CASE REPORT

# Disseminated classic Kaposi sarcoma on immunocompetent patient

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## ABSTRACT

Kaposi's sarcoma (SK) is a rare, solitary or multifocal angioproliferative tumor, which typically involves the skin or mucosal surfaces. There are four widely recognized types of Kaposi's sarcoma that are histologically indistinguishable but differ in their epidemiology and prognosis. The etiology is associated with infection of the human herpes virus type 8, which causes changes in endothelial cells, which are subjected to reprogramming and abnormal differentiation.

Classical SK occurs in men rather than women (2.5:1), generally elderly, without immunosuppression. Lesions are characterized by macules, papules, plaques and violaceous, red-bluish or brown nodules, which are prone to bleeding and ulceration; in more than 85% of cases, they are usually located on lower limbs.

The unusual clinical case of an 82-year-old female patient is presented. The patient has no significant pathological history and does not report any toxic habits. Her consult is due to multiple patches, papules, nodules and erythematoviolous tumors which she has been presenting for 2 years; the tumors, grouped and of papillomatous appearance, began on the dorsum of the feet and in a short time spread to the rest of the lower limbs, abdomen, thorax, neck and upper limbs.

This case report confirms that the disease does not depend only on the active infection by the human herpes virus 8, but also on other conditions of the patient, even if not well identified. It is believed that it will be useful for the medical community to know that there are specific cases of classic Kaposi's sarcoma that present as papillomatous tumors in patients without a pathological history.

## INTRODUCTION

Kaposi sarcoma (KS) is a rare, solitary or multifocal angioproliferative tumor, that typically involves skin or mucosal surfaces.[1] There are four widely recognized types of Kaposi sarcoma that are histologically indistinguishable but differ in their epidemiology and prognosis. These include classic or chronic KS, endemic or African, iatrogenic or immunosuppression-related and epidemic or AIDS-associated.[2]

Kaposi sarcoma (KS) was initially described in 1872 by Moritz Kaposi, physician and dermatologist. He described various cases involving a multifocal pigmented cutaneous sarcoma in elderly European men, all of which died within 2 years.[3]

In the last few years, a new subgroup of patients has been recognized: men who have sex with men (MSM);

they are generally young, HIV-seronegative and have no identifiable immunodeficiency. This fifth variant, termed nonepidemic, resembles to classic KS in presentation and prognosis.[4]

Etiology is associated with the human herpes virus 8 (HHV-8) infection, which alters endothelial cells, which undergo reprogramming and abnormal differentiation.[5]

Classic KS is seen in more men than women (2.5:1), generally older, without apparent immunosuppression.[6] Lesions are characterized by macules, papules, plaques and violaceous, red-bluish or brown nodules, which are prone to bleeding and ulceration; in more than 85% of cases, these are usually located on lower limbs; and in 68% of cases, these are exclusively located on that area. Other less common areas include upper limbs, thorax and abdomen, gastrointestinal tract, lymph nodes and mucosal surfaces on rare occasions.[7]

Biopsy that reveals characteristic angioproliferative features is required for definitive diagnosis. These are aberrant proliferation of blood vessels, spindle-shaped tumor cells, extravasated erythrocytes, and inflammatory infiltrates.[8] Immunohistochemical staining of biopsy specimens confirms diagnosis by detection of HHV-8 latent nuclear antigen within spindle cells.[9]

Classic KS manifests a chronic course. Half of the cases can be cured with treatment, twenty percent of the cases stabilize, a lower percentage is at risk for recurrence and progression. Nonetheless, the disease on its own has not resulted in mortality.[7,10]

A great percentage of classic KS patients show a partial or satisfactory response to therapy, including radiotherapy, surgical escision, laser therapy, chemotherapy, immunotherapy, among others.[11]

## CASE REPORT

The clinical case of an 82-year-old female patient is presented. The patient has no significant pathological history and does not report any toxic habits. Her consult is due to multiple patches, papules, nodules and erythematoviolous tumors which she has been presenting for 2 years; the tumors, grouped and of papillomatous appearance, began on the dorsum of the feet and in a short time spread to the rest of the lower limbs, abdomen, thorax, neck and upper limbs. These were asymptomatic at first. However, 3 months ago, the patient started complaining of pain at the bottom of the feet, particularly while standing. (Figs. 1, 2, 3, 4). Approximately, a year and a half ago, a biopsy was performed at another health center, which confirmed capillary hemangioma. The patient received no treatment.

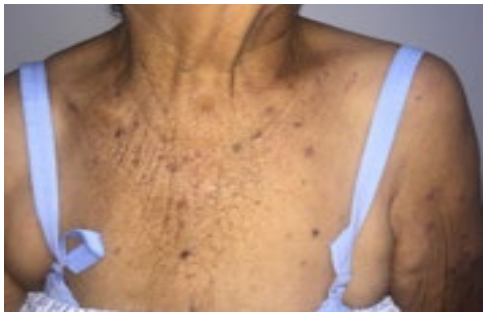

*Fig. 1. Patches, plaques and violaceous nodules on thorax and arms.*

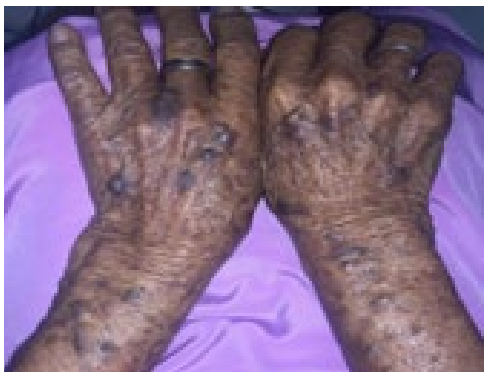

*Fig. 2. Patches, plaques and violaceous nodules on arms and hands.*

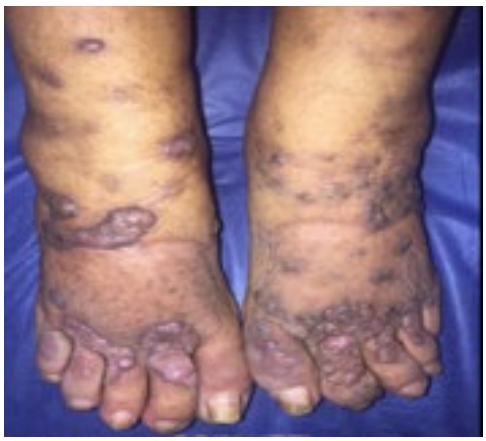

*Fig. 3. Papillomatous tumors and nodules on the feet.*

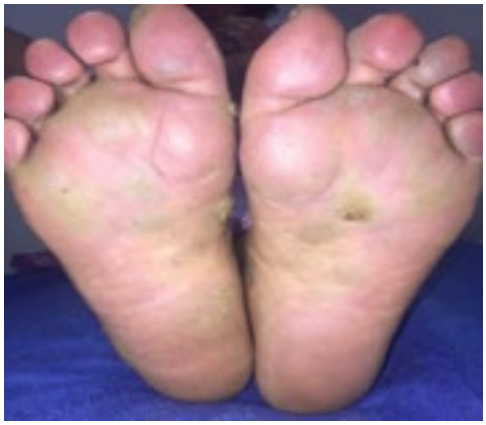

*Fig. 4. Multiple nodules at the bottom of the feet.*

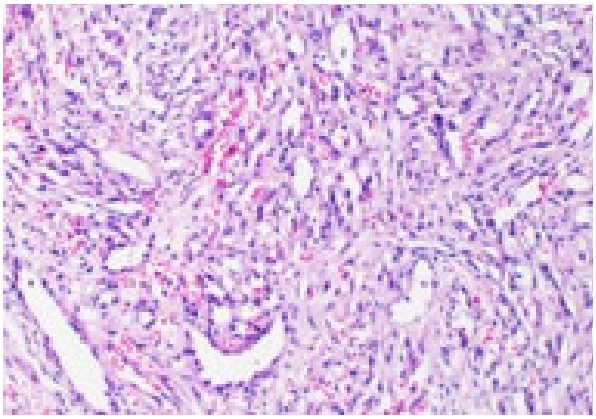

*Fig. 5. Dermal vessel proliferation, spindle vessels, extravasation.*

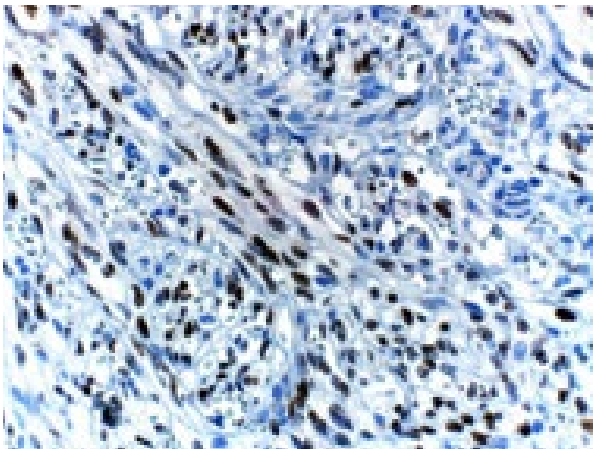

*Fig. 6. Nuclear powder in HHV-8 infected cells.*

A biopsy was performed. It was compatible with Kaposi sarcoma (Fig. 5). An immunohistochemical staining of biopsy was also performed. This resulted positive for herpes virus 8 (Fig.6). Furthermore, laboratory exams confirmed a negative result for HIV on two occasions. Such history deemed necessary for the patient to visit the oncology department at "Sociedad de Lucha Contra el Cáncer (SOLCA)" to receive adequate treatment.

## DISCUSSION

For epidemiologic features, our patient classifies for the variant of classic KS, as she is elderly and HIV-negative; but has an atypical presentation, as most of the time, lesions appear on lower limbs, rarely reaching the thorax and abdomen, as in this case.[1,10]

Since the nineties, the infectious origin of this pathology was believed to be independent from that of HIV. In 1994, the results of a scientific research, that lead to the discovery of HHV-8 as the cause of the disease, were discovered.[3,13]

Nowadays, it is known that KS is caused by a combination of virus infection and deterioration of the host immune system. However, and although AIDS and iatrogenic-related variants are clearly associated with a well-defined immunodepression, the deterioration of the immune system function within the classic variant is thought to be related to 'immunosenescence'; which refers to an aged immune system.[14] Apart from KS, HHV-8 causes two linfoproliferative disorders: Primary Effusion Lymphoma (PEL) and Multicentric Castleman Disease (MCD).[15]

Pathologic diagnosis is often made with hematoxylin and eosin staining in order to evaluate the basic features present, in varying degrees, within all the cases of the disease. These include vascular proliferation in the dermis (with cleft-like spaces without endothelium covering), a greater number of vessels without endothelial cell coating, the presence of extravasated blood that results in the formation of hyaline globules and hemosiderin accumulation. Spindle cell proliferation is also a distinctive feature of KS. Spindle cells are characterized by elongated nuclei and cytoplasm and containing hemosiderin inclusions on certain occasions. Although spindle cells are generally identified in sheets or fascicles, they may be difficult to distinguish in early lesions.[16]

Lately, immunohistochemistry has played an important role in KS diagnosis. KS lesions have an heterogenous cellular composition. Cellular immunohis-

tochemistry, which makes use of antibodies against vascular endothelial markers, such as the CD34, revealed a vascular nature, and the subsequent detection of lymphatic endothelial markers in the spindle cells, such as podoplanin and vascular endothelial growth factor receptor 3 (VEGF), suggested that KS has a lymphatic endothelial cell origin.[17,18] The majority of immunochemical tests and gene expression and experimental data nowadays suggest that spindle cells are lymphatic endothelial cells and/or endothelial cells that undergo reprogramming after HHV-8 infection to produce cells with an aberrant combined immunophenotype.[19,20] In addition to lymphocytes and plasma cells, histiocytes are abundant in KS lesions, which may be identified with immunohistochemistry; they have also contributed to our understanding of the cellular composition of this pathology and in the differential diagnosis of KS in rare and complicated cases.[21,22]

Immunochemical stains for HHV-8 antigens are very helpful to diagnose KS. Specifically, antibodies that recognize the latency-associated nuclear antigen (LANA) can be used in routine to confirm a KS diagnosis in difficult cases. These are routinely used nowadays. The proportion of infected cells is variable, ranging from <10% to >90% of the total cell population in lesional areas. LANA is considered positive when a punctate nuclear pattern is observed, which prevents it from being mistaken by cytoplasmic hemosiderin or melanin when a brown chromogen is used.[3,8,19]

Nowadays, it is thought that a KS diagnosis does not only require histology and immunohistochemistry, but also HHV-8 detection, using molecular biology techniques, as the antibody measuring and detection that are performed in blood samples and other biologic fluids may mark the virologic state even further (latent vs active).[8]

KS differential diagnosis is wide. Consequently, it is possible that early stage cutaneous lesions need to be differentiated from the targetoid hemosiderotic hemangioma, fibrous histiocytoma and annular granuloma. Lesions, that one could potentially mistake for nodular KS, include bacillary angiomatosis, spindle cell hemangioma and kaposiform hemangioendothelioma, fibrohistiocytic tumors, fibrous histiocytoma atypical variants, and dermatofibrosarcoma protuberans, spindle cell melanoma and other spindle cell mesenchymal neoplasms (cutaneous leiomyosarcoma). More advanced and aggressive variants of KS should be differentiated from angiosarcoma.[23]

On the other hand, one could establish as differential diagnosis other HHV-8 disorders. First, primary effusion lymphoma, which is a B cell lymphoma affecting most commonly the peritoneal, pleural and pericardial cavities.[24] Although it can rarely appear as solid lesions that are outside body cavities.[25] It is seen most frequently in young men with AIDS or HIV positive. On rare occasions, there have been cases with no relation to HIV, but most of these patients suffer from other type of immunodeficiency. Symptoms depend on the affected body cavity and are caused by the accumulation of liquid with malignant cell content.[26] In addition to being infected by HHV-8, tumor cells are frequently coinfected by the Epstein-Barr virus. Tumor cells, although they originate from B cells, do not frequently express immunoglobulin and other B cell antigens, but they do express plasmatic cell antigens. PEL tends to be extremely aggressive and presents dissemination in remote locations. Opportunist infections and HIV-related complication tend to be fatal. In rare HIV-negative cases, results may be better.[3,26]

In contrast, Multicentric Castleman Disease (MCD) is a lymphoproliferative disorder with generalized lymphadenopathy and systemic symptoms. It is believed that these symptoms are caused by excessive production of inflammatory cytokines, specially IL-6.[27] Most of MCD cases occur in patients with HHV-8 and HIV infection; less than half of MCD cases occur in people with HHV-8 but no HIV infection. There are distinctive pathologic features in lymph nodes, and HHV-8 infected cells can be identified; these have plasmablastic morphology and express immunoglobulin light chains.[28] HIV patients diagnosed with HHV-associated MCD are to be treated with rituximab, a monoclonal antibody and gold standard. Chemotherapy (etoposide or anthracycline) must be included in the treatment if there is organic insufficiency with potentially lethal consequences.[29]

Classic KS manifests a chronic course. If treated, the disease undergoes the following pattern: half of the cases can be cured with treatment, twenty percent of the cases stabilize, a lower percentage is at risk for recurrence and progression. Nonetheless, the disease on its own has not resulted in mortality.[7]

Consequently, a great percentage of classic KS patients show a partial or satisfactory response to therapy, including radiotherapy, surgical escision, chemotherapy, laser therapy, topic retinoids, topical imiquimod, topical timolol, immunotherapy, among others.[11] However, some cases of apparent remission have evidenced KS recurrence, as the virus latency, associated with Koebner phenomenon, has caused viral reactivation, with both mucosal and cutaneous lesions. A long-term follow-up of the patient is recommended.[12]

In contrast to non-classic and non-HIV Kaposi sarcoma (endemic, iatrogenic, non-endemic), classic KS' spontaneous resolution, as it is, has not been reported. This is consistent with other studies, which state that KS' physiopathology is not only caused by an HHV-8 active infection, but also by environmental factors, among which the immunological state seems to be the most important.[3,10]

## CONCLUSION

An unusual case of classic KS is presented. The patient is a woman with no significant pathological history. She does present disseminated cutaneous involvement. This clinical presentation has not been widely reported in the literature reviewed within reach.

Although the patient does not present any identifiable immunodeficiency and has denied, on several occasions, immunosuppressant topical application or intake, her clinical picture is compatible, both histologically and immunohistochemically, with disseminated classic KS, which could raise doubts in relation to the patient's involvement with any immunosuppressant that was not revealed in the questioning.

This case report confirms that the disease does not only depend on the active infection by HHV-8, but also on other conditions of the patient, which may not be fully identified. It is believed that this case will be useful for the medical community in order to know that there are specific cases of classic Kaposi sarcoma that present as disseminated and grouped tumors in immunocompetent patients.

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