HIV-Associated Kaposi Sarcoma Induced by Immune Reconstitution Inflammatory Syndrome Following Antiretroviral Therapy: A Case Report and Review

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Abstract

Classically, Kaposi sarcoma (KS) has been implicated as an HIV/AIDS-defining illness, presenting in patients with low CD4 counts and high viral loads. We present a case of an HIV-seropositive patient on antiretroviral therapy who developed KS lesions in the setting of an undetectable HIV-viral load and high CD4 T-cell count secondary to a paradoxical phenomenon known as immune reconstitution inflammatory syndrome (IRIS), in which lesions develop in parallel with an improved immune status. We will review the pathogenesis, diagnostic criteria and consequences of IRIS-induced HIV-KS following antiretroviral therapy.

Case Report

A 45-year-old, HIV-seropositive male presented to a private practice clinic complaining of a lesion on his left back, which had been enlarging over the course of one month. He also noted new lesions on the bilateral dorsal hands that had also developed over the course of a month. He denied pain, pruritus, burning, or bleeding of the lesions. Additional review of systems was otherwise negative. Review of medical history was significant for starting HAART approximately nine months prior to noticing the skin lesions. His viral load had been undetectable since beginning HAART, and his most recent CD4 count was reported as 704 cells/mm$^3$, an increase from his pre-HAART CD4 count of 658 cells/mm$^3$. History was additionally notable for same-sex encounters (MSM) and prior sexually transmitted disease, including treated syphilis and inactive genital herpes.

Physical examination revealed a solitary, well-demarcated pink nodule with overlying fine white scale on the left back (Figure 1). On his bilateral dorsal hands were discrete, 1 cm, pink-to-violaceous, round flat-topped plaques with overlying fine white scale (Figure 2). Provisional diagnoses for the scapular lesion included: dermatofibroma, hypertrophic scar, dermal nevus, prurigo nodularis, basal cell carcinoma, Merkel cell carcinoma, adnexal neoplasms, Spitz nevus, dermatofibrosarcoma protuberans, atypical fibroxanthoma, lymphomatoid papulosis, pyogenic granuloma, bacillary angiomatosis, B cell lymphoma and Kaposi sarcoma. The differential diagnosis for the dorsal hand lesions included: granuloma annulare, annular lichen planus, Kaposi sarcoma, sarcoidosis, erythema elevatum diutinum, deep erythema annulare centrifugum, subacute cutaneous lupus erythematosus, and pseudolymphoma.

A shave biopsy was performed on the lesions on the left back and left dorsal hand (Figures 3, 4). Both lesions shared similar histopathologic characteristics, with microscopic evaluation showing an intra-dermal, dense nodule composed of interweaving fascicles of spindle cells containing red blood cells. At the periphery of the nodules were granulation tissue, characterized by widely dilated blood vessels, a markedly edematous stroma, and a nuclear infiltrate containing plasma cells and siderophages (Figure 3). Immunostaining was positive for CD34 (Figure 4) and HHV8, highlighting hematopoietic origin of spindled cells and confirming the
diagnosis of KS, respectively.

Our patient was sent to oncology for further evaluation, with resultant laboratory studies and CT imaging negative for visceral disease. Since the lesions were limited to the skin, our patient elected to treat them locally with the vascular-specific pulse dye laser (585 nm) as an adjunct to continuing HAART. PDL was performed on lesions on his back and dorsal hands with the following parameters: 3 ms pulse duration, 13 joules/cm² fluence, and 7 mm spot size. Our patient tolerated the procedure well and has remained clinically stable with undetectable viral load and excellent CD4 count. The lesion on the back has remained quiescent after one treatment, and he continues to receive laser therapy to the dorsum of the hands.

Discussion

Kaposi sarcoma (KS) is an angio proliferative tumor capable of affecting the skin, lymph nodes or viscerla. There are four subtypes of KS: classic, African-endemic, HIV/AIDS-associated, and iatrogenic/immunosuppression-related. These subtypes share many common features, including history of human herpes virus 8 (HHV8) expression within lymphatic and vascular endothelial cells as well as a variable clinical presentation ranging from localized to disseminated mucocutaneous and/or visceral disease. Phenotypic expression of HHV8 within KS lesions is due to a complex multi-factorial relationship between several factors including HHV8 gene expression, HIV status, immune impairment, cytokine dysregulation and other yet-to-be identified factors. Histological features of KS do not vary between clinical subtypes, but they do vary by stage of lesion. Clinically, lesions tend to vary in severity but are typically erythematous-to-violaceous papulonodules that enlarge with time.

The most common presentation of KS is the HIV-related subtype. Historically, HIV-KS has been considered an AIDS-defining condition due to presentation in the setting of severe immunodeficiency demonstrated by associated low CD4 T-cell counts and high viral loads. The introduction of antiretroviral therapy has led to a decrease in the overall incidence and prevalence of HIV/AIDS-related KS secondary to recovery of host immune response and reduction of HIV and HHV-8 viral loads. Although HAART is mainly preventative and therapeutic for clinical HIV-KS, a subset of HIV-seropositive individuals will have onset of new, worsening, or recurrent KS lesions secondary to a paradoxical phenomenon known as immune reconstitution inflammatory syndrome (IRIS) following initiation of antiretroviral therapy. IRIS is defined as the paradoxical worsening or onset of an infection, inflammatory condition, or a proliferative disease (such as cancer) occurring in parallel with an improved immune status. IRIS-induced KS is not exclusively seen in the setting of HIV-seropositivity; it has also been described in association with iatrogenic KS upon discontinuation of immunosuppressive therapy with systemic steroids and cytotoxic chemotheraphy. The pathogenesis of HAART-induced IRIS-KS has been described as a dysregulation of the restored host ability to mount an inflammatory response, particularly involving the activity of HHV8 antigen. A HAART induced increase in CD4+ T cells and a decrease in HIV viral load are believed to promote the host production of inflammatory cytokines that trigger the expression of HHV-8 gene products into antigens. The production of HHV8 antigens influences a shift from Th2 (CD4+ T-cell dominant) to Th1 (CD8+ T-cell dominant) immune response. Subsequently, this encourages production of additional inflammatory cytokines as well as cytotoxic CD8+ T cells that specifically target HHV8 antigen. Overall, this dysregulation between the strengthened Th2 and Th1 arms of the immune system results in aberrant signaling for excessive inflammation, promotion of angiogenesis, and transformation of endothelial cells by the HHV8 antigen, all of which contribute to the angio proliferative manifestations of KS disease.

In the setting of HIV, risk factors that promote development of KS include sex between men, low CD4 T-cell count, high HIV and HHV8 viral loads, concurrent infections and history of sexually transmitted disease. It has been postulated that about 6.6% to 10% of subjects who are HIV-seropositive will develop IRIS-associated KS after HAART is initiated. Patients with greater immunodeficiency at initiation of HAART are at increased risk of developing IRIS, with an incidence reported as high as 25% in patients with a baseline CD4 T-cell count of <50 cells/mm³. Diagnostic criteria for IRIS-induced HIV-KS includes a patient on HAART with new, worsening, or recurrent KS lesions in the setting of increased CD4 count greater than or equal to 50 cell/mL or a two-fold increase, and a decrease in HIV-1 viral load greater than 0.5 log. The time frame for development of KS following initiation of HAART is not clearly defined, although several cases report cutaneous lesions developing within eight to 12 weeks of initiating therapy. While increased risk of IRIS is seen in the setting of advanced immunodeficiency, in recent years numerous case reports and retrospective studies have described initial KS lesions developing after initiation of antiretroviral therapy in patients with baseline CD4 counts >300 cells/mm³ and undetectable viral loads, much like our case report. The rising presentation of HIV-KS in the setting of optimally controlled HIV disease counters the traditional view that KS-lesions are a prognostic indicator specific to advanced HIV disease or that KS is an AIDS-defining illness. Prognosis in patients with IRIS-associated HIV-KS is promising, particularly in the setting of immunocompetence, with immunocompetence defined as undetectable viral loads and CD4 T-cell counts greater than or equal to 300 cells/mm³. These patients have been reported to have a less aggressive course and more localized disease when compared to those who have high viral loads and low CD4 T-cell counts, or those who were HAART naive at HIV-KS diagnosis. These patients were also found to be significantly less likely to die and demonstrated a better 15-year survival when compared to KS patients with lower CD4 counts and detectable HIV viral loads.

Opportune control of HIV infection by continuing HAART is an integral part of successful therapy, with recommended additional adjunctive local or systemic therapy depending on extent of disease. Response to HAART as monotherapy ranges from 20% to 80% based on stage of disease and level of pretreatment. Adjavan localized therapeutic options include radiotherapy, pulse-dye laser, pulsed CO2 laser, excisional surgery, and intralesional chemotherapy. These adjuvants provide limited benefit as they do not affect development of new lesions in untreated areas, making continued therapy with HAART the only treatment associated with long-lasting, complete resolution of lesions.

Conclusion

IRIS-associated HIV-KS is a paradoxical immunoinflammatory reaction brought about by improvement in immune status following antiretroviral therapy. In our current era of HAART-controlled HIV disease, dermatologists must remain suspicious of IRIS-associated HIV-KS, regardless of initial CD4+ T-cell count or HIV viral load. Judicious and appropriate screening is recommended for pre-existing KS lesions as well as for evidence of new eruptions following recovery of the immune system. This condition is best managed with continued disease control on HAART as well as adjunctive local or systemic therapy depending on clinical severity on a case-by-case basis.

References


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