Epithelioid haemangioendothelioma of bone

Katherine Humphris
Amy Charter
Kate Marks
William Merchant

Abstract

Epithelioid haemangioendothelioma (EHE) of bone often presents as a multifocal tumour with an affinity for cortical bone. Therefore, pathological fractures are common at presentation. They can be confused initially for metastatic carcinoma, given their potential to express cytokeratins. However, the diagnosis can now be clarified with to the discovery of a unique translocation that is found in the majority of EHE tumours.

Keywords bone tumour; vascular tumour

Case report

A male patient in his eighties presented with progressive unilateral thigh pain radiating to the knee, of a few months' duration. He had no past medical history of note. Initial cross-sectional imaging of the thigh showed multiple lytic lesions of the femoral shaft (Figure 1). Before further investigations could be performed he suffered a pathological fracture of his femur. Further imaging revealed multiple lesions throughout the right femur, tibia and foot (Figure 2).

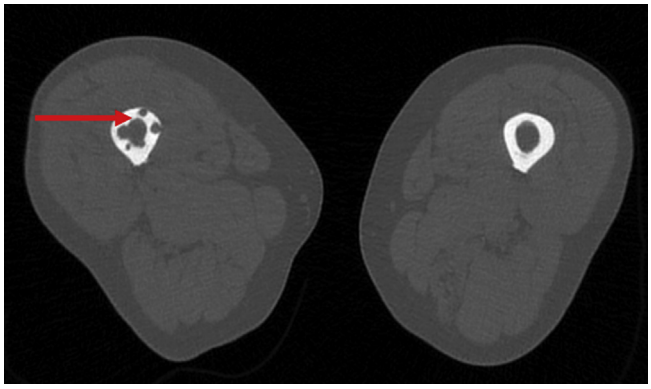

Figure 1 CT scan of right and left thighs showing decreased density lesions (red arrow) within the cortex of the right femur.

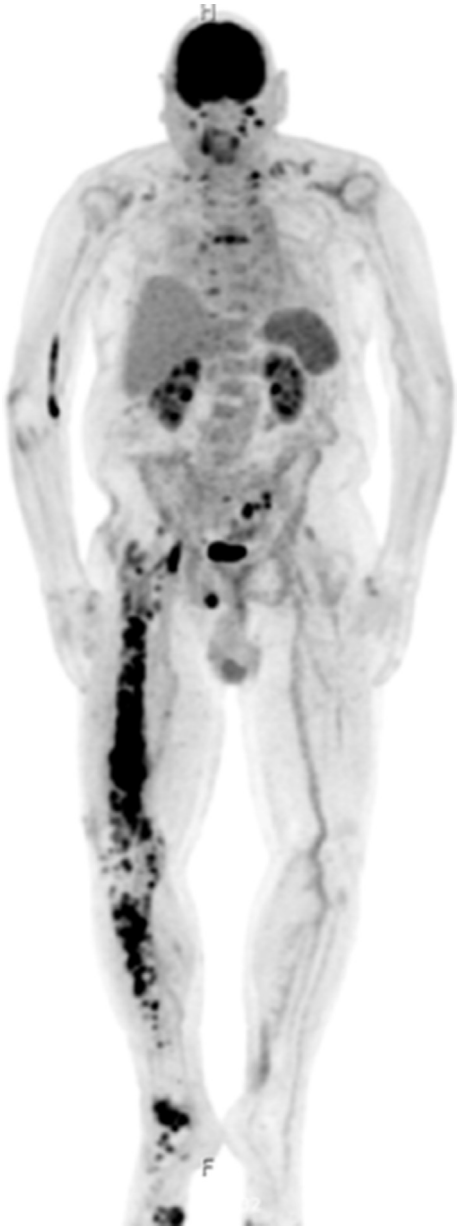

Figure 2 PET CT showing multiple lesions within right femur, tibia and foot.

Katherine Humphris *MA(Cantab) MB Bchir Histopathology Registrar, Department of Histopathology, St James's University Hospital, Leeds, UK. Conflicts of interest: none declared.*

Amy Charter *BSc MBBS Histopathology Registrar, Department of Histopathology, Bradford Royal Infirmary, UK. Conflicts of interest: none declared.*

Kate Marks *MBChB PhD Histopathology Clinical Research Fellow, Pathology and Data Analytics, University of Leeds, UK. Conflicts of interest: none declared.*

William Merchant *MBChB FRCPath Consultant Histopathologist, St James's University Hospital, Leeds, UK. Conflicts of interest: none declared.*

This Short Case is brought to you in association with the Pathological Society of Great Britain and Ireland. Each month we feature a Short Case written by a member of the Trainees' Subcommittee of the Pathological Society of Great Britain and Ireland. The Short Case includes a series of Test Yourself Questions at the end to check your understanding of the case. We hope you enjoy reading it.

Pathological Society
Understanding Disease — Guiding Therapy

© 2020 Published by Elsevier Ltd.

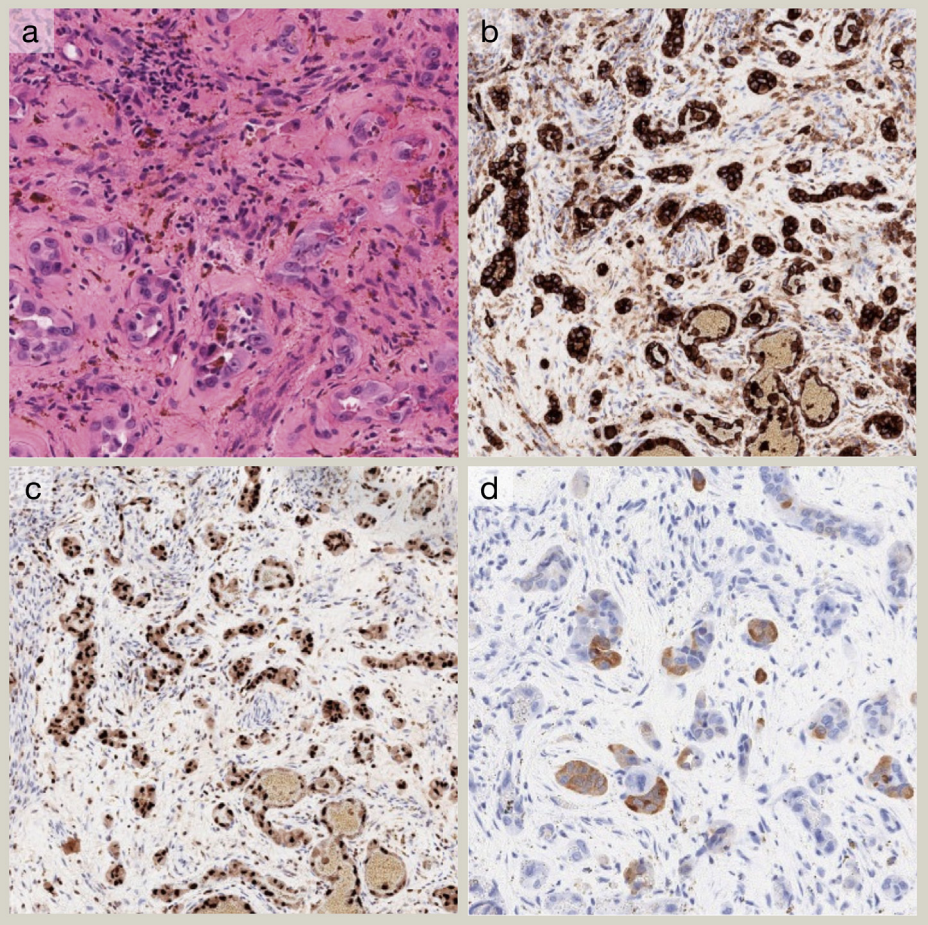

Figure 3 (**a**) H&E of tumour composed of nests and chords of cells with abundant eosinophilic cytoplasm and central rounded nuclei with a variable degree of nuclear atypia. (**b**) to (**d**) Immunohistochemistry: (**b**) CD31 staining; (**c**) CD34 staining; (**d**) Patchy positivity with CK7.

There were two specimens of bone reamings submitted to pathology. The first was very small and showed mainly new bone formation with small clusters of cohesive atypical cells which stained positively for AE1/3 and showed patchy CK7 staining. It was initially reported to be sufficient for a diagnosis of metastatic carcinoma, but the amount of tissue was insufficient for further assessment.

Microscopic examination of the second specimen revealed cords and islands of epithelioid cells within a fibromyxoid stroma (Figure 3a). The lesional cells had abundant eosinophilic cytoplasm and contained relatively uniform nuclei with open, vesicular chromatin and inconspicuous nucleoli. Variable vessel formation was noted. No solid architecture or necrosis was identified.

The cells stained strongly and diffusely for CD31 and showed patchy positivity for CD34 (Figure 3b and c). Weak positivity for AE1/AE3 and focal positivity for CK7 were seen (Figure 3d). Immunohistochemistry for CK20, PSA, TTF-1, CDX-2 and CK5/6 were negative. Given the clinical presentation and histological appearances, a diagnosis of epithelioid haemangioendothelioma with malignant features was made. Unfortunately, the patient's health then declined rapidly and they were treated palliatively.

Discussion

Epithelioid haemangioendothelioma (EHE) is a tumour which can arise in many different tissue types, with a prognosis which is hard to predict and variable across different clinical contexts. Any site or organ can be affected but the typical locations for EHE are the soft tissues, lung, liver and bone. Bone lesions are more likely to be multifocal at presentation.[1] Within the bone EHE has a particular affinity for cortical bone so pathological fractures are common and a source of morbidity[2] as unfortunately our patient knows all too well.

The tumour cell is an epithelioid endothelial cell with abundant eosinophilic cytoplasm and occasional cytoplasmic vacuoles. Erythrocytes may be seen within these vacuoles. The cells are arranged in nests or cords surrounded by a myxohyaline stroma.

Immunohistochemistry can be used to demonstrate the endothelial origins of the tumour cells - positivity with CD31, CD34, ERG, D2-40 and FLI1 is expected though can be variable.[1] Cytokeratins may be expressed, such as the focal CK7 positivity seen in this case. This can be a potential pitfall for an incorrect diagnosis of metastatic carcinoma, particularly as these tumours often present as multifocal disease.

As is the case in an increasing number of tumours, difficult diagnosis of EHE can now be aided with genetics. A unique translocation has been identified in the majority of EHE cases: t(1;3)(p36;q23-q25) resulting in *WWTR1-CAMTA1* gene fusion.[3] A small subset of cases has alternatively been found to have

 © 2020 Published by Elsevier Ltd.

YAP1-TFE3 gene fusion4. Both WWTR1 and YAP1 have a role in the Hippo cell signalling pathway.[4]

EHE is described as having intermediate features between a haemangioma and an angiosarcoma and has previously been described as a tumour with metastatic potential. In the recently published WHO blue book on soft tissue and bone tumours, EHE is described as a malignant vascular neoplasm.[1] Predicting the behaviour of this tumour is, however, still a challenge. Anatomic site is important, with tumours arising in lung or bone having a poorer prognosis.[1] Histopathology also plays a role, with increased mitotic activity and tumour size both thought to indicate poorer prognosis. However, severe cytological atypia, spindled morphology or the presence of necrosis have not been shown to be prognostic.[1] A multicentre cohort of 42 EHE patients found those with symptoms at diagnosis, tumour size >3cm and Ki67 index 10% had a poorer outcome.[5] Ki67 index was, however, unknown for 24 of the 42 patients and further research is required.

Our clinical colleagues have a challenging job selecting treatments for patients with EHE given the paucity of data on optimal treatment protocols. Management strategies reported in the literature include surgery, active surveillance, cytotoxic drugs, immunomodulatory drugs such as thalidomide, tyrosine kinase inhibitors and mTOR inhibitors.[2]

Conclusion

Diagnosis of EHE is challenging as it is a rare tumour with a range of clinical presentations and can easily be confused with metastatic carcinoma. As histopathologists our main role is providing the diagnosis which, thanks to the identification of a pathognomonic translocation, may be aided by molecular pathology if required. We can also provide information which may help clinicians with the tricky job of predicting prognosis and planning treatment. ◆

Practice points

- Epithelioid haemangioendothelioma can present with multifocal disease mimicking metastatic carcinoma
- Epithelioid haemangioendothelioma often affects cortical bone and therefore may present with pathological fracture
- This tumour is a malignant vascular neoplasm considered as having intermediate features between a haemangioma and an angiosarcoma
- These tumours can show variable positivity for cytokeratins which is a potential pitfall

Self-assessment multiple choice questions

1 Which translocation is found in most EHE tumours

A. EWSR1-NFATC1
B. *EWS-FLI1*
C. *WWTR1-CAMTA1*
D. *EWSR1-PBX3*
E. *NUP160-SLC43A3*

Answer C

2 Which of the following immunohistochemical stains is most often positive in EHE tumours?

A. CD31
B. AE1/3
C. CK7
D. Desmin
E. EMA

Answer A

3 Which of the following features is associated with poorer prognosis in EHE?

A. Necrosis
B. CAMTA1 expression
C. Cytological atypia
D. Tumour location
E. Spindled morphology

Answer D

REFERENCES

1 Soft Tissue and Bone Tumours. WHO classification of tumours, 5th Edition, vol. 3. WHO Classification of Tumours Editorial Board. ISBN-13: 978-92-832-4502-5.
2 Rosenberg A, Agulnik M. Epithelioid hemangioendothelioma: update on diagnosis and treatment. *Curr Treat Opt Oncol* 2018; **19**(4)**:** 19.
3 Errani C, Zhang L, Sung YS, et al. A novel WWTR1-CAMTA1 gene fusion is a consistent abnormality in epithelioid hemangioendothelioma of different anatomic sites. *Genes Chromosomes Cancer* 2011; **50:** 644–53.
4 Antonescu CR, Le Loarer F, Mosquera JM, et al. Novel YAP1-TFE3 fusion defines a distinct subset of epithelioid hemangioendothelioma. *Genes Chromosomes Cancer* 2013; **52:** 775–84.
5 Shiba S, Imaoka H, Shioji K, et al. Clinical characteristics of Japanese patients with epithelioid hemangioendothelioma: a multicenter retrospective study. *BMC Canc* 2018; **18:** 993.

© 2020 Published by Elsevier Ltd.