Immune Reconstitution Inflammatory Syndrome Associated with Kaposi Sarcoma during Potent Antiretroviral Therapy

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Rapidly progressive Kaposi sarcoma (KS) lesions with lymphadenopathy and tissue swelling occurred in a patient during antiretroviral treatment, despite an increased CD4+ lymphocyte count and decreased HIV-1 level and KS-associated herpesvirus replication, suggesting immune reconstitution inflammatory syndrome. Inflammation resolved coincident with decreases in the CD4+ lymphocyte count during paclitaxel treatment, whereas KS cleared only after prolonged antiretroviral therapy and chemotherapy.

Persons who are coinfected with Kaposi sarcoma (KS)-associated herpesvirus (KSHV) and HIV-1 are at high risk for KS. It has been hypothesized that HIV-1 infection promotes KSHV pathogenesis through the effects of HIV-1 proteins on KSHV replication and, indirectly, through CD4+ lymphocyte depletion and the production of inflammatory cytokines [1–3]. Although antiretroviral agents do not affect KSHV replication directly, a dramatic decrease in the incidence of AIDS-associated KS has coincided with the advent of HAART [4, 5]. HAART results in complete or partial resolution of KS lesions in 55%–60% of patients with AIDS-associated KS [6, 7]. These findings suggest that suppression of HIV-1 is often adequate for treatment of AIDS-associated KS, but little is known about the relationships between immune reconstitution, control of KSHV replication, and resolution of KS tumors during HAART.

Immune reconstitution inflammatory syndrome (IRIS) is an inflammatory reaction to an opportunistic pathogen and/or tumor antigen that occurs early after initiation of HAART and is temporally related to an increase in the host’s CD4+ lymphocyte count [8]. IRIS is most frequently observed in individuals with severe CD4+ T cell depletion and is believed to be due to reconstitution of immune responses to a previously existing (but clinically occult) pathogen or tumor antigen, rather than development or progression of opportunistic infections. Although KSHV is prevalent among HIV-1-infected persons, IRIS during antiretroviral treatment of AIDS-associated KS has been reported only twice [9, 10]. No measurements of KSHV load, however, were performed in these cases to distinguish them from progressive KS. Herein, we describe a case of rapidly progressive KS at the time of initiation of HAART, despite the patient having decreases in HIV-1 and KSHV replication, consistent with IRIS associated with AIDS-associated KS.

Case study. A 35-year-old white, homosexual man presented with KS and Pneumocystis jiroveci pneumonia. Physical examination revealed 36 cutaneous lesions consistent with KS that were concentrated on the face and torso and ranged from 0.3 to 3 cm in the largest dimension. Neither mucocutaneous KS nor symptoms of visceral involvement were present. The CD4+ lymphocyte count was 81 cells/mm3, and the plasma HIV-1 RNA level was >750,000 copies/mL. The patient was treated with anti-P. jiroveci pneumonia therapy for 3 weeks, was observed for 2 additional weeks, and started receiving stavudine, lamivudine, and coformulated lopinavir-ritonavir. No new KS lesions developed during the 5-week interval before commencement of HAART.

During the second week of HAART, face and neck swelling developed (figure 1A). Physical examination findings were notable for periorbital edema; multiple new, nontender cervical lymph nodes; and a more violaceous and nodular appearance of the preexisting KS lesions. CT of the neck and chest demonstrated multiple 1-cm anterior and posterior cervical lymph nodes, as well as subcutaneous edema, but neither mediastinal lymphadenopathy nor evidence of superior vena cava obstruction were noted. During the preceding month, the results of serum cryptococcal antigen tests had been negative, a rapid plasma reagin test was unreactive, antibodies for Toxoplasma gondii were not detected, the serum lactate dehydrogenase level was normal, and blood cultures were negative for mycobacteria. Fine-needle aspiration of a cervical node revealed a polymorphous population of lymphocytes, histiocytes, and acute inflammatory cells, without evidence of malignancy or granuloma. The results of bacterial cultures of the aspirate were...
Figure 1. A, Photograph of the patient 4 weeks after initiation of HAART, demonstrating extensive cutaneous KS-associated lesions and facial and periorbital edema. B, Photograph of the patient 32 months later. After 13 cycles of paclitaxel and almost 3 years of HAART, lesions have largely resolved. The circular lesion on the right cheek is a nevus.

negative, but an insufficient amount of the specimen was available to perform mycobacterial culture.

Examination of the patient 7 weeks after he had started receiving HAART revealed multiple cervical lymph nodes ranging in size from pea-sized to 2 cm in diameter, and there were 12 new lesions consistent with cutaneous KS on the anterior chest. The CD4+ lymphocyte count had increased to 319 cells/mm³ (figure 2A), and the plasma HIV-1 RNA level had decreased to 681 copies/mL (figure 2B). Paclitaxel therapy (135 mg/m² every 3 weeks) was begun at this time.

At week 10 of HAART, facial edema had resolved, cutaneous KS lesions were flattened and faded, and the CD4+ lymphocyte count had decreased to 133 cells/mm³. Three additional cycles of paclitaxel were given at 75% of the full dose because of myelosuppression, resulting in marked flattening and fading of KS lesions. Nevertheless, 4 weeks after the last dose of paclitaxel was administered, facial swelling, darkening of lesions, and cervical lymphadenopathy recurred. The CD4+ lymphocyte count had increased to 241 cells/mm³. Paclitaxel therapy (135 mg/m² every 3 weeks) was resumed. The patient observed that, after each cycle of chemotherapy, his facial swelling and cervical lymphadenopathy would disappear, but they would then reappear shortly before the next cycle. A cervical lymph node excisional biopsy performed after 7 cycles demonstrated classic features of KS, and the results of immunohistochemistry examination of the specimen were also positive for KSHV. On discontinuation of treatment with paclitaxel, after a total of 13 cycles, edema and lymphadenopathy did not recur. The CD4+ lymphocyte count was 210 cells/mm³, and it increased to 436 cells/mm³ over the ensuing 20 months. Many KS lesions were present at the time that chemotherapy was stopped; however, all but 2 small facial lesions resolved over the following 20 months (figure 1B).

Methods. At the first visit, the patient was enrolled in a study of the impact of HAART on KSHV replication. This study followed the US Department of Health and Human Services Guidelines for human experimentation and was approved by the Colorado Multiple Institutional Review Board (Denver). Plasma and PBMC KSHV DNA were quantified by real-time PCR amplification of a conserved region of the ORF 26 minor capsid gene, as described elsewhere [11]. In all assays, there was a linear relationship between the value of threshold cycle for the standards and the logarithm of minor capsid DNA copy number ($r^2 = 0.98$ for each assay). If the measured KSHV DNA level was $\geq 1$ copy, the result of the PCR reaction was considered to be positive. Negative controls included 2 PCR reactions that contained 2 µg of carrier DNA and 4 reactions that contained no DNA. In all assays, the measured fluorescence of the 6 negative controls did not exceed the threshold after 40 PCR cycles.

Results. Prior to receipt of HAART, KSHV DNA was detected in both plasma samples (median KSHV DNA level, 4518 copies/mL) and PBMCs (median, 10,700 copies/10⁵ cells) (figure 2C and 2D). Plasma KSHV DNA levels did not change from pretreatment levels during the first 4 weeks of HAART, although the plasma HIV-1 RNA level had decreased 2.5 log₁₀.
Figure 2. Effects of HAART on the immunologic and virologic parameters of peripheral blood CD4+ lymphocyte count (A), plasma HIV-1 RNA level (B), plasma Kaposi sarcoma–associated herpesvirus (KSHV) DNA level (C), and PBMC KSHV DNA level (D). Dashed lines, lower limits of detection; black arrow, start of paclitaxel therapy.

Copies/mL by week 4 (figure 2B). Between weeks 4 and 8 of HAART, the plasma KSHV DNA level decreased precipitously (a decrease of 2.2 log_{10} copies/mL from pretreatment levels). PBMC KSHV DNA levels decreased gradually over the first 17 weeks of antiretroviral therapy.

Discussion. We have described the sudden onset of facial edema, cervical lymphadenopathy, and new KS lesions in a patient shortly after initiation of HAART. Several features of this case suggest that the worsening symptoms and clinical findings represented IRIS rather than progressive KS. Importantly, there was no clinical progression of KS during the 5 weeks before initiation of HAART. The temporal relationship between the initiation of HAART, the increased CD4+ lymphocyte count, and the sudden onset of facial swelling and lymphadenopathy is consistent with IRIS [8]. The finding of inflammatory cells in the cervical lymph node aspirate is also consistent with IRIS, and other potential causes of cervical lymphadenopathy that were investigated were excluded. A decrease in the plasma KSHV DNA level that was temporally associated with initiation of HAART further suggests that KSHV-specific immune responses were reconstituted during this interval. The response of clinical symptoms to paclitaxel, an inhibitor of cell proliferation, and recurrence of symptoms after discontinuation of therapy are consistent with prior reports of anti-inflammatory therapy for other types of IRIS [8].

IRIS associated with AIDS-associated KS provides a unique opportunity to evaluate temporal relationships between immune reconstitution and dynamic changes in KSHV replication. The precipitous decrease in the plasma KSHV DNA level during the period of IRIS and increased CD4+ lymphocyte count suggest that productively KSHV-infected cells were rapidly cleared by reconstituted host antiviral responses during the early period of HAART. The more gradual decrease in the KSHV DNA level in PBMCs suggests that clearance of latently infected cells is slower and/or that this population is more numerous. Paclitaxel therapy resulted in rapid resolution of facial edema and in decreases in the CD4+ lymphocyte count. For this patient, chemotherapy likely served both to treat KS and to attenuate reconstituted immune responses, thereby alleviating symptoms of IRIS while KSHV antigen was being cleared by KSHV-specific host effector cells.

Initiation of HAART is usually associated with regression of KS [6, 7], not progression, as was observed in our patient. Our literature search revealed only 2 prior reports of IRIS associated with KS. In one case, laryngeal obstruction occurred in a patient with known KS shortly after initiation of HAART [9]. In the other case, parotid gland KS developed in an individual 2 years after initiation of HAART, despite there being good CD4+ lymphocyte reconstitution and virus suppression [10]. We found an additional report of rapidly progressive KS in a few individuals that occurred after initiation of antiretroviral therapy.
Although not recognized as such by the authors, these cases may represent additional examples of KS-associated IRIS. Thus, it is likely that KS-associated IRIS is more common than the literature reflects. With the advent of HAART in Africa, where KSHV is more prevalent and initiation of HAART is recommended at lower CD4⁺ lymphocyte counts than in the United States, it is likely that significantly more cases of KS-associated IRIS will be observed. It is important for clinicians to realize that IRIS does not indicate failure of HAART or a need for changes in antiretroviral regimen. Instead, chemotherapy in conjunction with HAART can effectively control the symptoms of IRIS as well as resolve KS.

Acknowledgments
We thank Joy Folkvord for assistance with photography.

Financial support. National Institutes of Health (grant CA79389; to T.B.C), Colorado Center for AIDS Research (grant AI054907), University of Colorado AIDS Clinical Trials Unit (grant U01 AI 32770), and University of Colorado Cancer Center Quantitative PCR Core.

Potential conflicts of interest. All authors: no conflicts.

References