Progressive kaposiform hemangioendothelioma and sirolimus-related severe thrombocytopenia

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Abstract

Kaposiform hemangioendothelioma is a locally invasive tumor and we were unable to find any previous reports of multifocal progression. Sirolimus, a mammalian target of rapamycin inhibitor, has been widely used to treat kaposiform hemangioendothelioma. Herein, we report a case of multifocal progressive kaposiform hemangioendothelioma, wherein sirolimus treatment caused severe thrombocytopenia. A 12-year-old East Asian girl presented with indurated dark-purple masses on her back. The patient had received three surgical interventions following the first appearance of the masses in 2012 and subsequent reappearances in 2014 and 2016. Kaposiform hemangioendothelioma was diagnosed based on radiological and pathological findings. Two more masses appeared in the following year. The patient was treated with oral sirolimus (2.5 mg/m^2/day) and developed grade 3 thrombocytopenia 8 days later. The patient was uneventfully relieved 5 days later after the withdrawal of sirolimus and the administration of appropriate medications. This rare case indicated that kaposiform hemangioendothelioma could be progressive with local metastatic characteristics in children. Besides, the severe sirolimus-induced complication highlights the importance of serum drug level monitoring during treatment. Physicians should be extremely cautious while treating kaposiform hemangioendothelioma patients with sirolimus.

Key words: Kaposiform hemangioendothelioma, sirolimus, thrombocytopenia

Introduction

Kaposiform hemangioendothelioma is a rare vascular tumor with intermediate-grade malignancy. Kaposiform hemangioendothelioma typically appears as a firm reddish-purple mass with ill-defined boundaries. This entity develops from cutaneous or subcutaneous tissues and is often likely to be locally infiltrative. We were unable to find any previous reports of distant metastasis of kaposiform hemangioendothelioma. Sirolimus, a mammalian target of rapamycin inhibitor, became the first-line drug of choice for treating kaposiform hemangioendothelioma owing to its strong efficacy.[1] However, when used as anticancer agents, mTOR inhibitors are associated with severe complications, including hyperlipidemia, nephrotic syndrome, stomatitis, anemia, microcytosis, hypertension and impaired wound healing.[2]

Herein, we report a locally multifocal progressive kaposiform hemangioendothelioma wherein sirolimus treatment caused severe thrombocytopenia.

Case Report

A 12-year-old East Asian girl first presented to our center in 2017 with indurated dark-purple masses on the upper vertebral, left deltoid and infrascapular regions of her back [Figures 1a and b]. She complained of localized itching but no pain or tenderness. The masses first appeared as purple nodules along the midline of the upper region of the back in 2012 and slowly grew with hypertrichosis. She had undergone three surgical resections at a local hospital in April 2012, June 2013 and May 2014 with recurrence following every surgery. In 2016, an isolated dark-purple mass appeared with large confluent areas of indolent erythema on her left infrascapular region [Figures 1a and b, solid black arrow] and another on the left deltoid region 2 months later [Figures 1a and b, hollow black arrow]. Fifteen months later, she presented with substantially enlarged masses and a newly grown mass on the left suprascapular (Figure 1 c-d, solid white arrows) and left lateral pectoral region of her back (Figure 1 c-d, hollow

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white arrows). On her first admission, she underwent a radiological examination to evaluate the depth and size of the tumor. Enhanced T1-weighted magnetic resonance imaging revealed a diffuse hyperintense lesion with ill-defined margins and reticular stranding on the skin and subcutaneous plane [Figures 2a and b]. Computed tomography showed lesions involving the T6–T11 vertebral bodies [Figure 2c]. Previous histopathological slides were independently reviewed by two experienced pathologists who confirmed the diagnosis of kaposiform hemangioendothelioma. On low magnification, they identified a tumor with a lobular and focally infiltrative growth pattern, infiltrating deep into the hypodermis and subcutaneous fat layer. The tumor also contained endothelial cells with a low degree of cytologic atypia intermixed with bland spindle-shaped endothelial cells, some pericytes and attenuated vessels with slit-like openings. Lymphatic-specific staining (D2-40 and Prox-1) showed neoplastic endothelial spindle cells and lymphatic channels adjacent to vascular lobules of the lesion [Figures 3e and f]. To assess the recurrence course and exclude the possibility of malignant transformation, we biopsied the lesion on her left infrascapular region [Figure 4]. Fluoroscopically-guided percutaneous core biopsy of the T6 vertebral body was also performed to exclude other diseases [Figures 2d solid white arrow], and the pathological results confirmed the diagnosis [Figure 5]. Based on radiological [Figures 2a and c] and histopathological analyses [Figures 3–5], we confirmed the diagnosis of kaposiform hemangioendothelioma with progressive lesions. There was no evidence of thrombocytopenia or coagulation disorders based on her previous blood examination reports.

Given the multiple instances of postsurgical recurrences and associated aggressive progression, we recommended sirolimus to control her tumor progression. However, her guardians refused the medication at first. Fifteen months later, considering the progress of her lesions, she was counselled and accepted to receive sirolimus at 2.5 mg/

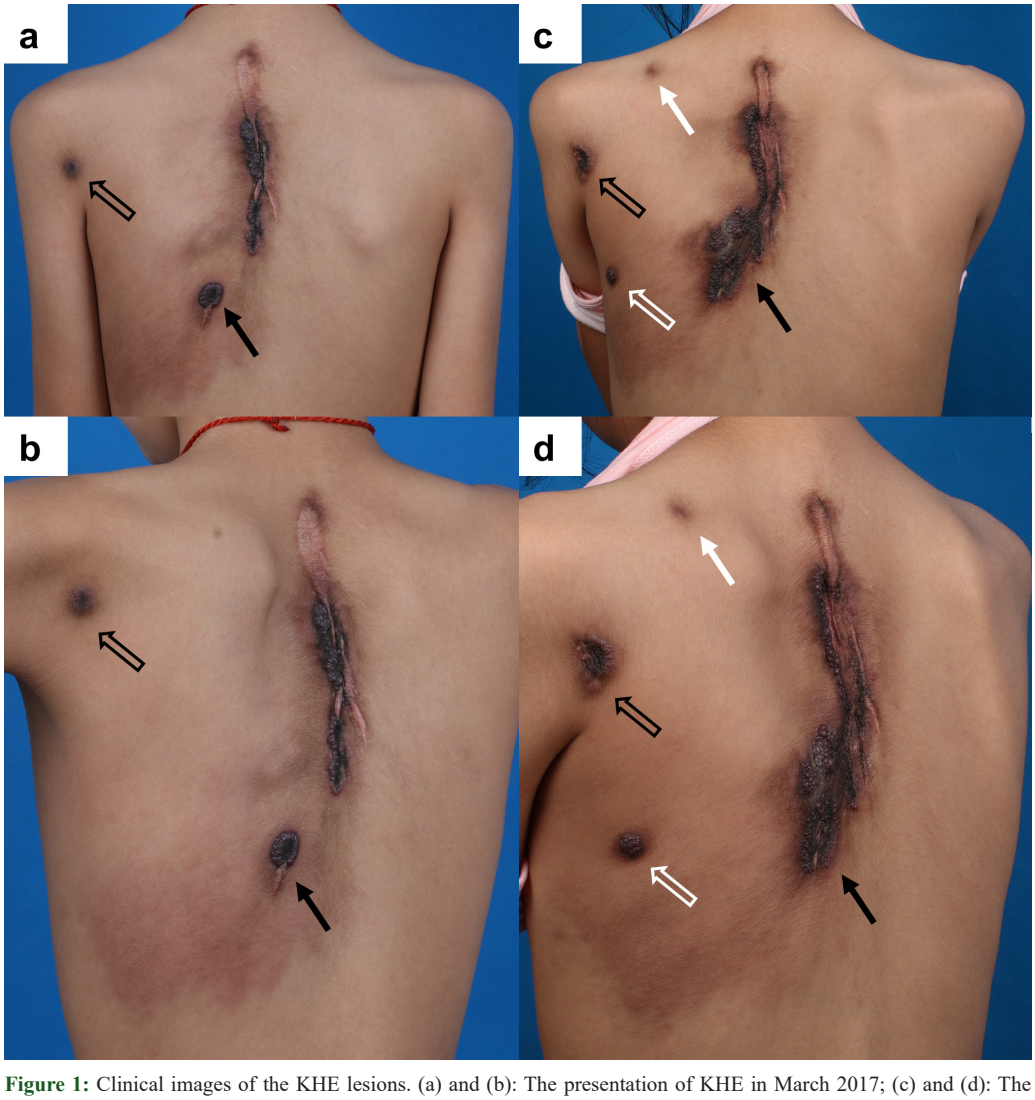

Figure 1: Clinical images of the KHE lesions. (a) and (b): The presentation of KHE in March 2017; (c) and (d): The presentation of KHE in August 2018. The black arrows indicate new masses that appeared in 2016, and the solid arrow indicates the KHE mass for biopsy in 2017 at our centre. The white arrows indicate the new lesions that appeared in 2018

m^2/day with no adjunct medication. Eight days after the onset of treatment, ecchymosis appeared on multiple areas of her body. Her platelet count dropped to 8,000/μL. Oral sirolimus was immediately discontinued and intravenous corticosteroids and immunoglobulins were administered to resolve internal bleeding. Infections, leucopenia and hepatic or coagulation function disorders were ruled out based on blood test results and clinical examinations. After 5 days of treatment, her platelet count recovered to 18,700/μL. She was free of thrombocytopenia and was discharged. There were no signs of progression and the lesions on her back were stable with no new masses identified atone-year follow-up.

Discussion

According to previous reports, kaposiform hemangioendothelioma shows intermediate-grade malignancy and locally aggressive characteristics but is usually free of distant metastasis.[3] Several case reports have described multifocal kaposiform hemangioendotheliomas; however, all of these cases involved the retroperitoneum and multiple visceral organs.[4,5] It is also necessary to differentiate the present diagnosis from kaposiform lymphangiomatosis, a complex lymphatic anomaly exhibiting features of both lymphatic malformation and neoplasia.[6] However, all kaposiform lymphangiomatosis cases involved multiple organs with

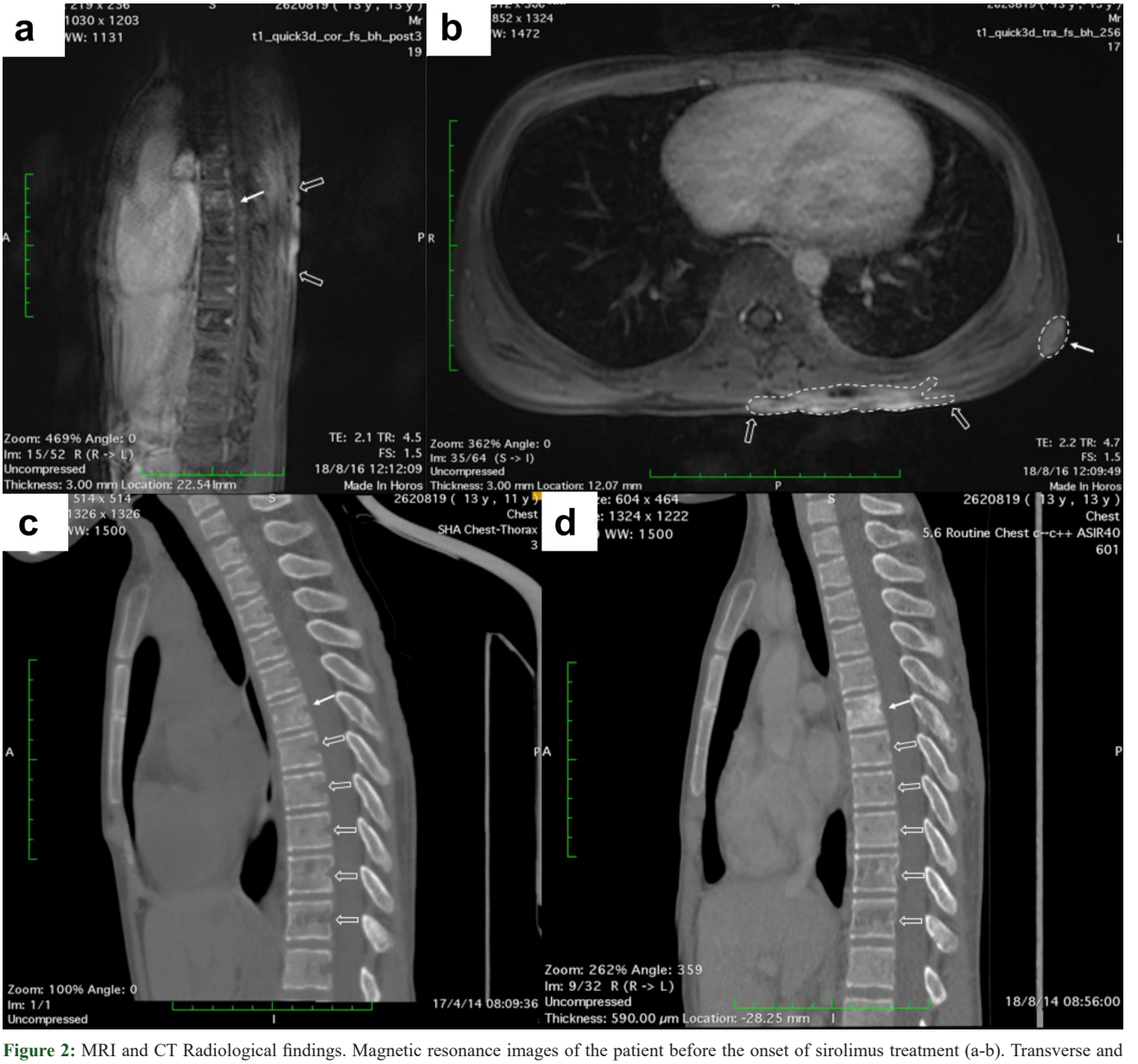

Figure 2: MRI and CT Radiological findings. Magnetic resonance images of the patient before the onset of sirolimus treatment (a-b). Transverse and coronal views of T1-weighted MRI with enhancement and fat-suppression sequence showed irregular margins and strong inhomogeneous enhancement of the mass on the midline of the upper back. Another isolated homogeneous mass with weak enhancement was also noticed in her left infrascapular region. The region of the lesions is highlighted by white arrows (a) and the dotted box (b). Coronal views of spinal CT in 2017 (c) and 2018 (d). CT scans in the sagittal plane of the patient's thoracic spine from T1 to T12 show mixed lytic and sclerotic changes of T6 to T11 vertebral bodies. The solid white arrows indicate T6, where the puncture biopsy was obtained

a predilection for the thoracic cavity, thereby causing pleural effusion that commonly led to respiratory distress and dyspnoea which were absent in our case.[7] In thiscase, radiological examinations showed that the midline kaposiform hemangioendothelioma lesions affected multiple vertebral bodies but with no infiltration into other surrounding tissues. These findings are beyond our understanding that kaposiform hemangioendothelioma is locally infiltrative and is prone to grow into surrounding tissues.[8] One possible explanation is that cutaneous lesion might metastasize to the spine via the blood, similar to the metastatic features of multifocal myeloma, hematological cancers or other metastatic lesions.[9] However, histopathological results indicated only mild cytological atypia and inconspicuous mitotic activity without the evidence of malignancy. Therefore, we could rule out malignant vascular tumors such as angiosarcoma or epithelioid hemangioendothelioma. Moreover, the absence of human herpesvirus 8 in the lesion further eliminated the possibility of Kaposi's sarcoma.

Thrombocytopenia in patients with kaposiform hemangioendothelioma (known as Kasabach-Merritt phenomenon) is more common in patients under 1 year of age; infections and vaccinations can also trigger thrombocytopenia. Kasabach-Merritt phenomenon is also often accompanied by a coagulation disorder, including elevated D-dimer and low fibrinogen levels. Recent studies have shown that sirolimus is effective and safe in treating kaposiform hemangioendothelioma patients.[1] When mTOR inhibitors were used as single therapies for treating other tumors, the incidence of drug-related high-grade thrombocytopenia was approximately 1.9%,[10] and thrombocytopenia was the most common dose-limiting toxicity when mTOR inhibitors were used for

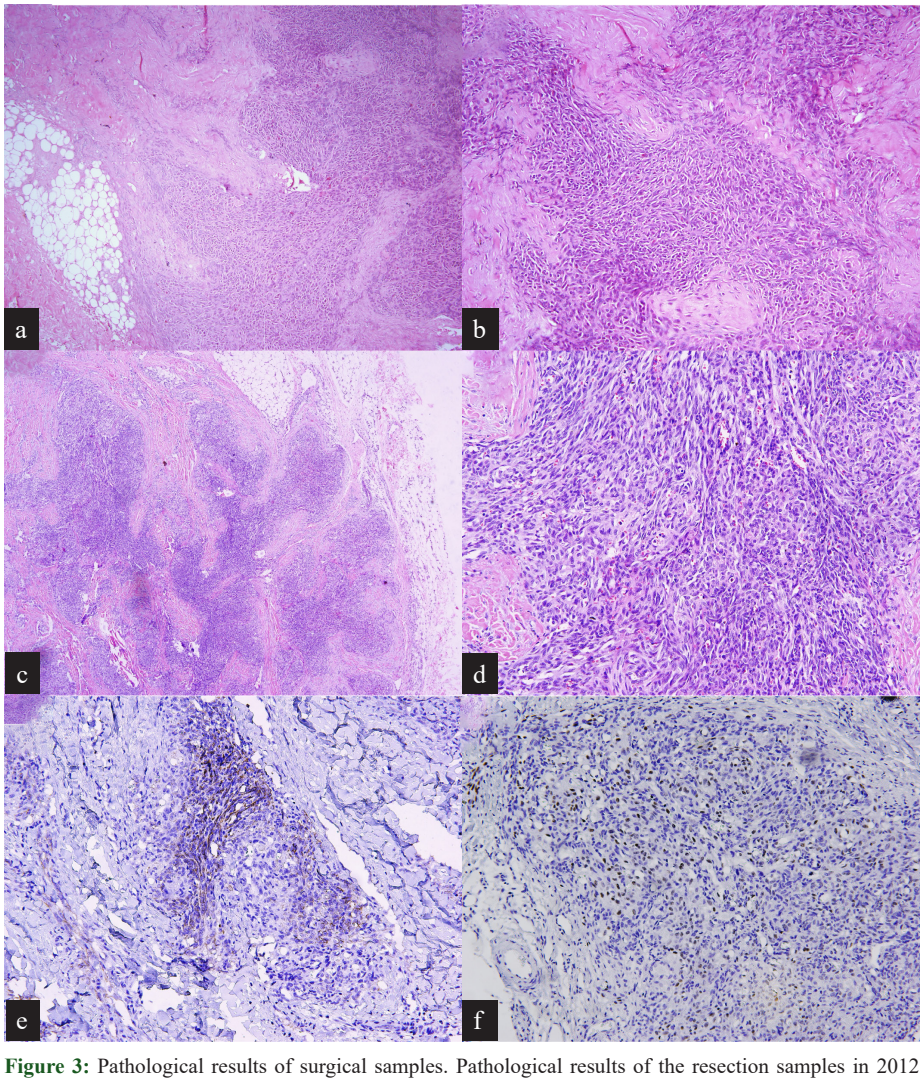

Figure 3: Pathological results of surgical samples. Pathological results of the resection samples in 2012 (a-b) and 2014 (c-f). Low-power view showing a tumour with lobular and focally infiltrative growth pattern, with infiltration deep into the hypodermis and subcutaneous fat layer (a, c, haematoxylin-eosin [HE], ×100). Tumour containing endothelial cells with a low degree of cytologic atypia, intermixed with bland spindle-shaped endothelial cells, some pericytes, and attenuated vessels with slit-like openings (b, d, HE, ×200). D2-40 (e, ×200) and Prox-1 (f, ×200) staining showing neoplastic spindle endothelial cells and lymphatic channels adjacent to vascular lobules of KHE

treating cancer or other medical conditions.[10] In this case, according to our treatment protocol, the patient's platelet and white blood cell counts were checked every week. To control the sirolimus target trough level between 10 and 15 ng/mL, the patient was asked to undergo monthly blood tests. However, she developed thrombocytopenia after 8 days of sirolimus treatment which was earlier than the onset dates in other cases.[10] Additionally, compared to previous reports, the dosage used in this patient was relatively low (2.5 mg/m^2/day); thus, the subsequent incidence of thrombocytopenia should be theoretically lower. We presumed that the observed severe thrombocytopenia might have occurred due to polymorphic variants of hepatic enzymes CYP3A4 and CYP3A5 which could cause an abnormal metabolic status, leading to the accumulation of sirolimus in the system and subsequent drug-related thrombocytopenia within a short time (around 7–10 days).[11] Thus, we hoped to restart low-dose sirolimus (0.1 mg/m^2/day) and continue monitoring her sirolimus trough levels weekly for dose adjustments but the guardians of the patient refused to restart sirolimus treatment because of their concerns regarding its severe side effects. Furthermore, topical sirolimus is effective for microcystic lymphatic malformation with minimal systemic absorption; therefore, topical sirolimus could be a choice for this patient to control the progression of her superficial lesion.[12]

To conclude, this case shows that kaposiform hemangioendothelioma can have multifocal progressive behavior in children. Severe sirolimus-induced thrombocytopenia highlights the importance of serum drug level monitoring during treatment. In addition, we recommend the screening of kaposiform hemangioendothelioma patients for liver enzyme variants

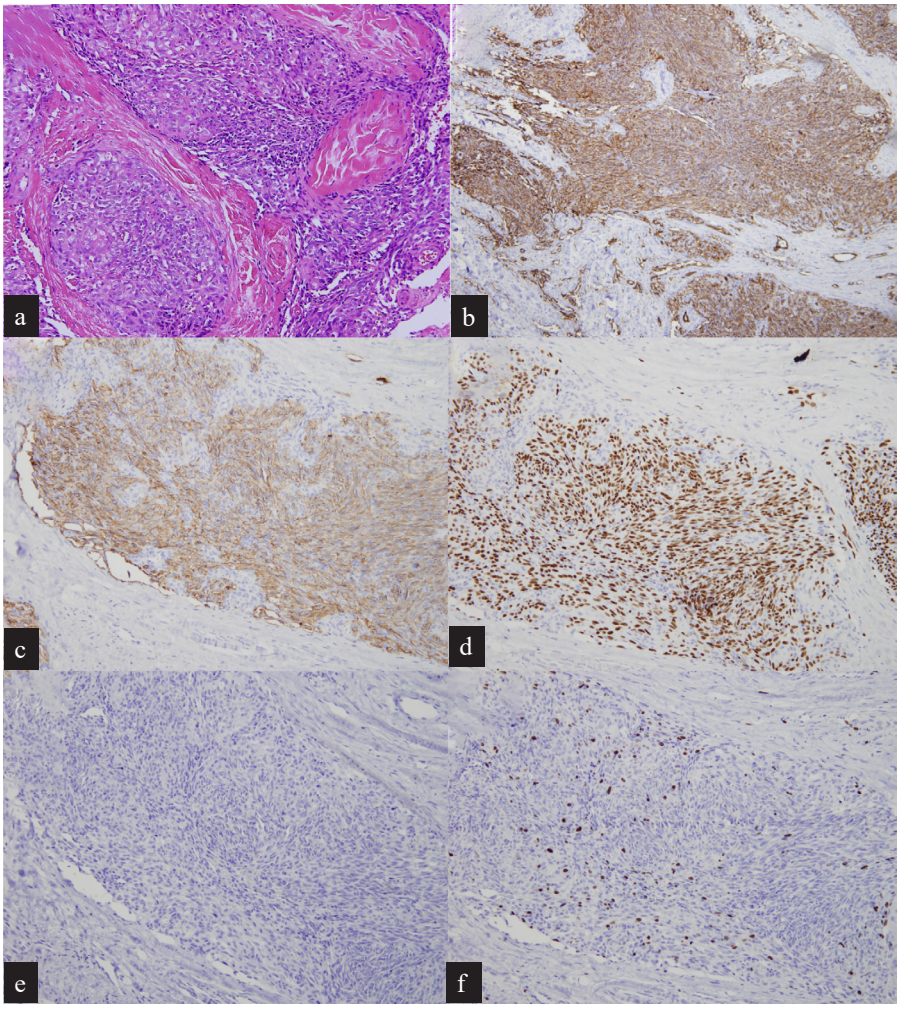

Figure 4: Histopathological results of the incisional biopsy from her back. High-magnification view showing foci exhibiting a glomeruloid pattern with central epithelioid tumour cells surrounded by spindle tumour cells with small central slit-like vessels. Cytological atypia was mild with inconspicuous mitotic activity (a, HE, ×200). Epithelioid and spindle tumour cells were strongly positive for CD31 (b, ×100). Most 0neoplastic cells and the surrounding dilated lymphatic vessels were positive for D2-40 (c, ×200) and Prox-1 (d, ×200). Absence of human herpesvirus 8 (HHV-8) in the lesion (e, ×200). Approximately 5% of nuclei were positive for Ki-67 (f, ×200)

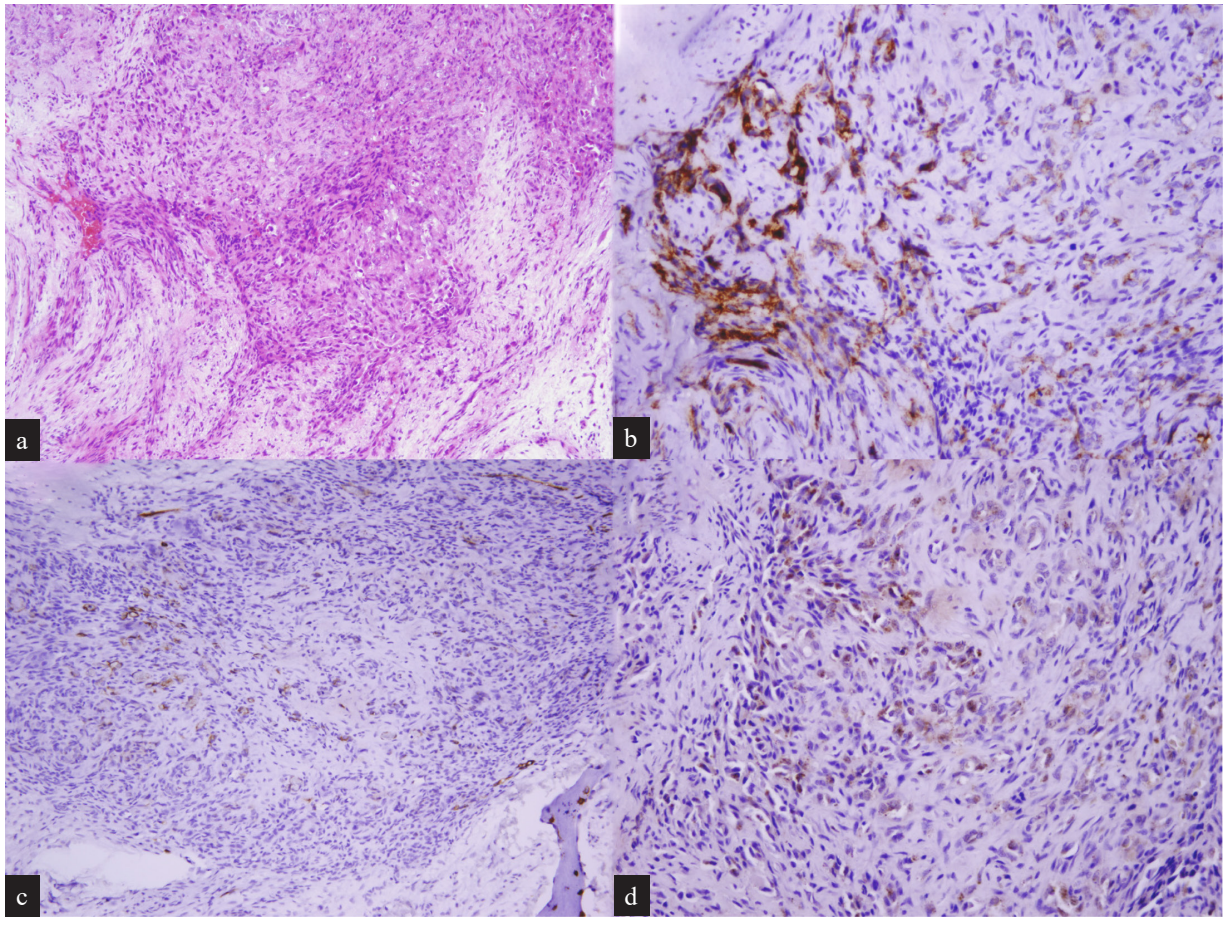

Figure 5: Pathological results of the needle aspiration biopsy obtained from the T6 vertebral body. Pathological examination of the T6 vertebral body biopsy specimen showing irregular infiltrative tumour nodules having a dense hyaline stromal response with minor cytological atypia (a, HE, ×200). Tumour cells showing strongly a positive expression of CD31 (b, ×400). D2-40-stained lymphatic channels in the lesion (c, ×200). Prox-1-stained lymphatic vessels and scattered endothelial cells (d, ×200)

before initiating sirolimus treatment to avoid severe dose-related complications.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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