential to fracture from progressive disease, warranted more immediate attention to avoid greater long term disability from a potential pathological fracture.

The patient subsequently received four cycles of doxorubicin and ifosfamide.

OUTCOME AND FOLLOW-UP

More than 2 years after completing his trimodality therapy, the patient remains fully functional in his profession as a police officer and is symptom free, with an Eastern Cooperative Oncology Group (ECOG) performance status of zero. He ambulates independently, and continues to be monitored with serial imaging and clinical examinations.

DISCUSSION

Definition and classification

Vascular tumours are tumours arising from the endothelial linings of blood vessels. Nearly one half to two thirds originate from a small vein.[1 3]

The WHO has classified vascular tumours of the bone as follows:

1. Haemangioma (benign)
2. EHE (locally aggressive)
3. EHE (intermediate grade)
4. Angiosarcoma (malignant)

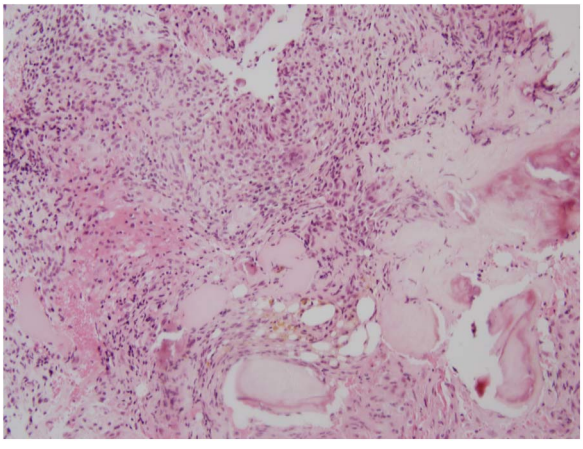

Figure 6 H&E staining of left third metatarsal biopsy showing epithelioid cells with minimal atypia or mitoses.

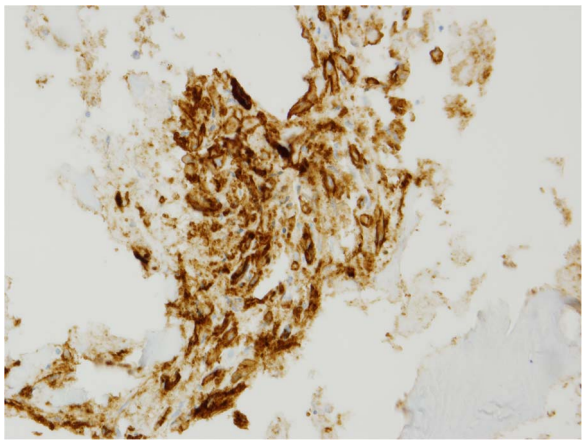

Figure 7 Immunostaining showing CD31 positivity in epithelioid tumour cells.

Synonyms

Intravascular bronchioloalveolar tumour, angioglomoid tumour, myxoid angioblastomatosis.[1]

Incidence

EHE is a rare tumour. Its precise incidence is undetermined.[1]

Age/sex distribution

The lesion occurs in nearly all age groups with the exception of early childhood years, and affects both sexes equally.[1]

Location

In descending order of frequency:[4]

1. Lower extremities: femur, tibia, fibula and small bones of feet—62%
2. Upper extremities: humerus, ulna, radius and small bones of hands—14%
3. Vertebrae—10%
4. Concurrent parenchymal tumours—18%

Clinical features

EHE of the bone is a tumour that has a tendency to multicentricity.[4] There is no clear distinction between multifocality and metastatic disease. Some authors have described multifocal

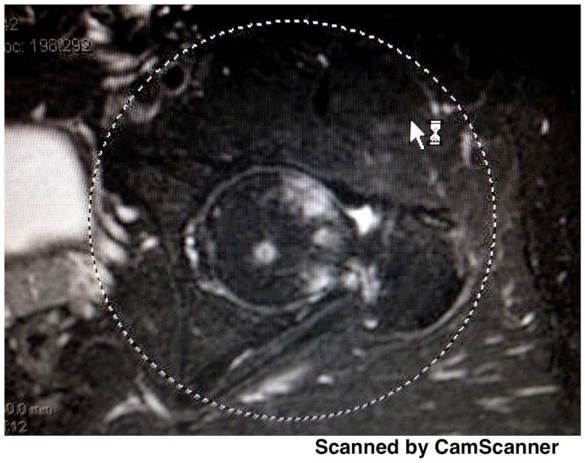

Figure 8 Left hip MRI showing metastatic disease in the left intertrochanteric region.

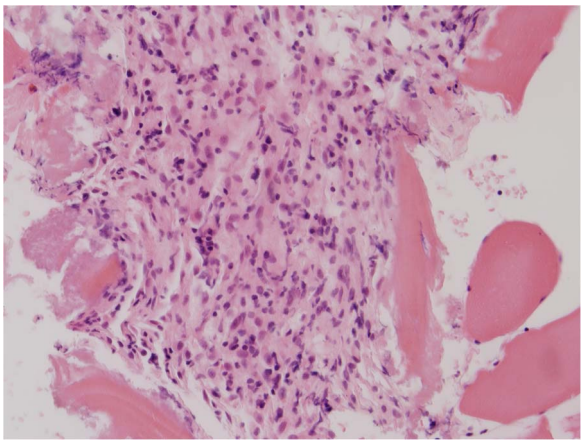

Figure 9 H&E staining of left hip biopsy showing epithelioid cells with minimal atypia or mitoses.

disease as that which occurs in the same limb. Most of the patients are asymptomatic at the time of the diagnosis but, if symptomatic, pain appears to be a common theme across all described reports. Pathological fractures and localised swelling may also occur. Because these tumours arise from blood vessels they may present with thrombophlebitis and extremity oedema.

Radiographic findings

CT scan and MRI show a well-demarcated osteolytic lesion with no periosteal reaction. These usually remain confined to bone but may invade into surrounding soft tissue. A honeycomb-like appearance with trabeculations can also be seen. Matrix mineralisation is uncommon.[5]

Bone scan may show doughnut-like lesions with increased radiotracer uptake of the isotope.[5]

Unni *et al* described a positive correlation between the radiographic picture and the histological grade. Low-grade tumours will show sharply demarcated margins and some bony trabeculae, whereas high-grade tumours have distinct and irregular margins.[3]

EHE has a high incidence of multicentricity. A complete skeletal survey is therefore recommended.[3]

Treglia *et al*[6] demonstrated the value of PET/MRI in the diagnosis of FDG-avid multifocal bony and soft tissue EHE. Davis *et al*[7] also reported on the presence of FDG avid lesions in their case report of a multifocal epithelioid sarcoma-like haemangioendothelioma involving the cuboid and calcaneus bones. These reports suggest that primary vascular tumours show FDG avidity and, therefore, including a PET-CT or PET/MRI as a part of the staging work up should remain a consideration. Given the multicentric tendency of these tumours, PET-CT may aid in detection of occult disease in critical sites such as the vertebral column, which may then warrant medical intervention.

Immunohistochemistry and cytogenetics

EHE of the bone expresses a variety of endothelial antigenic surface markers such as CD31, CD34 and FLI-1, which are more reliable than von Willebrand factor.[1]

EHE can show cytokeratin positivity in 38% of cases and can also focally express epithelial membrane antigen.[2 8]

Presence of translocations involving chromosome 1 and 3 [t (1; 3) (p36.3; q25)], resulting in a wwtr1-camta1 fusion product, is a consistent genetic abnormality of these tumors.[1]

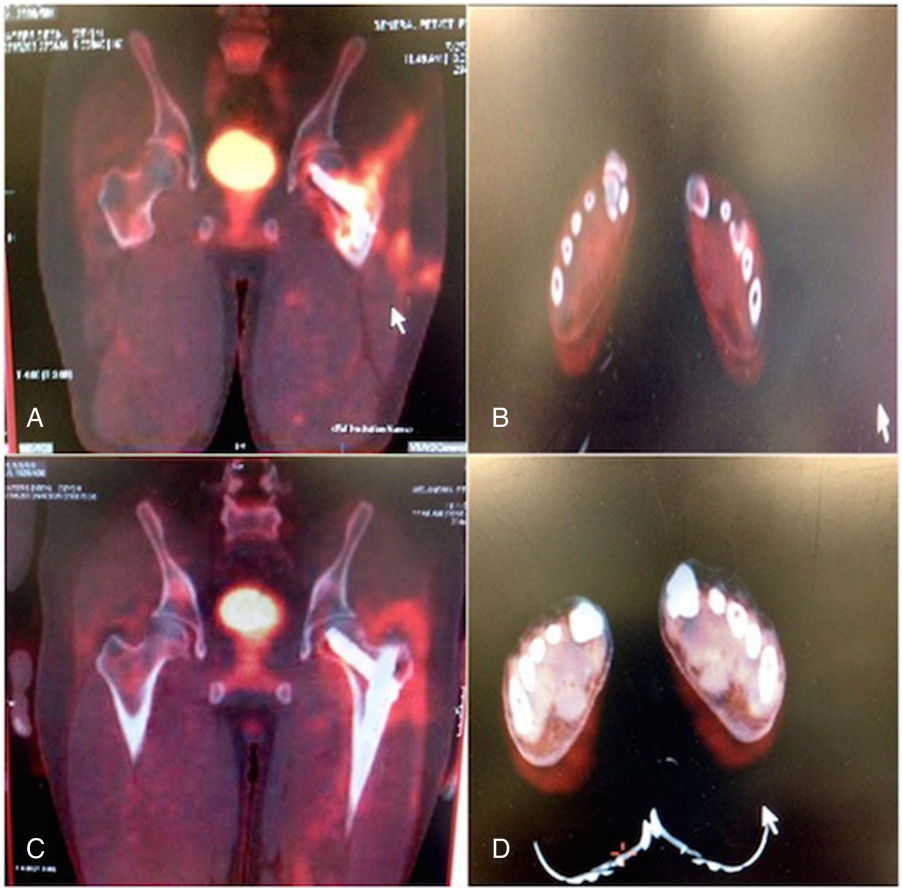

Figure 10 Positron emission tomography (PET-CT) showing moderate to intense fluorodeoxyglucose (FDG) activity in the left intertrochanteric region and mild FDG activity within the left foot. [A and B left to right upper row]. PET CT showing resolution of FDG avidity in left foot and left hip. [C and D left to right lower row].

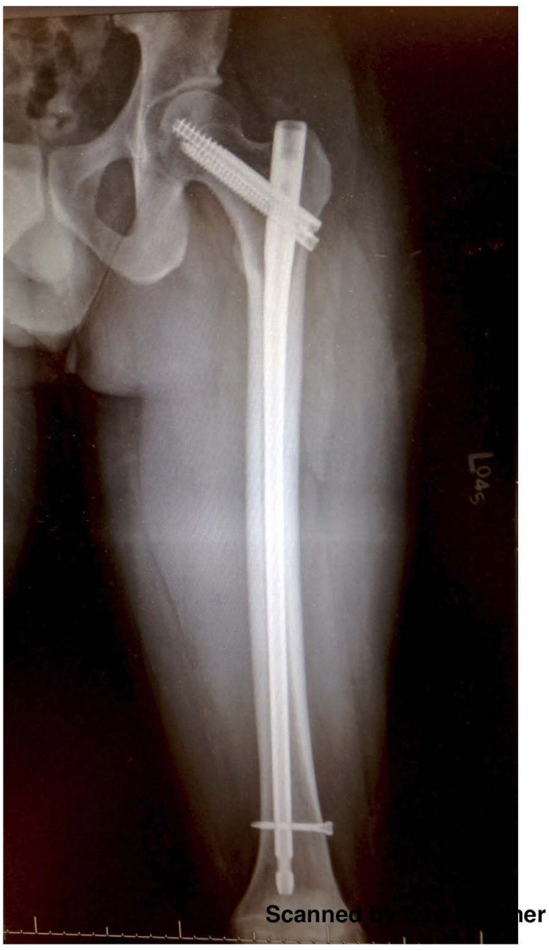

Figure 11 Radiographs of the left hip showing an uncomplicated appearance of the left femoral intramedullary nail.

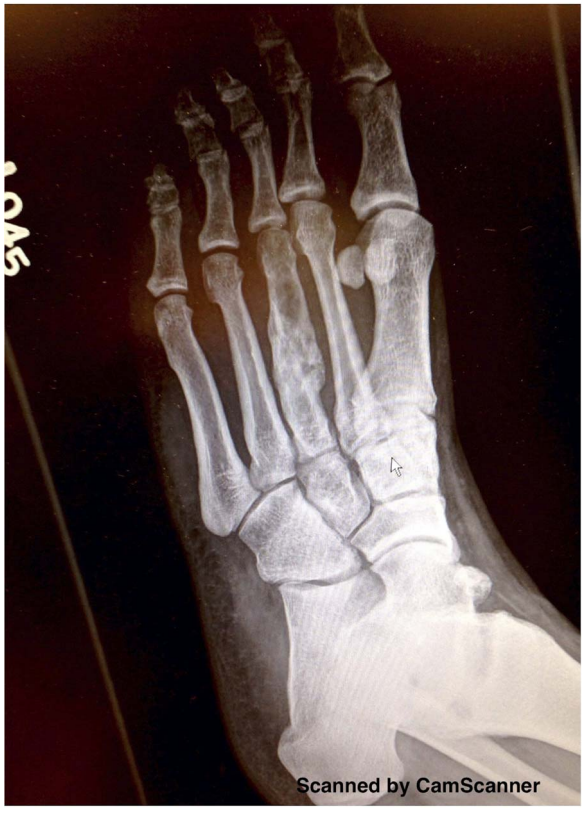

Figure 12 Radiographs of the left foot showing fracture union of the left third metatarsal shaft.

YAP1-TFE3 fusion has been noted in EHE, and these types show a higher degree of vasoformation and solid tumour growth, presence of TFE3 immunostaining and absence of the more typical t(1:3) translocation.[9]

Pathology

Gross appearance: these tumours usually consist of soft red nodular masses. The lesions can also be tan, solid and associated with bony fragments, which may obscure the vascular nature of the lesions.[4]

Histology

The histological hallmarks of EHE include nests and cords of spindle-shaped eosinophilic endothelial cells referred to as 'epithelioid or histiocytoid', and intracytoplasmic vacuoles (blister cells), myxoid/myxohyaline stroma and a low mitotic count.[4] A third of EHE show features suggesting malignant potential such as marked nuclear atypia, high mitotic activity (>1/hpf), spindle cells and necrosis.[1] Electron microscopy shows neoplastic cells situated on a distinct basal lamina and possessing surface-oriented pinocytic vesicles with occasional Weibel-Palade bodies. They differ from normal endothelium by the presence of numerous vimentin filaments.

Treatment

In our experience, multidisciplinary involvement with tumour board discussions involving oncosurgeons, medical oncologists, pathologists, case nurses and radiation oncologists, has resulted in patients achieving the best outcomes.

Role of surgery

The mainstay of treatment is complete surgical resection of the tumour with the aim to achieve negative margins. A wide local excision is recommended even for a low-grade tumour, since these can also act aggressively and have the ability to metastasise. Additionally, if the biopsy specimen is not representative of the entire tumour, the patient may be undertreated.[10]

Luzzati *et al*[11] proposed that wide local excision with negative margins is probably associated with a more favourable long term disease control and survival as compared to surgeries with positive margins or lesions treated with chemotherapy and radiation alone.

Role of radiofrequency ablation

Rosenthal *et al*[12] report that using radiofrequency ablation (RFA) as an adjunctive procedure can limit the requirement for surgery where wide resection would result in significant functional or cosmetic deficits. Davis *et al*[7] have reported on their successful use of RFA for multicentric bony epithelioid sarcomas, including haemangioendotheliomas, yielding a disease free survival (DFS) of 2 years at the time of publication.

Role of radiation and chemotherapy

Adjuvant chemotherapy and radiation have been used in combination when surgical margins are positive or when surgery is not an option due to multicentric involvement or locally advanced disease.[13]

Radiation

A definitive radiation dose for bony EHE has not been well studied. Intensity modulated radiation therapy (IMRT) has been used to avoid radiation exposure to normal surrounding tissues.[14] Drazin *et al*[13] used an adjuvant dose of 33 fractions of a total dose of 5940 cGy for a mastoid EHE with 8-year disease free survival. Yim *et al*[15] used a dose of 55 Gy in 32 fractions over 43 days to achieve remission for an unresectable cervical EHE. In their case report, EHE was reported to be sensitive to a radiation dose of 30–40 Gy. Gherman *et al*[16] used an adjuvant radiation dose of 60 Gy in 23 fractions for an EHE of the radius status postresection with negative margins. Angelini *et al*,[17] in their case series of 62 bony EHE, reported that, given the risk of radiation-induced sarcomas, radiation therapy should be utilised only in situations where wide surgery with negative margins cannot be obtained or when lesions are difficult to access surgically due to their location.

Chemotherapy

Kleer *et al*[5] reported, in his series of 40 cases from the Mayo Clinic, that the efficacy of adjuvant chemotherapy cannot be proven as too few patient have received this treatment modality. Chemotherapy has been used adjuvantly to treat tumours involving multiple bones or parenchymal organs.[5]

Carboplatin and paclitaxel in combination with bevacizumab for its vascular endothelial growth factor (VEGF) targeting properties have shown some success in bony EHE.[18] Another regimen used in multifocal tumours is six cycles of epirubicin and ifofosfamide, plus two cycles of etoposide.[17] A combination of doxorubicin and isosfamide has proved to be active in advanced soft tissue sarcomas as well and has been widely used.[18]

Thalidomide and, less frequently, lenalidomide, have been tried due to their antiangiogenic properties. Interferon α with its antiangiogenic properties has also shown activity in EHE.[19]

Because EHE expresses VEGF receptors, sorafenib, a small molecule BRAF and VEGF receptor inhibitor, is a logical candidate for the treatment of EHE. Chevreau *et al*[20] studied 15 patients, who were not candidates for curative surgery and radiotherapy, who received sorafenib. The 9-month progression-free rate was 30.7% (4 of 13 patients). No complete responses were observed.

Bally O *et al* have reported on a patient with liver and lung EHE whose disease responded to pazopanib with an 8-year progression free survival (PFS), which is unheard of in other sarcoma subtypes where the median PFS is about 4.5 months with this medication. This patient had progressed on prior therapies, including doxorubicin and brostacilline. Pazopanib is the only VEGF inhibitor approved for sarcomas. The 5-year survival rate after conventional chemotherapy is less than 30% in sarcomas.[21]

Role of biphosphonates

Pamidronate monotherapy has been used in an elderly patient with a unicentric low grade osteolytic EHE with complete response, which was sustained for 6 years.[22]

Prognosis

The prognosis in EHE of the bone depends on the extent of disease. Overall survival is 89–97% for localised disease and 50–74% for multifocal disease.[5] Microscopic findings that suggest a poor prognosis include marked nuclear atypia, high mitotic activity (>1/hpf), spindle cells and necrosis.[1]

Patient's perspective

When I was diagnosed with epithelioid haemangioma (EHE), I did not know what to expect. I know that the cancer can come back anytime so that is why I feel scared. Now the pain in my foot is very tolerable and that makes me feel safe. I feel safe in your hands as doctors. I thought chemotherapy was harsh on me. I was on very strong medications, which 5 days after still made me sick with nausea, vomiting, anxiety and hair loss. However, that was totally worth it because I am alive. I am very glad it was caught early; and the fact that you are telling PEOPLE ABOUT this CONDITION IS great.

Learning points

- Epithelioid haemangioendothelioma of the bone is a rare vascular tumour arising from the endothelial lining; it can be locally aggressive and have a tendency towards multicentricity.
- The prognosis will depend on the extent of disease and can be favourable, even with metastatic disease, with timely diagnosis and treatment involving a multidisciplinary team of surgeons, and medical and radiation oncologists.
- Wide local excision with negative margins has the highest chances of yielding a cure. Positive margins, unresectable or multicentric disease benefits from adjuvant radiation and chemotherapy.
- A treatment plan based on tumour board discussions improves final outcomes for the patient.

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Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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