Immune Reconstitution Inflammatory Syndrome Due to Pulmonary Kaposi Sarcoma Following Initiation of Highly Active Antiretroviral Therapy

Aimee N. French, MD, Mark Richman, MD, MPH, and Nader Kamangar, MD, FACP, FCCP, FAASM

Abstract: Pulmonary Kaposi sarcoma (KS) is a potentially fatal complication of AIDS/HIV infection. With the development of highly active antiretroviral therapy (HAART), the morbidity and mortality associated with AIDS/HIV have decreased significantly. However, a small number of patients started on HAART develop a severe inflammatory response to preexisting pathogens or antigens, known as immune reconstitution inflammatory syndrome. We describe a case of rapidly progressive pulmonary KS in a patient with AIDS who was recently restarted on HAART and provides a review of immune reconstitution inflammatory syndrome and its association with KS.

Immune reconstitution inflammatory syndrome (IRIS) represents a group of inflammatory disorders associated with paradoxical worsening of preexisting infectious and noninfectious processes following the initiation of highly active antiretroviral therapy (HAART) in HIV-infected individuals. IRIS occurs when the newly reconstituted immune system recognizes dormant antigens of preexisting infections. Kaposi sarcoma (KS) flare associated with initiation of HAART represents yet another protean manifestation of IRIS. IRIS associated with KS can be difficult to diagnose and a high clinical suspicion is pivotal. This entity raises important clinical implications for the management of KS in the HAART era as rapid initiation of appropriate antineoplastic therapy is crucial.

CASE REPORT

A 34-year-old homosexual male, diagnosed with HIV/AIDS in 2000, presented to the HIV clinic for routine follow-up complaining of dry cough, dyspnea, painful swelling of the groin and genitals, and a painful periodontal infection for 1 week. At the time of initial HIV diagnosis, the patient was treated at an outside HIV clinic and was taking HAART until 2 years prior, when treatment was discontinued secondary to intolerable side effects. The patient was lost to follow-up after discontinuation of therapy. Two weeks before admission, the patient presented to an outside HIV clinic and dental office, where he was found to have a CD4 count of 2 cells/mL and an HIV RNA of 325,000 copies/mL. Subsequently, he was restarted on HAART (lopinavir/ritonavir, emtricitabine-tenofovir).

The patient stated that in the past week his genital, groin, and periodontal lesions had become significantly more swollen and painful. At initial presentation, he was afebrile; his heart rate was 91, blood pressure 106/56, respiratory rate 20, and oxygen saturation 94% on room air. He was thin and fatigued with a hoarse voice and constant dry cough. He had hyperplasia and erythema throughout the gingival area, with two 1 cm violaceous nodular lesions on the skin of the right cheek. His pulmonary examination revealed bilateral coarse breath sounds that were decreased at the bases. The patient had bilateral tender inguinal lymphadenopathy, scrotal and genital edema, and multiple violaceous nodular lesions on the abdomen and genital area.

Laboratory studies revealed a CD4 count of 19 cells/mL and an HIV RNA that was undetectable. The patient had a white blood cell count of 2500 cells/mL, absolute neutrophil count of 1125 cells/mL, hemoglobin 11.7 mg/dL, and platelets 335,000 cells/mL. Chest radiography (Fig. 1) and thoracic computed tomography (CT) (Fig. 2) revealed dense bibasilar consolidation with marked peribronchial thickening, perivascular nodularity, nodules along interlobar fissures, and thickening of interlobular septa and bilateral pleural effusions. Pleural fluid analysis revealed an exudative process with many reactive mesothelial cells; culture did not grow any organisms. Brain CT was normal. The following studies were negative: sputum bacterial, mycobacterial, viral, and fungal stains, and cultures including Pneumocystis jiroveci pneumonia, cytomegalovirus, coccidioides, and cryptococcus; blood cultures for bacteria and fungus; and urine for histoplasmosis and legionella.

Although no obvious source of infection was apparent, empiric antibiotic coverage was started using trimethoprim/sulfamethoxazole and ceftriaxone. The patient continued HAART. On day 2 of admission, the patient underwent fiberoptic bronchoscopy that revealed multiple nodular muco-
cutaneous lesions in the proximal trachea. Biopsy revealed benign mucosa with squamous metaplasia, consistent with acute and chronic inflammation. Skin biopsy demonstrated KS.

During hospitalization, the patient’s condition deteriorated. He required up to 15 L oxygen by facemask to maintain adequate oxygen saturation. After one round of doxorubicin chemotherapy, the patient’s dyspnea and oxygen requirements improved. He was released from the hospital 3 weeks later for outpatient chemotherapy. Three weeks postinitiation of doxorubicin chemotherapy, chest CT demonstrated dramatic reduction in parenchymal disease (Fig. 3). In addition, the patient’s cutaneous KS regressed significantly and his oral lesions resolved. Despite lack of pulmonary tissue demonstrating KS, the diagnosis of pulmonary KS was made on the basis of classic radiographic findings, absence of other explanatory etiologies, and response to chemotherapy. Although the patient’s HIV RNA level decreased and CD4 count improved slightly with HAART, he subsequently experienced an outbreak of oral herpes and bacterial pneumonia. The patient developed respiratory distress and bilateral pneumothoraces, expiring 5 weeks after diagnosis.

DISCUSSION

The development of HAART has significantly reduced AIDS-related morbidity and mortality, particularly from bacterial pneumonia, opportunistic infections, and non-Hodgkin lymphoma.1–4 HAART is also responsible for the dramatic decline in the number of mucocutaneous and pulmonary KS cases seen in areas of the world where HAART is available. The Centers for Disease Control and Prevention estimates indicate the incidence of KS among HIV-infected patients in the United States declined from 4.8 per 100 person-years in 1990 to 1.5 per 100 person-years in 1997. This decline has been accelerated by HAART, with a correlation between the number of antiretroviral agents a patient takes and the patient’s risk of developing AIDS-KS, ranging from a 13% reduction with monotherapy or dual therapy to a 59% reduction with triple therapy.5

Although HAART therapy provides a protective immune response in addition to a profound decrease in HIV-1 viral load and increase in CD4 count, a small number of patients still develop AIDS-defining illness despite HAART, most commonly in the 3 months immediately after the initiation of HAART.6,7 It is believed that HAART, in the process of reactivating the immune system, triggers a profound pathologic inflammatory response to subclinical pathogens and
 residual antigens of dead/dying organisms already present, and, in the case of autoimmune activation, to innate antigens.\textsuperscript{2,4,6,8–11} This pathologic inflammation and dysregulation of the immune system, known as IRIS, results in clinical deterioration of AIDS-related infections and malignancies, as well as other noninfectious diseases such as Grave disease, non-Hodgkin lymphoma, and systemic lupus erythematosus.\textsuperscript{2,6,8–10} These are not accounted for by proliferation of organisms or malignant cells, but rather by an exuberant recruitment of inflammatory cells at the sites of existing pathogens and/or antigens.

Jacobsen and Race first described IRIS in their case reports of atypical manifestations of CMV retinitis and atypical abscess formation in HIV patients recently started on HAART therapy.\textsuperscript{12,13} An IRIS-like phenomenon was well described in the literature before HAART. Case reports of non-HIV patients treated for Mycobacterium tuberculosis (MTB) infection revealed anti-MTB therapy had contributed to the reversal of immunosuppression believed to be induced by MTB infections. Similar rationalization has been used to explain the recovery of immune cells after bone marrow transplant or chemotherapy.\textsuperscript{4}

With the widespread use of HAART in the late 1990s, the first cases of HIV-related IRIS-associated diseases were described. Most of the literature consists of case reports and small case series that have helped define the incidence, risk factors, and presentation of IRIS. To date, there are no prospective therapeutic studies concerning the management of IRIS.\textsuperscript{2,4} Based on published reports, 10% to 25% of patients beginning HAART will experience some degree of IRIS.\textsuperscript{14} It is believed that return of the CD4 cell count occurs in 2 phases.\textsuperscript{4} The first phase (redistribution) is associated with a rapid decline in HIV RNA levels that result in the reactivation of existing memory T-cells (CD4\textsuperscript{+}CD45RO\textsuperscript{+}) and redistribution of these cells from lymphoid tissue; this process may take weeks to months and accounts for the delay in CD4 count recovery. The second, slower phase (repopulation) involves the production of naive T-cells (CD4\textsuperscript{+}CD45RA\textsuperscript{+}CD62L\textsuperscript{+}), which does not occur until months after the initiation of HAART.\textsuperscript{4,6,14} IRIS occurs during the redistribution phase when the ability to mount an inflammatory response to previously indolent antigens is restored. Rapid decline of HIV RNA level is a stronger predictor of IRIS than rapid CD4 count recovery.\textsuperscript{4,6}

Retrospective studies indicate that patients most commonly present with activation of previously suppressed Mycobacterium avium complex, M tuberculosis, CMV, Hepatitis B and C, Cryptococcus neoformans, P jiroveci pneumonia, Herpes simplex, and other infectious and noninfectious etiologies such as KS.\textsuperscript{1,4} Mycobacterial and cryptococcal diseases each account for 30% of IRIS cases.\textsuperscript{15} Presentations of IRIS-associated illnesses may be atypical, including M avium complex lymphadenitis, CMV immune recovery vitritis, and immune recovery uveitis (IRU).\textsuperscript{11} The atypical manifestations and accelerated presentations may help differentiate IRIS from new opportunistic infections that occur on HAART before adequate immunity is restored.

Studies indicate that IRIS occurs more frequently in patients of younger age, a baseline CD4\textsuperscript{+} percentage of fewer than 10% of lymphocytes, and lower CD4:CD8 ratio before starting therapy.\textsuperscript{5,14} Other risk factors include lower baseline CD4 count, higher HIV RNA count; the strongest association is with a more rapid fall in HIV RNA counts within 90 days of initiating HAART.\textsuperscript{5} All reports indicate that male sex and recent or concurrent opportunistic infection increase the risk of IRIS.\textsuperscript{5,10,14}

Although most commonly documented with opportunistic infections, IRIS has also been associated with the acceleration of KS. KS is an angio proliferative tumor associated with endothelial cells, fibroblasts, infiltrating leukocytes, and spindle-shaped tumor cells; KS is an AIDS-defining illness.\textsuperscript{1} The sexually transmitted human herpes virus 8 (HHV-8), also known as KS-associated herpes virus, is the etiologic agent of KS.\textsuperscript{2} There is an interaction between gender and risk for KS, with the prevalence of KS among homosexual HHV-8/HIV-infected males over 20 times that of similarly infected females.\textsuperscript{1} There is a similarly low prevalence among heterosexual HIV-infected hemophiliacs.\textsuperscript{1} Those with CD4 counts below 200 cells/mL are at increased risk for both KS and IRIS-KS. As with our patient, those with CD4 counts <100 cells/mL have a shorter life expectancy and are more likely to develop IRIS-KS and pulmonary involvement by KS.\textsuperscript{5,16,17}

Pulmonary KS is an ominous sign of late-stage AIDS, seen in the presence of extensive mucocutaneous disease and rarely isolated to pulmonary lesions. Patients often present with complaints of dyspnea, cough, night sweats, and fever, making it difficult to distinguish between other pulmonary processes.\textsuperscript{1,16,17} Hoarseness, hemoptysis, dysphagia, and stridor have also been described in patients with pulmonary KS, indicating that the tumor involves the trachea or the larynx. In addition, KS-associated lower extremity lymph node involvement and edema make it difficult to walk, and cutaneous lesions can be painful. In severe cases, the pulmonary burden of tumor can result in respiratory compromise, hemorrhage, and death. Chest radiographic findings of pulmonary KS include reticular and nodular opacities, diffuse consolidation and/or ground-glass opacity, focal air-space consolidation, and/or atelectasis. In 50% of patients, there may be unilateral or bilateral pleural effusions. In 10% to 16% there may be enlarged hilar or mediastinal nodes. Patients with both AIDS and pulmonary KS experience an increased occurrence of opportunistic infections and a greater risk of death compared to those with isolated cutaneous KS or HIV/AIDS alone.

IRIS-associated KS has been described in only a few case reports and one cohort study conducted in 2005 at Chelsea and Westminster Hospital, London. The risk of IRIS was increased in individuals presenting with KS tumor-associated edema at the initiation of HAART, indicating an active inflammatory process before starting therapy. In addition, patients who were HAART-naive at the time of diagnosis of KS were also at increased risk. Location of KS was not associated with risk of IRIS. Although less than 10% of patients with preexisting KS developed IRIS, symptoms in those affected occurred within 2 months of starting HAART.
Compared with KS progression before HAART, all patients had documented acceleration of their KS.8

Strategies to prevent and manage IRIS are limited because randomized trials are lacking. The best prevention against IRIS is to ensure patients with low CD4 cell counts are appropriately treated with prophylactic agents against opportunistic infections before the initiation of HAART. Most case reports indicate that IRIS resolves within a few weeks if HAART is continued and the underlying disease treated. Because most patients with IRIS have an underlying opportunistic infection, treatment usually involves appropriate anti-infective therapy with or without the use of anti-inflammatory agents (NSAIDS or systemic corticosteroids) to suppress the inflammatory process.18 Studies of the management of TB-IRIS have used varying doses and duration of treatment, ranging from intravenous methylprednisolone 40 mg every 12 hours to prednisone 20 to 70 mg/d for 5 to 12 weeks. Likewise, steroids have been used to successfully diminish the inflammatory component of cryptococcal meningitis-IRIS.11 Interruption of HAART is unnecessary, except in severe or unresponsive cases of IRIS.

Treatment of IRIS-KS with cytotoxic chemotherapy agents, including etoposide, bleomycin, doxorubicin, vincristine/vinblastine, and paclitaxel, when used in combination with HAART, causes regression of KS. The most widely used chemotherapy regimen consists of adriamycin, bleomycin, and vincristine.17 Radiation therapy, local injection of chemotherapeutic agents, and topical retinoids are reserved for local and less aggressive forms of KS.16,17,19 Although our patient was initially treated with aggressive chemotherapy, the extent of our patient’s pulmonary disease and comorbid conditions contributed to his rapid demise.

CONCLUSION

Although HAART has had a pronounced effect on the occurrence of opportunistic infections and the progression of AIDS, it has also been linked to the pathologic inflammatory response resulting in IRIS. IRIS is an aggressive and potentially fatal complication of beginning HAART therapy in patients with advanced AIDS, particularly males and those known to have opportunistic infections. IRIS has been most commonly described in patients infected with M avium complex, M tuberculosis, C neoformans meningitis, CMV, and Herpes simplex. Patients with KS may experience fatal flaring of their cutaneous and/or visceral KS lesions shortly after initiating HAART. Patients with the most pronounced decline in HIV-1 RNA levels within 90 days of starting HAART are the most likely to develop IRIS. IRIS must, therefore, be considered in patients presenting with an opportunistic infection or progression of malignancy within 90 days of starting HAART. Studies to evaluate the incidence and outcomes of IRIS are much needed.

REFERENCES