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Epithelioid Angiosarcoma in a Patient with Klippel-Trénaunay-Weber Syndrome: An Unexpected Response to Therapy

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Key Words
Angiosarcoma · Chemotherapy · Chronic lymphedema · Klippel-Trénaunay-Weber syndrome · Stewart-Treves syndrome

Abstract
We present a rare case of Stewart-Treves syndrome characterized by a diffuse angiosarcoma of the leg in a 22-year-old man with a history of chronic lymphedema due to Klippel-Trénaunay-Weber syndrome. He underwent limb disarticulation and medical treatment with cycles of doxorubicin, oral thalidomide and sunitinib with a very good response after 12 months of follow-up.

Introduction

Angiosarcoma that develops on a limb with chronic lymphedema is called Stewart-Treves syndrome. Usually, this appears as a complication of a long course lymphedema located on the arm, after mastectomy and/or radiotherapy due to breast cancer. Other reported types of chronic lymphedema in the Stewart-Treves syndrome include congenital lymphedema and lymphedema caused by venous thrombosis, trauma, infection (e.g. filariasis) and arteriovenous fistulae. In the latter case, venous hypertension, ulcers, infections, lymphagitis and angiosarcoma may develop. We present one case of this syndrome. It is a rare case, since it included a diffuse angiosarcoma of the leg in a 22-year-old man with a history of lymphedema due to Klippel-Trénaunay-Weber syndrome (KTWS). He underwent limb disarticulation and medical treatment with cycles

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of doxorubicin, oral thalidomide and sunitinib with a very good response after 12 months of follow-up.

Due to the aggressive nature of this syndrome, knowledge and research on its treatment are necessary.

Case Report

A 22-year-old black male from Guinea-Bissau was admitted complaining of progressive enlargement of the right lower limb since he was 14 years old. In the last two years, he had had recurring episodes of bleeding and pain and infected skin ulcers in that limb. There were no family or positive epidemiologic findings. The physical examination showed gigantic hemihypertrophy of his right lower limb, with multiple variegated and grape-like, red or purple, firm subcutaneous nodules in the calf and thigh, pinpoint red macules, some in a circle around the limb and multiple infected skin ulcers with excessive bleeding (**fig. 1**). Laboratory tests revealed ferropenic anemia (Hb 6 g/dl; ferritin 3 ug/l). The search for microfilariae and filarial antibodies in the blood, serologies for HIV, HBV, and HCV, as well as VDRL and TPHA were negative. Serologic screening of HHV8 was positive. A culture of skin biopsy ruled out fungus and mycobacterium infections. A limb CT scan revealed marked thickening of the subcutaneous soft tissue, an increased intermuscular fat layer, lymphedema, extensive varicosities of the superficial and deep veins and massively dilated ileofemoral vessels (**fig. 2**). A chest CT scan and ecochardiogram showed high output cardiopathy with severe pulmonary hyperemia. Upper and lower endoscopy showed multiple vascular ectases of the stomach, descending colon and rectal mucosae. Arteriography revealed multiple pelvic and lower-limb arteriovenous fistulae. The diagnosis of KTWS was made. Because of uncontrolled bleeding of the lower right limb, persistent ulcer infections and excessive pain, he was submitted to limb disarticulation. Surprisingly, the histopathologic examination of a nodule revealed an epithelioid angiosarcoma (**fig. 3**), confirmed in other nodules, also from the contralateral leg. Repeated chest CT scan showed two new nodular lung images suspicious of being metastatic. Before starting treatment, we performed a PET scan that showed evidence of extensive disease with significant pelvic, left leg, upper abdomen and chest involvement (**fig. 4**). Chemotherapy was started with oral thalidomide 200 mg/day, liposomal doxorubicin 30 mg (20 mg/m^2 body surface) every 21 days (5 cycles), and sunitinib 25 mg/day for 4 weeks followed by 2 weeks off treatment (4 cycles) was started. Laser therapy over new patches was given. The nodules have regressed. Physical rehabilitation was made with adaptation to a prosthetic right limb and a great improvement in quality of life. A second PET scan at 4 months' follow-up showed active lesions just on the cicatricial area of the surgery.

Discussion

KTWS is a rare syndrome with about 1,500 cases recorded [1] that manifests itself at birth or during childhood or adolescence. The lower limb is the site of malformations in approximately 95% of the patients [2]. The enlargement of the extremity consists of bone elongation and circumferential soft tissue hypertrophy. Vascular malformations involving the gastrointestinal and genitourinary tracts have been described [3]. Complications include stasis dermatitis, coagulopathy, pulmonary embolism, congestive heart failure and bleeding from abnormal vessels, including the gut, kidney and genitalia. However, the mortality of this syndrome is about 1% [1]. In a majority of patients, treatment is conservative (graded compressive stockings or pneumatic compression devices), but surgical treatment (epiphysiodesis, excision of soft tissue hypertrophy, percutaneous sclerosis or stripping of superficial varicose veins) may be indicated. In this patient, an extreme example of the natural course of KTWS, the only therapeutic option to control bleeding and painful ulcer infections was limb disarticulation.

Soft tissue sarcomas are very rare tumors (1% of adult malignant neoplasias) [4]. Most cases of angiosarcoma are associated with chronic lymphedema (Stewart-Treves syndrome, congenital lymphedema, filariasis) or with radiation exposure. Arteriovenous fistulae result in venous hypertension that may be complicated with lymphedema, ulcers,

infection and lymphangitis. The lymphedematous region becomes an immunologically vulnerable area, predisposed to malignancy, because of the continual angiogenic stimulus [5]. The epithelioid angiosarcoma is a variant composed predominantly of large rounded 'epithelioid' endothelial cells with abundant amphophilic and eosinophilic cytoplasm and large vesicular nuclei [6]. Surgery in combination with radiotherapy is used for initial lesions. The chronic lymphedema-associated angiosarcoma has a very aggressive behaviour, with longer survival after radical amputation of the affected member [7]. Perfusion with tumor necrosis factor (TNF)-alpha and melphalan in the isolated limb has emerged as a new limb-salvage strategy [8]. Chemotherapy is indicated for disseminated tumours (doxorubicin, cyclophosphamide, methotrexate, vincristine) [9]. The prognosis is poor with a high recurrence rate, 84% at 5 years, and a high hematogenous metastasis rate [9]. One half of all patients may be expected to die within the first year after diagnosis with metastatic disease [6].

Our patient already had severe limb complications and disseminated disease. Owing to the rarity of the disease there are no treatment guidelines. We decided to start chemotherapy with doxorubicin (already approved for angiosarcoma) and thalidomide, which had already shown efficacy in four case reports [10–13]. The decision to add sunitinib, a novel tyrosine kinase inhibitor already approved for metastatic renal cell carcinoma and gastrointestinal stromal tumors, was based on its anti-tumor and antiangiogenic activities [14].

Conclusion

Our case illustrates an unexpected presentation of an epithelioid angiosarcoma, good therapeutic response with a 12-month survival and a great improvement in the quality of life. Interestingly, our patient gained 20 kg in 12 months and is actually on good health.

As far as we know, this is the first case of KTWS managed this way and with such good results. We wonder about the relationship between the HHV8 and angiosarcoma [15].

Authors' Contribution

AS, CM, RL, VB, ET and JPA cared for the patient during his hospital admission, researched the topic, wrote/organized the paper and prepared the images. All authors read and reviewed the final manuscript.

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Fig. 1. Photograph of the patient's right lower limb. Gigantic hemihypertrophy of the right lower limb, with multiple variegated and grape-like, red or purple, firm subcutaneous nodules in the calf and thigh, pinpoint red macules, some in a circle around the limb and multiple infected skin ulcers with excessive bleeding.

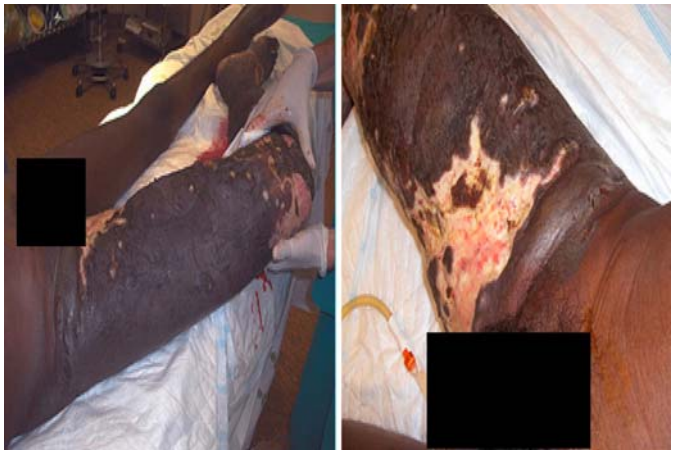

Fig. 2. Limb CT scan. Marked thickening of the subcutaneous soft tissue, increased intermuscular fat layer, lymphedema, extensive varicosities of the superficial and deep veins and massively dilated ileofemoral vessels.

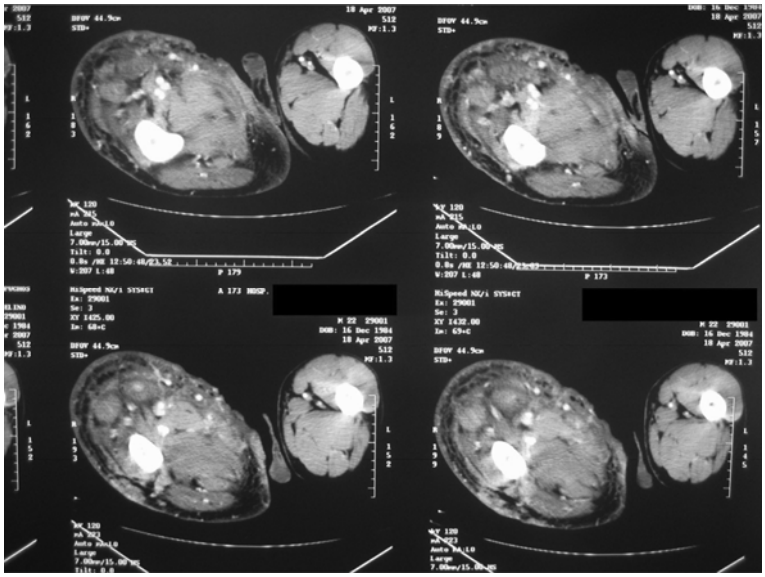

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Fig. 3. Histopathologic examination of a lesion. On the left (HE, 400×): dilated vascular spaces lined by plump, atypical endothelial cells. On the right (Factor VIII, 400×): Immunohistochemical positive stain for Factor VIII.

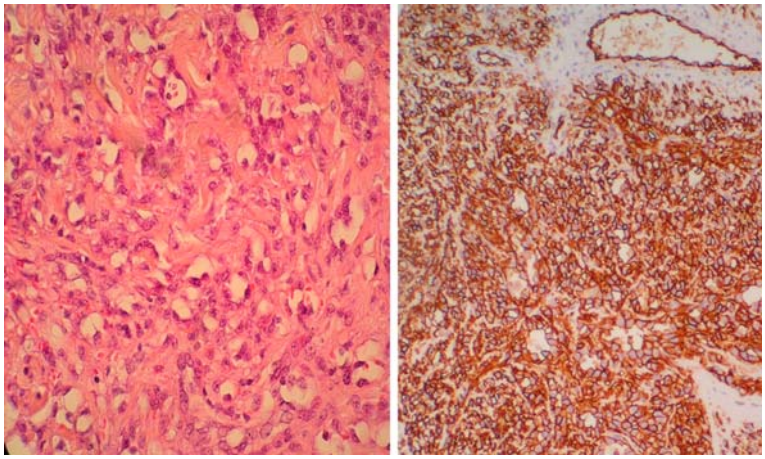
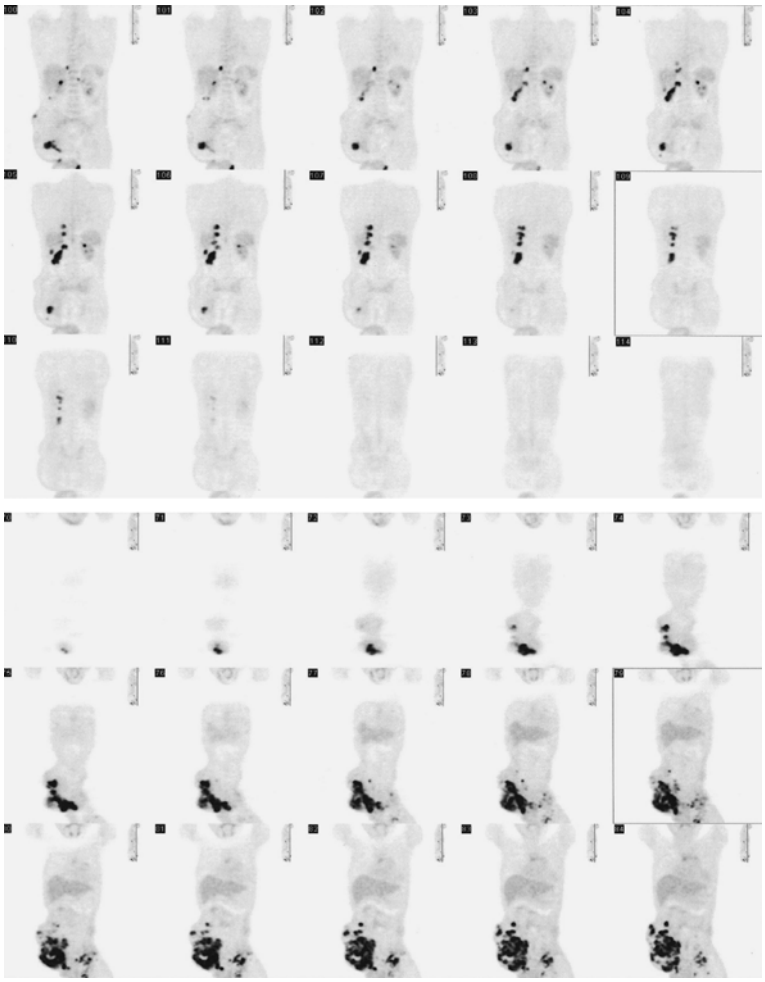


Fig. 4. PET scan. Extensive disease with significant pelvic, left leg, upper abdomen and chest involvement.



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