A Fatal Case of Kaposi Sarcoma Immune Reconstitution Syndrome (KS-IRIS) Complicated by Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS) or Multicentric Castleman Disease (MCD): A Case Report and Review

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Patient: Male, 28-year-old
Final Diagnosis: Kaposi sarcoma inflammatory cytokine syndrome (KICS)
Symptoms: Abdominal pain • anemia • dyspnea • fever • shock • thrombocytopenia
Medication: —
Clinical Procedure: Skin biopsy
Specialty: Infectious Diseases

Objective: Unusual clinical course
Background: Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS) is a relatively new syndrome described in patients co-infected with Human Immunodeficiency Virus (HIV) and Kaposi Sarcoma (KS) Herpes Virus (KSHV). KICS clinically resembles Multicentric Castleman disease (MCD) and both present with various degrees of lymphadenopathy, pancytopenia, HIV and KSHV viremia, and signs of systemic inflammatory syndrome (SIRS). KICS has higher mortality than MCD and is rarely recognized. Lymph node, bone marrow, or splenic biopsy can help differentiate between the 2 entities.

Case Report: We present a case of a 28-year-old African American man with advanced acquired immunodeficiency syndrome (AIDS) who was diagnosed with disseminated pulmonary and cutaneous KS. Following initiation of combined antiretroviral therapy (cART), rapid immunologic recovery occurred followed by rapid clinical deterioration (IRIS) with multiorgan failure, overwhelming SIRS, and ultimately death. The patient’s symptoms, signs, and laboratory findings during this episode could not be solely explained by KS-IRIS, and MCD versus KICS was diagnosed.

Conclusions: SIRS in patients with uncontrolled HIV viremia and CD4 lymphopenia has a broad differential diagnosis, including infectious and noninfectious causes. It encompasses sepsis due to common bacterial pathogens, various HIV-specific opportunistic infections, immunological conditions such as hemophagocytic lymphohistiocytosis (HLH), and IRIS, malignancies such as primary effusion lymphoma (PEL) and MCD, and finally KICS. Clinicians involved in treatment of these patients should have a high index of suspicion for less-known and recently described syndromes such as KICS to recognize it early and initiate timely treatment, which might improve the high mortality associated with KICS.

MeSH Keywords: Acquired Immunodeficiency Syndrome • Giant Lymph Node Hyperplasia • Herpesvirus 8, Human • HIV Kaposi Sarcoma Inflammatory Cytokine Syndrome • Systemic Inflammatory Response Syndrome

Full-text PDF: https://www.amjcaserep.com/abstract/index/idArt/926433
Cachectic man with a body mass index (BMI) of 17, in no distress, and in good spirits. He was alert and oriented to self, location, and time. A lung exam was significant for bilateral rhonchi, but without wheezes. Cardiac, abdominal, and neurologic exams were normal. A skin examination was notable for multiple violaceous and dark purple raised patches on the face, anterior chest, and back; but no genital ulcerations were identified. A lymphatic exam was notable for nontender inguinal lymphadenopathy. An oral exam was negative for ulcers or thrush, but several papulonodular dark purple masses were noted on the upper gingiva.

A complete blood cell count (CBC) showed white blood cell count (WBC) of 10.9×10^9/L with lymphopenia (2% lymphocytes), hemoglobin of 12.2 g/dL, and platelets of 197×10^9/L. Serum electrolytes, lactate dehydrogenase, and renal and liver function were normal. Rapid plasma reagin (RPR) was unreactive, procalcitonin was within normal range, CRP was 184 mg/L, and ESR was 59 mm/hr. EKG showed normal sinus rhythm without ischemic changes or arrhythmia. A chest X-ray (CXR) demonstrated bilateral interstitial infiltrates. Blood and sputum cultures were sent. The patient was admitted with a preliminary diagnosis of Kaposi sarcoma and either community-acquired pneumonia (CAP) or PIP in an immunocompromised host. Arterial blood gas showed an A-a gradient of 40 mmHg; therefore, prednisone 40 mg daily was added to trimethoprim-sulfamethoxazole (TMP-SMX) for empiric treatment of severe PIP. With supplemental oxygen and rest, he continued to be relatively asymptomatic with the exception of continued generalized fatigue and intermittent fevers. On the second day of admission, blood cultures remained without growth, and urine Legionella antigen and urine Streptococcus pneumoniae antigen were negative. Serum Cryptococcus neoformans antigen and Toxoplasma gondii antibodies returned negative as well. Sputum culture demonstrated normal respiratory flora. A Mycobacterial sputum culture was negative for acid-fast bacilli. Due to persistent fever, and to better characterize the infiltrates seen on CXR, a computerized tomography (CT) scan of the chest was obtained. The CT chest demonstrated significant hilar and mediastinal lymphadenopathy with lymph nodes measuring around 1cm; areas of ground-glass infiltrates in the lingual and right lower lobe; small-to-moderate bilateral pleural effusions; and peribronchial thickening with diffuse nodularity of the bronchovascular bundles consistent with radiological findings in pulmonary Kaposi sarcoma (Figure 1). Bronchoscopy with bronchoalveolar lavage (BAL) demonstrated airway edema with hypervascularity, and multiple, friable violaceous maculopapular lesions variable in size with scattered areas of alveolar hemorrhage consistent with KS. Biopsies were not taken due to an increased risk of bleeding, but qualitative HHV-8 PCR was sent from BAL, which returned positive, confirming the diagnosis of KS. He was started on cART with co-formulated bictegravir (BIC), tenofovir alafenamide fumarate (TAF), and emtricitabine (FTC). One of

**Background**

Kaposi sarcoma (KS)-associated herpesvirus (KSHV) or human herpesvirus 8 (HHV) is the etiological agent for a heterogeneous group of human disorders. It occurs mostly in those infected by human immunodeficiency virus (HIV), particularly in the presence of uncontrolled HIV viremia and CD4 lymphopenia [1–3].

KSHV-related malignancies include the following: KS, PEL, and Multicentric Castleman disease (MCD). Recently, a new syndrome named KSHV inflammatory cytokine syndrome (KICS) was described in patients co-infected with HIV and KSHV [4–6]. KICS is clinically indistinguishable from MCD as both manifest with various degrees of lymphadenopathy, pancytopenia, HIV and KSHV viremia, and signs of systemic inflammatory syndrome (SIRS). Lymph node, bone marrow, or spleen biopsy is required to differentiate between the 2 entities [3–7].

While pulmonary IRIS due to opportunistic pathogens such as Pneumocystis jiroveci (PIP), Cryptococcus neoformans, and Mycobacterium tuberculosis is commonly seen, KS pulmonary IRIS has been relatively rarely reported, but is associated with high mortality [8,11–14].

**Case Report**

The patient was a 28-year-old African-American man with AIDS and schizophrenia who required admission for dyspnea manifesting 2 months prior, but dramatically worsening over the week preceding admission. He denied fevers, chills, night sweats, and anorexia, but had lost a significant but unquantified amount of weight over the preceding 2 months. His social history was relevant for being a lifelong resident of New York City without recent travel, having sex with men (MSM), residing in city housing without pets, and smoking marijuana; but negative for vaping, illicit drug use, or heavy alcohol use. His medical history was significant for AIDS with HIV diagnosed 10 years prior, at which time cART (zidovudine, lamivudine, and efavirenz) was prescribed, but discontinued by the patient early in treatment due to nausea and disbelief in its efficacy. His medical history was also relevant for untreated schizophrenia, prior disseminated zoster, recurrent oral and genital HSV, and primary syphilis, which had been successfully treated at our facility years ago with benzathine penicillin. He had no prior surgeries.

Upon presentation, vital signs were normal, but he soon developed a fever of 38.5°C. He was dyspneic and exhibited exertional hypoxia after walking 20 feet, with oxygen saturations falling from 97% to 85%. A physical exam was remarkable for a cachectic man with a body mass index (BMI) of 17, in no...
the lesions on the back was biopsied, and pathology showed changes consistent with KS, with spindle cell proliferation, slit-like vascular spaces, and extravasated blood cells (Figure 2). The CD4 count was 7 cells/mm$^3$, and the HIV VL was 59 120 copies/ml. The quantitative serum polymerase chain reaction (PCR) KSHV viral load was 10 150 copies/ml.

Since BAL cultures remained negative, and direct fluorescent antibody (DFA) was negative for PJP, TMP-SMX and prednisone were discontinued as PJP was deemed an unlikely cause of his symptoms. The patient completed 5 days of ceftriaxone and azithromycin empirically for community-acquired pneumonia. His lymphadenopathy was felt to be due to disseminated KS or due to MCD, but he refused to have another biopsy. Discharge was delayed due to inability to arrange for home oxygen. The patient therefore remained hospitalized, and was continued on cART, which he tolerated well. Unfortunately, 3 weeks following the initiation of cART, he clinically worsened with progressive dyspnea, hypoxia at rest, intermittent hemoptysis, fevers, nausea, anorexia, and non-bloody diarrhea without abdominal pain or vomiting.

A CT of the chest was repeated in addition to a full infectious workup to exclude hospital-acquired infections. This demonstrated marked worsening of bilateral pulmonary opacities (Figure 3). Due to worsening hemoptysis and progressive hypoxia, repeat bronchoscopy was deemed too risky since the patient refused elective intubation for the procedure. Concomitantly, he developed tachycardia with heart rates ranging from 110 to 135 beats per minute, tachypnea with respiratory rates of 25–30 per minute, and high fever recurred at regular intervals, responsive to acetaminophen. These findings were consistent with SIRS. CBC showed new thrombocytopenia of 37×10$^9$/L, anemia worsened with nadir hemoglobin of

Figure 1. Coronal image of initial CT of the chest shows various parenchymal abnormalities, including small areas of ground-glass infiltrates in the lingual and RLL. There is significant peribronchial thickening and diffuse nodularity of the bronchovascular bundles, suggestive of pulmonary Kaposi sarcoma.

Figure 2. In this high-power image we can observe infiltrate consisting of atypical spindled endothelial cells forming vascular channels intersecting between collagen bundles. Promontory sign (normal vessel enveloped in atypical vascular space) is present in the black box. This characteristic is not specific for KS and can also be seen in other vascular neoplasms such as angiosarcoma.

Figure 3. Coronal image of repeated CT of the chest demonstrates interval worsening of patchy consolidative, ground-glass, and reticulonodular opacities in both lungs, greatest within the central portions of the lungs. Additionally, stable moderate right and mild interval increased moderate left pleural effusions are present.
8.5 g/dl, without evidence of internal or external bleeding. His renal function steadily deteriorated over the next few days with peak creatinine of 4.1 mg/dL and oliguria, necessitating continuous renal replacement therapy (RRT). A bladder scan and renal ultrasound revealed no obstruction. Additionally, he developed worsening aspartate-aminotransferase (AST) and alanine aminotransferase (ALT). Total bilirubin and alkaline phosphatase remained normal. LDH was mildly elevated at 250 U/L (upper limit normal ~150 U/L). There were no schistocytes on peripheral smear to suggest an intravascular hemolytic process. Levels of D-dimer, prothrombin time, and activated partial thromboplastin time were normal, and his fibrinogen level was 455 mg/dL (normal values 200–400 mg/dL), which was consistent with a severe inflammatory process rather than disseminated intravascular coagulation (DIC). Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) serologies showed evidence of prior infection, with quantitative PCR in blood for both viruses returning negative, thus ruling out active infection.

With respect to his renal failure, TAF-induced acute kidney injury (AKI) was felt unlikely, particularly given his young age, absence of comorbidities such as diabetes and hypertension, and short duration of TAF therapy. Moreover, TAF toxicity did not adequately explain his SIRS, acute liver injury, or worsening hypoxic respiratory failure. A drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome due to TMP/SMX was ruled out in the absence of eosinophilia or new rash. At this point, the differential diagnosis was expanded to include the following: severe sepsis due to hospital acquired pathogens, paradoxical KS-IRIS or “unmasked” IRIS secondary to a previously undiagnosed opportunistic infection, hemophagocytic lymphohistiocytosis (HLH), MCD, PEL, or KICS. The patient was started empirically on ceftzipime, metronidazole, and vancomycin. In a repeat infectious workup, urine, blood, and stool cultures all remained negative. His abdominal exam continued to be without tenderness, and stool sent for culture, ova, and parasites, and the Clostridioides difficile stool toxin PCR result was negative. HLH was felt to be unlikely as ferritin was 511 mcg/L, triglycerides were 120 mg/dl, and albumin was 2.9 g/dL. A repeat detailed physical exam failed to point towards a source of potential infection. His KS lesions did not change in the interim, apart from slight regression of his upper gingival changes. A repeat CD4 count had increased to 80 cells/mm³, and HIV VL decreased to 1100 copies/ml. A repeat plasma KSHV VL increased to 21 146 copies/ml (perioriented DNA extracted from blood using primers for ORF26 region by Focus Diagnostics, Cypress, CA). Additionally, human interleukin-6 (hIL-6) and interleukin 10 (IL-10) levels were sent for analysis. Thoracentesis was performed, yielding grossly bloody fluid (likely due to pleuropulmonary KS in combination with thrombocytopenia), but the absence of malignant cells excluded PEL.

Our leading diagnosis at this juncture was pulmonary KS-IRIS in addition to either MCD or KICS. Over the subsequent 48 h, the patient further deteriorated, and developed progressive hypotension refractory to maximal doses of norepinephrine, vasopressin, and epinephrine, necessitating discontinuation of renal replacement therapy. He required emergent intubation for refractory hypoxic respiratory failure due to acute respiratory distress syndrome (ARDS). In light of his rapid clinical deterioration and multiorgan failure refractory to aggressive therapy, he was deemed an unsuitable candidate for empiric chemotherapy for MCD/KICS. His family transitioned him to comfort care, and he was terminally extubated. His family refused autopsy, but provided consent for publication of the case report. The IL-6 and IL-10 levels were found to be 200.5 and 111.8 pg/ml, respectively (normal levels less than 86 pg/ml and 10 pg/ml for IL-6 and IL-10, respectively, by ELISA kit for cytokine detection, Thermo Fisher Scientific, Waltham, MA).

Discussion

KS, a cytokine-mediated angioproliferative disease, is a low-grade malignancy most commonly affecting the skin and mucosa, but it can metastasize to involve virtually any internal organ [11]. Visceral involvement has been described in about 25% of patients, with the gastrointestinal system being the most commonly affected, followed by the lungs. Pulmonary KS is more likely to occur in patients with extensive cutaneous disease, and portends a worse prognosis [2,12]. KSHV exhibits a lifecycle with 2 phases: latent and lytic. Following primary infection, KSHV establishes an intracellular latency phase which helps it survive long-term by evading immune recognition of with by the host [14]. In co-infected patients, HIV machinery directly promotes KSHV replication while CD4 cell depletion and cytokine secretion indirectly contribute to KSHV proliferation [15–17]. Combined, these processes lead to KSHV survival within the infected cells and ongoing infection, which ultimately results in malignant transformation. Furthermore, coinfection with HIV can diminish T cell response to KSHV, which contributes to KS progression [9,18]. Despite its lack of activity against KSHV, cART leads to resolution of KS lesions in about 60% of patients by reducing HIV VL and by promoting CD4 cell recovery [16].

IRIS occurs in up to 30% of therapy-naive HIV patients, with mortality ranging between 5% and 30%, and both are higher in Africa than in Europe [19,20]. The incidence of KS-related IRIS has been reported to be 6% to 29% depending on the study population and the country [11,21–23]. In a retrospective study from the U.S., IRIS was more common in those with PJP at the time of cART initiation (28%) than in those with Mycobacterium avium complex (MAC) infection (4%). Among patients with visceral KS, 16% developed KS-IRIS and this group had higher...
morbidly and mortality than IRIS due to the above-described opportunistic infections [23]. Pulmonary KS seems to have particularly poor prognosis, and patients commonly deteriorate rapidly, precluding eligibility for chemotherapy. In a recent retrospective study, all patients who died from KS-IRIS had pulmonary involvement [14], which stands in stark contrast to another case series where none of the patients had pulmonary involvement and all survived [10]. There is no diagnostic test for IRIS. Diagnosis is made by taking into account information regarding pre-existing opportunistic infection or tumor in correlation with timing and response to cART. Clinical deterioration can occur due to worsening of the known opportunistic infection or tumor (paradoxically). Alternatively, reconstitution of the host’s immune system can “unmask” a previously undiagnosed infection, which can prove more challenging to diagnose [8]. Our patient’s relatively rapid development of IRIS after 3 weeks of therapy may be explained by his treatment with an integrase inhibitor-based regimen (BIC), which has high potency and is known to be associated with more IRIS development compared to other regimens. Predictors of IRIS development include: younger age at diagnosis, higher HIV VL and lower CD4 count at the start of cART, and hematocrit of <30%. Predictors for KS-IRIS development include pre-treatment presence of KS lesions and detectable KSHV viremia [10,11,15,22]. Our patient had all the risk factors associated with an increased risk for development of KS-IRIS, including high KSHV viremia. In addition to pulmonary KS, which is associated with higher mortality, another grim prognostic sign was the development of thrombocytopenia, which has been described to predict high mortality [11].

As our patient’s HIV VL decreased from 59 120 to 1100 copies/ml, and his CD4 count markedly increased (from 7 to 80 cell/mm), we were confident his diagnosis was KS-IRIS with pulmonary involvement, as described in Figures 1 and 2. Furthermore, qualitative HHV-8 PCR from sputum was positive, which confirmed the diagnosis despite the lack of endobronchial lesion biopsy. Nevertheless, overwhelming SIRS, worsening thrombocytopenia and anemia, acute renal failure, and acute liver injury were not compatible with KS-IRIS. Results of an extensive infectious workup remained negative, the criteria for HLH were not met, and the absence of malignant cells in pleural fluid excluded PEL. By excluding these diagnoses, we were left with 2 possibilities: MCD or KICS. Unfortunately, due to lack of lymph node biopsy, the definite secondary diagnosis could not be confirmed. There were a few manifestations, however, which favored KICS over MCD. While not absolutely diagnostic, discussion of these differences might help in future research in regard to differentiation between these overlapping entities.

In 2010, Uldrick and co-authors from the National Institutes of Health (NIH) described a new entity of IL-6-mediated SIRS syndrome. TAFRO was ruled out, however, as this syndrome is a variant of HHV-8-negative MCD in immunocompetent hosts, and requires the presence of ascites (which was absent in our patient). Moreover, it has been described thus far mostly in Japanese patients, and has not been reported in blacks [26,27].
Therapy of KS-IRIS depends on the severity of the disease. Mild cutaneous disease is expected to resolve with reconstitution of the immune system, and cART is usually adequate. The timing of cART in the setting of KS has not been studied, but the general consensus is that therapy should not be delayed [8,9,13]. For disseminated cutaneous disease and visceral KS, chemotherapy (usually doxorubicin and paclitaxel) is recommended in addition to cART. Cardiotoxicity of doxorubicin might be a limiting factor for continuation of therapy, which is sometimes needed for prolonged period of time, up to years [23]. We did not initially start the patient on chemotherapy due to his reluctance to immediately start chemotherapy and his/teams hope that his lesions would improve if not completely resolve with cART. Unlike IRIS due to opportunistic bacterial or fungal pathogens, KS-IRIS should not be treated with steroids due to potential for accelerating KSHV replication and further tumor growth [13,28]. Our patient did receive 3 days of prednisone therapy empirically for presumed PJP, and this may have contributed to worsening of KS with development of IRIS, and MCD vs. KICS.

Presently, the treatment modalities for MCD and KICS are similar. Rituximab and doxorubicin have been used successfully in combination. Rituximab targets B cells producing cytokines and containing KSHV, while doxorubicin helps to eliminate KS spindle cells and prevents the aggressive KS proliferation that can occur with rituximab monotherapy [7,23]. Valganciclovir has activity against KSHV and has been used in conjunction with high doses of zidovudine, although this combination is associated with more relapses than the rituximab-based regimen [23]. In the only case report of post-transplant KICS in an HIV-negative patient, recovery was achieved by a combination of foscarinet and rituximab in addition to modification of anti-rejection therapy by substituting tacrolimus with everolimus, which has activity against KSHV [27]. Interestingly, although IL-6 might be the key cytokine in KICS-IL-6, to the best of our knowledge, antagonists such as tocilizumab have not been evaluated in this setting.

Frequently, as illustrated in our case, patients are too ill to tolerate chemotherapy, and death might be due to the overlapping of 2 of these entities (MCD and KICS). Further research is needed to better understand the differences between these 3 entities (MCD, PEL, and KICS) and for improved diagnosis. We postulate that our patient, in addition to KS-IRIS, also had KICS, which contributed to his rapid deterioration and death.

Conclusions

SIRS in patients living with HIV and AIDS (PLWH), particularly in those with uncontrolled HIV viremia and low CD4 count, has a broad differential diagnosis, including: sepsis due to common community- or hospital-acquired infections, various opportunistic infections, HLH, IRIS, PEL, MCD, and KICS. By reporting this case, we aim to increase awareness among clinicians involved in the care of PLWH about these rare yet life-threatening complications. We also wish to further educate regarding the newly-reported KICS, particularly as it relates to the challenging differential diagnosis within this group of KSHV-related diseases.

Our case report has certain limitations. Most importantly, we did not obtain a lymph node biopsy, so we were unable to determine whether the second process leading to overwhelming cytokine storm with SIRS was MCD or KICS. Additionally, our laboratory was unable to test for viral encoded vIL-6, which, if elevated, would further support our hypothesis.

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