

CLINICAL CARE CONUNDRUMS

A Double-Edged Sword

The approach to clinical conundrums by an expert clinician is revealed through the presentation of an actual patient's case in an approach typical of a morning report. Similarly to patient care, sequential pieces of information are provided to the clinician, who is unfamiliar with the case. The focus is on the thought processes of both the clinical team caring for the patient and the discussant.



This icon represents the patient's case. Each paragraph that follows represents the discussant's thoughts.

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A 40-year-old man with human immunodeficiency virus (HIV) infection and a CD4 count of 58 cells/ μ L was admitted to the hospital with 1 month of fevers, night sweats, a 5-kg weight loss, several weeks of progressive dyspnea on exertion, and a nonproductive cough. He denied headaches, vision changes, odynophagia, diarrhea, or rash. He had no history of opportunistic infections, HIV-associated neoplasms, or other relevant past medical history. He was diagnosed with HIV 3 years ago and had been off antiretroviral therapy (ART) for the last 10 months. Two weeks prior to this presentation, he was seen in clinic but did not report his symptoms. He was prescribed trimethoprim/sulfamethoxazole (TMP/SMX) for prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP). He had recently moved from New York City to San Francisco, had quit smoking within the last month, and denied alcohol or illicit drug use.

At a CD4 cell count of 58 cells/ μ L, the patient is at risk for the entire spectrum of HIV-associated opportunistic infections and neoplasms. The presence of fevers, night sweats, and weight loss suggests the possibility of a disseminated infection, although a neoplastic process with accompanying B symptoms should also be considered. Dyspnea and nonproductive cough indicate cardiopulmonary involvement. The duration of these complaints is more suggestive of a nonbacterial infectious etiology (e.g., PCP, mycobacterial or fungal disease) than a bacterial etiology (e.g., *Streptococcus pneumoniae*). Irrespective of CD4 count, patients with HIV are at increased risk for cardiovascular events and pulmonary arterial hypertension, although the time course and presence of constitutional symptoms makes these diagnoses less likely. Similarly, patients with HIV are at increased risk

for chronic obstructive pulmonary disease (COPD), and the patient does have a history of cigarette smoking, but the clinical history and systemic involvement make COPD unlikely.



On physical examination, the patient was in no acute distress. The temperature was 36°C, the blood pressure 117/68 mm Hg, the heart rate 106 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% on ambient air. No oral lesions were noted, and his neck was supple with nontender bilateral cervical lymphadenopathy measuring up to 1.5 cm. There was no jugular venous distension or peripheral edema. The cardiovascular exam revealed tachycardia with a regular rhythm and no murmurs or gallops. His lungs were clear to auscultation. The spleen tip was palpable. No rashes were identified. The neurological examination, including mental status, was normal.



The white blood cell count was 2400/mm³, the hemoglobin 7 g/dL with mean corpuscular volume of 86 fL, and the platelet count 162,000/mm³. Basic chemistry, liver, and glucose-6-phosphate dehydrogenase (G6PD) tests were within the laboratory's normal range. The HIV viral load was 150,000 copies/mL. Chest radiography revealed bibasilar hazy opacities, and computerized tomography (CT) of the chest revealed a focal nodular consolidation in the right middle lobe along with subcentimeter bilateral axillary and mediastinal lymphadenopathy. There were no ground-glass opacities.

The patient's physical examination does not support a cardiac disorder. Lymphadenopathy is nonspecific, but it is consistent with a potential infectious or neoplastic process. Leukopenia and anemia suggest potential bone-marrow infiltration or suppression by TMP/SMX. Although the pulmonary exam was nonfocal, chest imaging is the cornerstone of the evaluation of suspected pulmonary disease in persons with HIV. The focal nodular consolidation on chest CT is nonspecific but is more characteristic of typical or atypical bacterial pneumonia, mycobacterial disease such as tuberculosis, or fungal pneumonia than PCP or viral pneumonia. A lack of ground-glass opacities also makes PCP and interstitial lung diseases less likely.



The patient was treated for community-acquired pneumonia with ceftriaxone and doxycycline with improvement in dyspnea. Antiretroviral therapy with darunavir, ritonavir, tenofovir, and emtricitabine was initiated. Azithromycin was

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started for prophylaxis against *Mycobacterium avium* complex (MAC). The TMP/SMX was changed to dapsone, given concern for bone-marrow suppression. Blood cultures for bacteria, fungi, and mycobacteria were negative. Polymerase chain reaction from pharyngeal swab for influenza A and B, parainfluenza types 1–3, rhinovirus, and respiratory syncytial virus were negative. Several attempts to obtain sputum for acid-fast bacillus staining and culture were unsuccessful because the patient was unable to expectorate sputum. Serum interferon-gamma release assay for *M. tuberculosis* and the following serologic studies were also negative: cytomegalovirus, Epstein-Barr virus, parvovirus, *Bartonella* species, *Coccidioides immitis*, and *Cryptococcus neoformans* antigen. Given his improvement, the patient was discharged from the hospital on ART, doxycycline for community-acquired pneumonia, and prophylactic azithromycin and dapsone with scheduled outpatient follow-up.

☐ Ten days later, he was seen in clinic. Though his dyspnea had improved after completing the doxycycline, he noted a persistent dry cough and daily fevers to 40°C. The physical exam was unchanged, including persistent cervical lymphadenopathy. Laboratories revealed a white blood cell count of 2400/mm³, hemoglobin of 4.8 g/dL, and a platelet count of 122,000/mm³. The absolute reticulocyte count was 21,000/μL (normal value, 20,000–100,000/μL). A peripheral blood smear was unremarkable, and serum lactate dehydrogenase (LDH) was within normal limits. The direct antiglobulin test (DAT) was negative. The patient was readmitted to the hospital.

The initial improvement in dyspnea but persistent fevers and cough and worsening pancytopenia are suggestive of multiple processes occurring simultaneously. Dapsone can cause both hemolytic anemia and aplastic anemia, although the peripheral smear, normal LDH and G6PD, and negative DAT are not consistent with the former. Bone-marrow suppression from a combination of ART medications and dapsone cannot be ruled out. An infiltrative process involving the bone marrow, including tuberculosis, MAC, disseminated fungal infection, or malignancy, remains a possibility. Repeat chest imaging is warranted to assess the prior right middle lobe consolidation and to further evaluate the persistent respiratory complaints.

☐ Prophylaxis of PCP with dapsone was switched to atovaquone due to persistent anemia. A repeat CT of the chest and a concurrent abdominal CT revealed interval enlargement of mediastinal lymph nodes with multiple periportal, retroperitoneal, and hilar nodes not present on prior chest imaging, in addition to new bilateral centrilobular nodules and interval development of small bilateral pleural effusions. The abdominal CT also showed hepatosplenomegaly with splenic-vein engorgement. Empiric treatment for disseminated MAC infection with clarithromycin and ethambutol was initiated in addition to vancomycin and cefepime for possible healthcare-associated pneumonia. Over the next several days, the patient continued to have daily fevers up to 39.8°C. A repeat CD4 count 3 weeks after starting ART was 121 cells/μL. The HIV RNA level had decreased to 854 copies/mL.

The patient has developed progressive, generalized lymphadenopathy, worsening pancytopenia, and persistent fevers in the setting of negative cultures and serologic studies and

despite treatment for MAC. This constellation, along with the radiographic findings of hilar lymphadenopathy and pleural effusions, is suggestive of non-Hodgkin lymphoma (NHL). Alternatively, Kaposi sarcoma (KS) or tuberculosis can have a similar radiographic and clinical presentation, although pancytopenia from KS seems unusual. The lymphadenopathy could be consistent with multicentric Castleman disease or bacillary angiomatosis (BA), although the latter diagnosis would be unlikely given recent antibiotic therapy. At this time, a careful search for other manifestations and reasonable targets for biopsy is warranted. An appropriate suppression of the HIV viral load after initiation of ART, with improvement in CD4 count, is the proper context for the immune reconstitution inflammatory syndrome (IRIS), which is characterized by paradoxical worsening or unmasking of a disseminated process.

☐ A bone-marrow biopsy revealed marked dysmegakaryopoiesis and mild dyserythropoiesis, but no other abnormalities. Flow cytometry and histoimmunohistochemical staining did not show evidence of lymphoproliferative disorder in the marrow. Smears and cultures of the bone marrow for bacteria, acid-fast bacilli, and fungi were negative. A right cervical lymph node biopsy was performed, with multiple fine-needle aspiration and core samples taken. Bacterial, fungal, and acid-fast bacilli tissue cultures were without growth, and initial pathology results were concerning for high-grade lymphoma. A monoclonal proliferation of lymphocytes was noted on flow cytometry of the tissue sample. The patient developed progressive dyspnea, tachypnea, and hypoxemia. A chest x-ray revealed worsening perihilar and basilar opacities.

The possibility of bone-marrow sampling error must be considered in a patient that has such a high pretest probability for lymphoma or infection, but staining, immunological assays, cultures, and direct assessment by pathologists generally give some suggestion of an alternative diagnosis. The bone-marrow findings are compatible with HIV-related changes, but continued vigilance for infection and malignancy is warranted. Although the diagnosis of NHL based on the cervical biopsy result is only preliminary, the patient's rapidly deteriorating clinical status warrants initiation of treatment with steroids while awaiting definitive results, particularly given his poor response to aggressive management of potential infectious causes. A bronchoscopy should be considered given the predominance of pulmonary symptoms and his rapid respiratory decline.

☐ Approximately 1 week after admission, high-dose systemic corticosteroids were administered for presumed aggressive lymphoma. Over the next 48 hours, the patient's hypoxemia worsened, and he was intubated for hypoxic respiratory failure. A repeat chest CT (see Fig. 1) showed bilateral peribronchovascular patchy consolidations and pleural effusions without evidence of pulmonary embolism. The patient was also noted to have a single, discrete violaceous nodule on the hard palate as well as a nodule with similar appearance on his upper chest (neither lesion was present on admission). A skin biopsy was obtained. Despite steroids, antibiotic therapy, and aggressive critical-care management, severe acidosis, progressive acute kidney injury, and anuria ensued. Continuous venovenous hemodialysis was initiated.

Discrete violaceous nodules with mucocutaneous localization in the context of AIDS are virtually pathognomonic for KS. Rarely, BA may be misdiagnosed as KS, or they may occur

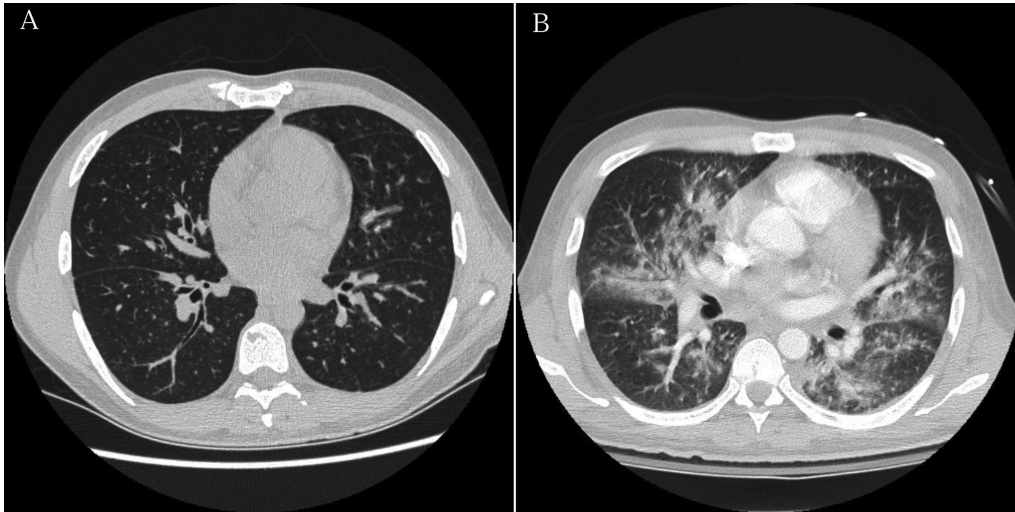



FIG. 1. Comparison of axial views of initial computerized tomography (CT) of the chest (A, left side) and repeat CT of the chest (B, right side) after the administration of corticosteroids 1 month later. There was development of bilateral peribronchovascular patchy infiltration in the context of underlying hilar lymphadenopathy and centrilobular nodules.

concurrently. The patient's current clinical deterioration, radiographic findings, and development of new skin lesions in the setting of response to ART are concerning for KS-related IRIS with visceral involvement. It is likely that systemic corticosteroids are potentiating KS-related IRIS. At this point, there is compelling evidence of 2 distinct systemic disease processes: lymphoma and KS-related IRIS, both of which may be contributing to respiratory failure. Steroids can be highly effective in the treatment of high-grade lymphoma but can be harmful in patients with KS, where they have been shown to potentially exacerbate underlying disease. Given the patient's worsening respiratory status, discontinuation of corticosteroids and initiation of chemotherapy against both opportunistic malignancies should be considered.

 The patient's condition deteriorated with progressive acidosis and hypoxemia, and he died shortly after being transitioned to comfort-care measures. Review of the skin biopsy revealed KS. Autopsy revealed disseminated KS involving the skin, lymph nodes, and lungs, and high-grade anaplastic plasmablastic lymphoma infiltrating multiple lymph nodes and organs, including the lungs (see Fig. 2). There was no evidence of infection.

COMMENTARY

This case demonstrates the simultaneous fatal progression of 2 treatable HIV-associated malignancies in an era in which the end-stage manifestations of untreated HIV are becoming less common, particularly in developed countries. Modern ART—the centerpiece of progress with HIV—has yielded dramatic improvements in prognosis, but in this case, by precipitating KS-IRIS, ART paradoxically contributed to this patient's demise. Similarly, high-dose systemic corticosteroids, which were deemed necessary to stabilize the progression of his high-grade lymphoma, likely accelerated his KS. This corticosteroid-mediated worsening appears to be unique to KS given that corticosteroids are often recommended to treat severe presentations of IRIS in other diseases (eg, tuberculosis, MAC, PCP).

Immune reconstitution inflammatory syndrome is the paradoxical worsening of well-controlled disease or progression of previously occult disease after initiation of ART.¹

Although infectious diseases—including mycobacteria, cytomegalovirus, cryptococcosis, or PCP—are best known for their ability to recrudescence or manifest with a recovering immune system, opportunistic malignancies such as KS can do the same. Risk factors for development of IRIS are low pre-ART CD4 count, high pre-ART viral load, and rapid response to ART.² In 1 large series, the median time to diagnosis of IRIS was 33 days.² Immune reconstitution inflammatory syndrome is a clinical diagnosis without specific pathologic findings. Because IRIS is a diagnosis of exclusion, other explanations for worsening disease, including drug resistance, drug reactions (eg, abacavir hypersensitivity syndrome), and poor adherence to medications, should be ruled out before making the diagnosis.

Kaposi sarcoma is a vascular tumor associated with infection by human herpesvirus 8 (HHV-8). The incidence of AIDS-related KS has declined substantially in the post-ART era.^{3,4} The classic radiographic presentation of pulmonary KS includes central bilateral opacities with a peribronchovascular distribution as well as pulmonary nodules, intraseptal thickening, mediastinal lymphadenopathy, and associated pleural effusions.^{5,6} Kaposi sarcoma-related IRIS has been described as developing within weeks of ART initiation and is associated with substantial morbidity and mortality, particularly in the context of pulmonary involvement, with 1 recent series showing 100% mortality in patients who did not receive chemotherapy.⁷⁻⁹

Human immunodeficiency virus-associated KS can respond well to ART alone. Indications for systemic chemotherapy for KS include extensive mucocutaneous disease, symptomatic visceral disease, or KS-related IRIS.¹⁰ The main chemotherapeutic agents used systemically for KS are liposomal anthracyclines such as doxorubicin or daunorubicin, or taxanes such as paclitaxel.¹¹ An association between corticosteroids and progression of KS has been previously described, even as early as several days after steroid administration.¹²⁻¹⁴ Recently, revised diagnostic criteria for corticosteroid-associated KS-IRIS have been proposed; this patient met those criteria.¹⁵

Plasmablastic lymphoma is a highly aggressive systemic NHL seen predominantly in HIV-positive patients. There is a strong association with Epstein-Barr virus; HHV-8 is more variably associated and is of unclear significance.¹⁶ Most HIV-infected patients have extranodal involvement at

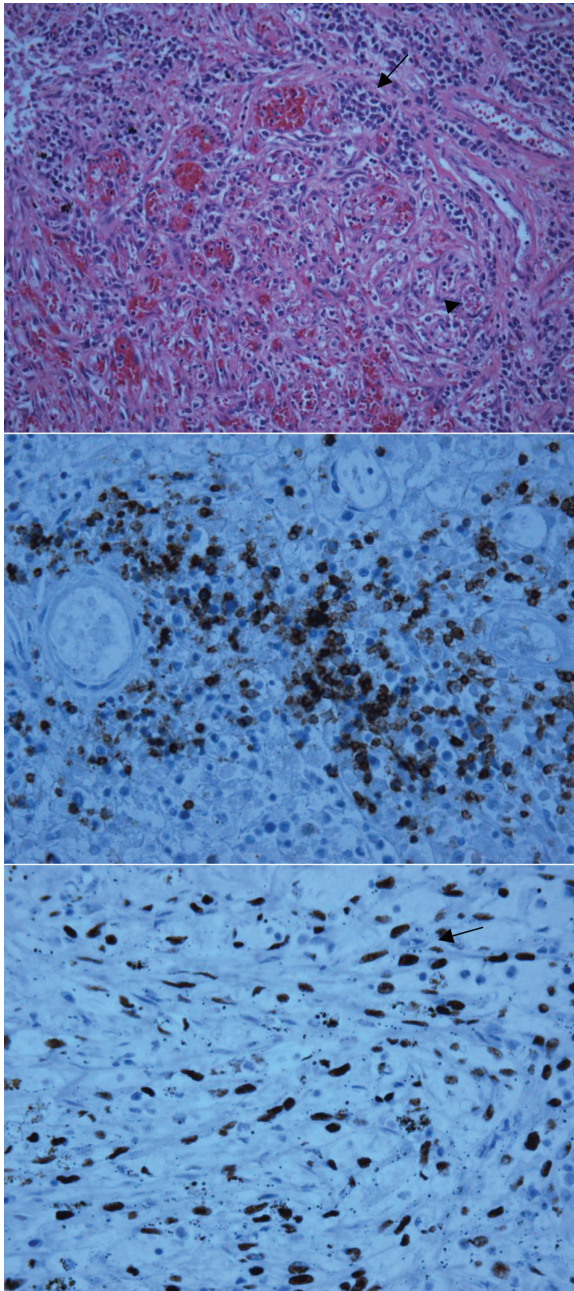


FIG. 2. The top panel (A) is a standard hematoxylin and eosin staining of a sample of lung tissue visualized at 20× magnification that reveals evidence of lymphoma cells (arrow) and Kaposi sarcoma (arrowhead). The middle panel (B) demonstrates immunoperoxidase staining for CD138, which is diffusely positive in this section (see dark brown–stained areas), consistent with plasmablastic lymphoma. The bottom panel (C) demonstrates immunohistochemical staining for human herpesvirus 8 (arrow), which is consistent with Kaposi sarcoma.

diagnosis; in a series of 53 HIV-positive patients, the oral cavity was the most frequent site, and lung involvement was seen in 12%. The prognosis is poor, with a mean survival of approximately 1 year.¹⁷

Treatment for systemic NHL in HIV-positive patients generally consists of a chemotherapy regimen while ART is continued or initiated.¹⁸ The most commonly used chemotherapy combination is cyclophosphamide, doxorubicin, vincristine, and prednisone, often supplemented with the anti-CD20 monoclonal antibody rituximab. In the case of aggressive systemic NHL, more intensive treatment regimens

are often utilized, though it remains unclear if they are associated with improved outcomes.^{17,19} Antiretroviral therapy is continued, as it has been shown to reduce the rate of opportunistic infections and decrease mortality.²⁰

Despite the remarkable progress that has been made in the past 30 years, HIV/AIDS remains a devastating and remarkably complex disease. As the landscape of HIV/AIDS evolves, clinicians will continue to be faced with new challenging and vexing decisions. Perhaps no greater challenge exists than the presence of 2 simultaneous, rapidly fatal malignancies with directly competing therapeutic strategies, as in this case, where the ART and steroids employed to address NHL fostered widespread KS-IRIS. This case reminds us that a single unifying diagnosis can often be the exception rather than the rule in the care of patients with advanced HIV. It also illustrates how the mainstay of HIV treatment, ART, can be a double-edged sword.

KEY TEACHING POINTS

- In HIV/AIDS patients receiving ART who become paradoxically more ill despite improvements in their CD4 counts, consider IRIS.
- Though corticosteroids are a hallmark of treatment for most types of IRIS—and for aggressive lymphomas—they can worsen KS.

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