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Brief Communications

Kaposi Sarcoma Inflammatory Cytokine Syndrome (KICS): A Rare but Potentially Treatable Condition

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Disclosures of potential conflicts of interest may be found at the end of this article.

Abstract

Kaposi sarcoma inflammatory cytokine syndrome (KICS) is a newly-described condition affecting individuals who are HIV-positive and are infected with human herpesvirus 8 (HHV-8). This is a syndrome that in some ways mimics severe sepsis with associated acute respiratory distress syndrome, possibly requiring a ventilator and vasopressor support. However, unlike severe sepsis, antibiotics provide no benefit. Management of KICS has not been fully elucidated because of its high mortality rate. However, the syndrome has been successfully treated in some cases with immunomodulatory therapy. It is crucial for oncologists to be able to recognize this syndrome and to institute the appropriate therapy. ***The Oncologist*** 2017;22:623–625

Introduction

We present a patient with a case of presumed KICS to alert oncologists about this condition and to avoid misdiagnosis, potentially leading to disastrous consequences. We discuss the patient's presentation and relevant laboratory findings. We perform a review of the available literature regarding KICS, multicentric Castleman disease (MCD), immune reconstitution inflammatory syndrome (IRIS), and primary effusion lymphoma (PEL), and discuss new treatment modalities that have been proposed to manage this condition.

Case Presentation

A 23-year-old male with advanced AIDS and cutaneous Kaposi sarcoma (KS) was admitted to Grady Memorial Hospital in Atlanta, Georgia, with generalized malaise, frontal headache, nasal congestion, nausea, vomiting, fevers, and chills for 2 days—concerning for meningitis. His CD4 count was 207. He had completed 15 cycles of liposomal doxorubicin prior to admission to maintain control of his KS, with relative success, as there were no active KS lesions on admission. He was febrile at 38.7°C with tachycardia and hypotension—concerning for sepsis.

Initial laboratory results revealed a white blood count of 10.7, hemoglobin of 4.6, and a platelet count of 128,000. The patient's presentation was most concerning for acute anemia and sepsis, possibly secondary to meningitis. He received IV fluids and underwent a lumbar puncture to analyze for an infectious etiology. Given the high suspicion for sepsis, the patient was started on broad-spectrum antibiotics. Unfortunately, his clinical status declined with progressive anemia (reaching hemoglobin of 3 g/dL despite multiple transfusions), and he developed respiratory failure, requiring intubation, and hypotension, requiring vasopressor support. Once the results of the cerebrospinal fluid studies were received, he was found to be positive for Epstein-Barr virus and was initiated on ganciclovir. Despite this, hemodynamic shock persisted together with fever and tachycardia and he remained intubated due to respiratory failure.

Given the overwhelming respiratory failure, anemia, and hemodynamic shock, the possibility of KICS was considered. His IL-6 levels were found to be elevated to 20.16 (normal reference range between 0.31–5.0). Additionally, his low albumin level on admission of 2.3, which then ranged between 1.8 to 1.9 during his hospitalization, along with his elevated C-reactive protein level of 20.84 on admission, further raised the concern for KICS. One option for the treatment of KICS is to use rituximab, liposomal doxorubicin along with antiviral therapy—the current mainstay of treatment for KS herpesvirus infection (KSHV)-associated MCD [1]. If rituximab is given alone, it can cause a flare of KS, hence the necessity of coupling this treatment with liposomal doxorubicin. Unfortunately, the patient's poor liver function (total bilirubin of 20.9) prohibited the use of liposomal doxorubicin, as it is hepatically metabolized. Rituximab was therefore initiated as monotherapy. In the week following the initiation of rituximab, the patient was extubated and no longer required vasopressor support. His bilirubin also improved, although remained elevated at 10.8. He received 4 weekly doses of rituximab. His total bilirubin trended downward from 10.8 to 2.8 from week 2 to week 3 of rituximab treatment, and his direct bilirubin also trended downward (from 7.0 to 1.4 from week 2 to week 3).

Ultimately the patient's poor liver function prohibited the use of liposomal doxorubicin until the fourth and final dose of

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rituximab, at which point it was dosed at a 75% dose reduction. Despite the clinical improvement following initiation of rituximab, he then began to deteriorate. After completing four doses of rituximab, he developed bilateral pleural effusions that were thought to be due to progression of KS, and so he was treated with another dose of liposomal doxorubicin, this time at 50% dose reduction.

The patient's entire course was complicated by the need to balance control of KICS with rituximab while attempting to avoid exacerbation of KS with the use of liposomal doxorubicin. He improved sufficiently to be stable on the general medical floor for several weeks. His bilateral pleural effusions then increased and he again developed hypotension and respiratory failure. Ultimately, the patient passed away 6 weeks after admission.

Discussion

KICS is an entity recently described in patients with KSHV. Patients with KICS show a high KSHV viral load and increased levels of IL-10. They also tend to have elevated viral and human IL-6, although in recent cases this has not been consistently found [1–3]. An increase in production of interleukin-6 can cause cytopenia, fevers, cachexia, hyponatremia, and hypoalbuminemia [4]. The diagnosis of KICS is achieved by exclusion of other entities. It requires the elimination of MCD by pathology, as well as excluding serious recurrent infections. Among patients who have both KSHV and HIV, KICS may be an important cause of morbidity and mortality. It is hypothesized that KS may be resistant to therapy in patients who have coinciding KICS due to an excess of cytokine release, which in itself can help promote KS cell proliferation [5]. This was not the case in our patient, as the patient had KS prior to being diagnosed with KICS.

KICS and MCD have similar presentations, typically differentiated by biopsy. MCD is associated with splenomegaly and lymphadenopathy, as opposed to KICS, in which these are not prominent features [6]. Due to the patient's extremely tenuous clinical condition requiring vasopressors, a biopsy was not pursued, particularly in light of the fact that it is unlikely to have significantly changed management. Additionally, due to his poor hepatic function, he was not deemed eligible for cytotoxic chemotherapy but was a candidate for rituximab. For this reason, he was given rituximab alone, without pathologic confirmation.

IRIS, which describes inflammatory disorders associated with a paradoxical worsening of preexisting infectious processes following the initiation of highly active antiretroviral therapy (HAART) in HIV-infected individuals, can also have similar features. Typically, preexisting infections in individuals with IRIS could have been previously diagnosed and treated, or they may be subclinical and later unmasked by the host's regained capacity to mount an inflammatory response [7]. There are no universal criteria to define IRIS. The presence of AIDS with a pretreatment CD4 count of fewer than 100 cells/microL (except in patients with tuberculosis), a positive virologic and immunological response to ART, along with a temporal association between initiation of HAART and the onset of clinical features, are strongly correlated with IRIS. The patient's negative cultures, CD4 count of 207 on presentation, lack of improvement on antibiotics, lack of correlation between starting HAART and the patient's presentation made IRIS a less likely diagnosis [8–11].

PEL as a cause of the patient's worsening dyspnea could have also been a concurrent ailment in this patient, though less likely with a CD4 count of 207. PEL is a rare HIV-associated non-Hodgkin's lymphoma (NHL) accounting for about 4% of all HIV-associated NHL. Patients are typically HIV-positive men with a decreased CD4 T-cell count at diagnosis. In addition, a significant portion has pre-existing Kaposi's sarcoma or MCD, as they are both known manifestations of HHV-8 infection. PEL typically presents as lymphomatous growth in a liquid phase in body cavities, without associated extra-cavitary tumor masses. Symptoms are usually secondary to mass effects from the malignant effusion. Hence, patients typically present with dyspnea from pleural or pericardial disease, or abdominal distension from the peritoneal disease [12]. Due to the patient's dire presentation requiring pressor support, a pleural tap was not pursued as the patient was not a candidate for cytotoxic chemotherapy due to poor hepatic function.

Conclusion

There are minimal data guiding clinicians on how to treat KICS. It has been hypothesized that treating the underlying tumor may decrease KSHV-associated cytokines. However, in situations where this syndrome is present, treating the original sarcoma is not easy due to related comorbidities. However, it is justifiable to employ therapeutic modalities for KICS similar to those that are used for KSHV-MCD, including drugs such as rituximab. It may be used in order to destroy B cells that contain KSHV or which may be producing cytokines themselves. Another drug that may be used is ganciclovir, which has activity against KSHV. Finally, liposomal doxorubicin can be used to eliminate KS spindle cells and prevent the aggressive proliferation of KS lesions with concurrent rituximab treatment. Further research is required in this newly described syndrome in order to optimize treatment regimens. Patients presenting with KICS are noted to have a high mortality rate, increasing the need for further research on the condition and correctly identifying this syndrome as of paramount importance for practicing oncologists [13].

Disclosures

The authors indicated no financial relationships.

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For Further Reading:

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Implications for Practice:

Human immunodeficiency virus (HIV)-infected patients are at increased risk of developing cancer, particularly in the later stages of acquired immune deficiency syndrome (AIDS). Despite the advent of highly active anti-retroviral therapy (HAART), malignancy in this population is a leading cause of morbidity and mortality. Kaposi's sarcoma (KS) and AIDS-related non-Hodgkin's lymphoma (ARL) are the most common AIDS-defining malignancies. AIDS-related KS varies from minimal to fulminant disease. Treatment decisions for AIDS-related KS are guided largely by the presence and extent of symptomatic disease. In addition to HAART, excellent treatments exist for both localized disease (topical gel, radiotherapy, and intralesional therapy) and advanced disease (liposomal anthracyclines, paclitaxel). Novel therapies that have become available to treat AIDS-related KS include angiogenesis inhibitors and antiviral agents. ARL comprises a heterogeneous group of malignancies. With the immune restoration afforded by HAART, standard-dose chemotherapies now can be safely administered to treat ARL with curative intent. The role of analogous treatments used in HIV-negative patients, including monoclonal antibodies and autologous stem cell transplantation, requires further clarification in HIV-positive patients. HIV-infected patients also appear to be at increased risk for developing certain non-AIDS-defining cancers, such as Hodgkin's lymphoma and multiple myeloma. Although the optimal treatment of these neoplasms is at present uncertain, recent advances in chemotherapy, antiretroviral drugs, and supportive care protocols are allowing for more aggressive management of many of the AIDS-related cancers. This article provides an up-to-date review of the epidemiology, pathogenesis, clinical features, and treatment of various AIDS-related malignancies that are likely to be encountered by an oncologist practicing in the current HAART era.