HIV-associated lymphoma

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A 39-year-old man with AIDS experienced worsening shortness of breath, cytopenia, and fever and was admitted to Baylor University Medical Center. The patient also reported symptoms of anorexia, diarrhea, abdominal pain, and generalized body pain. The physical examination showed cachexia; a large perineal Kaposi sarcoma tumor, as well as scattered Kaposi sarcoma lesions on his face, neck, back, and chest; dependent edema in the legs and scrotum; a scrotal ulcer; and abdominal distension with ascites and tenderness. No lymphadenopathy or hepatosplenomegaly was noted. A lung infiltrate and right-sided pleural effusion were evident, and the possibility of parapneumonic effusion was considered.

A complete blood count demonstrated leukopenia (white blood cell count, 500 K/uL), anemia (hemoglobin, 8.6 g/dL), and thrombocytopenia (platelet count, 19,000 K/uL), with a virtual absence of CD4⁺ cells (<1%). The absolute lymphocyte count was 288 cells/L. HIV-1 RNA quantification by polymerase chain reaction was <50. The patient's blood cultures were also positive for *Streptococcus viridans*. The source of the infection was believed to be the skin, in association with Kaposi

Figure 2. High-power view (×40, H&E) of primary effusion lymphoma. Note the multinucleated tumor cell with prominent macronucleoli (arrow) in a background of highly atypical pleomorphic mononuclear cells.

sarcoma. The patient was treated with broad-spectrum antibiotics, and follow-up blood cultures showed resolution of the infection.

The pleural effusion was drained and sent for cytologic evaluation. Results showed highly atypical, pleomorphic lymphoid cells (*Figures 1 and 2*). Usual B and T cell markers (CD3, CD5, CD10, CD15, CD20, CD79a, PAX5) were negative, and activation markers (CD30 and MUM1) were positive in this tumor. CD138 showed a minimal to no staining pattern (although most PELs show a positive reaction). The tumor proliferation marker MIB-1 (Ki-67) showed strong positivity, with staining of 75% of cells (*Figure 3*). The cells were positive for human herpesvirus 8 (HHV8) and Epstein-Barr virus (EBV) (*Figure 4*). The EBV copy number in the pleural fluid was 105,000/mL.

Although the differential diagnosis based on the clinical findings would include pyothorax-associated lymphoma, Burkitt lymphoma, lymphomatous effusion of disseminated

Figure 1. (a) Highly cellular smear with multiple aggregates of mononuclear cells (×10, hematoxylin and eosin stain [H&E]). (b) Note the pleomorphic nature of the cells (×20, H&E). (c) Some of the cells show plasma cytoid features with perinuclear hof (single arrow) (×40, H&E). (d) This tumor has high cellular turnover, prominent mitotic activity, and cellular apoptosis (double arrow) (×40, H&E).

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Figure 3. Immunohistochemistry results showed positive staining ($\times 10$) for (a) CD30, (b) MUM1, and (c) MIB1 (75%).

Figure 4. (a) Primary effusion lymphoma with a distinct, strong positive reaction to HHV8 ($\times 10$). (b) Epstein-Barr virus-encoded small RNAs (EBER) staining showed scattered, slightly positive cells ($\times 10$).

lymphoma, malignant melanoma, and pleomorphic non-small cell carcinoma, the absence of HHV8 in each of these lymphomas eliminated them from consideration. Primary effusion lymphoma (PEL) was diagnosed.

DISCUSSION

Lymphoma is common among HIV-positive patients: they have a 60- to 200-fold increased risk of non-Hodgkin lymphoma and an up to 8-fold increased risk of Hodgkin lymphoma compared with the general population (1). HIV-associated lymphomas are aggressive and heterogeneous, consisting of both systemic and central nervous system types. The systemic lymphomas (as opposed to the central nervous system lymphomas) often occur among HIV patients with an otherwise good clinical status—i.e., 75% of patients have CD4 counts $>50/\text{mm}^3$ at presentation, and many patients have no history of prior opportunistic infections (2).

The type of non-Hodgkin lymphoma found in this case—PEL—is considered an AIDS-defining illness. Along with plasmablastic lymphoma of the oral cavity, it is one lymphoma that occurs primarily in HIV-positive individuals (*Table*). There have been some cases in HIV-seronegative patients with no prior history of transplantation; in these individuals, the disease tends to occur in advanced age, at least 2 to 3 decades later than it does in HIV-positive patients. PEL is rare, comprising 4% of AIDS-related lymphomas and $<1\%$ of non-AIDS-related large-cell lymphomas (3, 4).

PEL was first acknowledged as a distinct entity in 1995 based on its consistent association with HHV8. In this malignancy, neoplastic cells proliferate within one or more of the major body cavities (pleural, peritoneal, and pericardial) and generally are restricted to those cavities. On rare occasions, the

cells infiltrate into the lymphatic system or subserosal tissue and form mass lesions, generally in the gastrointestinal tract or soft tissue.

PEL represents an advanced stage (preplasmacytic) of B-cell differentiation but typically lacks any immunophenotypic evidence of B- or T-cell differentiation by conventional im-

munochemistry or flow cytometry methods. Pan B-cell markers (CD19, CD20) are negative, but cells are positive for CD45 and activation-associated antigens CD30, CD38, CD71, and EMA. PEL cells rarely exhibit genotypic infidelity with biphenotypic B- and T-cell expression (positive B- and T-cell gene rearrangements) (4).

HHV8 is integral to the pathologic definition of PEL. In North America, only 1% to 3% of the population is infected with HHV8 (although the seroprevalence is as high as 50% to 70% in the Mediterranean region) (4), but those infected with HIV have a high prevalence of coinfection with HHV8 (5). Other manifestations of HHV8 infection include Kaposi sarcoma and multicentric Castleman disease; patients with those conditions are more likely to get PEL and vice versa (3).

Like HHV8, EBV is a member of the gamma herpes virus family. Most HIV-positive patients with PEL also show evidence of EBV infection. However, the role of EBV in PEL oncogenesis remains unclear. HHV8 appears to play the dominant role in lymphomatous transformation for PEL, with EBV playing a supportive role (4). For other AIDS-related malignancies, such as primary central nervous system lymphoma, EBV plays a primary role (3), and overall it is identified in 60% of HIV-related lymphomas (1).

The pathogenesis of PEL and its relation to HHV8 are still being determined. Several studies have suggested that viral interleukin-6 acts as an autocrine growth factor for PEL cells

Table. Categories of HIV-associated lymphomas*

Category	Examples
Lymphomas also occurring in immunocompetent patients	Burkitt lymphoma: classical, with plasmacytoid differentiation, and atypical Diffuse large B-cell lymphoma: centroblastic, immunoblastic Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue type (MALT lymphoma) (rare) Peripheral T-cell lymphoma (rare) Classical Hodgkin lymphoma
Lymphomas occurring more specifically in HIV+ patients	Primary effusion lymphoma Plasmablastic lymphoma of oral cavity
Lymphoma also occurring in other immunodeficiency states	Polymorphic B-cell lymphoma (PTLD-like)

*From Jaffe et al, 2001 (1). Reprinted with permission.

(6, 7) and accelerates angiogenesis through production of vascular endothelial growth factor-A (8). In addition, three latent gene products of HHV8 may play a role in oncogenesis; these include latency-associated nuclear antigen-1, viral cyclin, and viral FLICE inhibitory protein (4).

PEL has a poor prognosis, with a median survival time of about 6 months (4). Simonelli et al (9) reported on their 11 patients with PEL—in the context of 277 cases of HIV-associated non-Hodgkin lymphoma. Eight of these 11 patients were treated with a regimen of cyclophosphamide, doxorubicin, vincristine, and prednisone, and 42% reached complete remission. Still, the median survival time was only 6 months—lower than that for other types of non-Hodgkin lymphoma. At the onset of the disease, the PEL patients did not differ from the other patients in terms of CD4 number, HIV viremia plasma levels, and clinical characteristics. The cause of death in PEL patients is not only lymphoma progression but also opportunistic infection and complications of HIV (4).

Nador et al (10) had a lower response rate of only 3 to 4 months in 15 PEL patients. The difference could have been related to the absence of highly active antiretroviral therapy (HAART), which has been shown in multivariate analysis to be associated with a better prognosis (11). Even HAART by itself has been reported to produce remission of PEL (12, 13).

Palliative local radiation therapy to the body cavity has been suggested (3), and other drugs have been used for PEL, including high-dose methotrexate (14), parenteral azidothymidine and interferon-alpha (6, 15), and bortezomib (16).

Despite therapy, including HAART, the patient's EBV copy number in the blood continued to increase dramatically over several days—from 5,860 to 21,500 copies/mL—and he continued to experience severe abdominal, perianal, and generalized pain. His condition deteriorated rapidly due to the disseminated Kaposi sarcoma, PEL, edema, and ascites. In conjunction with his family, he decided to institute a do not resuscitate and do not intubate order. He was treated with comfort measures only and died a week after discharge.

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