

Fatal HIV-Associated Anaplastic Large-Cell Lymphoma

Liron Pantanowitz, MD; Jorge Castillo, MD; John K. Freeman, MD; Bruce J. Dezube, MD

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Lymphoma is a well-known complication of HIV infection. Such AIDS-defining lymphomas are usually aggressive B-cell lymphomas. However, epidemiological data have also linked HIV infection with an increased risk of T-cell lymphoma.¹ Therefore, it is easy to appreciate why the number of AIDS-related T-cell lymphoma case reports has increased in the literature.² We present an interesting case of fatal anaplastic large-cell lymphoma of T-cell phenotype associated with Epstein-Barr virus (EBV) infection in a patient with AIDS.

A 42-year-old Hispanic man with HIV infection diagnosed 4 years earlier had a recent medical history significant for *Mycobacterium avium-intracellulare* pneumonia. He had been treated with ethambutol and azithromycin and also had been given *Pneumocystis jirovecii* pneumonia prophylaxis. He had been nonadherent to his antiretroviral treatment regimen.

On presentation, he complained of vomiting, diarrhea, 1 week of fever (temperature of 38.8°C [101.9°F]), weakness, and a 2-day history of urinary incontinence unrelated to a neurological cause. His absolute CD4⁺ cell count was 63/μL, and his HIV RNA level was 227,637 copies/mL. Physical examination revealed dehydration, oral thrush, parotid enlargement, and nontender left cervical lymphadenopathy.

Results of laboratory testing showed a white blood cell count of 2300/μL, with 13% lymphocytes (normal, 15% to 43%); hemoglobin level of 8.8 g/dL (normal, 14 to 18); platelet count of 121,000/μL (normal, 150,000 to 460,000); abnormal findings on urinalysis (3+ albuminuria, 3+ hemoglobinuria, and casts); normal electrolyte levels and renal function; serum albumin level of

2.6 g/dL (normal, 3.4 to 4.8); total bilirubin level of 0.1 mg/dL (normal, 0.0 to 1.0); and lactate dehydrogenase level of 878 U/L (normal, 94 to 250). *M avium-intracellulare* was found in a bronchoalveolar lavage specimen. A blood culture grew *Bacteroides thetaiotaomicron*.

Despite cefepime therapy, the patient remained febrile. Respiratory distress developed, and he became hypotensive with ensuing acute renal and liver failure. Diffuse airspace disease was noted on a chest radiograph. He died soon afterward, and an autopsy was performed.

Postmortem examination revealed anaplastic large-cell lymphoma involving his cervical, mediastinal, peri-aortic, mesenteric, and peripancreatic lymph nodes as well as multiple organs, including the lungs, heart, kidneys, adrenal glands, esophagus, stomach, and liver (Figures 1, 2, 3, and 4). His cervical lymph nodes measured up to 2.5 cm. In addition, several deep visceral lymph nodes were enlarged and measured up to 1.0 cm; most of these lymph nodes were grossly replaced by lymphoma. His lungs were firm and noncrepitant on gross examination and were notable for multiple white tumor nodules bilaterally on the visceral pleura and within the parenchyma (Figure 1A). Apart from extensive pulmonary involvement by lymphoma, there was also diffuse alveolar damage (Figure 1B) but no evidence of mycobacterial infection.

The lymphoma cells were immunoreactive for the T-cell markers CD45RO and CD30 (Figure 5) but failed to stain with CD20, CD79a, PAX5, CD3, CD15, CD56, CD57, ALK, epithelial membrane antigen, and latent nuclear antigen 1 (for human herpesvirus 8). In situ hybridization for EBV-encoded RNA was strongly positive. T-cell receptor (T-gamma) gene rearrangement by polymerase chain reaction analysis was positive for a clonal T-cell gene rearrangement.

The risk of T-cell lymphoma has been estimated to be 15-fold higher in HIV-positive persons. Although HIV-associated T-cell lymphoma was recognized relatively early in the AIDS epidemic,³⁻⁵ its occurrence in the pre-HAART era was believed to be rare.⁶ Many earlier cases of T-cell lymphoma have been grouped with B-cell lymphomas in larger series of AIDS-related lymphoma. The exact pathogenesis of T-cell lymphoma in the setting of HIV infection is uncertain but appears to be related to both immuno-

Dr Pantanowitz is assistant professor of pathology in the department of pathology at Baystate Medical Center, Tufts University School of Medicine, Springfield, Mass. Dr Castillo is assistant professor of medicine, Brown University Warren Alpert Medical School, division of hematology and oncology, The Miriam Hospital, Providence, RI. Dr Freeman is assistant professor of pathology and director of hematopathology in the department of pathology, Baystate Medical Center, Tufts University School of Medicine. Dr Dezube is associate professor of medicine in the department of medicine (hematology-oncology division) at Beth Israel Deaconess Medical Center, Harvard Medical School, Boston. Drs Pantanowitz and Dezube are the editors of this column.

suppression and viral co-infection (eg, with EBV).²

Several concomitant HIV-induced T-cell abnormalities are believed to predispose patients to natural killer/T-cell lymphomas. For example, some authors believe that the preponderance of CD8⁺ lymphocytes seen with chronic HIV infection may facilitate their neoplastic transformation.⁷ While the frequency of EBV in anaplastic large-cell lymphoma not associated with HIV is low,⁸ there have been several reports showing a high frequency of EBV

detection in anaplastic large-cell lymphoma associated with HIV infection.⁹⁻¹¹ It has been suggested by some authors that EBV infection may mediate progression of other non-Hodgkin lymphomas to CD30⁺ anaplastic large-cell lymphoma.¹² Interestingly, cases of anaplastic large-cell lymphoma associated with EBV infection ap-

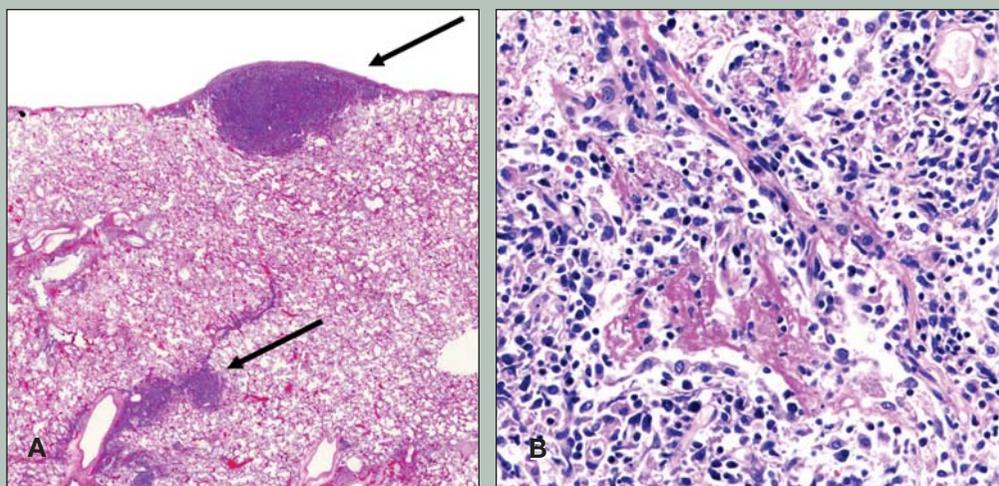


Figure 1. A: Lymphoma nodules (arrows) are shown on the visceral pleura and in the lung parenchyma along the septum (hematoxylin and eosin stain). B: Anaplastic lymphoma cells are seen extensively infiltrating the lung parenchyma admixed with intra-alveolar eosinophilic (pink) fibrin deposition in keeping with an exudative (acute) phase of diffuse alveolar damage (hematoxylin and eosin stain, original magnification $\times 400$).

pear not to be associated with ALK gene expression because of the classic chromosomal translocation involving chromosomes 2 and 5, ie, t(2;5).¹³ In support of this observation, the EBV-associated anaplastic large-cell lymphoma in our HIV-positive patient was ALK-negative.

AIDS-related T-cell lymphomas usually present at

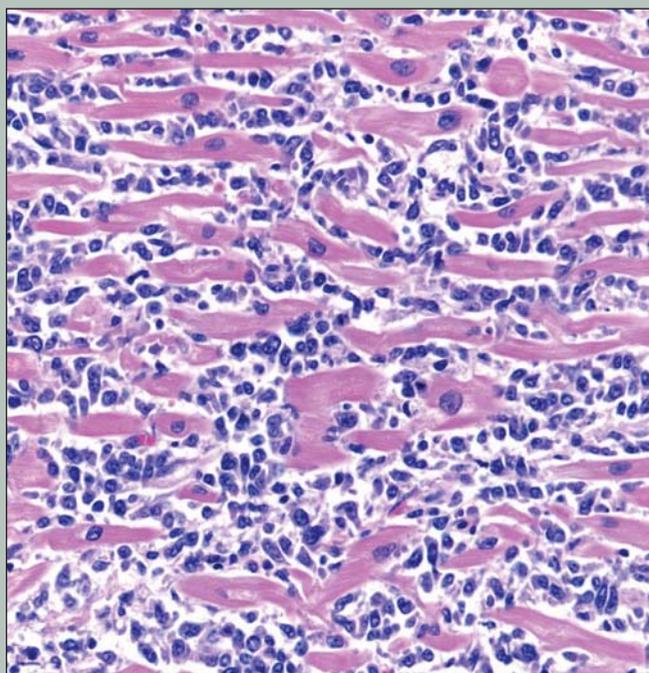


Figure 2. Anaplastic lymphoma cells can be seen diffusely infiltrating between myocytes in the heart (hematoxylin and eosin stain, original magnification $\times 400$).

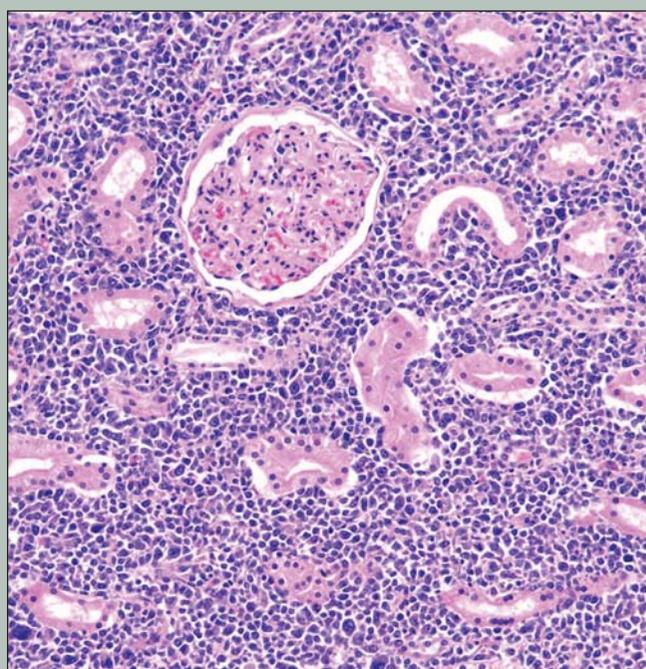


Figure 3. The kidney interstitium is densely packed with malignant lymphocytes growing between renal glomeruli and tubules (hematoxylin and eosin stain, original magnification $\times 200$).

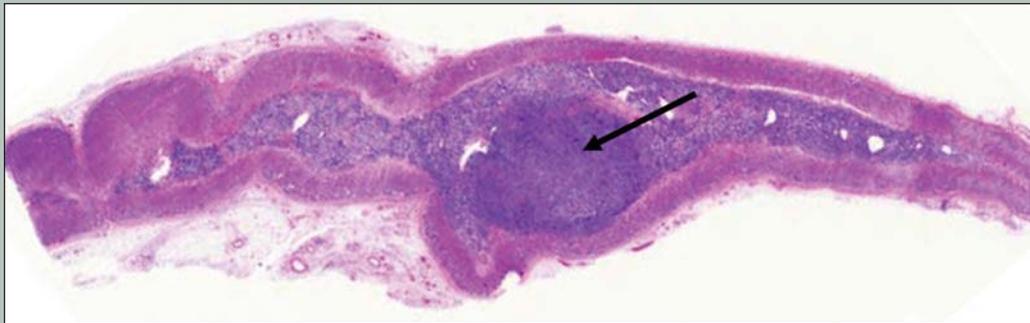


Figure 4. A large lymphoma nodule (arrow) is shown within the medulla of an adrenal gland (hematoxylin and eosin stain).

an advanced lymphoma stage in patients with marked immunosuppression and prior AIDS-defining illness.² Such patients commonly have B symptoms (eg, weight loss, night sweats, fever), lymphadenopathy, and extranodal disease. Many of the clinical manifestations of T-cell lymphoma, such as fever, can be related to cytokine expression from lymphoma cells. In general, systemic AIDS-related T-cell lymphomas exhibit an aggressive clinical course with a poor prognosis.

In one series involving 4 patients with CD30⁺ T-cell anaplastic large-cell lymphoma, similar to that seen in our patient, investigators reported aggressive disease with patients dying within a median of 3 months from their lymphoma diagnosis.¹⁴ Factors that likely contribute to the aggressive clinical behavior of these malignancies include advanced clinical lymphoma stage at presentation, marked HIV-related immunosuppression, and chemotherapeutic resistance. A standard therapeutic approach is required in order to address these emerging AIDS-defining T-cell neoplasms, for which prognosis remains poor even in the HAART era.²

Finally, autopsy rates for patients dying in hospitals have declined dramatically over the past 50 years.¹⁵ This case clearly demonstrates the clinical value of post-mortem examination. Autopsies should be reasserted as a tool for investigation and quality improvement in modern medicine. □

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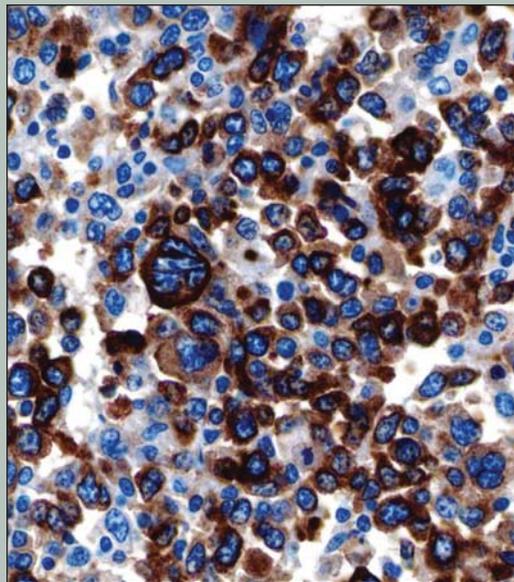


Figure 5. Lymph node effacement caused by anaplastic lymphoma cells (immunohistochemical stain for CD30, original magnification $\times 600$).

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