Primary effusion lymphoma (PEL), formerly known as body cavity–based lymphoma, is a high-grade B-cell non-Hodgkin’s lymphoma associated with Kaposi’s sarcoma and human herpesvirus 8 infection. It usually affects serous body cavities and results in recurrent lymphomatous effusions. PEL is often diagnosed in patients with HIV infection and carries a poor prognosis, with median survival near 6 months. We describe a patient who presented with symptomatic pericardial effusion, secondary to newly diagnosed PEL, and no prior history of HIV infection.

A 44-year-old homosexual white man with a significant past medical history of Crohn’s disease presented to Baylor University Medical Center’s emergency department in January 2008. The patient complained of a 4-month history of Pel-Ebstein fever, which was characterized by recurrent episodes of daily high fever separated sometimes by days without fever. Other symptoms included a 10-pound weight loss, intermittent dry cough, increasing dyspnea, chills, and severe fatigue. On admission the patient was febrile with a temperature of 103.2°F, tachycardic with a pulse of 120 beats per minute, and normotensive with a blood pressure of 107/61 mm Hg. He was mildly cachectic, and his skin was moist secondary to sweating. The patient had a small jugular vein distention with no carotid bruit. He had palpable lymphadenopathy on examination, with a pea-sized right supraclavicular lymph node, a right cervical lymph node (1.5 cm in diameter, soft, rubbery, and nontender), and bilateral inguinal lymphadenopathy (approximately 1 cm in diameter and rubbery). The patient’s lungs were clear except for an occasional crackle at the right base that cleared with deep breathing. His heartbeat was regular without murmur. The abdomen was nontender, but a spleen tip was palpable. On skin examination, the patient had a small, 1-cm, nontender, gray-bluish, slightly raised skin papule on his left shin and a similar lesion on the right forearm.

The patient was found to have cardiomegaly and possible pleural effusion on a chest x-ray, severe anemia (hematocrit, 19.5%), and thrombocytopenia (platelets, 63,000/mm³). He was admitted to the hospital for a blood transfusion and further evaluation.

A computed tomography (CT) scan of the abdomen and pelvis confirmed a large pericardial effusion, small right pleural effusion, splenomegaly, and extensive mildly enlarged (estimated to be 1-cm diameter) retroperitoneal and bilateral iliac lymphadenopathy (Figure 1). A transthoracic echocardiogram demonstrated a left ventricular ejection fraction of 60% and confirmed...
was biopsied and confirmed HHV8 and Kaposi’s sarcoma (Figure 4). There was no evidence of lymphoma in the lymph node.

On hospital day 7, the patient was started on highly active antiretroviral therapy (HAART) with emtricitabine/tenofovir and lopinavir/ritonavir for his new diagnosis of HIV. On hospital day 8, he was treated with CHOP chemotherapy (cyclophosphamide, doxorubicin, vincristine, and prednisone) for the primary effusion lymphoma (PEL). Prior to discharge, a CT scan confirmed that the pericardial effusion had not reaccumulated (Figure 5). The patient’s fevers and fatigue had completely resolved by discharge, 11 days after admission. Subsequently, the patient received two more cycles of CHOP chemotherapy.

At 7-month follow-up, he was asymptomatic; his HIV RNA by PCR was undetectable, and his CD4 count was improving. He continued on HAART.

**DISCUSSION**

PEL accounts for 4% of all HIV-associated non-Hodgkin’s lymphomas (1). The other HIV-associated lymphomas include Burkitt’s or Burkitt’s-like lymphoma, diffuse large B-cell lymphoma, and plasmablastic lymphoma, which includes multicentric Castleman’s disease (2).
Since 1985 the development of a non-Hodgkin’s lymphoma has been classified as an AIDS-defining illness (3). There are rare case reports of PEL in individuals who do not have HIV (4); these cases occurred in elderly men who had evidence of HHV8 infection and patients receiving immunosuppression after organ transplantation (5, 6). PEL was first described by Knowles and associates in 1989 (7), and since then we have learned that it is usually associated with Kaposi’s sarcoma (8).

PEL affects serous body cavities, which are body cavities that are lined by serous membranes, and results in recurrent lymphomatous effusions. For a PEL diagnosis, concomitant infection with HHV8 must be documented. In over 90% of HIV-associated cases, EBV has also been found. The mechanism by which HHV8 and EBV lead to PEL has not been delineated. Three gene products—latency associated nuclear antigen-1, viral cyclin, and viral FLICE inhibitory protein—appear to play an important role and are under investigation (9).

Patients who present with PEL are usually HIV-positive men with a decreased CD4 count and often with evidence of Kaposi’s sarcoma or Castleman’s disease. Our patient was unique in that the pericardial effusion from the PEL eventually led to the diagnosis of HIV and Kaposi’s sarcoma. Only one other case report was found in which PEL was diagnosed from a symptomatic pericardial effusion (10). Clinically, these patients have lymphomatous pleuritis, pericarditis, and/or peritonitis, without extracavitary masses. Symptoms are due to the mass effects of increasing accumulation of the effusion and include dyspnea, cough, chest pain, abdominal distention, and abdominal pain. Patients also may have typical “B symptoms,” including fever, diaphoresis, and weight loss.

The diagnosis is based on cytological study of the involved effusion or biopsies of the tissue lining the cavity where the effusion is present. The malignant cells usually are large with round or irregular nuclei, conspicuous nucleoli, and moderate to abundant basophilic cytoplasm, some with cytoplasmic vacuoles (11). Also, in one series of 19 cases, every PEL cell case had coarse chromatin, large numbers of apoptotic bodies, and high mitotic activity (12). HHV8 must be detected in the malignant cells for the diagnosis of PEL. Serological tests for HHV8 can be done by immunohistochemical staining for latency-associated nuclear antigen. Quantitative real-time PCR to measure peripheral blood or the affected effusion for HHV8, as done in our patient, can be helpful to quickly obtain a diagnosis, determine viral load and thus toxicity, and assist in expedient initiation of treatment. The presence of EBV should be evaluated, usually with PCR for EBV DNA. PEL cells usually express CD45 but not B or T cell markers such as CD19, CD20, CD79a, CD3, CD4, or CD8. Markers of lymphocyte activation are present, such as CD30, CD38, HLA DR, and CD 71. A marker for plasma cell differentiation, CD138, is also present (13, 14).

In suspected cases, initial workup should include a history and physical, complete blood count, comprehensive metabolic panel, and lactate dehydrogenase test. Imaging with either a CT scan of the chest, abdomen, and pelvis or a whole-body positron emission tomography scan is warranted. A bone marrow biopsy should be performed for staging, although it rarely shows malignancy. Since a malignant effusion is present, these patients are considered Ann Arbor stage IV.

Typically the patients have a poor prognosis, and median survival prior to HAART was 3 months. With the addition of HAART, median survival has improved to 6 months. In addition, some case reports have documented long-term survival with HAART alone (15, 16). The most recent multicenter series of 28 patients showed a median survival time of 6.2 months and 1-year overall survival of 39.3%, which is similar to results from small patient series (17). In that multicenter study, Boulanger et al concluded that the only two negative prognostic factors in HIV-related PEL were poor performance status and absence of HAART prior to PEL diagnosis. However, one might expect that absence of HAART prior to diagnosis may be a favorable prognostic sign, as HAART may have activity against PEL. The most frequent causes of death are progression of lymphoma, HIV-related complications, and opportunistic infection. Therefore, prolonged neutropenia should be treated with granulocyte colony-stimulating factor, and patients should receive prophylaxis for *Pneumocystis carinii* pneumonia and close monitoring for cytomegalovirus reactivation (18).

Due to the rarity of PEL, no prospective studies have evaluated the best therapy for these patients. The first-line therapy most commonly reported is CHOP chemotherapy (1). Some case reports include the addition of methotrexate, but one must be careful of the accumulation of this agent in the effusions and subsequent toxicity (19). Since patients with PEL do not express CD20, rituximab treatment does not have a significant role. In one case report, a patient with PEL treated with HAART and rituximab had a complete response at 1 month, but this response may have been due to HAART alone (20). There have been two case reports of autologous stem cell transplant for PEL but not enough data to recommend this treatment (21, 22). In other case reports, the effusions were treated with directly injected cidofovir, which was associated with a several-month remission in one patient (23, 24). Two potential experimental therapies are bortezomib, a proteasome inhibitor, and drugs such as LY294002, which inhibit the phosphatidylinositol 3’-kinase/AKT pathway. Both therapies have been shown to induce apoptosis in PEL cell lines (25, 26). Matta demonstrated that the activity of bortezomib was associated with inhibition of nuclear factor kappa-B pathways, upregulation of p53, p21, and p27, and activation of the caspase cascade (27). Bortezomib was also shown to work synergistically with cytotoxic chemotherapy on PEL cell lines. Another promising regimen that has shown activity against the nuclear factor kappa-B pathway in PEL cell lines is a combination of arsenic trioxide combined with interferon (28). Buger and colleagues were able to inhibit clonal growth of PEL in vitro and in animal models by using antibodies to IL-6 (29). Future approaches may include silencing the *LANA-1* gene with small RNA transcripts or using RNA interference to inhibit viral cyclin or viral FLICE inhibitory protein (30, 31).


