A 22-Year-Old Man With AIDS Presenting With Shortness of Breath and an Oral Lesion

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Since the development of combination antiretroviral therapy (cART), the incidence and mortality associated with Kaposi sarcoma (KS) have been reduced, although not eliminated. Clinical presentations of KS range from simple skin involvement to disseminated disease, including involvement of the oral cavity and viscera, which portends a more ominous prognosis. Multiple case reports and data from clinical trials indicate that administration of systemic corticosteroids may aggravate KS. We present a case of disseminated KS following administration of prednisone for presumed immune reconstitution inflammatory syndrome (IRIS) associated with fungal pneumonia in an HIV-infected individual. The discussion that follows outlines the pathophysiology and clinical presentations associated with KS and existing data for the role of corticosteroids in promoting KS progression.

CASE PRESENTATION

A 32-year-old man with a past medical history of HIV/AIDS and remote tobacco abuse presented to our facility with a chief complaint of shortness of breath and persistent cough, which began three months prior to admission. He initially tried over-the-counter cough suppressants, which provided little relief. Over the next four weeks, he had progressive fatigue, decreased appetite, night sweats, shortness of breath, dry cough, and oral thrush with chest pain on swallowing. Approximately two months prior to admission, he presented with the above symptoms and was noted to be afebrile with normal values for pulse oximetry at rest. His CD4+ T-cell count was 8 cells/mm$^3$ (228-2,290 cells/mm$^3$). A chest radiograph revealed mild bilateral, centrally located interstitial infiltrates, and blood cultures were negative. Based on the duration of his illness, his lack of prophylaxis for Pneumocystis jirovecii pneumonia (PJP), and the appearance of his chest radiograph, he was treated presumptively for both PJP and candida esophagitis.

Approximately one-and-a-half months prior to admission, the patient was seen in the HIV outpatient clinic for hospital follow-up visit. He had not received cART for the previous two years. cART therapy was initiated, along with prophylactic trimethoprim-sulfamethoxazole, azithromycin, and oral fluconazole treatment for diffuse oral candidiasis. Following this outpatient clinic visit, his shortness of breath and cough persisted, and he presented to another hospital approximately three weeks prior to admission, where he was noted to be hypoxic with multilobar infiltrates on chest radiography that were more extensive than those seen during his prior hospitalization. He received a diagnosis of multilobar community-acquired pneumonia and was started on levofloxacin. Bronchoscopy with bronchoalveolar lavage (BAL) revealed no endobronchial lesions, a negative evaluation for PJP, negative Gram stain and bacterial cultures, negative AFB cultures, and negative KOH stain. He was discharged on levofloxacin, high-dose fluconazole, and a prednisone taper for presumed pneumonia in the context of an immune reconstitution inflammatory syndrome (IRIS). Fungal cultures from the BAL subsequently grew a few colonies of Paecilomyces species, and serum cryptococcal antigen was negative.

One week prior to admission, he was again seen in the HIV outpatient clinic, where he was noted to have a violaceous, fungating lesion on the hard palate (Figure 1). On further questioning, the patient stated that a much smaller form of this lesion had been present for the past three months, although masked by severe overlying thrush. In addition, he had worsening shortness of breath and cough now productive of copious brown sputum. Repeat CD4+ T-cell count was 31 cells/mm$^3$ at this time. Outpatient computed tomography (CT) of the chest revealed diffuse lung parenchymal opacities, with areas of nodularity and...
consolidation (Figure 2). Due to these findings and the lack of improvement, he was sent to the emergency department (ED).

In the ED, he was visibly short of breath but without thrush or odynophagia. Review of systems was significant for decreased appetite, fatigue, night sweats, and cough productive of a large amount of thick, brown sputum. He was afebrile, with a normal blood pressure and pulse. Oxygen saturation on room air by pulse oximetry was 83%. The oropharyngeal examination was significant for the lesion on the hard palate previously noted, as well as a similar but smaller lesion on the maxillary gingival mucosa. Lung exam revealed diffuse crackles and rhonchi in all lung zones, with decreased breath sounds at the bases. He had no skin lesions and no significant lymphadenopathy. The remainder of the physical exam was unremarkable. Initial laboratory assessment revealed a total protein of 5.9 g/dL (6.0-8.0 g/dL), an albumin of 2.7 g/dL (3.4-5.0 g/dL), a mild normocytic anemia, and mild hypokalemia. His white blood cell count was 9,200/µL (4,500-11,000/µL) with a normal differential.

The patient was admitted to the hospital with a diagnosis of multilobar fungal pneumonia and suspicion
for oropharyngeal Kaposi sarcoma (KS). The infectious disease consultants recommended use of liposomal amphotericin for the treatment of Paecilomyces infection, as well as a biopsy of the hard palate lesion. Oral prednisone was continued due to concerns for ongoing IRIS. The biopsy revealed proliferation of atypical spindle cells forming fascicles, bundles, and cleft-like structures lined by mildly atypical endothelial cells. Red cells were noted between the spindle cells and vascular lumina (Figure 3). Immunohistochemical stains for human herpesvirus-8 (HHV-8), CD31, CD34, and Factor VII were strongly positive, supporting the diagnosis of KS (Figure 4).

Oncology was consulted and recommended bronchoscopy and colonoscopy for staging. Bronchoscopy revealed several new, violaceous, submucosal endobronchial lesions suggestive of KS. The lesions were not biopsied due to concern for bleeding. Gram stain performed on BAL fluid revealed a few yeast colonies which did not grow in culture. Routine cultures for bacteria and acid-fast bacilli were negative. Colonoscopy revealed a rectal lesion suggestive of KS, further confirming the disseminated nature of the illness in this patient.

Because of the concern for his concomitant fungal pneumonia, chemotherapy was held until his pneumonia had improved. After an 18-day hospital stay, he was discharged home. Steroids were tapered off, liposomal amphotericin was discontinued, and voriconazole was initiated with a minimum of six additional months of antifungal therapy planned. At the time of hospital discharge, his productive cough had ceased, and he was no longer requiring supplemental oxygen. On outpatient follow-up, he continued to improve. Repeat CT scan of the chest eight weeks following discharge showed improvement in the basilar consolidations and decreased size of several of the nodular lesions (Figure 5).

KS EPIDEMIOLOGY

Prior to 1981, the estimated annual incidence of KS in the United States was between 0.02 and 0.06 cases per 100,000. In June 1981, numerous case reports of KS began to surface in large metropolitan areas of New York and California. In contrast to previous cases, these patients were typically young men (39 years old on average) who were homosexual or bisexual. In addition, these tumors behaved more aggressively. These cases led to the establishment of the Task Force on KS and Opportunistic Infec-

Figure 4: (HHV-8 immunostain 100x) Low-power image of atypical spindle cells in fascicles showing strong nuclear immunostaining for HHV-8.

Figure 5: Follow-up CT of the chest showing improvement in the basilar consolidations and decreased size of several of the nodular lesions.
tions, which eventually led to the discovery of AIDS in 1982. While the causative agent of AIDS was determined in 1984, it was not until a decade later that the viral etiology of KS, the Kaposi sarcoma-associated herpesvirus (KSHV; or HHV-8), was identified. Four subtypes of KS have been described, including classic, endemic, iatrogenic, and AIDS-related KS. Current estimates of the prevalence of KS among AIDS patients vary. A study in 1989 showed that the prevalence among homosexual men with AIDS was 21% and only 1% in AIDS patients who had contracted the virus by way of blood transfusion. The cumulative incidence in HIV patients has since fallen from 14.3% in 1980-1989 to 1.8% in 1996-2006, mostly due to the emergence of cART.

RISK FACTORS AND TRANSMISSION OF HHV-8

Several epidemiologic studies indicate that sexual contact is the most common mode of transmission for HHV-8. Higher circulating viral loads have been associated with homosexual activity, increasing number of sexual partners, commercial sex work, and attendance at STD clinics. Viral DNA has been detected in the semen and prostatic fluid of HIV-positive men, but higher viral loads in saliva relative to anal and genital tissue/fluid samples support saliva exposure as the most likely mode of transmission. Salivary transmission is further supported by observation of horizontal transmission of HHV-8 among children and relatives in endemic regions. Recipients of blood transfusions and solid organ transplants are also at greater risk of HHV-8 acquisition if the donor is seropositive for HHV-8. Although all patients with KS are infected with HHV-8, only about 0.03% of men and 0.02% of women infected with the virus will develop KS annually. Immunosuppression, either inherited, acquired, or iatrogenic, is a well-documented risk factor for the development of KS. Male gender, lower total lymphocyte count, lower CD4+ T cells, and a history of systemic and topical corticosteroid use have all been associated with development of KS.

PATHOPHYSIOLOGY OF KS AND CORTICOSTEROIDS

HHV-8 is grouped in the human gamma-herpesvirus family, which also includes Epstein-Barr virus. Members of this family cause tumors in both humans and animals by induction of uncontrolled cellular proliferation. Target cells for infection include endothelial cells, epithelial cells, macrophages, and B lymphocytes. A host of factors have been shown to activate latent virus, including inflammatory cytokines, immunosuppression, and tissue hypoxia. Inflammatory cytokines, including IL-6, induce proliferation of KS cells in vitro through the gp130 protein pathway, and increased inflammation associated with immune reconstitution inflammatory syndrome (IRIS) may explain the induction or KS tumors in patients recently started on cART. However, the exact mechanism is unknown. Some HIV-positive patients with undetectable viremia and normal CD4+ T-cell counts also develop KS, implicating mechanisms other than immunodeficiency in KS progression, including chronic inflammation associated with HHV or other co-existent opportunistic infections.

Clinical observations strongly suggest that corticosteroids not only increase the risk of KS, but can also exacerbate existing KS. Dexamethasone has been shown to stimulate proliferation of cultured KS cells in vitro. KS cells possess an unusually high concentration of corticosteroid receptors, which can be further upregulated with corticosteroid treatment in a positive feedback mechanism. Inflammatory cytokines also synergize with corticosteroids to induce proliferation of KS cells.

Recognition of these associations is important due to the frequent use of systemic corticosteroids in HIV-infected patients for illnesses such as PJP and cryptococcal meningitis. Before initiating steroids in these patients, it is important to perform a thorough examination of the skin and oral cavity to identify suspicious lesions. We would advocate that if suspicious lesions are present, corticosteroids should generally be held until the diagnosis has been ruled out by biopsy. Sexual history is also important, as men who have sex with men have a much higher risk of acquiring HHV-8 and subsequently, KS relative to other risk groups. The association of steroid treatment with KS appears to have been demonstrated in our patient, who developed clinically evident disease of the oral cavity and progressive pulmonary distress after receiving prednisone for IRIS. Further, our patient improved after the discontinuation of steroids, although it is unclear to what degree this was due to antifungal therapy and cART.

CLINICAL FEATURES AND DIAGNOSIS

In contrast to other subtypes of KS, AIDS-related KS is generally more fulminant, with a higher incidence of widespread disease. Typical lesions are purple, red, or brown, highly-vascular papules, although many morphological variants exist. The most common sites of clinically apparent disease include the extremities, face, oral mucosa, and genitalia, although virtually any tissue in the body can be affected. The presentation is variable, including mild disease limited to the skin and more severe disease involving the lymph nodes and visceria. Although cutaneous disease precedes dissemination in most cases, disseminated or visceral disease may be present in the absence of skin involvement. Prior to the emergence of CART, most patients who developed KS would eventually develop disseminated disease, most often of the oral cavity, GI tract, and respiratory tract, which is associated with a high mortality rate. The most important clinical mimic is bacillary angiomatosis (BA), which can present as multiple, red, vascular skin lesions and also involve visceral organs. Although uncommon, BA has a higher prevalence among HIV-infected individuals than the normal population.
Histopathologic assessment is needed for diagnostic confirmation of KS. The typical stages include the macular, patch, and nodular stages, each with different degrees of angiogenesis, inflammation, and proliferation.\textsuperscript{37} Immunohistochemical staining using monoclonal antibodies targeting the HHV-8 latent nuclear antigen-1 (LNA-1) is considered the gold standard for diagnosis of KS, as it has a very high sensitivity and specificity.\textsuperscript{38} Staining with D2-40, CD31, and CD34 are used as adjunct stains, although the specificity for these markers is lower.

**STAGING AND TREATMENT**

AIDS-related KS patients are stratified into risk categories based on three parameters: Extent of tumor (T), Immune status (I), and Severity of systemic illness (S). Patients are given a zero or one in each category. This staging system was developed by the AIDS Clinical Trial Group (ACTG) of the National Institute of Health in 1989 and revised in 1997.\textsuperscript{39,40} This staging should only be used for AIDS-related KS, and there is currently no universally accepted staging system for the other subtypes.

cART is recommended for all patients with AIDS-related KS. In the mid-1990s, the incidence and overall survival with KS dramatically changed with the introduction of cART. A French cohort study of HIV patients showed that the incidence fell from 32 per 1,000 person-years in 1993 to 3 per 1,000 person-years in 1999.\textsuperscript{41} A similar study in 2011 showed that the cumulative incidence of Kaposi sarcoma was 14.3% from 1980 to 1989, 6.7% from 1990 to 1995, and 1.8% from 1996 to 2006.\textsuperscript{42} Similarly, patients with KS showed significantly higher survival rates in the cART era as compared to the pre-cART era.\textsuperscript{43}

The improvement in prognosis may in part be explained by overall immune reconstitution, rather than regression of tumor. A small number of patients (6%-14%) may develop worsening of their disease after the initiation of cART, which is thought to be due to the IRIS.\textsuperscript{43,44} Most patients who develop IRIS-induced KS flares are able to tolerate continuation of cART.\textsuperscript{45}

Systemic chemotherapy is usually reserved for patients with more extensive or rapidly progressive disease. The 2008 British HIV Association guidelines for HIV-associated malignancies recommend that the decision to use systemic chemotherapy should be based on a number of parameters, including prognostic index, initial response to cART, patient performance status, and end organ function.\textsuperscript{46} Furthermore, disseminated tumors (widespread skin involvement, extensive oral involvement, tumor-associated edema or ulceration, visceral involvement) and those with IRIS-induced KS flares should be considered for chemotherapy.\textsuperscript{47} Liposomal anthracyclines (doxorubicin, daunorubicin) and taxanes (paclitaxel) are the mainstay of treatment.\textsuperscript{48} Despite the use of cART and standard chemotherapy, Stage III disease (T\textsubscript{3}, I\textsubscript{2}, S\textsubscript{3}) portends a particularly poor prognosis, with a median survival of only 15 months.\textsuperscript{49} Ganciclovir has demonstrated activity against HHV-8 and may be useful in the prevention of KS in high-risk patients.\textsuperscript{46} Local therapy with intralesional vinblastine, radiation, and other topical agents is typically used for cosmesis or reduction in symptoms associated with bulky lesions but does not prevent progression of disease in other tissues.

**PAECILOMYCES**

*Paecilomyces* is a filamentous fungus common in the environment, inhabiting the soil, decaying plants, and food products. Although often viewed as a contaminant, it has been known to cause a variety of diseases in humans and animals, including pneumonia in immunocompromised hosts. While there are only a handful of case reports, the most commonly reported species linked to respiratory infections are *P. variotii* and *P. lilacinus*. Respiratory tract infection with *P. lilacinus* is usually characterized by pleural effusions and pulmonary abscesses, while *P. variotii* can present with hiliar lymphadenopathy, cavitary lesions, confluent patchy opacities, and pulmonary nodules. It is important to differentiate species as they display different resistance patterns to antifungal therapy, with reports of poor susceptibility to amphotericin B, itraconazole, and echinocandins for *P. variotii*.\textsuperscript{50} It is unclear if *Paecilomyces* played a role in our patient’s disease process. However, his clinical and radiographic improvement with antifungal therapy leads us to believe his respiratory symptoms were at least partly due to fungal pneumonia.

**CONCLUSION**

KS was one of the most feared complications in the early AIDS epidemic. A once rare disease exploded onto the scene in the early 1980s and was quite morbid and potentially fatal to those afflicted. Advances in cART in the mid-1990s have been essential to reducing the prevalence, morbidity, and mortality associated with this disease. The discovery of HHV-8 as the cause for KS in 1994 was critical to understand its pathophysiology. Although the exact mechanism of transmission has yet to be proven, studies suggest sexual transmission, possibly by exposure to saliva, as the most likely vector. Inflammation and immunosuppression in the setting of HHV-8 infection have been shown to cause KS proliferation leading to tumor formation. Corticosteroids can induce KS tumorigenesis and exacerbate pre-existing lesions, often leading to disseminated disease. Consequently, steroids should be avoided if there is reasonable suspicion for the presence of KS. Clinical presentations range from focal skin involvement to extensive involvement of visceral organs. More fulminant presentations are more common in HIV-infected patients, particularly those who are not on cART. While a clinical diagnosis can be made by observing classic lesions, definitive diagnosis is made by histology and immunohistochemical staining to identify HHV-8 latent nuclear antigen-1. Staging is based on the extent of tumor burden, immune status, performance status, and coexisting
systemic illness. Antiretroviral therapy continues to be a mainstay of treatment, along with systemic chemotherapy for patients with more severe disease. However, patients with advanced stage disease have a poor prognosis, even with cART and chemotherapy.

REFERENCES


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