Presentation of Case

A 41-year-old man was admitted to the hospital because of shortness of breath and fever. He had been well until 7 months earlier, when a rash and wheezing developed after he had eaten shellfish. He was seen in the emergency room of another hospital and treated for an allergic reaction; his symptoms improved.

Eighteen days later, cough and shortness of breath developed, and he returned to the same emergency room. Laboratory-test results are shown in Tables 1 and 2.

A chest radiograph was normal. Albuterol and clarithromycin were administered, and he was discharged. One week later, temperatures ranging from 39.4 to 40.0°C, chills, sweats, and dyspnea on exertion developed, and he was readmitted to the hospital. The tonsils were enlarged. The abdomen was soft, with mild tenderness in the right upper quadrant, and the spleen was palpable. The remainder of the examination was normal. Chest radiography was normal, and computed tomographic (CT) scanning of the abdomen revealed splenomegaly. Epstein–Barr virus (EBV) and cytomegalovirus-specific antibodies were consistent with past infection; serologic testing for brucella and parvovirus, cytomegalovirus antigenemia, tularemia agglutination, and rapid plasma reagin were negative. Results of other laboratory tests are shown in Tables 1 and 2. During the hospitalization, cervical, axillary, and inguinal lymphadenopathy developed, along with hepatomegaly, rash, anemia, and thrombocytopenia. A bone marrow biopsy revealed that the marrow was hypercellular. The patient’s symptoms gradually improved. Cultures of blood, stool, and urine were negative. He was discharged home 1 week after admission with a presumptive diagnosis of acute EBV infection.

Four months before admission to this hospital, temperatures up to 39.7°C, fatigue, myalgias, arthralgias, rhinorrhea, enlarged cervical nodes, and shortness of breath developed. On outpatient evaluation at another hospital, cervical and inguinal lymphadenopathy was present; axillary lymph nodes were smaller than on previous examinations. Results of laboratory tests are shown in Tables 1 and 2. During the next 3.5 months, the patient did not regain his previous level of vigorous activity. He lost 13.6 kg of weight, and a cough developed that was associated with several episodes of post-tussive vomiting.

Two weeks before admission, the patient traveled to Florida. During the visit,
Table 1. Hematologic Laboratory Data.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Emergency Visit to Other Hospital, 7 Months before Admission to This Hospital</th>
<th>One Week Later, on Admission to Other Hospital</th>
<th>Outpatient Visit to Other Hospital, 4 Months before Admission to This Hospital</th>
<th>On Admission to This Hospital</th>
<th>Second Hospital Day</th>
<th>Third Hospital Day</th>
<th>Normal Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematocrit (%)</td>
<td>27.4</td>
<td>23.9</td>
<td>32.3</td>
<td>19.9</td>
<td>18.6</td>
<td>26.7</td>
<td>41.0–53.0</td>
</tr>
<tr>
<td>Hemoglobin (g/dl)</td>
<td>9.3</td>
<td>7.9</td>
<td>11.7</td>
<td>6.5</td>
<td>5.7</td>
<td>8.9</td>
<td>13.5–17.5</td>
</tr>
<tr>
<td>White-cell count (per mm³)</td>
<td>4800</td>
<td>6,300</td>
<td>5,000</td>
<td>6,600</td>
<td>5,800</td>
<td>6,300</td>
<td>4500–11,000</td>
</tr>
<tr>
<td>Differential count (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutrophils</td>
<td>50</td>
<td>61</td>
<td>71</td>
<td>71</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Band forms</td>
<td>23</td>
<td>29</td>
<td>6</td>
<td>8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymphocytes</td>
<td>12</td>
<td>7</td>
<td>13</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monocytes</td>
<td>14</td>
<td>1</td>
<td>9</td>
<td>11</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eosinophils</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metamyelocyte</td>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelets (per mm³)</td>
<td>Low 136,000</td>
<td>62,000</td>
<td>83,000</td>
<td>67,000</td>
<td>81,000</td>
<td>150,000–350,000</td>
<td></td>
</tr>
<tr>
<td>Mean corpuscular volume (μm³)</td>
<td>85</td>
<td>82</td>
<td>83</td>
<td>78</td>
<td>80</td>
<td>79</td>
<td>80–100</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin (pg/red cell)</td>
<td>29.0</td>
<td>27.1</td>
<td>30.0</td>
<td>25.5</td>
<td>24.6</td>
<td>26.3</td>
<td>26.0–34.0</td>
</tr>
<tr>
<td>Mean corpuscular hemoglobin concentration (g/dl)</td>
<td>33.9</td>
<td>33.1</td>
<td>36.2</td>
<td>32.8</td>
<td>30.8</td>
<td>33.4</td>
<td>31.0–37.0</td>
</tr>
<tr>
<td>Red-cell distribution width (%)</td>
<td>15.4</td>
<td>15.7</td>
<td>13.5</td>
<td>19.3</td>
<td>19.5</td>
<td>17.8</td>
<td>11.5–14.5</td>
</tr>
<tr>
<td>Reticulocytes (%)</td>
<td>0.7</td>
<td></td>
<td>2.4</td>
<td>2.0</td>
<td>0.5–2.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Erythrocyte sedimentation rate (mm/hr)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>138</td>
<td>0–17</td>
<td></td>
</tr>
<tr>
<td>Prothrombin time (sec)</td>
<td>15.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>11.1–13.1</td>
</tr>
<tr>
<td>Partial-thromboplastin time (sec)</td>
<td>29.8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>22.1–35.1</td>
</tr>
<tr>
<td>Prothrombin time (international normalized ratio)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
his symptoms persisted, he had a near syncopal episode, and his temperature rose daily to a maximum of 39.4°C. During the week before admission, dyspnea occurred with minimal activity. He returned home. On the day of admission, he had chest pain and blurred vision. He was referred by his primary care physician for evaluation at this hospital, where he appeared to be acutely ill, and he was admitted to the hospital through the emergency department.

The patient had had pyelonephritis and mononucleosis during childhood. Testing for human immunodeficiency virus (HIV) had been negative 5 years earlier. He had no known drug allergies and was taking no medications. There was no history of tick bites, travel other than to Florida, or exposure to animals, raw milk, cheese, or persons with tuberculosis or other illnesses.

The patient had been divorced 4 years earlier and lived with his father and a pet dog. He had had 16 sexual partners during his lifetime; since the divorce he had had sexual contact with 6 women, 5 in the year before his illness began, about whom he knew little. He did not use condoms regularly. He had had no homosexual contacts or exposure to sex workers. He was unemployed and had previously worked in the construction industry. He had used cocaine and alcohol, but he had stopped both 8 months earlier. He had never used tobacco or intravenous drugs. His mother had had chronic obstructive lung disease and diabetes mellitus, and she had died at the age of 63 years. His father and a 5-year-old daughter were both well.

On examination, the patient appeared to be fatigued and became short of breath during the interview. The temperature was 39.3°C, the pulse 125 beats per minute, and the blood pressure 97/57 mm Hg; the respirations were 18 to 22 breaths per minute and rose to 40 per minute with minimal exertion. The oxygen saturation was 94 percent while he was breathing ambient air. The conjunctivas were pale, and soft, nontender lymph nodes (1 to 3 cm in diameter) were palpable in the anterior and posterior cervical, axillary, and inguinal chains. Bibasilar crackles were heard in the lungs (more in the left than in the right), and the heart sounds were rapid, with a hyperdynamic precordium. The liver and spleen were palpable. The remainder of the examination was normal. Laboratory-test results are shown in Tables 1 and 2. Urinalysis showed 1+ albumin, 0 to 2 red cells,
5 to 10 white cells, and a few bacteria per high-power field. Specimens were sent for tests for HIV antibody, brucella agglutination, fungal antibodies, and urinary legionella antigen, and cultures of the urine, blood, and stool were obtained. One unit of packed red cells was transfused. Oral iron supplementation was started, and a tuberculin skin test was performed.

A biopsy specimen of the bone marrow was hypercellular, with trilineage hematopoiesis. There were no granulomas or lymphoid aggregates. Stains and cultures for fungi, acid-fast bacilli, and common bacteria were negative. Flow cytometry revealed an inverted ratio of CD4+ and CD8+ T cells and phenotypically normal B cells.

CT scanning of the thorax, abdomen, and pelvis, performed after the oral and intravenous administration of contrast material, showed diffuse thickening of the distal esophageal wall and a 3-mm nodular opacity within the lower lobe of the left lung. Both the liver and spleen were enlarged, and the spleen measured 16 cm in an anteroposterior view. Multiple enlarged lymph nodes were seen in the porta hepatis, peripancreatic space, and left paraaortic region and along the iliac vessels bilaterally, with no evidence of necrosis or calcification.

On the third hospital day, a second unit of red cells was transfused. Results of additional laboratory tests are shown in Tables 1 and 2. A diagnostic procedure was performed.

**Differential Diagnosis**

**Dr. David T. Scadden:** May we review the radiology studies and the bone marrow–biopsy specimen?

**Dr. Victorine V. Muse:** A contrast-enhanced CT scan of the chest, abdomen, and pelvis shows marked hepatosplenomegaly (Fig. 1A) and enhancing axillary lymphadenopathy (Fig. 1B), with abdominal lymph nodes up to 2 cm in greatest dimension (Fig. 1C). Pelvic and inguinal lymphadenopathy is also seen.

**Dr. Robert P. Hasserjian:** The bone marrow–biopsy specimen was markedly hypercellular (Fig. 2A). Erythroid and myeloid elements were present in a normal ratio and showed maturation. Megakaryocytes were increased, and included frequent small forms with hypolobated nuclei (Fig. 2A, inset). Eosinophils and plasma cells were also increased in number. Lymphoid aggregates were not identified. A reticulin stain (Fig. 2B) demonstrated a moderate diffuse increase in reticulin fibers. Some binucleated erythroid forms were noted on the marrow aspirate.

The presence of hypercellular marrow in the setting of thrombocytopenia and anemia with a low reticulocyte count suggests ineffective hematopoiesis, which may be caused by a metabolic deficiency, a primary stem-cell defect such as a myelodysplastic syndrome, or an abnormal bone marrow microenvironment. Whereas the presence of dysplasia in the megakaryocytic series and some dyserythropoiesis in this case raised the possibility of a myelodysplastic syndrome, this diagnosis should be rendered only after the exclusion of other possible causes of ineffective hematopoiesis with abnormal maturation. Autoimmune and infectious causes, in particular HIV infection, should be considered in a young patient such as this one. In fact, the results of bone marrow flow cytometry showed an inverted ratio of CD4+ to CD8+ T cells. The bone marrow findings in this case are within the spectrum of those reported in patients who have HIV infection with cytopenia (Table 3).

**Dr. Scadden:** Although I am aware of the diagnosis in this case, the differential diagnosis in the case of a patient with recurrent febrile episodes, lymphadenopathy, splenomegaly, cytopenia, weight loss, and respiratory symptoms is broad. Possible causes include infection, neoplasms, and autoimmune diseases. The history of unprotected intercourse with multiple partners raises the suspicion of sexually transmitted infections. The absence of localized symptoms or physical findings suggests a viral process; however, subacute bacterial diseases and fungal diseases such as tuberculosis or histoplasmosis cannot be ruled out.

Infection with HIV type 1 is a primary consideration in this patient. He had had a negative test for anti-HIV antibodies 5 years earlier, but he had had multiple sexual partners since his divorce 4 years earlier, so he could have been infected with HIV at any time during that period. Acute HIV infection is characterized by a mononucleosis-like syndrome with fever and lymphadenopathy, during which the viral load is high and antibodies are typically absent. CD4 counts, which transiently drop during acute infection, return to baseline levels when the infection is partially controlled by the immune response. Although the illness diagnosed as EBV infection 6 months before admission was consistent with acute HIV in-
The severity of the patient's symptoms on admission suggests a longer duration of HIV infection. The finding on the bone marrow aspirate of an inverted ratio of CD4+ to CD8+ T cells makes the diagnosis of HIV disease highly likely in this patient.

This case illustrates one important manifestation of HIV infection, bone marrow dysfunction, and suggests the presence of another complication, an opportunistic neoplasm. Although antiretroviral therapy has reduced the frequency of such manifestations, they remain important in the setting of either unrecognized HIV infection, as in this case, or in advanced disease.

The patient had progressive anemia and thrombocytopenia. Although sequestration in his enlarged spleen could explain these abnormalities, the low hematocrit and reticulocyte counts suggest an abnormality in red-cell production. The discrepant finding of cytopenia with normal-to-increased bone marrow cellularity is characteristic of HIV disease. HIV appears to affect hematopoietic cell function through alterations in the microenvironment in which blood-cell production occurs. Many cell types within the bone marrow that probably contribute to hematopoietic regulation can be infected with HIV, including monocytes, macrophages, T cells, mesenchymal cells, and endothelial cells. Bone marrow dysfunction owing to HIV infection is reversible with effective antiretroviral therapy.

In addition to pancytopenia, this patient had lymphadenopathy and hepatosplenomegaly for at least 6 months. Persistent generalized lymphadenopathy owing to reactive lymphoid hyperplasia may occur in patients in the early stages of
the acquired immunodeficiency syndrome (AIDS), possibly caused by a combination of B-cell dysregulation in the setting of T-cell dysfunction and viral antigenemia associated with immune suppression. However, the severity of the clinical symptoms in this patient raises the possibility of cancer occurring in the setting of HIV infection.

HIV is one of several human viruses associated with cancer. Human papillomavirus, EBV, human herpesvirus 8 (HHV-8) (also known as Kaposi's sarcoma herpesvirus), and human T-cell leukemia virus type 1 are capable of directly inducing neoplastic transformation. In contrast, HIV, like hepatitis C and hepatitis B, provides a context in which malignant transformation may arise but rarely, if ever, directly transforms cells. HIV infects T cells, but T-cell tumors are rare in HIV disease; B-cell malignant tumors are common, although the virus does not infect B cells.

Table 3. Reported Bone Marrow Findings in Patients with HIV Infection and Cytopenia.a

<table>
<thead>
<tr>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypercellularity</td>
</tr>
<tr>
<td>Morphologic dysplasia (particularly in erythroid and megakaryocytic lineages)</td>
</tr>
<tr>
<td>Reticuloendothelial iron blockade with increased storage iron</td>
</tr>
<tr>
<td>Plasmacytosis, lymphoid aggregates, and granulomas</td>
</tr>
<tr>
<td>Reticulin fibrosis</td>
</tr>
<tr>
<td>Hypocellularity with serous atrophy (in advanced infection)</td>
</tr>
</tbody>
</table>

*a Data are from Delacretaz et al.² and Karcher and Frost.³

Reactivation of latent herpesvirus infections is common in HIV infection. Many cases of non-Hodgkin's lymphoma and most cases of Hodgkin's lymphoma in this setting, as well as the cases of leiomyosarcoma that occur rarely in HIV-infected children, are associated with the presence of EBV in tumor cells.¹⁵,¹⁶ In this patient with lymphadenopathy, lymphoma is a consideration. However, lymphomas in HIV-positive patients are typically aggressive Burkitt's lymphoma or large B-cell lymphomas, and the waxing and waning course of this patient's disease during 6 months would be unusual.

Kaposi's sarcoma and multicentric Castleman's disease are caused by HHV-8, as is primary effusion lymphoma, which is often also associated with EBV.¹⁸ Multicentric Castleman's disease presents with persistent fever, splenomegaly, and anemia in virtually all patients, with lymphadenopathy in approximately 90% of cases, marked weight loss in 70%, and pancytopenia in 35%.¹⁹ The development of fever, lymphadenopathy, weight loss, and splenomegaly in this patient may reflect acute HHV-8 infection and would be consistent with the sequence of events that occurred during the 6 months before admission.²⁰ That illness may have represented acute infection with HHV-8 or reactivation of HHV-8 in a setting of increasing immune suppression caused by progressive AIDS.²¹ However, the cytopenia of acute HHV-8 infection is associated with bone marrow that appears aplastic, distinctly different from the appearance of this patient's bone marrow.²²

HHV-8 produces homologues of many chemokines and cytokines that promote B-cell proliferation and survival and probably have a role in the pathogenesis of disease, including viral interleu-
kin-6 (a B-cell growth factor); viral homologues of the chemokines macrophage inhibitory proteins 1, 2a, and 2b; and viral Bcl-2 and cyclin D homologues that may enhance cell survival and proliferation. HHV-8 infection is prevalent, with seropositivity rates estimated at about 4% in North America, 25% in the Mediterranean basin, and up to 89% in sub-Saharan Africa. The frequency of HHV-8-related disease is nonetheless very low, since the virus is generally well controlled by the immune system.

Kaposi’s sarcoma occurs commonly with multicentric Castleman’s disease. Respiratory symptoms in this patient could reflect pulmonary involvement by Kaposi’s sarcoma. The characteristic appearance of lung involvement by Kaposi’s sarcoma (peribronchiolar cuffing and patchy infiltrates and effusions) was not evident on the chest CT images in this case. Respiratory problems could also reflect infection in an immunocompromised patient.

In summary, this patient probably acquired an infection with HIV between 1 and 4 years before admission, and as the infection progressed to AIDS, he either became infected with HHV-8 or the virus became reactivated in the 6 months before admission, causing multicentric Castleman’s disease.

**DR. DAVID T. SCADDEN’S DIAGNOSES**

AIDS, caused by HIV infection.

Multicentric Castleman’s disease, caused by HHV-8 infection.

**PATHOLOGICAL DISCUSSION**

Dr. Hasserjian: After the bone marrow–biopsy specimen was reviewed, the results of an HIV antibody test were reported to be positive. The viral load was 589,000 RNA copies per milliliter of plasma, and the peripheral-blood CD4 cell count was 101 cells per microliter.

The diagnostic procedure was a biopsy of the right and left cervical lymph nodes. The findings were similar in the two nodes. The lymph node capsule and subcapsular sinuses contained multiple expansile nodules of spindle cells (Fig. 3A), with slit-like spaces containing red cells (Fig. 3B).

**Figure 3. Biopsy Specimen of the Cervical Lymph Node.**

The specimen shows subcapsular nodules of spindled cells (Panel A). On higher magnification (Panel B), the spindled cells enclose slit-like vascular spaces containing red cells. Some cells contain eosinophilic hyaline globules (inset). These features are diagnostic of Kaposi’s sarcoma. The lymph node also contains scattered atrophic-appearing germinal centers (Panel C), surrounded by a hypervascular paracortex containing sheets of mature plasma cells; large plasmablasts replace much of the follicle mantle areas (Panels A, B, and C, hematoxylin and eosin; Panel C, inset, Giemsa). With immunohistochemical staining (Panel D, HHV-8 immunoperoxidase stain), the plasmablasts express HHV-8 antigen. In situ hybridization studies reveal monotypic staining of the plasmablasts for lambda (Panel E) with no staining for kappa light chain (Panel F). The surrounding reactive mature plasma cells show polytypic staining for immunoglobulin light chains.
Some of the spindle cells contained refractile hyaline globules, reflecting degenerated red cells (Fig. 3B, inset). An immunohistochemical study for HHV-8 was positive in the nuclei of the tumor cells. These findings are diagnostic of Kaposi’s sarcoma.

In the remaining lymph node tissue, the medullary cords were expanded by sheets of mature-appearing plasma cells (Fig. 3C). Many lymphoid follicles displayed small, atrophic germinal centers and mantle zones expanded by large plasma blasts with vesicular nuclei, prominent central nucleoli, and abundant, eccentrically placed amphophilic cytoplasm (Fig. 3C, inset). These cells were HHV-8–positive on immunohistochemical analysis (Fig. 3D) and expressed monotypic IgM lambda on both immunohistochemical analysis and in situ hybridization (Fig. 3E and 3F). These features are characteristic of the plasmablastic variant of multicentric Castleman’s disease. Castleman’s disease was originally described in these Case Records more than 50 years ago by Benjamin Castleman. Currently, two histologic types are recognized. The hyaline vascular type is usually localized and has atrophic, hyalinized follicles. The plasma-cell variant is characterized by follicular hyperplasia with variably atrophic germinal centers in a background of mature plasma cells. Multicentric involvement, systemic symptoms, and immunologic abnormalities often occur (multicentric Castleman’s disease). In the plasmablastic variant of multicentric Castleman’s disease, the abnormal follicles are surrounded by enlarged plasmablasts, as in this case; the condition occurs both in persons with HIV infection and in those without HIV infection. In nearly all cases in which the patient is HIV–positive and in about half the cases in which the patient is HIV–negative, HHV-8 is detectable in the plasmablasts.

An unusual feature of the plasmablastic variant of multicentric Castleman’s disease is that although the plasmablasts express monotypic IgM lambda light chain, these cells display a polyclonal repertoire of immunoglobulin gene rearrangements (Table 4). Plasmablastic lymphomas, which are both monotypic and monoclonal, subsequently develop in a high proportion of HIV-positive patients with plasmablastic multicentric Castleman’s disease.

### Table 4. Herpesvirus-Associated Plasmablastic and Immunoblastic Proliferations.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Common Sites</th>
<th>Association with HIV Infection</th>
<th>Viruses in Tumor Cells</th>
<th>Immunoglobulin Status</th>
<th>B-Cell Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasmablastic multicentric Castleman’s disease</td>
<td>Lymph node, spleen</td>
<td>Mostly</td>
<td>HHV-8</td>
<td>Polyclonal, monotypic IgM λ</td>
<td>Naive</td>
</tr>
<tr>
<td>Plasmablastic lymphoma of the oral cavity</td>
<td>Oral cavity</td>
<td>About 75%</td>
<td>EBV</td>
<td>Monoclonal, monotypic κ or λ</td>
<td>Terminally differentiated</td>
</tr>
<tr>
<td>Primary effusion lymphoma</td>
<td>Serous cavities</td>
<td>Mostly</td>
<td>Both HHV-8 and EBV</td>
<td>Monoclonal, Ig not expressed</td>
<td>Germinal center</td>
</tr>
<tr>
<td>Germinotropic lymphoproliferative disorder</td>
<td>Lymph node</td>
<td>No</td>
<td>Both HHV-8 and EBV</td>
<td>Polyclonal, monotypic κ or λ</td>
<td>Germinal center</td>
</tr>
</tbody>
</table>

* Data are from Du et al., Colomo et al., and Du et al. Ig denotes immunoglobulin.

### Discussion of Management

**Dr. Scadden:** Multicentric Castleman’s disease in the HIV-infected patient is often a devastating illness, and treatment is difficult. Therapies that have been reported to have some effect include single-agent and low-dose etoposide, thalidomide, interferon alfa, retinoids, anti–interleukin-6 antibody, combination chemotherapy, and rituximab. Anti-herpesvirus medications affect HHV-8 only in its lytic phase, and there are insufficient data to recommend this therapy. The effect of anti-HIV therapy is modest and variable.

The contribution of Kaposi’s sarcoma to this patient’s clinical symptoms is unclear. Although there was no radiographic evidence of pulmonary involvement, given the devastating nature of this complication and the prominence of respiratory symptoms, treatment for Kaposi’s sarcoma would be reasonable. Paclitaxel has been shown to be a highly potent medication against the disease, even when given in modest doses of 100 mg per square meter of body-surface area.

**Dr. Hasserjian:** On the fourth hospital day, the patient’s respiratory status suddenly deteriorated. The trachea was intubated, and he was transferred to the medical intensive care unit. An echocardiogram showed an ejection fraction of 40% and
a hypokinetic left ventricle. A chest radiograph showed new right lower lobe infiltrates, and sputum cultures grew *Staphylococcus aureus*; he was treated with vancomycin. During the next week, his condition improved, and the trachea was extubated. One dose of paclitaxel was administered; pancytopenia developed, which resolved slowly. Two and a half weeks after admission, antiretroviral therapy (lamivudine, stavudine, lopinavir, and ritonavir) was begun, and the patient was discharged home 3 weeks after admission, receiving antibiotic therapy intravenously. Two days later, he was readmitted because of fever and shortness of breath. On admission, he was hypotensive and hypoxemic, and had bulky bilateral cervical lymphadenopathy. A chest radiograph showed new pulmonary infiltrates with possible cavitation, and a sputum culture grew *S. aureus*.

**Dr. Muse:** Multiple chest radiographs revealed consolidations in the right lower lobe initially and then bilaterally, with pleural effusions. CT scanning of the chest delineated a mixture of multifocal ground-glass opacities, confluent air-space disease, and thick-walled cavities (Fig. 1D).

**Dr. Hasserjian:** Respiratory failure, refractory metabolic acidosis, hypotension, and multiorgan failure developed, and despite aggressive management, the patient died 5 days after readmission. An autopsy was performed.

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**PATHOLOGICAL DISCUSSION**

**Dr. Hasserjian:** The autopsy was limited to the chest. Both lungs were heavy, with extensive fibrin deposition in intraalveolar spaces and focal abscess formation, consistent with *S. aureus* infection. There was cardiomegaly with biventricular hypertrophy, consistent with HIV cardiomyopathy. The mediastinal lymph nodes were enlarged and showed persistent, but partly regressed and scarred, Kaposi’s sarcoma and persistent plasmablastic multicentric Castleman’s disease.

**Dr. Nesli Basgoz** (Infectious Diseases): Could this patient’s sudden clinical deterioration after discharge from the hospital have been due to an immune reconstitution inflammatory syndrome? Could an exacerbation of his HHV-8–related Kaposi’s sarcoma or Castleman’s disease have occurred after the treatment with antiretroviral therapy, since he had not had effective cytoreductive chemotherapy?

**Dr. Scadden:** This syndrome is typically seen in patients with mycobacterial and cytomegalovirus infection, in whom infection abruptly worsens after the initiation of antiretroviral therapy. It has been reported in patients with Kaposi’s sarcoma, who had progressive disease after the initiation of antiretroviral therapy. However, the interval from the initiation of antiretroviral therapy to the patient’s clinical deterioration in this case was less than a week, and usually the syndrome occurs after at least several weeks of therapy.

**Dr. Hasserjian:** Although the autopsy was limited, neither progressive Kaposi’s sarcoma nor any of the pathogens usually associated with an immune reconstitution inflammatory syndrome were identified.

**Dr. Nancy Lee Harris** (Pathology): Could the illness 7 months earlier have been acute HIV infection?

**Dr. Scadden:** I think the episode 7 months earlier was probably a seafood allergy rather than acute HIV infection; atopic events occur more commonly in HIV-infected persons. The presence of both anti-HIV antibodies and a very low CD4 cell count at the time of admission and profound hematologic abnormalities suggest prolonged HIV infection — at least a year, and probably longer.

**Dr. Bruce D. Walker** (Infectious Diseases): Two HIV-infected patients in whom the infection progressed to AIDS less than a year after the development of acute infection have been reported. Such rapid progression is unusual, however, and I agree with Dr. Scadden that the patient under discussion probably had been infected for longer than 6 months.

**Dr. Harris:** As this case comes to publication, we have just passed the 25th anniversary of the first reports of HIV–AIDS. By coincidence, the first case of AIDS that was diagnosed in Massachusetts, in 1981, was a case of lymphadenopathic Kaposi’s sarcoma associated with Castleman’s disease, reported in these Case Records.

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**ANATOMIC DISSECTION**

HHV-8–associated multicentric Castleman’s disease and Kaposi’s sarcoma associated with HIV infection.

**Dr. Scadden** reports having received consulting fees from Alexion Pharmaceuticals and Genzyme. No other potential conflict of interest relevant to this article was reported.
REFERENCES

29. Dupin N, Diss TL, Kellam P, et al. HHV-8 is associated with a plasmablastic variant of Castleman disease that is linked to HHV-8-positive plasmablastic lymphoma.


