

## EXTENSIVE, RAPIDLY PROGRESSIVE CLASSIC KAPOSI SARCOMA – CASE REPORT

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### Summary

*Kaposi sarcoma (KS) is an angioproliferative condition of multifactorial etiology. Human herpes virus 8 infection is necessary, but not sufficient for the development of KS. Various genetic, social, immunologic and endocrine factors also play a role. KS encompasses four clinical subtypes: classic (sporadic) KS, endemic KS that occurs in Sub-Saharan Africa, epidemic KS, which develops in patients with human immunodeficiency virus (HIV) infection and iatrogenic KS, associated with the chronic use of immunosuppressive drugs.*

*Unlike KS arising in HIV-positive patients, there is no generally accepted staging system or treatment guideline for classic KS. No systemic treatment is specifically approved for this form of the disease and randomized trials comparing drug efficacy are lacking, therefore the management of these patients often represents a real challenge for clinicians.*

*We present the case of a 61 year-old HIV-negative male patient with no personal history of malignancy or immunosuppression diagnosed in our clinic with rapidly progressive classic KS with generalized cutaneous lesions and oral mucosa involvement and discuss the treatment strategies in such cases.*

**Key words:** Kaposi sarcoma, human herpes virus 8 infection, systemic treatment.

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### Introduction

Kaposi sarcoma (KS) is an angioproliferative condition first described by Moritz Kaposi in 1872 [1]. Uncertainty persists regarding the cell of origin in KS, but the results of most studies suggest it derives from a pluripotent mesenchymal progenitor cell. Its etiology is multifactorial. Human herpes virus (HHV) 8 infection is necessary, but not sufficient for the development of KS [2, 3]. Various genetic, social, immunologic and endocrine factors also play a role.

KS encompasses four clinical subtypes: classic (sporadic) KS that usually affects middle-aged or elderly Mediterranean or Jewish men, endemic KS that occurs in Sub-Saharan Africa, epidemic KS, which develops in patients with

acquired immunodeficiency syndrome (AIDS) and iatrogenic KS, associated with the use of immunosuppressive drugs, especially in transplant recipients.

Classic KS manifests as violaceous, red or brown macules, papules, plaques or nodules that usually affect the lower limbs, but can be generalized. The lesions gradually enlarge and can coalesce. They are generally asymptomatic, except for those located on the soles, which are often painful. Lymphedema develops as a result of lymphatic vessels obstruction. The oral mucosa is frequently involved. Lymph node or visceral involvement (especially gastrointestinal and pulmonary involvement) can also occur [4, 5]. It has an indolent course, the patients

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usually dying with, not of KS [6]. However, up to one third of patients develop a second neoplasm, particularly hematologic malignancies [5].

The diagnosis is based on the clinical picture and the histopathologic examination of lesional skin samples. Depending on the stage of the disease, the histopathologic examination reveals various degrees of angiogenesis, with the formation of slit-like vascular spaces in the upper dermis, the presence of an inflammatory infiltrate composed of lymphocytes, plasma cells, and macrophages, and spindle cell proliferation [4, 7]. The angioproliferative pattern is more pronounced in the patch and plaque stages, whereas nodules are mainly composed of fascicles of spindle-shaped endothelial cells [8]. Immunohistochemical studies show positivity for factor VIIIa in the cells lining the vascular spaces and for HHV 8 latent antigen, CD34 and CD 31 in spindle cells [7, 9].

Unlike KS arising in human immunodeficiency virus (HIV) positive patients, there is no generally accepted staging system for classic KS. Although multiple such systems have been developed, the most commonly used are those proposed by Mitsuyasu and Brambilla et al. [10, 11].

Mitsuyasu classified KS into 4 stages:

- Stage I: localized nodular KS in elderly men in North America and Europe.
- Stage II: localized, invasive, and aggressive KS.
- Stage III: disseminated mucocutaneous KS in African children and men who have sex with men.
- Stage IV: Stage III with visceral involvement [10].

The classification recommended by Brambilla et al also comprises 4 stages, as follows:

- Stage I (the maculonodular stage): small macules and nodules primarily confined to the lower limbs.
- Stage II (the infiltrative stage): plaques mainly involving the lower limbs, sometimes associated with a few nodules.
- Stage III (the florid stage): multiple angiomatous plaques and nodules involving the lower extremities that are often ulcerated.

- Stage IV (the disseminated stage): multiple angiomatous nodules and plaques extending beyond the lower extremities [11].

The management of classic KS should be individualized. Radiation therapy is the mainstay of treatment. A series of local treatments are also employed in case of unaesthetic lesions or as palliation therapy for symptomatic, locally advanced lesions. Given its immunomodulatory and antiviral properties, interferon (IFN)-alpha is also efficient in KS, but it is only approved in Romania for the treatment of HIV-associated KS. The use of antiherpetic drugs, like foscarnet, ganciclovir, and cidofovir in classic KS cases has ensued contradictory results. Chemotherapy, either as monotherapy or combined regimens is usually reserved for advanced cases, with visceral involvement [4, 12, 13].

We present a case of rapidly progressive classic KS with generalized cutaneous lesions and oral mucosa involvement and discuss the treatment strategies in such cases.

## Case report

A 61 year old male patient was referred to our clinic for the presence of widespread violaceous, elevated, indurated, irregularly shaped papules, plaques, and nodules of varying sizes, ranging from 3 mm to more than 10 cm. The lesions had a tendency to coalesce into large, infiltrated plaques (fig. 1). The patient also presented violaceous, indurated, slightly elevated plaques of approximately 1.5 cm in diameter on the hard and soft palate. Both the cutaneous and the mucous lesions were asymptomatic, except for the plantar plaques and nodules, which were painful. The skin lesions were accompanied by moderate lower limb edema. The lesions first appeared 18 months previously on the soles and rapidly extended and generalized. The rest of the physical examination did not reveal pathologic findings.

The patient had no personal history of malignancy or immunosuppression, but suffered from arterial hypertension, dyslipidemia, hyperuricemia and was receiving chronic treatment with antihypertensive and hypolipemiant drugs.



*Fig. 1. Widespread violaceous, elevated, indurated, irregularly shaped papules, plaques, and nodules of varying sizes*



A skin biopsy was performed and the histopathologic examination confirmed the clinical suspicion of KS, showing elongated/fusiform cells, frequent hemosiderin deposits and increased vascularization in the superficial dermis with small sized vessels (a purpura-like aspect) (fig. 2). Immunohistochemical studies showed positivity for HHV 8 latency-associated nuclear antigen (LANA) 1, CD34 and CD31 in spindle cells and for factor VIIIa in the cells lining the vascular spaces.

Laboratory tests results were within normal limits. Screening for HIV infection was also negative. Cerebral, thoracic, abdominal and pelvic CT scan did not reveal lymph node or visceral involvement.

The patient was referred to an oncologist and radiotherapist. Radiotherapy was initiated, targeting the skin lesions located on the soles. The clinical improvement was, however, minimal.

## Discussions

There is no curative treatment for KS, but disease control can be achieved and maintained for long periods of time. The therapeutic options approved for classic KS are limited. Moreover, there is currently no consensus regarding the indications of systemic therapy in classic KS.

Radiation therapy is the treatment of choice in most cases of classic KS. Electron beam radiation therapy is highly efficient for superficial

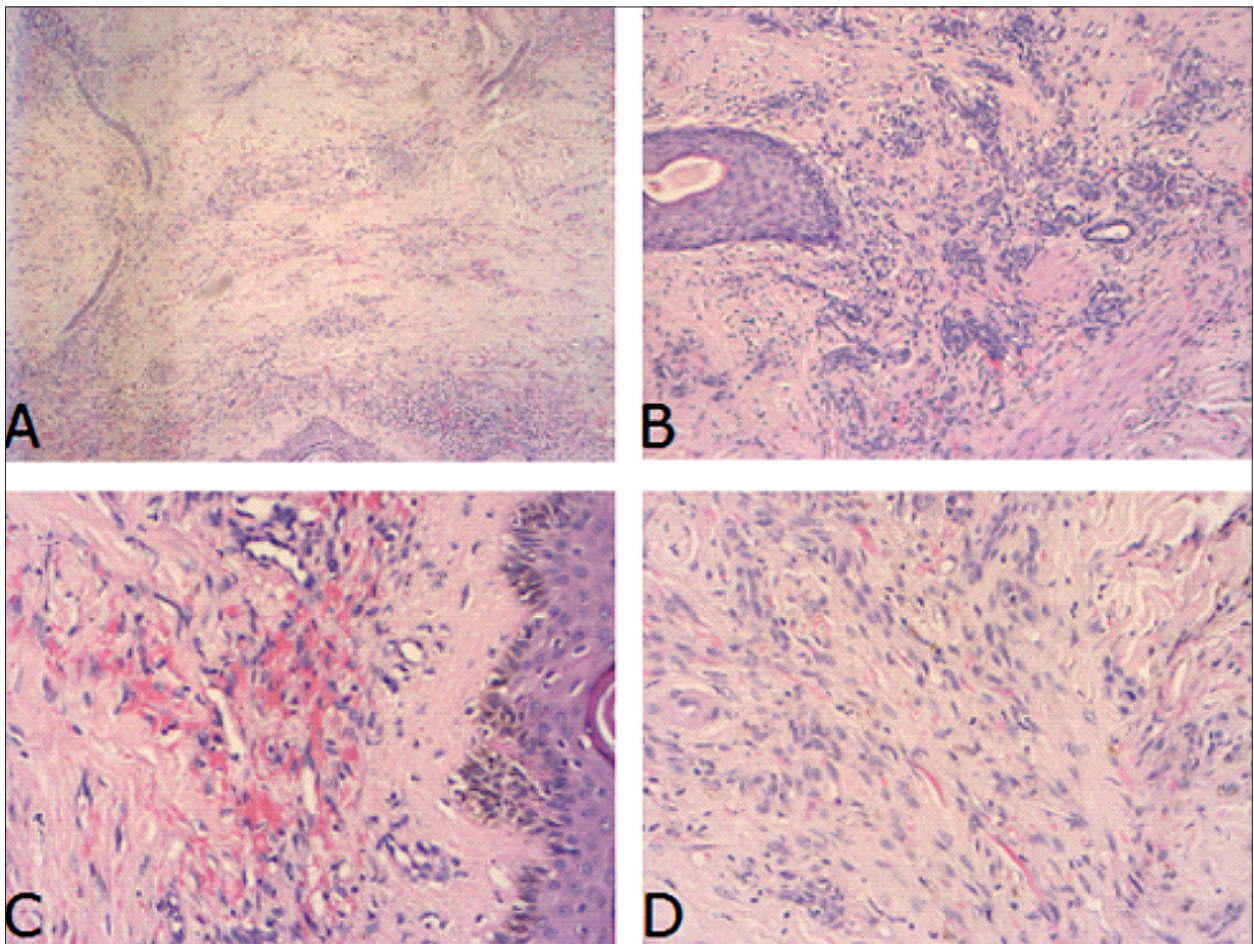


Fig. 2. Haematoxylin & eosin stain (A) magnification x 40, (B) magnification x 100, (C,D) magnification x 200 showing elongated/fusiform cells, increased vascularization in the superficial dermis with small sized vessels and intracellular hyaline globules



lesions, whereas standard radiotherapy is indicated for deeper cutaneous lesions [12]. Low-voltage (100 kV) photon radiation, high-dose-rate brachytherapy have also been employed with good results [14, 15]. Unfortunately, new lesions often form in nonirradiated areas, therefore many experts recommend extended-field radiotherapy, which ensures a better outcome [4]. In patients such as ours with generalized skin lesions, the benefits of radiation therapy are limited.

For bleeding, painful or unaesthetic cutaneous lesions, or in cases with few nodular lesions local palliative treatments, such as cryotherapy, laser therapy, electrocauterization, surgical excision, photodynamic therapy, topical retinoids, topical 5% cream and intralesional injection of vinca alkaloids or bleomycin are indicated [4, 12, 13]. These treatments do not influence the progression of KS and are associated with high local recurrence rates. Compression bandages or stockings are useful in reducing associated lower limb edema [16].

IFN-alpha has proven efficient in classic KS, both in high and low doses due to its antiproliferative, anti-angiogenic, immunomodulatory and direct antiviral effects [17,18]. However, it is only approved in AIDS-associated KS and our patient could not benefit from it. Off-label use of other immunomodulatory and anti-angiogenic drugs like thalidomide and pomalidomide have been reported as efficient in classic KS [19, 20].

Even though no cytotoxic drug is specifically approved for classic KS, various chemotherapeutic agents approved for AIDS-associated KS or other neoplasms, like vinblastine, vincristine, pegylated liposomal doxorubicin, liposomal daunorubicin, etoposide, taxanes and gemcitabine as monotherapy or combination therapy (doxorubicin, bleomycin and vincristine) have also been used in classic KS [4,13]. Their efficacy has not been compared in randomized clinical trials

[4]. There is no consensus as to the optimal dose regimen and duration of treatment. Regression of signs and symptoms is generally rapidly obtained [4, 12]. Nevertheless, given the significant toxicity of prolonged courses of such treatments, the risk of HHV 8 reactivation, the risk of opportunistic infections, and the predisposition of these patients to the development of other neoplasms, chemotherapy is reserved for advanced cases of KS, characterized by visceral involvement or for rapidly progressive mucocutaneous disease [4].

HHV 8 plays a central role in the etio-pathogenesis of KS, but the studies assessing the efficacy of antiherpetic agents like foscarnet, ganciclovir, and cidofovir in the treatment of KS have yielded contradictory results [4].

The search for new treatment modalities continues. Several anti-angiogenic drugs have shown encouraging results. These include vascular endothelial growth factor (VEGF)-inhibitors bevacizumab and sorafenib. [4] Case reports of successful treatment of classic KS patients with mammalian target of rapamycin (mTOR) inhibitor, sirolimus [21,22], imatinib mesylate [23], or immune checkpoint blockade with nivolumab or pembrolizumab [24] have recently been published.

## Conclusions

The particularity of the case presented herein is the rapid progression of KS and the extent of skin and oral mucosa lesions in a middle aged, HIV-negative patient with no prior history of malignancy or chronic immunosuppression. The lack of evidence based treatment guidelines, the paucity of therapeutic strategies approved for classic KS and the significant toxicity associated with systemic treatments make the management of such patients a real challenge for clinicians.

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Conflict of interest  
NONE DECLARED

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