Kaposi Sarcoma in an HIV-Negative Filipino with Myasthenia Gravis and Anterior Mediastinal Mass*

***Karen B. Mabilin-Prieto MD*[1]**
Rei Joseph P. Prieto MD[2]
Marita B. Dantes MD FPNA[3],
Elizabeth P. Prieto MD FPDS[4]

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[1]Resident, Department of Dermatology, East Avenue Medical Center, Quezon City
[2]Resident, Department of Internal Medicine, National Kidney and Transplant Institute, Quezon City
[3]Consultant, Department of Internal Medicine, National Kidney and Transplant Institute, Quezon City
[4]Consultant, Department of Dermatology, East Avenue Medical Center, Quezon City

ABSTRACT

Kaposi sarcoma (KS) is a rare vascular tumor derived from endothelial cell lineage with four clinical variants: classic, endemic, HIV-associated and immunosuppression-associated Kaposi sarcoma. Immunosuppression-associated Kaposi sarcoma has been reported among organ transplant recipients and those who are receiving immunosuppressive therapy for a variety of medical conditions that include myasthenia gravis.

A 44-year-old HIV-negative Filipino male, diagnosed with myasthenia gravis and an anterior mediastinal mass who was maintained on pyridostigmine and prednisone presented with a two-month history of non-tender, non-pruritic, bluish to violaceous papules, nodules and plaques over both feet. The patient mechanically manipulated the lesion over the right plantar foot, which resulted in right leg swelling that was eventually managed as cellulitis. Skin punch biopsy done over the violaceous plaque on the right medial foot revealed histopathologic findings consistent with Kaposi sarcoma, patch stage. This was confirmed by CD34 immunostaining. A final diagnosis of immunosuppresion-associated Kaposi sarcoma was made. The consensus was to perform excision of the anterior mediastinal mass before initiating treatment of Kaposi sarcoma. The patient expired before the plan could be carried out.

Immunosuppression-associated Kaposi sarcoma responds well to cessation of immunosuppressive therapy however management decisions should be made based on the presentation and coexistent systemic problems of each patient.

Keywords: *Kaposi sarcoma, immunosuppression-associated Kaposi sarcoma, HHV-8, myasthenia gravis, anterior mediastinal mass*

INTRODUCTION

Kaposi sarcoma (KS) is a rare neoplasm of lymphatic endothelial cells frequently evident as multiple vascular cutaneous and mucosal nodules.[1] It has been linked to Kaposi Sarcoma associated herpesvirus also known as human herpesvirus 8 (HHV-8).[2,3]

Before the AIDS epidemic, Kaposi sarcoma was regarded as extremely rare in all areas of world, with exceptionally elevated rates observed in certain population of Mediterranean, middle Eastern, or Eastern European descent, and more notably in sub-Saharan Africa populations.[4]

There are four clinical variants of Kaposi sarcoma, the classic, African-endemic, AIDS-associated and the iatrogenic or immunosuppression-associated type. The classic KS, most often seen in middle-aged and elderly men tends to run an indolent course.[3] AIDS-associated KS is one of the most common neoplasms among homosexual and bisexual men with AIDS and runs a rapidly progressive course.[3] African endemic KS has been implicated in 10% of malignancies in Central Africa.[3] Iatrogenic KS or immunosuppression-associated KS is seen among transplant recipients and in those taking corticosteroids or other immunosuppressants.[3]

Lesions initially develop on the distal lower extremities as unilateral or bilateral bluish red or purplish macules which later progress into firm plaques and nodules. Aside from the skin, it may also arise and may be confined to the oral cavity, genitals, lymph nodes and visceral organs. [2]

CASE REPORT

The patient is a 44-year old Filipino male, single, Roman Catholic, from Tabuk, Kalinga Apayao, Philippines who was referred to our institution due to papules and nodules over the distal upper and lower extremities. The patient was diagnosed with myasthenia gravis in 2012 when he was admitted in another government institution due to progressive dysphagia and dyspnea. He was subsequently managed as myasthenic crisis. Results of work-up included a plain chest CT scan which, revealed a 2.0x1.0 cm ovoid soft tissue density in the anterior superior mediastinum at the level of the aortic arch for which a consideration of thymoma was made. He was discharged with home medications of pyridostigmine and prednisone at 60 mg/day (1 mg/kg/day), with plans for biopsy of the mass once medical condition further improved. Prednisone was gradually tapered to 50 mg/day. However, he failed to follow-up for four months during which time he continued taking prednisone at the same dose.

During these four months, the patient noted a solitary, non-tender, non-pruritic, round, violaceous "hematoma-like" patch over the plantar aspect of the right foot. There were also few violaceous papules over the toes and medial aspect of the right foot. There was no history of trauma or manipulation prior to appearance of the lesions. No consultation was done. No medications were taken or applied. One month prior to consultation, there was noted increase in the size of the lesions. The patient manipulated the lesion on the plantar right foot. A few days later, there was erythema and inflammation with swelling of the right leg. This was accompanied by undocumented febrile episodes and occasional throbbing pain on the right foot. This prompted consultation and subsequent admission at another government hospital where a working impression of cellulitis on top of chronic venous insufficiency and myasthenia gravis, in stable remission was made. Acid-fast bacilli stain and 10% potassium hydroxide examination were negative. Arterio-venous duplex ultrasound of the lower extremities revealed deep venous insufficiency. Skin punch biopsy over the plaque on the medial right foot was done. Repeat chest CT scan showed an anterior superior mediastinal mass measuring 1.8 x 3.8 x 3.6 cm suggestive of thymoma *(figure 1)*. A chest radiograph was done and showed subsegmental atelectasis versus fibrosis of both lower lung fields. The patient was started on ampicillin-sulbactam 750 mg/tab once day, cotrimoxazole 160mg/180mg tablet twice a day, and enonaxaparin 0.4 cc subcutaneously once a day. Prednisone for the myasthenia gravis was gradually tapered off. Patient discharged with stable and improved condition. The histopathology result revealed a vascular tumor. Hence referral to our institution for further evaluation and management was done.

The review of systems was unremarkable. The past medical history was negative for thyroid disease and diabetes. However, he developed steroid-induced Type II diabetes mellitus subsequently. The family medical history was non-contributory. The patient previously worked as a helper in a rice meal and laboratory aide in an organic fertilizer production factory. He is single, non-promiscuous with only one heterosexual partner in the past. He denied a history of sexually transmitted infections or recent sexual contact.

The physical examination including neurological examination was unremarkable except for cutaneous examination which revealed several, ill-defined, irregularly shaped, erythematous to violaceous slightly raised plaques and nodules over the 2nd to 5th proximal toes extending to the dorsum of the feet *(figure 2)*. There were well-defined round violaceous and hyperpigmented plaques topped with crusts and scales over the medial and plantar aspect of the right foot *(figures 3)* and few well-defined, oval-shaped hyperpigmented nodules over the right forearm and left hand *(figure 4)*.

The initial working impression was vascular tumor probably Kaposi sarcoma. The differential diagnoses were acroangiodermatitis of Mali or pseudokaposi sarcoma, bacillary angiomatosis and angiosarcoma *(Table 1)*.

Recent laboratories showed mild anemia. Urinalysis and blood chemistries were normal. HIV Elisa was requested and showed a negative result. Histopathology slide review revealed an increase in the number of blood vessels throughout the dermis, and foci of extravasated erythrocytes. Spindle-shaped cells were disposed around the blood vessels, adnexal structures and interstitial dermis *(figure 5)*. Immunohistochemistry studies showed positive CD31 and CD34 expression in the perivascular spindle shaped cells confirming the diagnosis of Kaposi sarcoma *(figure 6 and 7)*.

Prednisone, which had been tapered down to 25 mg/day was continued as prescribed by the attending neurologist. Proper foot care and leg elevation was advised.

After the diagnosis was established, the patient was presented in a multidisciplinary conference where the consensus was to perform resection of the anterior mediastinal mass once the patient achieved optimal medical condition before initiating treatment of Kaposi sarcoma lesions with localized vinblastine. Prednisone was decreased to 20 mg/day.

Two months later, the patient again failed to follow-up. At this time, new papules and nodules appeared on the back, groin and posterior thigh with further increase in size of the plaques over both feet. Patient was admitted at a government tertiary hospital for resection of the mass.

During his hospital stay, new lesions continued to appear on both feet *(figure 8)*. Laboratory tests revealed persistent thrombocytopenia. The patient was referred to a hematologist. Bone marrow aspiration biopsy was done and findings were consistent with a reactive marrow, possibly immunologic in etiology, for which reason biopsy of the anterior mediastinal mass was deferred. While work-up was being done, he developed generalized body weakness, fever, chest heaviness, and tachypnea, which was diagnosed and managed as pneumonia. On the 17th hospital day, he developed severe respiratory difficulty and his condition rapidly deteriorated. He eventually expired. There was no consent for autopsy.

Final impressions were Kaposi sarcoma, immunosuppression-associated type, myasthenia gravis, with acute respiratory failure probably secondary to pulmonary embolism versus acute myocardial infarction as the cause of death.

DISCUSSION

Kaposi sarcoma (KS) is a lymphoangioproliferative disease often caused by human herpesvirus 8 (HHV-8). Although HHV-8 determination was not done in this patient, the diagnosis of Kaposi sarcoma in this patient was based on the clinical, histopathologic findings and confirmed by CD34 immunostaining. The patient having an anterior mediastinal mass, myasthenia gravis maintained on immunosuppressive therapy, and the HIV-negative status are features consistent with immunosuppression associated Kaposi sarcoma.

The pathogenesis of KS begins with HHV-8 infection. HHV-8 expresses viral oncogenes that, through the action of endothelial growth factors, promote inflammation and angiogenesis.[3,5,6] HHV-8 infection has been an essential factor in the pathogenesis of Kaposi sarcoma. Not all HHV-8 infected individuals develop the disease and co-factors in the development of KS have been postulated.[3]

Significant risk factors in the development of Kaposi sarcoma in this patient are the presence of a possible neoplasm (anterior mediastinal mass probably thymoma), autoimmune disorder (myasthenia gravis) and immunosuppressive therapy (prednisone).

Several studies have been published supporting the relationship of Kaposi sarcoma and corticosteroid therapy.[7,8,9] In the study of Guo et al[3], Kaposi sarcoma tumor cells and have shown that exogenous glucocorticoids stimulate their proliferation. They demonstrated that the glucocorticoid receptors are present at high levels on Kaposi sarcoma lesions and these receptors can be upregulated by exogenous glucocorticoid and inflammatory cytokines.

Likewise, Hudnall et al[8] have reported increased viral replication and activation of lytic cycle of HHV-8 after glucocorticoid administration in infected cells. Thus the effects of glucocorticoids are two-fold, the upregulation of Kaposi cell proliferation and the activation of HHV-8.

A study by Perez et al[10] found that Kaposi sarcoma has been reported in association with a second neoplasm in 37% of cases. The most frequently observed are lymphoproliferative disorders such as thymoma. The imbalance between CD34 and CD8 T lymphocytes has been considered responsible for the immunosuppression in the patients with thymoma. Coexisting Kaposi sarcoma and thymoma have been related to myasthenia gravis.[10]

Mantero et al[11] reported a case of myasthenia gravis developing in an HIV-negative patient with Kaposi sarcoma. The potential correlation between Kaposi sarcoma and myasthenia gravis is through immunological mechanism: Myasthenia gravis as paraneoplastic manifestation of Kaposi sarcoma and the role of antitumoral agent as treatment for both conditions.

The study of Ulbright et al[12] concludes that either a naturally occurring (thymic neoplasia or autoimmune disorder) or iatrogenically induced immunodeficiency (long term corticosteroid therapy) gives a background of a deranged immune status and likely predisposes patients to Kaposi sarcoma. [12]

Evaluation of Kaposi sarcoma should include a complete history and physical examination. Laboratory studies tend to be within normal limits. Occasionally eosinophilia has been noted in African-endemic and homosexual patients whom parasitosis may be common. Serum glucose levels may reflect an increased incidence of diabetes mellitus with classic Kaposi sarcoma.

The diagnosis of Kaposi sarcoma rests on the biopsy findings and identification of HHV-8 infection.[3] However assays for HHV-8 have been challenging and no universally accepted method exists.[13] Hence immune-histochemical stains are more reliable methods for confirming the diagnosis.

Histopathologically, Kaposi sarcoma lesions typically show proliferation of spindle cells and vascular structures in a network of collagen and reticular fibers. The epidermis is usually normal. Identification of endothelial cell markers CD31 and CD34, allow differentiation of Kaposi sarcoma from non-spindle cell vascular proliferations such as acroangiodermatitis.[3] In this patient, CD34 immunostaining is positive.

Unlike other malignancies, Kaposi sarcoma does not lend itself to the conventional TNM classification. Schwartz et al[2] proposed the currently preferred staging in 2008 *(Table 2)*.

Treatment for Kaposi sarcoma depends on the disease stage, the pattern and distribution of the lesions, the KS variant, and the patient's immune status.[3] Management modalities for Kaposi sarcoma include non-intervention, surgical excision, intralesional chemotherapy, laser therapy, cryotherapy, immunotherapy, antiviral drugs or cessation of immunosuppressive therapy.

In patients with only limited disease confined to the skin, local therapies aimed at eliminating

individual lesions are frequently used as initial treatment. Chemotherapy including doxorubicin, bleomycin, vincristine, etoposide, dacarbazine alone or in combination has been given to patients with progressive or widespread classic Kaposi sarcoma especially if internal organs are involved.[2]

Studies in HIV-infected patients and transplantation recipients have shown that immune restoration is the best treatment for Kaposi sarcoma in these patients. For patients with AIDS, highly active anti-retroviral therapy should be initiated to decrease incidence of AIDS-associated Kaposi sarcoma. However, HAART alone is not sufficient to control Kaposi sarcoma that has already advanced. Thus, addition of chemotherapy is required. In immunosuppression-associated Kaposi sarcoma, the goal of treatment is discontinuation or reduction of immunosuppressive therapy.[14] In this patient, the goal of treatment is discontinuation of immunosuppressive therapy. The initial plan is resection of the anterior mediastinal mass, negating the need for the corticosteroids as treatment for myasthenia gravis, thus controlling progression of Kaposi sarcoma. This will be followed by intralesional chemotherapy for the localized lesions.

The best prognosticator is the clinical classification of Kaposi sarcoma. Immunosuppression associated Kaposi sarcoma with regression of lesions after discontinuation of the immunosuppressive therapy gives an excellent prognosis. Cases of Kaposi sarcoma remission have been reported after a decrease in the use of corticosteroid medication. Mortality is most often secondary to other unrelated causes. [2,3]

CONCLUSION

A rare case of immunosuppression-associated Kaposi sarcoma in an HIV-negative Filipino male with myasthenia gravis and anterior mediastinal mass is presented. Immunosuppressive therapy such as corticosteroids may trigger the development of Kaposi sarcoma in patients who possess several other pathogenic factors such as the presence of deranged immune status and presence of human herpesvirus 8. Naturally occurring or iatrogenic immune-deficiency likely predisposes patients to Kaposi sarcoma. Immunosuppression associated Kaposi sarcoma responds well to cessation of immunosuppressive therapy however management decisions should be made astutely based on the presentation and coexistent systemic problems of each patient.

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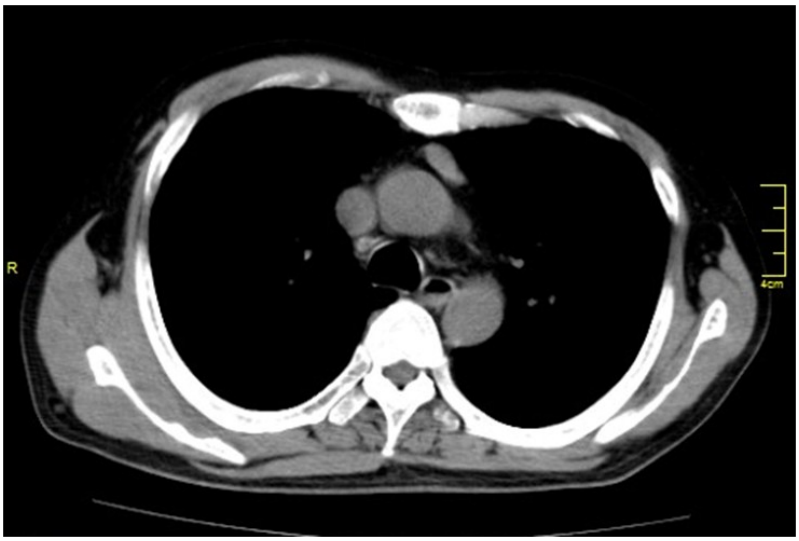

Figure 1. Chest CT scan showing the anterior mediastinal mass

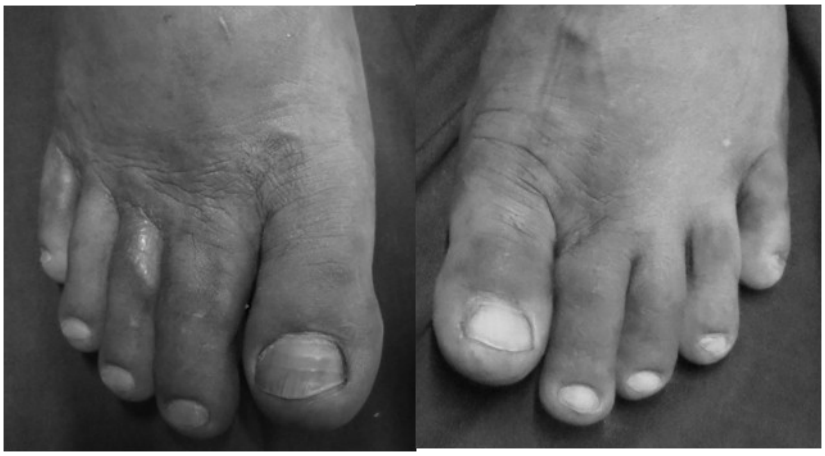

Figure 2. Several, ill-defined, irregularly shaped, erythematous to violaceous papules, slightly raised plaques and nodules over the 2nd to 5th proximal toes extending to the dorsum of the feet.

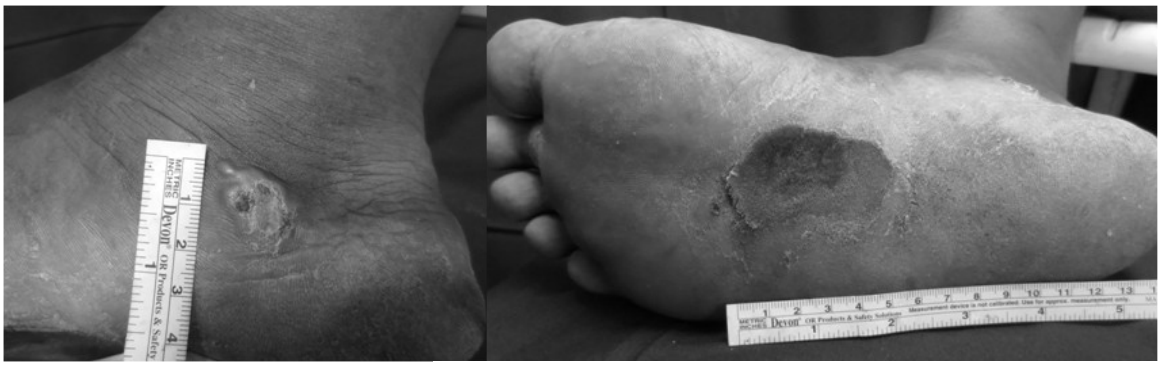

Figure 3. Round to oval, violaceous and hyperpigmented plaques topped with crusts and scales over the (a) medial and (b) plantar aspect of the right foot

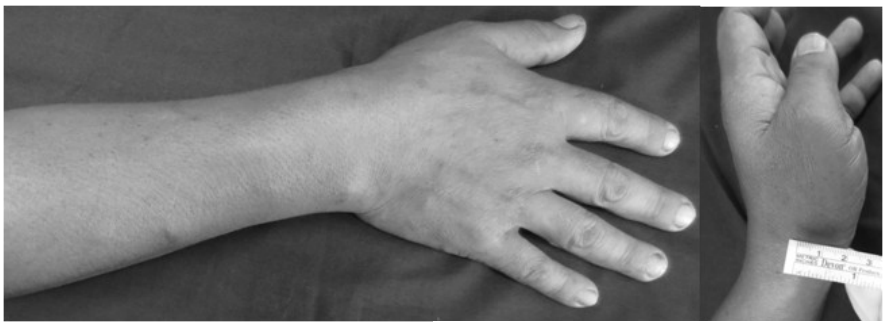

Figure 4. Few well-defined, oval-shaped, violaceous to hyperpigmented nodules over the (a) right forearm and (b) left hand.

Table 1. Differential diagnoses

CRITERIA	INDEX PATIENT	KAPOSI SARCOMA	ACROANGIODER-MATITIS OF MALI (PSEUDO-KAPOSI)	BACILLARY ANGIO-MATOSIS	ANGIOSARCOMA
Age and Gender	44 year old ; Male	Adult ; Male	Elderly ; Male	Any Age ; No gender predilection	>40 years old ; Highest incidence among the elderly
Clinical findings	Red to violaceous or bluish papules, nod-ules and plaque; Initially unilateral	Red-violet to bluish macules or papules that may form large plaques or develop into nodules; Initially unilateral	Brown or violaceous nodules and plaques which become verru-cous or ulcerates; Bilateral	Violaceous papules, nodules and plaques; Pedunculated with collarettte scaling and central umbilication	Single or multifocal bluish or violaceous papules nodules and lichenoid plaques
Associated signs and symptoms	Asymptomatic	Asymptomatic	Pain and edema	Lesions are tender and bleed easily	Lesions bleed easily; facial swelling and edema
Location	Distal extremities	Distal lower extremities	Extensor surface of the lower extremities	Any body part (rare on palms, soles or mouth)	Head, scalp, face and neck
Associated factors	Known case of myasthenia gravis maintained on corti-costeroid therapy	May be immunosuppres-sion associated	Associated with chronic venous insuffi-ciency	Exposure to flea-infested cats; responds to antibiotics	Increase incidence in skin with chronic lym-phedema
Association with HIV infection	HIV-negative	With or without associ-ated HIV infection	Not associated with HIV	With or without associ-ated HIV infection	Not associated with HIV

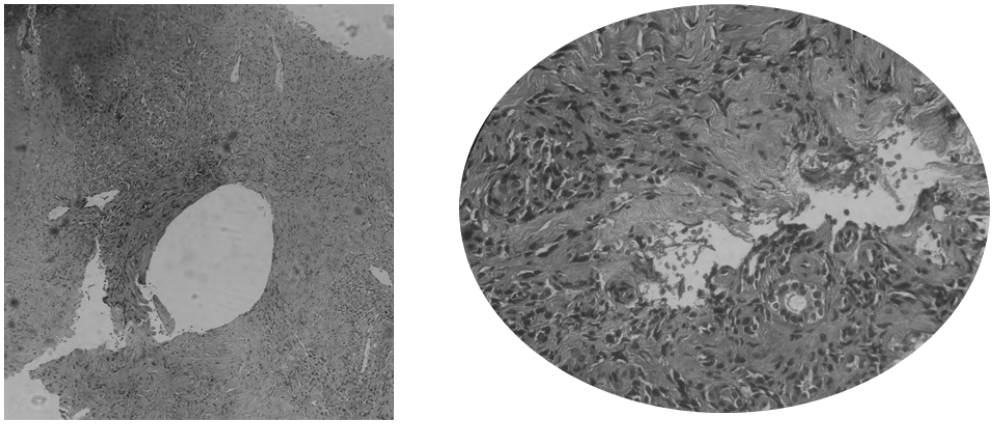

Figure 5. Hematoxylin and eosin staning revealed (a) an increase in number of blood vessels throughout the dermis, and (b) foci of extravasated erythrocytes and spindle-shaped cells are disposed around the blood vessels, adnexal structures and interstitial dermis

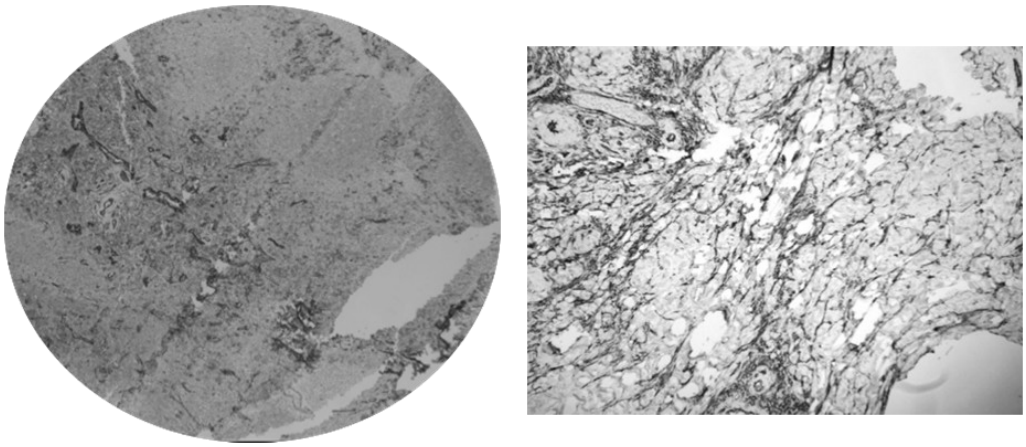

Figure 6. CD31 immunostaining shows a strong positive staining of the spindle cells insinuated between the collagen bundles throughout the dermis.

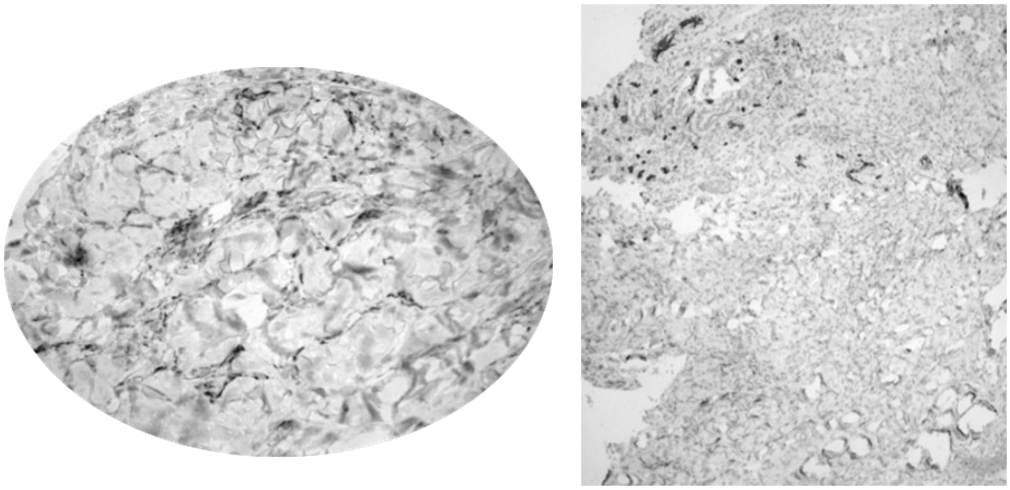

Figure 7. CD 34 shows strong positive staining of the spindle cells mainly located in the lower half of the dermis

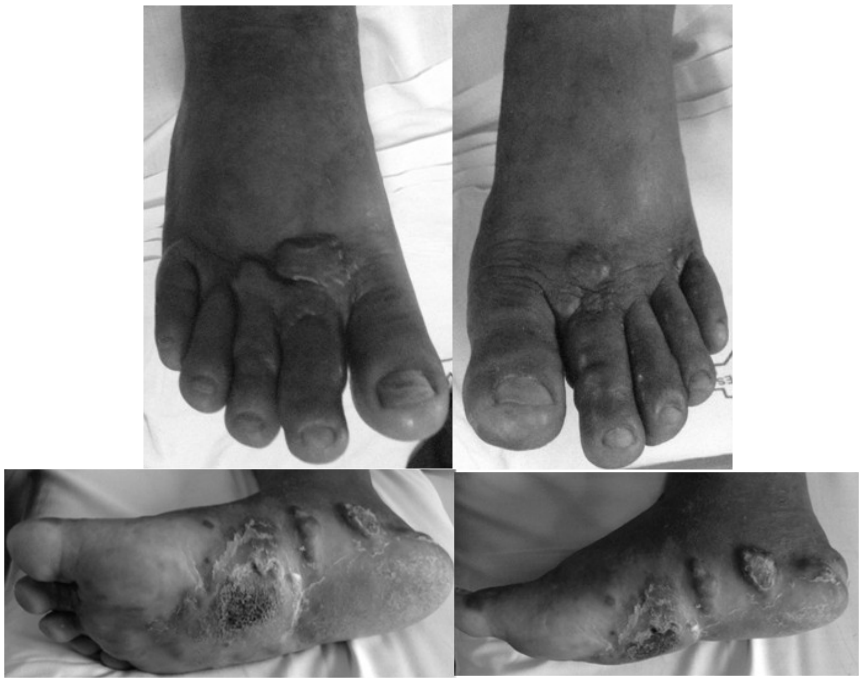

Figure 8. Progression of multiple, well defined, round to irregularly shaped bluish to violaceous nodules and plaques some topped with scales over both feet. Figure 8. Progression of multiple, well defined, round to irregularly shaped bluish to violaceous nodules and plaques some topped with scales over both feet.

Table 2. Kaposi sarcoma staging based on Schwartz et al in 2008

STAGE	DESCRIPTION
Stage I	Localized nodules Kaposi sarcoma (KS) <15 cutaneous lesions or involvement restricted to one bilateral anatomic site, and few, if any, gut nodules
Stage II	Includes both exophytic destructive KS and locally infiltrative cutaneous lesions and locally aggressive KS or nodular KS, or > 15 cutaneous lesions or involvement of more than one bilateral anatomic site and few or many gut nodules
Stage III	Generalized lymphadenopathic KS Widespread lymph node involvement, with or without cutaneous KS but with limited if any visceral involvement
Stage IV	Disseminated visceral KS Widespread KS usually progressing from stages II or III, with involvement of multiple visceral organs with or without cutaneous KS