Primary epithelioid hemangioendothelioma of the Spine: A first in Africa. A case report and literature review

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Introduction

Epithelioid hemangioendothelioma (EHE) is a rare vascular tumour that originates from vascular endothelial or pre-endothelial cells. Its demographic characteristics are unclear and there is no racial and sex predilection·[8]The overall incidence of EHE is 0.230 per 1000000 person-years.[8] EHE in general affects patients in the age range 16-74 years but EHE of the bone is more prevalent in the third and fourth decade of life.[2,3,5]EHE can develop in any part of the body but is reported to more frequently in the liver (34%), lungs (21%), bone (19%) and other sites (26%). [1.,2] It was first described and named in 1982 by Weiz and Enzinger and is classified in the 2020 WHO classification of bone tumours as a low-to-intermediate grade neoplasm.[2.,3] Malignant vascular bone tumours are rare and constitute less than 1% of primary bone tumours.[3] Bone involvement usually involves the lower extremity (62%), upper extremities (14%) and vertebra (10%)[3.] As such primary EHE of the spine is very uncommon, with the thoracic spine most likely to be involved followed by cervical, lumbar, and sacral levels in order of decreasing frequency[3.]

Here we report on a 26-year-old female with thoracic T2 and T3 lesions in keeping with primary EHE of the spine, her clinical presentation, work up including laboratory, immunohistopathological and imaging studies. We also conclude on her management and current condition. There are currently no prior clinical case reports on primary EHE of the spine in South Africa or Africa as a whole.

Statement of Ethics

Informed consent and assent were obtained from the patient to proceed with writing and publishing this report. Every effort has been made to exclude information that may identify her.

Case Presentation

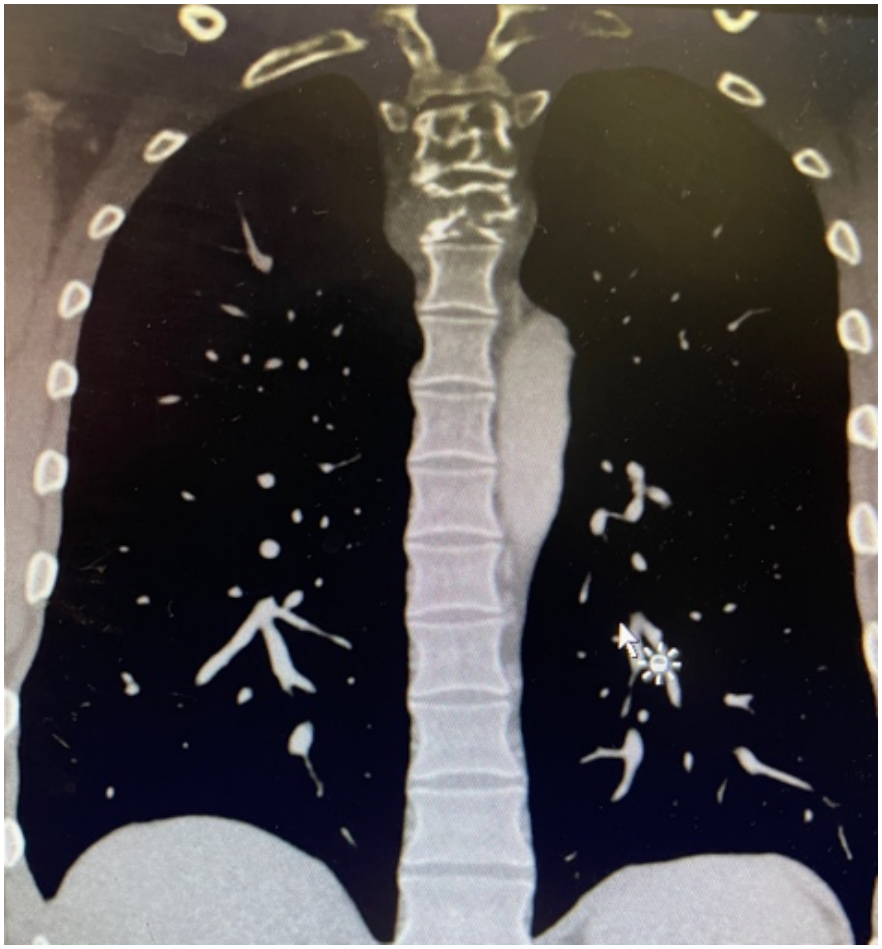
History

A 26-year-old female, born as twin A of a set of twins, presented from a peripheral hospital with a 2-month history of progressive lower limb weakness. She had initially mobilised with crutches with gradual deterioration and at time of review was wheelchair bound with associated bladder and bowel incontinence. She had no known medical comorbidities, no prior history of trauma or fever.

Examination

On general exam, patient noted to have a thyroid nodule and hirsutism. She was well oriented with intact cranial nerves and normal upper limb function. She however had features of thoracic myelopathy with increased lower limb reflexes, clonus, hypertonia, Babinski sign and paraparesis (worse on right side). There was a T4 sensory level and diminished anal sphincter tone and peri-anal sensation. No obvious tenderness or steps on her back and nor features of sepsis or inflammation.

Initial imaging: Computed Tomography (CT) Scan



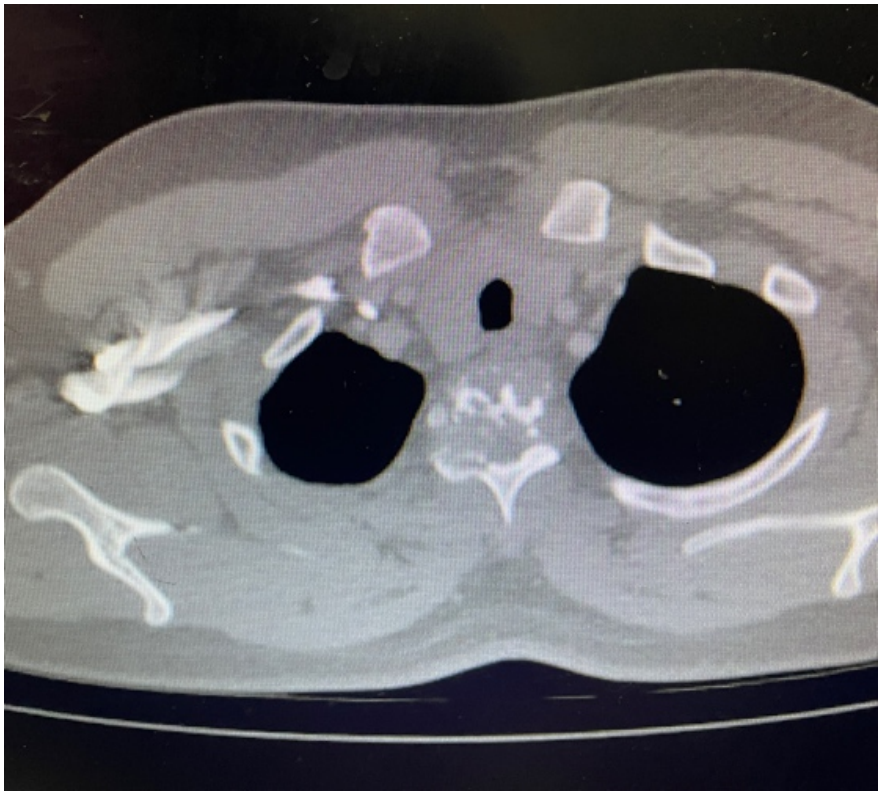
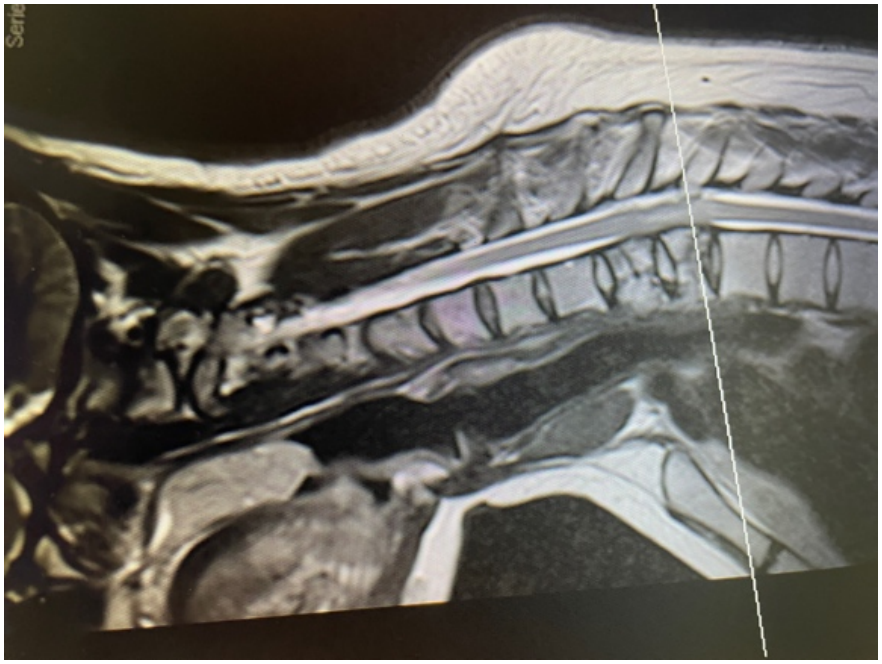


Figure 1. A. B

Coronal(A) and axial (B) CT images showing expansile osteolysis and collapse of T3 and T4 vertebral bodies with residual bony trabeculae, sclerotic rim and segmental kyphosis.

NB Surveillance CT scans of the chest (including neck), abdomen and pelvis did not show any primary. A solitary thyroid nodule was noted. On thyroids ultrasound: TIRADS classification of 5.

Magnetic Resonance Imaging (MRI) findings



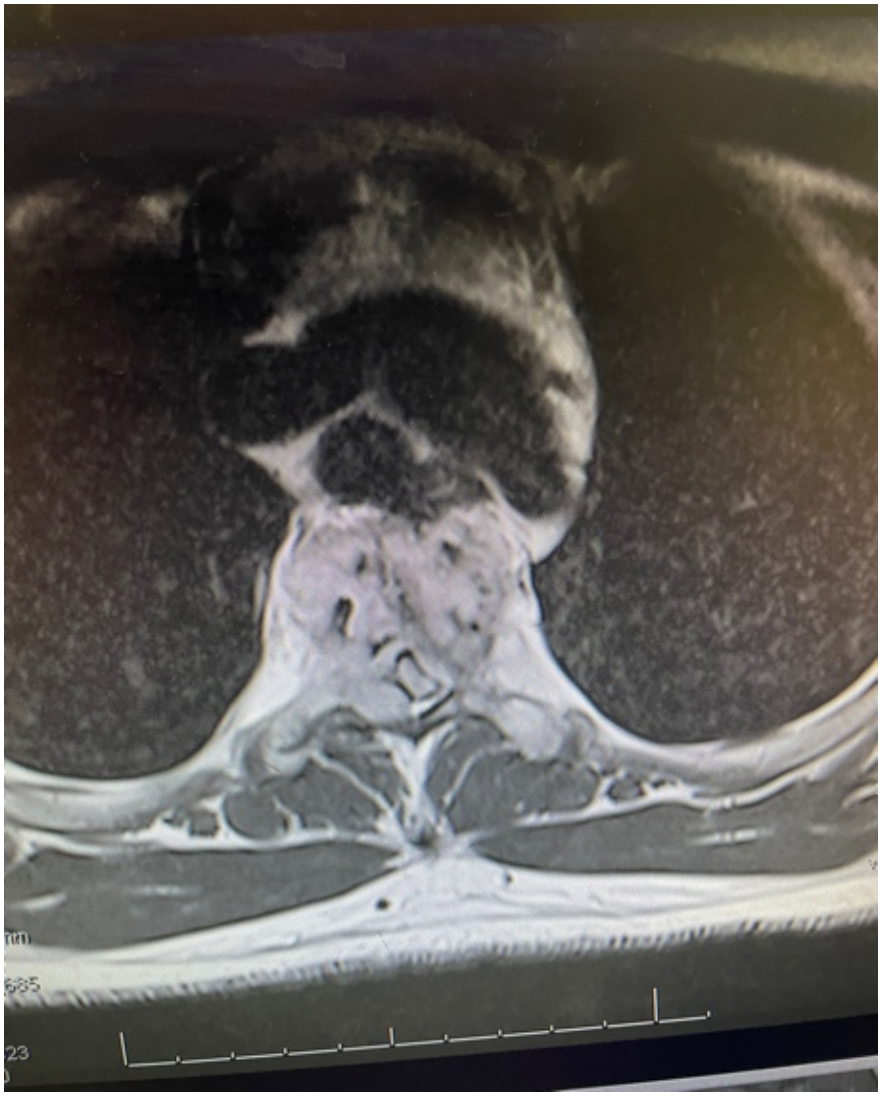


Figure 2: A B

Sagittal(A) and axial (B) views T2 and T3 vertebral body collapse with involvement of posterior elements and high-grade cord compression. Lesions are T1 isointense to grey matter and slightly T2 hyperintense and enhance with gadolinium contrast.

Laboratory work up:

- CEA (Carcinoembryonic antigen) negative, Anti-nuclear antibodies (CTD) negative, HIV negative
- Normal: Thyroid hormones (TSH/T4/T3), Parathyroid hormone, CA-125, CA 19-9, Full blood count, urea and electrolytes, Erythrocyte sedimentation rate, glycated haemoglobin, liver enzymes, and lactate dehydrogenase.
- Urine electrophoresis: normal urine creatinine, protein < 0.04g/L, Bence-jones protein 0

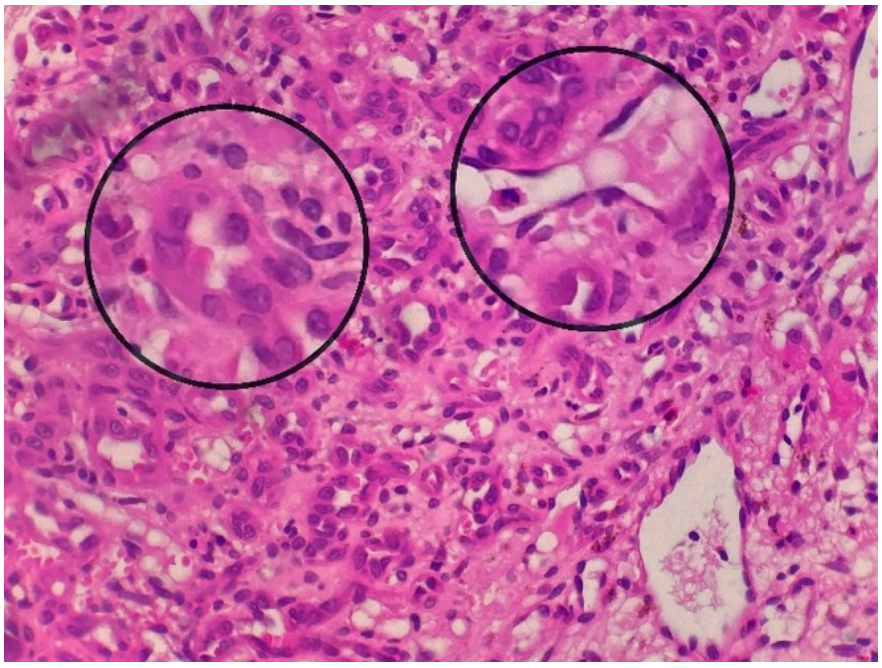
Clinical Course – Treatment and Outcome

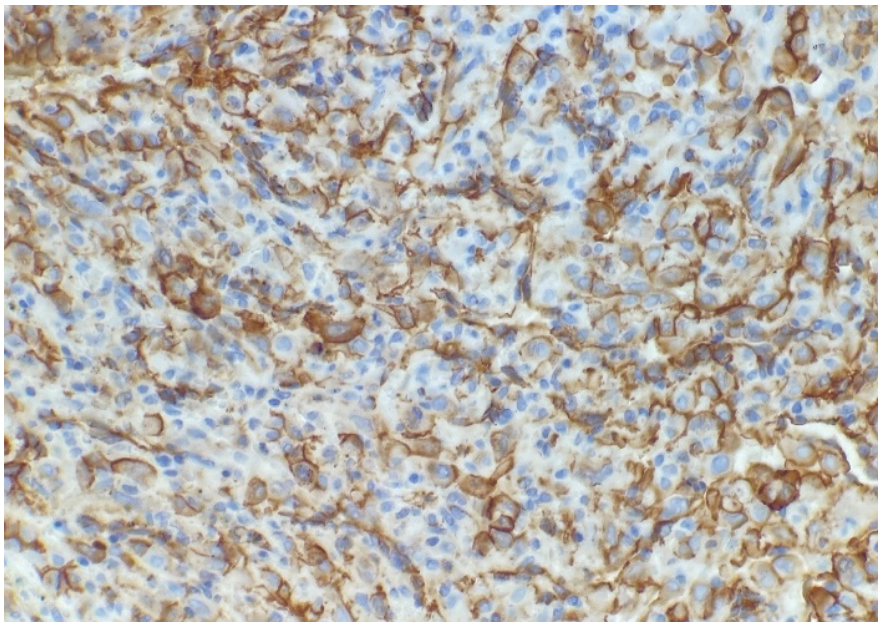
Patient initially taken for CT guided biopsy of the thoracic lesion as well as fine needle biopsy of the thyroid nodule.

Ultrasound guided thyroid nodule FNA:

Atypical epithelial cells with microfollicular arrangement. These cells also show nuclear inclusions, nuclear irregularity, and nuclear grooves. These features are in keeping with papillary thyroid carcinoma.

CT guided biopsy of thoracic lesion for immunohistopathology :





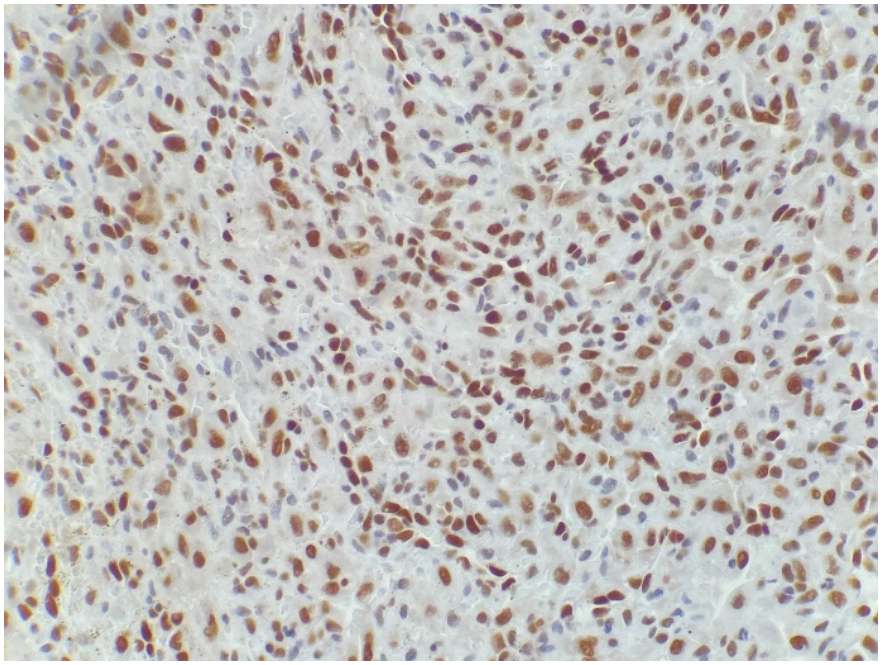


FIGURE 3: A , H&E image of EHE with plump neoplastic atypical vascular endothelial cells (inset 1, arrow) compared to admixed normal benign flattened and spindle endothelial cells (inset 2, star).**B.** CD31 immunostain highlighting membranes of neoplastic cells. C, FLI-1 immunostain highlighting large irregular nuclei of neoplastic cells. A horseradish peroxidase-diaminobenzidine (HRPO-DAB) detection system was used. Original magnification of A-C (400x).

A wide panel of antibodies was employed to further characterise this lesion. CD34, CD31 and FLI-1 immunopositivity confirmed vascular endothelial origin. Metastatic carcinoma was ruled out by negative staining for AE1/AE3 and Cam5.2 (cytokeratins). In light of thyroid nodule, additional TTF-1 and PAX8 stains were employed to rule out metastatic PTC; these were both negative. They are crucial for thyroid organogenesis and differentiation and are thus invariably positive in the presence of thyroid metastasis[9]. Less likely entities such as epithelioid sarcoma and haemangioblastoma were excluded by negative immunostaining results for INI-1 and inhibin, respectively.

As the lesion showed well-formed vessels as opposed to the more classic blister cells and myxohyaline stroma, a TFE3 antibody was employed to assess for the presence of a YAP1-TFE3 gene fusion which is characteristic in this subset of EHE. The TFE3 results were, unfortunately negative.

There is no locally available FISH platform to assess the presence of the WWTR1-CAMTA1 gene fusion nor is there a locally available fusion specific antibody.

Overall the architectural, cytomorphological atypia and immunohistochemical features are that of an atypical vascular lesion. The features are more atypical than that haemangioma but fall short of the significant atypia of angiosarcoma. Therefore a consensus diagnosis of EHE was reached.

Surgical plan:

Patient was taken for T2 and T3 separation surgery with C7 to T6 posterior instrumented fusion. Intraoperatively a highly vascular reddish-brown tumour that was encountered. Post operative MRI showed adequate tumour debulking. The histopathology examination was identical to that following the CT guided biopsy and in keeping with an Epithelioid hemangioendothelioma.

On follow up review, patient is recovering well and ambulating independently. She was discussed at a multi-disciplinary meeting with pathology, radiology, radiation-oncology and neurosurgery and a collective decision to offer radiation therapy was decided upon. She has done the pre-radiation planning and will receive a total of 54Gy in 30 fractions over 6 weeks.

She is due to follow up with the endocrine surgical service for the thyroid papillary carcinoma at their outpatient service and is planned for elective thyroid lobectomy.

Discussion

EHE is a rare low grade malignant neoplasm with potential for metastasis. Only 20% of the cases present with metastasis[1.,5.] It originates from vascular endothelial or pre-endothelial cells. Although it can develop anywhere in the body it most reported in the liver, lungs and bone. Primary EHE of the bone is rare constituting only 1% of all malignant tumours of the bone[1,2,5.], as such primary involvement of the spine in EHE is very rare [5.] Spinal EHE has a non-specific clinical presentation, usually with pain (mostly radicular or mechanical in nature) or neurological deficits attributable to compression of the spinal cord and/or nerve roots. There is a paucity of literature on EHE in Africa with only a few case reports on pulmonary, hepatic and pleural EHE and none for primary EHE of the Spine[6,7.] It occurs equally in both males and females with no racial predilection[1.]Weissferdt et al describes better overall survival for unicentric tumour as compared to multifocal disease (89% and 50% respectively) and a mortality rate of 20%. The median survival is at 1.3 years and 5-year survival of 33% after disease progression[5.]

Although EHE of the spine has no pathognomic features that are specific enough to be used as the sole means of diagnosis, most if not all cases show an expansile osteolysis with bony trabeculae and lack a sclerotic margin. There is usually vertebral body collapse with segmental kyphotic deformity[1,2,3,4,5.] On MRI the lesions are usually isointense to grey mater on T1 weighted imaging, slightly hyperintense on T2 weighted imaging with increased uptake of contrast on contrasted sequences[1.] Chen P et al., suggests that^{18}F-FDG PET/CT scan may be of some use in difficult cases (especially those with multifocal disease) with hypermetabolism, but this is not pathognomic and as such cannot be used in solitude to confirm diagnosis of EHE or its dissemination[2.]

Macroscopically the tumour a reddish-brown mass with tendency to bleed. The diagnosis of EHE rests mostly on the histopathological analysis. Microscopically the tumour cells appear as round, polygonal or fusiform with a central nucleus and intracytoplasmic vacuolations but with the absence of increased mitotic activity or necrosis[2,3,4,5,8.] Immunohistochemically EHE stains positive for CD31, CD34, EGR, Factor VIII related antigen and FLI-1[2,3,4,5,8.] Cytogenetic analysis can be used to show chromosomal translocation involving chromosomes 1 [t(1;3) and 3 (p36.3;q25) that results in WWTRI-CAMTAI fusion. This is present in approximately 90% of the cases with EHE[2,3.] A subset of patients with EHE may show YAP-1 TFE 3 fusion[10.]

The mainstay of treatment for patients with EHE of the spine seems to be multimodal with surgery, total resection where feasible, as the centrepiece.[2,3,5] Pre-operative embolization to reduce the vascularity of the tumour and radiation and chemotherapy are also described. Given the rarity of EHE, especially EHE of the spine, there currently exists no universally accepted treatment guidelines with clearly defined outcomes.

Conclusion

Our case is the first ever described case of spinal EHE in Africa. Our patient shows the previously described features in EHE of the spine. The clinical presentation, radiological features, microscopic and immunohisto-chemical features are congruent with those of the other cases of spinal EHE described from elsewhere. EHE remains a rare entity and EHE of the spine ultra-rare. The treatment modalities though not standardised, show that multimodality treatment with surgery and adjuvant radiotherapy remain the most plausible.

Author contributions

Bakang Kgaodi: Conceptualization, data curation, formal analysis, investigation, methodology, project administration, writing and editing of manuscript.

Jed Lazarus: Conceptualization, formal analysis, review and editing.

Brendon Price: Formal analysis, methodology, writing and review.

Stefan Kruger: Investigation, methodology, project administration, reviewing of manuscript.

Crispin Thompson: Conception and supervision of case write up process.

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