Durable complete response of classic Kaposi’s sarcoma of the supraglottis with pegylated liposomal doxorubicin

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Abstract
Introduction
Classic-type Kaposi’s sarcoma is a human herpesvirus 8 linked low-grade angioproliferative disease—not related, however, to the impairment of host-immune response—and typically occurring in older adults (males) in Mediterranean and Eastern European regions. The most frequent presentation is multifocal in mucocutaneous sites, especially lower extremities, trunk and oropharyngeal mucosa. We are reporting a case of a young Caribbean patient without immunodeficiency, and with a locally aggressive form of classic-type Kaposi’s sarcoma limited to the supraglottis, along with a 3-year complete response to treatment with pegylated liposomal doxorubicin.

Case report
A 41-year-old black male born in the Dominican Republic and living in Spain for the past 3 years was admitted to our hospital with a history of 1 month of progressive hoarseness in voice and urge to cough. He brought with him two 1-cm masses, which he coughed with a small amount of blood. He underwent laryngeal microsurgery; both lesions were removed and symptoms disappeared. Three months later he developed hoarseness again and new, bigger lesions were observed. He underwent additional surgical procedure to remove the tumours, with histopathological diagnosis of Kaposi’s sarcoma, but 2 months later a new recurrence appeared. The patient was diagnosed with primary classic Kaposi’s Sarcoma (Type I) limited to the supraglottis.

Conclusion
Classic-type Kaposi’s sarcoma is usually slow growing and does not impair quality of life and survival in the short term, but aggressive forms may be life threatening and should be treated urgently. Systemic chemotherapy with pegylated liposomal doxorubicin is an effective and well-tolerated strategy also for limited-stage disease with rapid progression, however.

Introduction
Kaposi’s sarcoma (KS) is a vascular endothelial low-grade neoplasia widely associated with acquired immunodeficiency syndrome (AIDS). Classic Kaposi’s sarcoma (CKS) is one of the four distinct clinical presentations of KS—not related to immunodeficiency, however, but requiring for its development the infection with human herpes virus 8 (HHV-8; also known as Kaposi’s-sarcoma-associated Herpes virus—KSHV). The highest incidence rates worldwide correspond to Mediterranean countries and Eastern Europe and the areas these individuals migrate to. This distribution corresponds to areas of prevalence of HHV-8 infection; however, not all infected persons develop CKS, and this implies existence of unknown cofactors along with the HHV-8 infection. The most likely transmission route identifies salivary shedding and practices that facilitate saliva passage, but other environmental factors related to skin hygiene or skin disease may also influence the development. There is a clear predominance in males aged 70 years or older, with only 4% to 8% of cases developed in relatively younger individuals, that is, those aged below 50 years.

Histopathologically all four types of KS are comprised of both distinctive spindle cells of endothelial origin, angiogenesis and a variable inflammatory infiltrate. Three stages can be identified (patch, plaque and nodular) as the inflammatory infiltrate becomes more dense; the spindle cells increase in number and accumulate around the areas of angioproliferation, and extravasated erythrocytes and macrophages present between spindle cells. Vascular structures are positive for factor VIII and spindle cells stain for CD34 and CD31. Gene products of HHV-8 affect both cell-cycle regulation and the control of apoptosis, and segments of the HHV-8 genome contain viral oncogenes.

The most frequent location of these lesions is the skin of the lower extremities, face, trunk and genitalia, but oral, gastrointestinal or endobronchial mucosa have also been described. We are reporting a case of a young Caribbean patient without immunodeficiency, but with a locally aggressive form of CKS limited to the supraglottis, along with a durable complete response to treatment with pegylated liposomal doxorubicin (PLD).

Case report
A 41-year-old black male born in the Dominican Republic and living in Spain for the past 3 years was admitted to our hospital with a history of 1 month of progressive hoarseness in voice and urge to cough. He brought with him two 1-cm masses,
which he coughed with a small amount of blood. Fibrolaryngoscopy showed two other 10-mm nodule-like masses originating from the right false vocal cord and arytenoid, occupying the anterior 2/3 of the glottis. The patient underwent laryngeal microsurgery, and both lesions were removed and symptoms disappeared.

Histopathology study of all the specimens revealed large fascicles of spindle-shaped endothelial cells with compact vascular slits and extravasated erythrocytes and macrophages present between spindle cells, all consistent with KS. Immunophenotype proved positive for CD31, CD34 and D2-40, and HHV-8 latent antigen was present within the spindle cells, thus confirming the diagnosis.

Three months later, the patient developed hoarseness again and new, bigger lesions were located. He underwent an additional surgical procedure to remove the tumours, based on the histopathological diagnosis of KS; however, 2 months later a new recurrence appeared (Figures 1 and 2). After extensive evaluation with body-CT scanners, bronchoscopy and colonoscopy, skin examination and laboratory tests—all excluding other lesions and immunodeficiency—the patient was diagnosed with primary Classic Kaposi’s Sarcoma (Type I) limited to the supraglottis. He had never been treated with immunosuppressant drugs.

Due to this locally aggressive behaviour and the possibility of massive bleeding to airways, the patient was immediately treated with PLD 20 mg/m² every 2 weeks for a total of 6 cycles, which resulted in excellent tolerance and immediate improvement of hoarseness. Response was assessed; there was a major response after three cycles (>50% reduction; see Figure 3) and complete response (CR) after 6 cycles (Figure 4). At the time of finalization of this report, and 36 months post-treatment, the patient was still in CR.

**Figure 1:** Pre-chemotherapy bronchoscopic view of a friable erythematous nodule of Kaposi’s sarcoma located in the supraglottis

**Figure 2:** CT scan contrast-enhancing nodule
Discussion

This case report is interesting in different aspects: it relates to a non-HIV heterosexual young patient with a locally aggressive form of non-disseminated CKS limited to the supraglottis.

First, this is an unusual presentation. CKS has been reported at virtually all anatomic sites, but available clinical evidence in non-AIDS-related KS after a HIV epidemic in this location is not found in databases. Extracutaneous involvement is rare as initial presentation, and visceral and mucosa involvement is rare in HIV-negative patients. Typical findings include solitary patches or nodules distributed along the skin of the lower limbs, and when the lesions are mucosal, there is simultaneous skin involvement in 84% of cases.

Second is the epidemiologic observation. Our patient is originally from an area with low seroprevalence of HHV-8 infection if we look at the reported rate of incidence in other Caribbean countries like Jamaica (5%).

Third is the natural history of the disease. CKS is typically a slow-growing malignancy with a long indolent course, and thus, mainly appearing in older populations and not compromising survival; however, clinical evaluations may vary. In our patient, the behavior was locally aggressive from the beginning, with rapid evolution in each progression. In this stage, lymphedema and ulceration are frequent and tumors may bleed easily. A recently proposed staging system set our patient in Stage IV condition (disseminated stage; multiple angiomatous nodules and plaques extending beyond the lower extremities), which always indicates rapid disease progression needing urgent treatment.

Management of KS depends on the extent of lesions and their evolution. Rapid evolution is considered an increase in the total number of nodules/plaques or in the total area of plaques in 3 months after examination. Given the scarcity of prospective randomized trials, different strategies have been used to manage CKS, with the goal of achieving symptom palliation and decreasing the size of cutaneous or visceral lesions and delaying or preventing disease progression. For localized lesions radiotherapy, cryotherapy, laser excision, and systemic chemotherapy have been used. pegylated liposomal doxorubicin is a new option for non-HIV infected patients and it is being studied in randomized clinical trials in HIV positive patients.

Figure 3: Fibrolaryngoscopic view after 3 cycles of PLD showing >50% shrinkage in size.

Figure 4: Complete response and disease-free larynx, eleven months after 6 cycles of PLD
or intrallesional injections of vinblastine have been used and, in particular, chemotherapy shows good responses in disseminated cases. Radiotherapy is frequently used for oral cavity KS with complete remission in about 85% of cases with a fractionated regimen to a total dose of 15 to 45 Gy. The excellent durable complete response and tolerance in our patient with PLD show this approach to be an effective and safe choice in the treatment of localized CKS. As there are no effective treatments available at this time to eradicate latent HHV-8 infection, follow-up of these patients is very important since medical practitioners are still debating whether this is a curable disease.

**Conclusion**

In conclusion, we report a unique case of a Type I CKS in a non-HIV young patient with a very peculiar presentation (coughing out a KS nodule), origin (supraglottis) and behaviour (locally aggressive). CKS is usually slow growing and does not impair quality of life and survival in the short term, but aggressive forms may be life-threatening and should be treated urgently. Systemic chemotherapy with PLD is an effective and well-tolerated strategy also for limited-stage disease with rapid progression.

**Consent**

Written informed consent was obtained from the patient for publication of this case report and accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

**References**