CASE REPORT

Rare Primary Effusion Lymphoma Associated with HHV-8 in Japan

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Abstract

We describe a 62-year-old man infected with human immunodeficiency virus (HIV)-1 who developed primary effusion lymphoma (PEL). Pleural effusion contained atypical lymphoid cells with human herpesvirus (HHV)-8 latent nuclear antigen (LANA)+. Radiological examination revealed pleural and pericardial effusion, but no evidence of tumor mass or lymph node enlargement. The patient was administered with highly active anti retroviral therapy (HAART) and THP-COP therapy, resulting in complete remission. The prevalence of HHV-8 infection among HIV positive individuals is higher than in the general population in Japan. Although PEL is extremely rare in Japan, the incidence might increase in the future.

Key words: primary effusion lymphoma, HIV, AIDS, HHV-8, Kaposi’s sarcoma

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Introduction

Primary effusion lymphoma (PEL) is a rare type of B-cell lymphoma presenting as serous effusion without obvious tumor masses. It usually occurs in patients infected with human immunodeficiency virus (HIV), and human herpesvirus 8 (HHV-8) is also thought to play a causative role (1). Several Japanese reports have described HHV-8-negative lymphomas of the body cavities of immunocompetent patients as PEL (2). The HHV-8-positive PEL cell line TY-1 was derived from a Japanese patient with AIDS (3), but a patient with HHV-8-associated PEL has never been reported in Japan, as far as we know. Here, we describe a patient with HHV-8 and HIV-positive PEL who responded well to highly active anti retroviral therapy (HAART) and chemotherapy.

Case Report

A 62-year-old man was admitted to a hospital due to shortness of breath for four weeks and a non-productive cough since March 2009. Chest x-rays and echocardiography revealed bilateral pleural and large pericardial effusions. In May 2009, cardiac tamponade resulted in impaired consciousness and he was referred to our hospital (Fig. 1, Table 1). We collected 300 mL of purulent pericardial fluid and 900 mL of non-purulent pleural effusions by puncture. Cytological analysis of the pericardial effusion revealed predominant polymorphonuclear leukocytes and coagulase-negative Staphylococci. Bacterial pericarditis and congestive heart failure were diagnosed. The symptoms and effusion were resolved by antibiotics and continuous pericardial drainage.

Serological findings were positive for anti-HIV and HCV antibodies. The CD4+ lymphocyte count in the peripheral blood was 73 cells/μL and plasma HIV-RNA was 31,000 copies/mL. Shortness of breath and palpitations developed again in June 2009. A chest x-ray detected bilateral pleural effusion, and a cytological evaluation revealed large atypical lymphoid cells with large nuclei and prominent nucleoli with abundant cytoplasm (Fig. 2). Immunohistochemical analysis showed that a cell block prepared from the pleural effusion was negative for CD3, L26, CD79a, CD30, CD138 and EBER, and positive for LCA and HHV-8 latent nuclear antigen (LANA) (Fig. 2). Southern blotting showed clonal rearrangement of the immunoglobulin heavy chain gene (Fig. 3). Systemic computed tomography confirmed the absence of tumorous lesions and enlargement of the liver.
Figure 1. Clinical course of the patient. Pleural effusion and plasma HHV-8 viral load decreased by THP-COP therapy and HAART.

Figure 2. Cytological study of pleural effusion. Large atypical lymphoid cells with large irregular nuclei and prominent nucleoli have abundant basophilic cytoplasm (A, Papanicolaou stain ×1000; B, May-Grünwald stain ×1000). Immunohistochemical analysis shows that cell block from pleural effusion indicates LCA+ (C), CD3- (D), L26- (E), and HHV-8 (F) latent nuclear antigen (LANA)+.

Figure 3. Analysis of DNA from cells in pleural effusion. Southern blots show gene rearrangement using probes to detect JH gene to immunoglobulin heavy chain (C, control human placenta; P, patient). Three bands are evident with probes 2 and 3.

Figure 4. Systemic computed tomography findings. Image shows lateral pleural and large pericardial effusions, but no tumor mass or enlargement of lymph nodes, liver and spleen.

The patient was diagnosed with acquired immunodeficiency syndrome (AIDS) and PEL. The plasma HHV-8 DNA load was 11,000 copies/mL. The patient was started on HAART, comprising abacavir sulfate (ABC), lamivudine (3TC) and lopinavir/ritonavir (LPV/RTV) in late June, 2009. Two weeks later, he was administered pirarubicin hydrochloride (33 mg/m²), cyclophosphamide, orlymphnodes (Fig. 4). The patient was diagnosed with acquired immunodeficiency syndrome (AIDS) and PEL. The plasma HHV-8 DNA load was 11,000 copies/mL. The patient was started on HAART, comprising abacavir sulfate (ABC), lamivudine (3TC) and lopinavir/ritonavir (LPV/RTV) in late June, 2009. Two weeks later, he was administered pirarubicin hydrochloride (33 mg/m²), cyclophosphamide,
phamide (500 mg/m²) and vincristine (0.9 mg/m²). The dosage of chemotherapy was reduced because of his poor performance status and renal insufficiency. He received 200 mg fluconazole and trimethoprim sulfamethoxazole (80 mg of trimethoprim and 400 mg of sulfamethoxazole) for the prophylaxis of fungal and Pneumocystis jirovecii infections. G-CSF was administered subcutaneously in a dose of 2 μg/kg to reduce the duration and degree of neutropenia. Pleural effusion transiently increased on day 8, but disappeared from day 15. Plasma HHV-8 DNA disappeared after two cycles of THP-COP therapy were completed. As of the time of the writing (February 2010), the patient remains free of HHV-8 DNA and eight cycles of THP-COP therapy were completed. After three cycles of THP-COP therapy, PET/CT demonstrated the absence of abnormal uptake. The patient thus achieved and sustained complete remission for 7 months.

Discussion

Non-Hodgkin’s lymphoma (NHL) is 60- to 200-fold more prevalent among HIV-positive, than immunocompetent individuals and PEL accounts for about 4% of HIV-associated lymphoma (4).

HHV-8 is a member of the Gammaherpesvirinae subfamily of Herpesviridae and it is associated with the pathogenesis of Kaposi’s sarcoma (KS), PEL and multicentric Castleman’s disease (5). Latency-associated nuclear antigen-1 and viral cyclin might also play roles in the pathogenesis of PEL (6). PEL is a large B-cell neoplasm usually presenting as serous effusions without detectable tumor masses. On the other hand, HHV-8-associated solid lymphomas in the absence of lymphomatous effusions have been termed as extra-cavitary PEL (1), and have been reported in Japan (7, 8).

To our knowledge, no Japanese patient with HHV-8-associated PEL has been described, which might be due to the low prevalence of HHV-8 infection in the general population varies throughout the world, being highest in Sub-Saharan Africa, where >50% of the population is infected (9). Seroprevalence is approximately 5-20% in the Mediterranean region (9), whereas the reported seroprevalence of HHV-8 among the general Japanese population is 1.4 - 2.2% (10, 11). The incidence of HHV-8 among seropositive HIV-negative Japanese blood donors according to assays for anti-LANA antibodies is 0.2% (12). Multiplex PCR assays have also indicated the prevalence of HHV-8 to be 0.2% (13). This extremely low-prevalence of HHV-8 could explain why PEL is rare in Japan. In fact, KS among individuals with HIV/AIDS was extremely rare in Japan until 1990 (Fig. 5).

Despite the present rarity of PEL in Japan, this could change as more individuals become infected with HIV-1 every year. The cumulative numbers of patients infected with HIV-1 and of those with AIDS reported by the Ministry of Health and Welfare of Japan at the end of December 2008 were 10,522 and 4,899, respectively. Furthermore, the prevalence of HHV-8 infection is higher among HIV-positive individuals than in the general population in Japan (12). In fact, the number of new instances of KS among HIV-positive patients has increased (Fig. 5).

Although combination chemotherapies such as CHOP are usually administered to patients with PEL, the prognosis is extremely poor. A retrospective study has shown that the median survival is only 6.2 months, and the 1-year overall survival rate is 39.3% (14). CD20 is not usually expressed on PEL cells, and rituximab (anti-CD20 monoclonal antibody) does not play a role in PEL therapy (14). The present patient achieved complete remission due to chemotherapy. Furthermore, HHV-8 DNA also disappeared from plasma after chemotherapy, indicating that HAART therapy combined with chemotherapy might result in a better response (14), although more patients undergoing such treatment are needed to support this notion.
Table 1. Laboratory Findings on Admission

<table>
<thead>
<tr>
<th>Hematology</th>
<th>Blood chemistry</th>
<th>Serology</th>
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<tbody>
<tr>
<td>RBC 268 × 10^6/μL</td>
<td>TP 9.6 g/dL</td>
<td>HbsAg (+)</td>
</tr>
<tr>
<td>Hb 7.3 g/dL</td>
<td>ALB 2.9 g/dL</td>
<td>HCVAb (+)</td>
</tr>
<tr>
<td>WBC 3920/μL</td>
<td>T-bil 0.6 mg/dL</td>
<td>HIVAb (+)</td>
</tr>
<tr>
<td>Neut. 45.9%</td>
<td>AST 16 IU/L</td>
<td>EBVCAlgM &lt;10</td>
</tr>
<tr>
<td>Lymp. 38.3%</td>
<td>GPT 12 IU/L</td>
<td>EBVCA IgG ×640</td>
</tr>
<tr>
<td>Mono. 11.0%</td>
<td>ALP 235 IU/L</td>
<td>EADRIgG ×20</td>
</tr>
<tr>
<td>Eosino. 3.8%</td>
<td>γ-GTP 33 IU/L</td>
<td>EBNA IgG ×10</td>
</tr>
<tr>
<td>baso. 1.0%</td>
<td>LDH 216 IU/L</td>
<td></td>
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<tr>
<td>PLT 17.0 × 10^5/μL</td>
<td>BUN 27.3 mg/dL</td>
<td>Immunological findings</td>
</tr>
<tr>
<td>CD4+ 104/μL</td>
<td>Cr 1.78 mg/dL</td>
<td>IgG 4,369 mg/dL</td>
</tr>
<tr>
<td>Na 134 mEq/L</td>
<td>IgA 803 mg/dL</td>
<td></td>
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<tr>
<td>K 4.4 mEq/L</td>
<td>IgM 402 mg/dL</td>
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<tr>
<td>Cl 108 mEq/L</td>
<td>sIL2R 1940 U/mL</td>
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<tr>
<td>CRP 4.28 mg/dL</td>
<td>BNP 393 pg/mL</td>
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In conclusion, we describe HHV-8-associated PEL that developed in a patient who was infected with HIV. Although PEL is presently rare in Japan, the incidence might increase in the future.

References