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Case report

Successful treatment of an HIV-positive patient with unmasking Kaposi's sarcoma immune reconstitution inflammatory syndrome

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ABSTRACT

Background: Kaposi's sarcoma (KS) continues to be the most common human immunodeficiency virus (HIV)-associated neoplasm with considerable morbidity and mortality. While lesions normally resolve upon initiation of antiretroviral therapy (ART), recrudescence or unmasking of KS lesions may occur as part of immune reconstitution inflammatory syndrome (IRIS). Treatment of unmasking KS-IRIS is not yet standardised.
Objectives: To report the successful treatment of a patient with fulminating mucocutaneous unmasking KS-IRIS by maintaining ART and using pegylated liposomal doxorubicin (PLD).
Study design: The patient, a 39-year-old HIV-positive male with no previous history of KS presented with a 2-week history of cutaneous and oral KS lesions that had disseminated rapidly over the preceding 4 days. The KS lesions appeared 8 weeks after recommencing ART. At the time of this presentation, his CD4+ count was 742 cells/mm^3 with a HIV viral load <400 copies/ml. ART was maintained and treatment with PLD commenced.
Results: Despite the rapid dissemination of KS lesions, virus was undetectable in plasma. In a late-stage vasoformative lesion, immunohistochemistry (IHC) for human herpesvirus 8 (HHV-8) antigen was light and diffuse, with stippled deposits within endothelial cell nuclei. Virus extracted from the lesion was HHV-8 subtype A. The patient responded well to PLD, relapsed a year later, but after further PLD, has remained well for the following 5 years.
Conclusion: Despite the absence of HHV-8 viraemia, this is clearly a case of unmasking KS-IRIS. It demonstrates that this entity can be successfully treated by maintaining ART and administering PLD.

1. Introduction

Kaposi's sarcoma (KS), was first described by Dr. Moritz Kaposi in 1872 as an "*idiopathic multiple pigmented sarcoma of the skin*" in five elderly Jewish men of Mediterranean origin.[1] After the onset of the HIV/AIDS epidemic, a disseminating form described as AIDS-associated-KS (AIDS-KS) appeared in both homosexual and bisexual HIV-positive populations of both developed and developing countries.[2] KS continues to be the most common HIV-associated neoplasm worldwide with considerable morbidity and mortality.[3] In most cases, initiation of antiretroviral therapy (ART) resolves KS. However, in a small subset of patients, the initiation of ART can cause an intense rebound of inflammatory responses including those to non-HIV viral infections, a situation now widely recognised as immune reconstitution inflammatory syndrome (IRIS). IRIS occurs in two forms. If an opportunistic infection worsens despite successful treatment of HIV this is called *paradoxical IRIS*, whereas the emergence of a previously absent infection is called *unmasking IRIS*.[4] When KS is associated with IRIS, this is called KS-IRIS. Studies from the USA,[5] UK[6] and Mozambique[7] have described paradoxical KS-IRIS in 6–11% of newly diagnosed HIV-positive patients initiating ART, but apart from a single study which reported unmasking KS-IRIS in 5% (2/36) of ART naive patients in Mozambique,[7] little is known about this latter condition. Paradoxical KS-IRIS can occur anywhere on the body, and monitoring HHV-8 viraemia can

Abbreviations: AIDS-KS, AIDS-associated Kaposi's sarcoma; ART, antiretroviral therapy; HIV, human immunodeficiency virus; HHV-8, human herpesvirus 8; IHC, immunohistochemistry; IRIS, immune reconstitution inflammatory syndrome; KS, Kaposi's sarcoma; PBMC, peripheral blood mononuclear cells; PLD, pegylated liposomal doxorubicin.

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provide insight to disease progression.[8] In most cases of paradoxical KS-IRIS, ART should not be stopped as lesions may resolve over time without additional therapy and, if necessary, can be controlled effectively by additional treatment with cytotoxic drugs or with interferon-alpha: nevertheless in some cases KS-IRIS can be fatal.[9] On the other hand, unmasking KS-IRIS is rare and there is little information on how this should be managed. The present case illustrates a successful regimen.

2. Case report

A 39-year-old homosexual HIV-positive male, with a stable partner, presented in 2005 with a 2-week history of cutaneous lesions over his chest and limbs which had rapidly progressed over the preceding 4 days. This was associated with gingival hypertrophy, generalised lymphadenopathy, dyspnoea and dysphagia. He had neither fever nor chills but complained of a sore throat and cough with blood-stained sputum and recent episodes of epistaxis. He was a smoker and past intravenous amphetamine user. He was on ART, and at the time of presentation his CD4+ count was 742 cells/mm^3 with an HIV viral load < 400 copies/ml.

His HIV was diagnosed 4 years earlier in 2001. At that time, his CD4+ count was 533 cells/mm^3. HIV genotyping showed a minor protease inhibitor mutation (A71V) and he was treated with pulsed ART as part of a clinical trial. The regimen during this period was lamivudine, didanosine and a boosted protease inhibitor, indinavir/ritonavir initially, followed by saquinavir/ritonavir. Fifteen months of ART was completed with two periods of a month each off therapy before treatment ceased in 2003, after randomisation to the drug conservation arm of that trial. His CD4+ count at cessation of ART was 970 cells/mm^3 with an HIV viral load of 69 copies/ml. In 2005, he recommenced therapy with lamivudine, nevirapine and tenofovir at a CD4+ count of 310 cells/mm^3 and an HIV viral load > 750,000 copies/ml. Eight weeks later he presented with the cutaneous lesions. He had no prior diagnosis of KS.

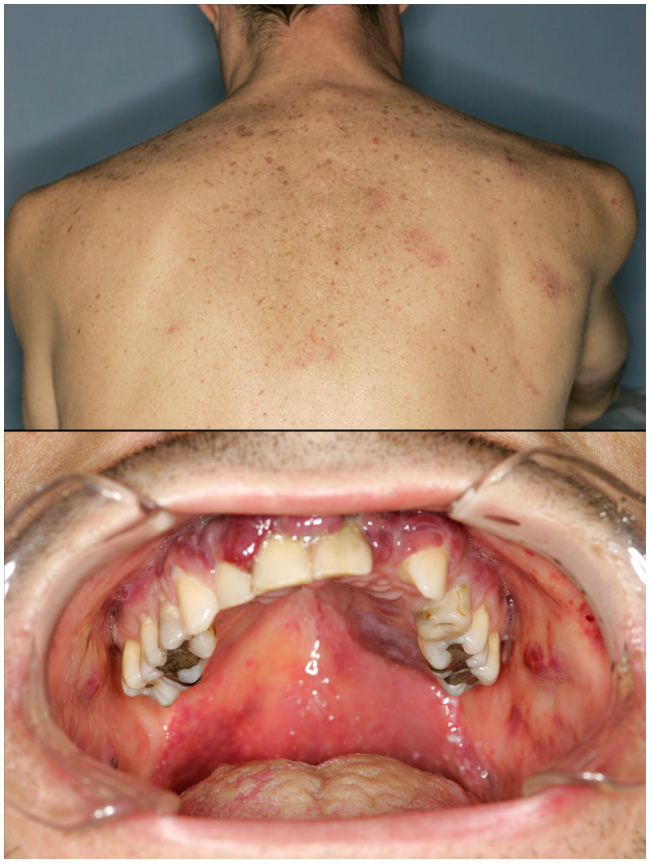

Fig. 1. Unmasking KS-IRIS lesions: Multiple round, purple patches on the back and large purple nodules on the gingival and hard palate.

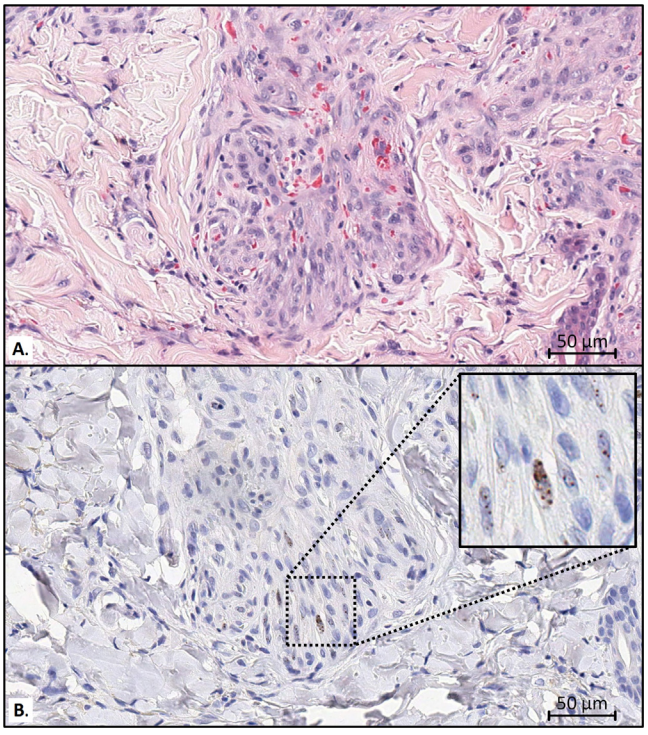

Fig. 2. Histological and immunohistochemical staining of KS-IRIS biopsy from the skin of the chest. Histological staining (A, H&E) shows clumps and strands of endothelial cells with vesicular nuclei dissecting between bundles of collagen fibres. There is a degree of nuclear pleomorphism and hyperchromatism, but no unequivocal mitotic figures. There is minimal canalisation, but characteristic extravasation of erythrocytes, some of which have coalesced. HHV-8 IHC (B) shows that approximately 20% of endothelial cells in this field stain positively for the HHV-8 antigen. These present as between 1 and 10 or more discrete dots within the nuclei, each presumably representing a small aggregation of virions.

On examination, the lesions were raised, macular and pigmented, consistent with KS, and appeared on the back, chest, upper and lower limbs and nose (Fig. 1). There was mucosal involvement, with nodular lesions of buccal mucosa and palate, and extensive subconjunctival haemorrhage of his right eye, with no visual deficits. A CT scan confirmed widespread lymphadenopathy within the neck, chest, abdomen and pelvis with nodular lesions within the lungs. Clinically, these findings were consistent with KS, stage T1-IO-S0 according to the AIDS Clinical Trial Group Oncology Committee staging criteria.[10]

A punch biopsy of a chest lesion showed a late-stage vasoformative lesion involving both dermis and subdermis, with areas of spindle cell proliferation, erythrocyte extravasation, a high degree of collagen dissection and the presence of multiple hyaline bodies, and some vascular invasion. Nuclei of the spindle cells stained positively by CD31 and for HHV-8 antigen by immunohistochemistry (IHC). The HHV-8 IHC staining pattern was light and diffuse, with 2–8 discrete granules per nucleus of infected cells, confirming the diagnosis of KS (Fig. 2). Plasma and peripheral blood mononuclear cells (PBMCs) samples collected prior to recommencement of ART and when he presented acutely with KS, were sent to the reference laboratory for HHV-8 PCR analysis. No HHV-8 could be detected in all specimens tested.

He was treated with pegylated liposomal doxorubicin (PLD) at 20 mg/m^2 with dexamethasone 20 mg o.d. which resulted in