MAJOR ARTICLE

New Onset of Kaposi Sarcoma in a Human Immunodeficiency Virus-1-Infected Homosexual Man, Despite Early Antiretroviral Treatment, Sustained Viral Suppression, and Immune Restoration

Amrei von Braun,[1] Dominique L. Braun,[1] Jivko Kamarachev,[2] and Huldrych F. Günthard[1]

Divisions of [1]Infectious Diseases and Hospital Epidemiology and [2]Dermatology, University Hospital Zurich, University of Zurich, Zurich, Switzerland

This is a rare case of new onset Kaposi sarcoma in a man infected with human immunodeficiency virus (HIV) and receiving antiretroviral treatment since primary HIV infection, with normal $CD4^+$ cell count and suppressed viral load. The presentation questions the general understanding of Kaposi sarcoma as an acquired immune deficiency syndrome-defining disease occurring predominantly in severely immunocompromised patients infected with HIV.

Keywords. HHV-8 reactivation; immune restoration; Kaposi sarcoma; primary HIV infection.

CASE REPORT

A 45-year-old white man infected with human immunodeficiency virus (HIV) presented with an acute onset of a dark patchy skin lesion on his left foot (Figure 1A) and a smaller dark papule on his penis (Figure 1B). The painless lesions had developed within a few days. He otherwise felt healthy and denied further symptoms. He had neither engaged in risky sexual behavior nor had he traveled recently. On physical examination no other physical abnormalities were seen.

The patient is an MSM (men who have sex with men) and was diagnosed with primary HIV-1 infection in April 2009. At that time, he presented with symptoms of an acute retroviral syndrome, had a negative HIV screening test in November 2008, and the HIV Western blot was positive for 3 of 5 bands in the presence of a detectable p24 antigen. His baseline $CD4^+$ cell count was 512/μL with a viral load of 4 million HIV-1 RNA copies/mL plasma. He was immediately started on early antiretroviral treatment (ART) consisting of ritonavir-boosted darunavir combined with tenofovir and emtricitabine as part of the Zurich Primary HIV Infection Study [1]. Under antiretroviral therapy, the patient's $CD4^+$ cell count remained stably above 500/μL until today (range, 606/μL–1002/μL; 29%–34%). His viral load has been consistently undetectable (<20 HIV-1 RNA copies/mL plasma) for more than 4 years.

Because HIV-associated Kaposi sarcoma (KS) was suspected, skin biopsy of the lesion on his left foot was performed. The histology showed a dermal tumor consisting of spindle cells with some irregular vessel lumina formation, as well as plasma cells and erythrocyte extravasates in the tumoral stroma yielding the diagnosis of KS (Figure 2A). Immunohistochemistry proved the lymph vessel origin of the tumor by showing positivity for the lymph vessel marker d2-40. Further human herpesvirus 8 (HHV-8) immunochemistry staining was positive in the spindle cells (Figure 2B), thus confirming the histological diagnosis. Based on

Received 20 January 2014; accepted 3 March 2014.

A. v. B. and D. L. B. contributed to the manuscript equally.

Correspondence: Amrei von Braun, University Hospital Zurich, Division of Infectious Diseases and Hospital Epidemiology, Raemistrasse 100, CH-8091 Zurich, Switzerland (Amrei.vonbraun@usz.ch).

Open Forum Infectious Diseases

DOI: 10.1093/ofid/ofu005

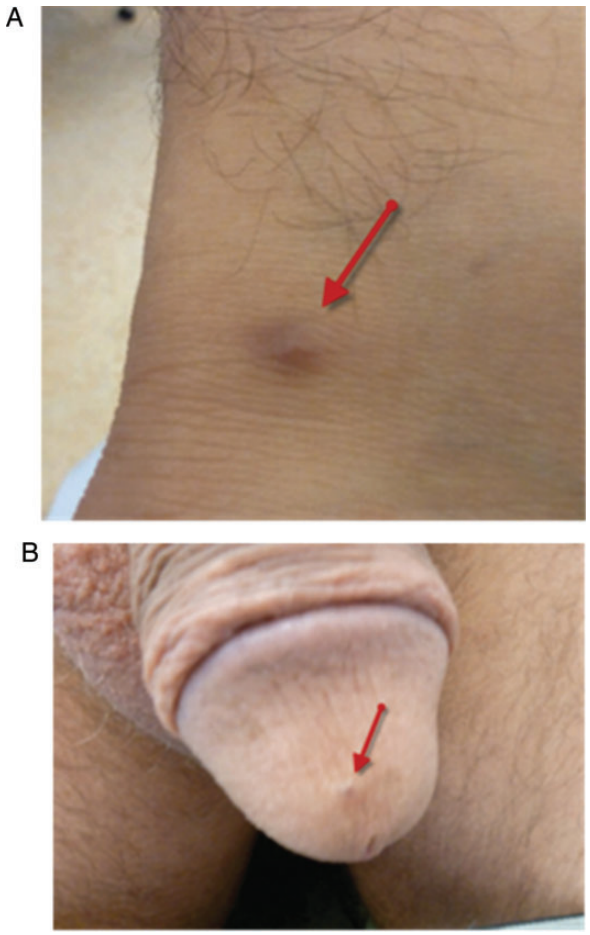

Figure 1. (A) Left foot, malleolar. Dark brown patchy lesion measuring 3 × 5 mm. (B) Glans penis. Dark brown papule measuring 2 × 2 mm.

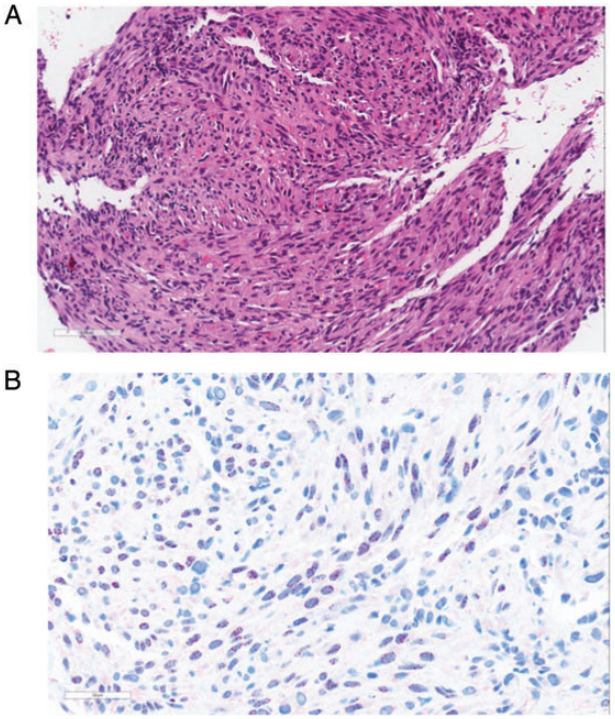

Figure 2. (A) Hematoxylin-eosin stain. Dermal tumor consisting of spindle cells with irregular vessel lumina formation, plasma cells, and erythrocyte extravasates in the tumoral stroma. (B) Human herpesvirus 8 (HHV-8) stain. Positive HHV-8 immunochemistry staining in spindle cells.

its clinical aspect, the genital lesion was considered to be KS as well. Laboratory results showed normal C-reactive protein, blood count, and liver and kidney function. Syphilis was ruled out by serology. The HIV-1 viral load was fully suppressed and his $CD4^+$ cell count measured 620/μL (30%). Differentiation of T cells showed increased expression of immune activation markers such as increased CD4/38 of 25/μL (normal, 4–22/μL) and CD8 HLA-DR of 135/μL (normal, 6–108/μL). Human herpesvirus 8 serologies and polymerase chain reaction (PCR) were performed retrospectively from a blood sample collected in April 2009 when the patient was first diagnosed with primary HIV-1 infection. The immunofluorescence assay revealed immunoglobulin (Ig)G antibodies against latent and lytic antigens in both samples, whereas IgM was negative, reflecting former HHV-8 infection. The HHV-8 PCR was negative in April 2009 but showed 593 copies/mL plasma at the onset of KS. To screen for possible further organ involvement gastro-oesophagoduodenoscopy and colonoscopy were done, both showing no visceral lesions. A chest x-ray was normal as well. The patient's current ART consisting of ritonavir-boosted darunavir combined with tenofovir and emtricitabine was continued. After visceral KS had been ruled out, the lesion on the left foot was treated locally with cryotherapy. The genital lesion disappeared spontaneously after 8 weeks and repeat HHV-8 PCR was negative. The patient continues to be seen at our hospital regularly and is doing well at 6 months. The lesion on his right foot has healed completely. No further lesions have appeared in the meantime. He remains stable on ART with suppressed viral load and high $CD4^+$ cell count.

Kaposi sarcoma is considered an acquired immune deficiency syndrome (AIDS)-defining neoplastic disease in patients infected with HIV [2] and is caused by HHV-8. The vascular nodules of the angioproliferative tumor appear on the skin, mucous membranes, and rarely in visceral organs (especially gastrointestinal [GI] tract, lungs). Lymph node involvement is common. Clinical findings range from single or multiple skin lesions as seen in our case to vastly disseminated disease. Diagnosis is based on the clinical aspect of the lesion and the biopsy, which histologically shows a proliferation of spindle cells and endothelial cells, extravasation of red blood cells, and hemosiderin-laden macrophages [2]. The development of KS in patients infected with HIV has historically been associated with low $CD4^+$ cell counts (usually <200/μL) and the absence of ART. Although KS was common in patients infected with HIV in the

1980s and 1990s, occurring in up to 67% of patients diagnosed with HIV [2], today it is rarely seen in countries with widespread distribution of effective ART [3]. Most patients who develop KS while on ART began treatment with low $CD4^+$ cell counts and develop KS within the first 6 months since initiation of ART [4]. A retrospective study by Daly et al [5] aimed to investigate the characteristics of patients infected with HIV with $CD4^+$ cell counts of >300 cells/μL and the presence of histologically confirmed KS. Of the 23 cases described, 7 (30%) presented with new onset KS while showing $CD4^+$ cell counts >300/μL. All of the cases were MSM with a median age of 39 years (range, 26–66 years), and only 2 of the patients were on ART at the time of diagnosis. This last fact prompts the authors to rule out immune reconstitution through ART as the sole cause of new onset KS in patients with high $CD4^+$ cell counts. Crum-Cianflone et al [6] evaluated longitudinal rates of KS and trends in $CD4^+$ cell counts during the HIV epidemic (1985–2008). The group was able to demonstrate an increase of the proportion of KS cases in patients with higher $CD4^+$ cell counts (>350/μL) in a setting with widespread access to ART, which further highlighted the importance that clinicians should be aware of the occurrence of Kaposi's sarcoma despite robust $CD4^+$ cell counts.

Human herpesvirus 8, also referred to as KS-associated herpesvirus, was identified in 1994 as the etiological agent of KS [7]. Human herpesvirus 8 infection is necessary but not sufficient for the development of KS. Human immunodeficiency virus coinfection and immunosuppression significantly increase an HHV-8-seropositive patient's risk of developing a KS [8]. Similar to other herpesviruses, it is transmitted through close person-to-person contact and establishes persistent infection. We were able to show a sudden and transient HHV-8 viremia in our patient at the time of onset of KS. Because the blood sample collected in 2009 already revealed seropositivity, a primary HHV-8 infection could be ruled out at the onset of disease. Sullivan et al [9] found an HHV-8 seropositivity rate of 69%–75% in MSM in Switzerland without KS, suggesting widespread exposure to this virus in Swiss MSM. We conclude that viral reactivation of unknown origin most likely contributed to the development of new onset KS in our patient. A further possible explanation for the patient's transient HHV-8 viremia could be superinfection with a different HHV-8 strain. Beyari et al [10] were able to demonstrate multiple HHV-8 infection in a study population from Malawi. Whether multiple HHV-8 carriage reflects simultaneous coinfection with more than one strain or superinfection remains unclear however. Most likely both options are possible.

So far, defined staging guidelines for KS do not exist. Most management recommendations by clinical HIV societies do not include routine staging investigations such as computed tomography scan, bronchoscopy, or GI endoscopy in the absence of symptoms [11]. We decided to perform a chest x-ray as well as upper and lower GI tract endoscopy before initiating a treatment strategy since single skin lesions can be treated locally.

Independently of any other factor, all HIV-infected patients diagnosed with KS should receive ART [8]. Effective antiretroviral regimens reduce the incidence of AIDS-related KS and are associated with histological regression of existing lesions in most cases. Limited local disease may be treated with a variety of therapies depending on size and location including cryotherapy, laser therapy, radiation, and intralesional chemotherapy (eg, vinblastine). Systemic therapies for disseminated disease approved by the US Food and Drug Administration include 2 liposomal anthracyclines (doxorubicin and daunorubicin) and the taxane paclitaxel.

The development of KS in patients infected with HIV with high $CD4^+$ cell count—as seen in our case—is rare. Although, theoretically, KS may occur at any stage of HIV infection, to our knowledge so far only a few case reports of KS in patients with high $CD4^+$ cell count were published [12]. Our case is the first one published on the occurrence of KS in a patient effectively treated with early ART since diagnosis of primary HIV infection. What triggers the development of KS in patients under successful ART with formally normal immune function is still unknown. Increased immune activation may be a possible cofactor. As mentioned above, laboratory investigations found signs of immune activation in our patient. However, whether KS itself leads to immune activation or vice versa remains unclear.

The answer to the question why some individuals are able to successfully control persistent HHV-8 infection and thereby prevent the onset of KS whereas others are not most likely lies in the HHV-8-specific immune responses, which are still poorly understood [13]. Lambert et al [14] compared the HHV-8 specific $CD8^+$ T cell responses in transplant recipients and patients infected with HIV with and without KS. The patients who did not develop KS clearly had more frequent anti-HHV-8 T cell responses. Because the cellular response to cytomegalovirus, a further latent virus, was similar in both patient groups, the author's findings do not seem to reflect global $CD8^+$ dysfunction [14]. The observations show lower HHV-8-specific $CD8^+$ T cell response and lower response to HHV-8-specific antigens in patients progressing to KS. A study published by the Swiss HIV Cohort Study was able to show that the humoral immune response to HHV-8 increases after 24 months of highly active ART (HAART), even in MSM without KS [9]. This humoral immune response together with changes in cellular immunity explains the protection against KS offered by HAART. The occurrence of KS in a patient started on HAART during primary HIV infection is even more remarkable because initiation of HAART at a very early stage of infection is associated with preserved immune function [14]. One could hypothesize that this fact should have contributed to a sufficient control of latent HHV-8 infection.

Luckily, KS has become a rare malignancy in the era of ART, at least in developed countries. Today, the incidence of KS is less than 10% of the incidence reported in 1994 [4]. Nonetheless, by presenting this case we emphasize the importance of keeping

the possibility of KS in mind even in patients infected with HIV with high $CD4^+$ cell count and on ART in order not to miss this potentially devastating disease. Our patient's case challenges the common perception of KS as an AIDS-defining illness in patients with normal $CD4^+$ cell counts.

Notes

Acknowledgments. We thank the patient for participating in the Zurich Primary HIV Infection Study.

Financial support. This work was supported by the University of Zurich's Clinical Research Priority Program (CRPP) "Viral infectious diseases: Zurich Primary HIV Infection Study"

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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