Primary effusion lymphoma (PEL) is a rare and newly defined form of non-Hodgkin’s lymphoma (NHL) which only involves the body cavities, causing lymphomatous effusions in the absence of lymphadenopathy or organomegaly. PEL develops in a serous body cavity such as the pleural, pericardial and abdominal cavities, and subarachnoid space. Previous studies suggested that PEL occurs almost exclusively in human immunodeficiency virus (HIV)-infected patients, first described in association with Kaposi’s sarcoma. More recently, several studies have demonstrated that PEL develops in non-AIDS patients with human herpesvirus type 8 (HHV-8) infection, suggesting that HHV-8 infection plays a key role in PEL. Several reports showed that PEL could occur in patients with hepatitis C virus (HCV) infection.

We report a case of PEL with underlying hepatitis B virus (HBV)-related liver cirrhosis.

**Case Report**

The patient was a 54-year-old man with chronic hepatitis B for more than 25 years, in whom liver cirrhosis was diagnosed 3 years ago. He received...
lamivudine from December 2000 for elevated alanine aminotransferase (ALT). Hepatitis B surface antigen (HBsAg) was positive. Hepatitis B e antigen (HBeAg) was negative, and antibody to HBeAg (anti-HBeAg) was positive. Antibody to HCV (anti-HCV) was negative. Lamivudine was discontinued in June 2001 with persistently normal ALT and undetectable HBV DNA. Lamivudine was restarted in January 2002 because of relapse of hepatitis (ALT, 397 U/L; HBV DNA, 523 pg/mL). Lamivudine was discontinued in October 2002 after the HBV activity subsided. Again, ALT became elevated (483 U/L) in March 2003. Lamivudine was resumed and continued thereafter.

However, progressive abdominal distension was noted in October 2003 and was aggravated rapidly in February 2004. He was admitted to our hospital in March 2004. Body weight increased from 82 to 92 kg in 5 months. On examination, the patient was chronically ill-looking. Consciousness was clear. The body temperature was 36.8°C, pulse rate was 112/minute and respiratory rate was 22/minute. The blood pressure was 130/80 mmHg. The conjunctivae were mildly pale and the sclerae were anicteric. The pupils were isocoric with prompt light reflex. The neck was supple without lymphadenopathy or jugular vein engorgement. Breath sounds were clear over bilateral lung fields. The abdomen was ovoid with shifting dullness. Neither tenderness nor rebound pain was noted. The liver was impalpable.

The hemogram showed normocytic anemia (8.8 g/dL). Biochemistry showed hypoalbuminemia (3.2 g/dL), impaired renal function (creatinine, 2.0 mg/dL) and high lactate dehydrogenase level (740 U/L). Other biochemistry data including serum ALT and bilirubin level were within normal limits. The prothrombin time was normal.

Abdominal sonography showed liver cirrhosis with patent portal vein, mild splenomegaly and massive ascites. Abdominal magnetic resonance imaging showed cirrhotic change of the liver with marked ascites without vascular obstruction. Paracentesis was performed and 1030 mL bloody ascites was drained. Cytology of the ascites revealed large and medium sized lymphoid cells with prominent nucleoli. Some had round vacuoles in their cytoplasm (Figure 1). The immunophenotyping of the lymphoma cells was positive for CD138, negative for CD19, cytoplasmic immunoglobulin (both k and λ) and cytoplasmic CD3. Chromosome study showed complex cytogenetics. All of the 13 mitotic cells showed clonal aberrations including add(1)(q22), −2, +3, +der(4)t(1;4)(q23;q21), del(4)(q31q35), +5, add(7)(p22), add(8)(p22), del(8)(q24), add(9)(q32), add(10)(q26), add(11)(q25), add(11)(q23), add(12)(q24), +del(13)(q31q34), del(13), +add(14)(q32).

Figure 1. Cytology of primary effusion lymphoma. (A) The tumor cells in ascites show predominance of large lymphocytes exhibiting anisonucleosis, round nuclei, coarse chromatin and increased nuclear and cytoplasmic ratios. Some round vacuoles are present in the cytoplasm (hematoxylin & eosin stain; original magnification 400x). (B) Tumor cells in pleural effusion.
add(14)(q32), der(14)(14;15)(q24;q22), +15, der(21)(q10), and add(21)(q22). The cell block of the ascites showed MuM-1 (−), VS38C (+), EBER (−). The nuclei of the lymphoma cells were positive by immunohistochemistry for the HHV-8-associated latent protein. During admission, massive pleural effusion developed. Pleural tapping revealed similarly abnormal cells that were found in the ascites. However, the second abdominal tapping revealed very few lymphoma cells in the ascites. Instead, the lymphoma cells could be easily detected in the pleural effusions. Sediments from the pleural effusions and second ascites were sent for polymerase chain reaction (PCR) to detect HHV-8 DNA. Direct sequencing was done to validate the correctness of PCR products. As shown in Figure 2, HHV-8 DNA could be detected in the lymphoma cells of pleural effusions. However, HHV-8 DNA was not detected in the second ascites specimen. We did not perform HHV-8 PCR in the first ascites sample.

A bone-marrow aspirate and trephine biopsy showed no evidence of lymphoma involvement. Computed tomography scan from neck to pelvis showed no pathologic lymphadenopathy. The result of exploratory laparoscopy was negative. The serology of HIV was negative. Based on the cytology, immunophenotyping and genetics, PEL was diagnosed.

The patient was given CHOP (I) (cyclophosphamide 1500 mg on D1, doxorubicin 100 mg on D1, vincristine 2 mg on D1, and prednisolone 100 mg/day on D1–D5) on April 30, 2004 and CHOP (II) on May 17, 2004. The two courses of chemotherapy were complicated with febrile neutropenia, spontaneous bacterial peritonitis, and Pseudomonas aeruginosa related sepsis. The infection episodes subsided under granulocyte-colony stimulating factor and adequate antibiotics. Cytology showed remarkable reduction of lymphoma cells in ascites after the therapy. Intraperitoneal injection of Picibanil (OK-432) (10KE every Monday and Thursday since May 31, 2004 for a total of six times) was given. CHOP (III) and CHOP (IV) were given on June 17, 2004 and on July 14, 2004. Again, the chemotherapy was complicated by spontaneous bacterial peritonitis and sepsis. The follow-up cytology of ascites was negative. Unfortunately, the cytology of ascites became positive 1 month later.

The patient was admitted again in September 2004 for spontaneous bacterial peritonitis. Blood culture yielded Enterobacter cloacae. However, the liver function progressively deteriorated with ALT elevated to 234 U/L, bilirubin 3.62 mg/dL and prothrombin time 18.4 seconds (control, 12.9 seconds). HBV DNA level was 9274 pg/mL. YIDD mutation was detected. Adefovir was added. However, the liver function deteriorated rapidly, resulting in hepatic encephalopathy and hepatorenal syndrome. The patient died of sepsis and hepatic failure.

**Discussion**

PEL typically involves only one body cavity. It is rare that both pleural and abdominal cavities are involved, as in our case. Though the original description of PEL is a rare form of NHL which only involves the body cavities in the absence of lymphadenopathy or organomegaly,1,2 it has recently
been argued that Kaposi’s sarcoma-associated herpes virus/HHV-8-positive solid lymphomas could be a tissue-based variant of PEL. In contrast, not all lymphomas localized to the body cavities are PELs. Burkitt’s lymphoma, pyothorax-associated lymphoma, anaplastic large cell lymphoma and lymphomatous effusion secondary to gastrointestinal tract lymphoma might also present with lymphoma in the body cavities. To make the diagnosis of PEL, it is important to rule out these possibilities. In our case, we had carefully excluded these possibilities by endoscopic, surgical and imaging studies.

The lymphoma cells of PEL exhibit variable polymorphism, from large immunoblastic or plasmablastic cells to anaplastic cells. Nuclei are large and round with prominent nucleoli. The cytoplasm is abundant and deeply basophilic with clear vacuoles occasionally. The cells express leukocyte common antigen (CD45) but are usually negative for pan-B-cell and pan-T-cell markers. Activation and plasma cell-related markers such as CD30, CD38 and CD138 are usually demonstrated. The lymphoma cells in our case were positive for CD138 and negative for CD19 and CD3 by flow cytometry. This phenotype is inconsistent with the typical presentation of PEL cells. In Carbone et al’s study, the expression of MUM-1/IRF4 (multiple myeloma 1/interferon regulatory factor 4) in PELs is 100%, strongly implicating its role in the disease pathogenesis. Immunohisto logically, the lymphoma cells in the ascites of this case were negative for MUM-1/IRF4, but the lymphoma cells in the pleural effusion were positive for MUM-1/IRF4. This paradoxical finding might be caused by the small number of lymphoma cells in the second paracentesis.

Epidemiologically, the majority of PELs arise in the setting of HIV infection. Most patients are young to middle aged homosexual males. The disease also occurs in the absence of HIV infection. HIV-seronegative patients with PEL might have an underlying immunodeficiency due to advanced age or associated conditions such as cirrhosis or cancer, or come from areas with high prevalence of HHV-8 infection such as the Mediterranean. Failure to detect HHV-8 DNA sequences precludes a diagnosis of PEL, although there were a few cases of HHV-8 negative PEL reported.

In Taiwan, the infection rate of HHV-8 is 19.2% between the ages of 21 and 40. The HHV-8-infected population rarely presents diseases except in the group of patients of old age, AIDS, cancer or impaired immunity. Although there are several peritoneal PELs reported in association with HCV-related liver cirrhosis, no PELs associated with HBV-related liver cirrhosis have been reported. The HBV-related cirrhosis probably played the role of impairing immunity in our patient. However, we need more cases to clarify the role of HBV in PEL.

The treatment of PEL is not well established because of small case numbers. Generally, the prognosis is extremely unfavorable even with high-dose chemotherapy and autologous stem cell reinfusion. Some case reports show complete remission of PEL in HIV-seropositive patients after antiviral therapy. An HIV-seronegative patient who achieved durable remission has been reported. Our patient, like in typical PEL, did not achieve durable remission and died within 6 months of diagnosis. Thus, whether chemotherapy is the treatment of choice in PEL needs to be established. Targeting HHV-8 is a new idea of treatment but it has not entered clinical trials.

It is not surprising that YMDD mutant developed in our patient because lamivudine was used for more than 1 year. However, the liver function deteriorated rapidly even when he was started on adefovir. The course of our patient was more fulminant than that in most patients with YMDD mutants. One of the possible explanations was that our patient was immunocompromised related to PEL, leading to unchecked HBV replication and final hepatic failure even with the use of adefovir.

In conclusion, when cirrhotic patients rapidly develop ascites, non-hepatic origins should also be considered in addition to liver cirrhosis per se. Among the non-hepatic origins, the differential diagnosis should include PEL. Once PEL is diagnosed, the treatment should be carefully
considered. Novel therapy may be better than conventional chemotherapy.

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References


