A 40-year-old heterosexual man presented with symptoms of pleuritic pain, nonproductive cough, and exertional dyspnea, which he had experienced for 3 weeks. There were no other symptoms of note. The patient’s medical history included AIDS, IV drug use, seizures, Pneumocystis carinii pneumonia, and infections with hepatitis B and C viruses.

Physical examination showed a cachectic man who was not in any distress. Vital signs included the following: temperature, 38°C; pulse, 100 beats/min; respiratory rate, 18 breaths/min; and BP, 110/70 mm Hg. Lung examination revealed dullness and decreased breath sounds over the left thorax. There was no evidence of lymphadenopathy or organomegaly.

Laboratory findings were the following: WBC count, $3.2 \times 10^9$/L (normal range, 4.7 to 6.1); hemoglobin level, 5 g/dL (normal range, 14 to 18); hematocrit, 15% (normal range, 42 to 52); and CD4 cell count, 7/μL (normal range, 400 to 1,770). Serum electrolyte levels were normal, and the serum lactate dehydrogenase level was 1,236 U/L (normal range, 60 to 225). The results of arterial blood gas tests on room air were the following: pH, 7.44 (normal range, 7.35 to 7.45); PaCO₂, 31 mm Hg (normal range, 35 to 45); PaO₂, 72 mm Hg (normal range, 80 to 100); and oxygen saturation, 95%. The results of smears and cultures of sputum for acid-fast bacilli were negative.

A chest radiograph (Fig 1) showed pleural effusion in the left lung more than in the right lung, partial atelectasis of the left lung, and an enlarged mediastinum with right shift. Contrast-enhanced chest and abdominal CT scans (Fig 2) showed pericardial and bilateral pleural effusions, ascites, and no evidence of lymphadenopathy. A procedure was performed.

What is the diagnosis?
Diagnosis: Primary Effusion Lymphoma or Body Cavity-Based Lymphoma

Examination of the pleural fluid showed the following: RBC count, 459/μL; WBC count, 730/μL, with 58% lymphocytes and 42% monocytes; pH, 7.26; serum lactate dehydrogenase level, 970 U/L; protein level, 6.4 g/dL; and glucose level, 57 mg/dL. The results of all cultures were negative. Pathologic analysis of the pleural fluid by polymerase chain reaction showed an absence of clonal rearrangement. Southern blot analysis for the presence of human herpes virus (HHV)-8 and Epstein-Barr virus (EBV) revealed that both viruses were present in high copy number, which is consistent with primary effusion lymphoma (PEL) or body cavity-based lymphoma (BCBL). Due to the patient’s advanced AIDS and poor candidacy for aggressive systemic chemotherapy, treatment was palliative with left chest tube thoracostomy for drainage of pleural effusion. Our patient is still alive 6 months after presentation, in comparison with the median survival for patients reported by Ansari et al (2 months) and Cesarman et al (3 months).

PEL/BCBL is a rare non-Hodgkin’s lymphoma (NHL) that grows in liquid phase in the serous body cavities in the absence of solid tumors. HIV-related NHLs, a major cause of morbidity and mortality among HIV-infected patients, are derived from B cells and are classified into Burkitt’s lymphoma, diffuse large cell lymphoma, anaplastic large cell lymphoma, and PEL/BCBL. PEL/BCBL represents about 3% of all AIDS-related NHLs. Among immunocompetent hosts, PEL/BCBL is rare, since it accounts for <1% of cases of high-grade NHL.

Gaidano et al reported a consistency of HHV-8 infection in PEL/BCBL and multicentric Castleman’s disease. HHV-8 occurs in 100% of AIDS-related cases and in 40% of cases unrelated to AIDS. These and other findings by Arvanitakis et al suggest that HHV-8 plays a pathogenic role in these disorders. Further molecular studies by Gessain et al of 250 cases of lymphoproliferative malignancies confirmed that HHV-8 is present at a high copy number in the PEL/BCBL cells and that HHV-8 is not pathogenic for other lymphoid neoplasms. Thus, HHV-8 infection represents a consistent and specific marker of PEL/BCBL, and its presence is now conventionally assumed to be a sine qua non for diagnosis. The detection of HHV-8 in lymphoid tumors other than PEL/BCBL is due to infection of bystander cells that contaminate the tumor clone.

Several studies have revealed that HHV-8 carries several genes that may putatively behave as oncogenes. Infections are highly selective for lymphoid neoplasms, the copy number of HHV-8 genomes harbored by PEL/BCBL cells is high, the PEL/BCBL genes with potential activity, namely, open reading frames, cellular D-type cyclines (ORF72/cyclin D), and ORF74 G-protein coupled receptor, are expressed by PEL/BCBL cells, and finally, PEL/BCBL cell lines produce large amounts of virus Interleukin 6, which is thought to support PEL/BCBL growth via the induction of human interleukin 1.

The molecular pathogenesis of PEL/BCBL is characterized by distinct genetic pathways, including chromosomal rearrangements of c-myc and bcl-6 genes in HIV-related Burkitt’s lymphoma and diffuse large cell lymphoma, respectively.

Studies by Gaidano et al to evaluate the role of microsatellite instability (MSI) in the development of PEL/BCBL showed that MSI represents a clonal genetic lesion affecting virtually all PEL/BCBL cells, which suggests that MSI may be involved in the pathogenesis of AIDS-related BCBL.

In addition to infection by HHV-8, a patient with PEL/BCBL is also frequently infected by EBV. In contrast to HHV-8 infection, which is present in all cases of PEL/BCBL, infection by EBV may be absent in some cases. Analysis by Karcher et al of the clinical and pathobiological features of 58 cases showed that PEL/BCBL is a unique neoplasm with a strong propensity for body-cavity involvement without mass lesions and with little or no dissemination; poor prognosis; high-grade, usually immunoblastic, morphology; late B-cell phenotype and genotype, no associated c-myc gene rearrangement; frequent presence of EBV genome; and uniform association with HHV-8. Considering these features, Karcher et al concluded that HHV-8 and EBV share a role in inducing PEL/BCBL, which indicates a role for antitherpes or anticytokine agents in the treatment of this lymphoma.

Ansari et al reported five patients with advanced AIDS who developed PEL/BCBL. All patients were homosexual men with multiple AIDS-related opportunistic infections. The range of CD4 cell counts was 25 to 130/μL. Three of the patients had preexisting Kaposi’s sarcoma diagnosed before diagnosis of the PEL/BCBL. Four of the patients presented with pleural effusions, and one presented with ascites. There was no evidence of a body-cavity mass, lymphadenopathy, or organomegaly. The median survival was 2 months.

Morassut et al studied the chest radiographs and CT scans of six patients with PEL/BCBL and discovered thickening of the parietal pleura in all patients and a pericardial thickening in four patients. Pericardial effusion and abdominal effusions were
present in five and two patients, respectively. There was no evidence of solid tumors or parenchymal abnormalities.

As seen on autopsy or in CT scans, PEL/BCBL presents as multiple, small tumor foci that cause irregular thickening of the serous membrane. The tumor may spread extensively so that it is difficult to determine whether the neoplasm originated in the pleura, the pericardium, or the peritoneum. PEL/BCBL involvement of superficial and deep lymph nodes, as well as soft tissue and organs other than serous body cavities, have been reported.

Finally, Nador et al. and Ceserano et al. suggested the designate of BCBL as PEL, since the latter term describes the condition more accurately and avoids confusion with other malignant lymphomas that occur in the body cavity.

CONCLUSION

PELs/BCBLs are a clinically and biologically distinct entity. They are predominantly, but not exclusively, found in patients with advanced AIDS and manifest a unique combination of morphologic, immunophenotypic, and genotypic features that are combined with the presence of HHV-8 and EBV. Since the growth of lymphoma cells in the body cavity may be the first and sole manifestation of the disease, PEL/BCBL must be included among the differential diagnoses of serous effusions detected in HIV-infected patients. Clinical trials are needed to design treatment using local therapy to the body cavity or drugs that concentrate preferentially to the body cavity to minimize further systemic immunosuppression.

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