Human Herpes virus 8-negative primary effusion lymphoma with *BCL6* rearrangement in a patient with idiopathic CD4 positive T-lymphocytopenia

Primary effusion lymphoma (PEL) was initially designated as a body-cavity-based lymphoma and recognized as a distinct clinical entity without a contiguous tumor mass. PEL was first reported in patients with acquired immunodeficiency syndrome (AIDS) and the distinctive feature of PEL originally reported as a B-cell neoplasm characterized by infection of the tumor cells by human herpes virus 8 (HHV-8).[1] However, there have recently been several reports of PEL in patients without human immunodeficiency virus (HIV) or HHV8 infection.[2-4]

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A 78-year-old male was admitted to our hospital for dyspnea. A computed tomographic scan of the chest and abdomen showed pericardial and pleural effusion, but there was no evidence of tumor masses, lymph node enlargement, or hepatosplenomegaly. Cytologic examinations of the effusion revealed large-sized lymphoid cells with immunophenotypes positive for CD19, CD20, CD22, IgM, IgD. Results of PCR analyses using the cells were positive for EBV, but negative for HHV8. BCL-6 gene rearrangement was detected by Southern blotting and FISH. The counts for leukocytes, lymphocytes and $CD4^+$ lymphocytes in his peripheral blood were 4000, 840 and 126×10^9/L, respectively, without evidence of immunodeficiency. The patient was diagnosed as PEL associated with idiopathic $CD4^+$ T-lymphocytopenia (ICL).

The patient was treated with rituximab and THP-COP regimen, and achieved remission. At the time of this report he had been free from PEL for more than 30 months after the chemotherapy although the low level of T lymphocytes continues persisted.

This is the first case of PEL developed in a patient with ICL. In contrast to PEL associated with HIV infection, the lymphoma cells were negative for HHV8 infection but positive for *BCL6* rearrangement and Ig expression, and successfully treated with chemotherapy.

Introduction

Idiopathic $CD4^+$ T-lymphocytopenia (ICL) is a rare condition which is manifested by peripheral $CD4^+$ T-cell depression without any evidence of causative agents such as HIV infection.[5] Previous reports of ICL have described unexpected severe infections, such as tuberculosis,[6] cryptococcosis,[7] candidiasis[8] or other pathogens.[9] However, non Hodgkin's lymphoma (NHL) in patients with ICL has rarely been described[10-14] and PEL in patients with ICL has never been reported.

Here we describe a case of HHV-8-negative EBV positive PEL with *BCL6* gene rearrangement in an HIV-negative elder patient associated with ICL.

Case report

A 78-year-old male with no special disease in his medical history was admitted to a hospital in April 2004 because of exertional dyspnea and detected with pleural and pericardial effusions. Physical examination revealed weakness of breath sound on the left and pitting edema on the legs. The liver was slightly enlarged, but no lymphadenopathy or splenomegaly was detected. Laboratory data were as follows; serum lactic dehydrogenase 268 IU/L (normal 119 to 229), alubumin 3.4 g/dL (normal 4.0 to 5.0), asparate-aminotransferase 65 IU/L (normal 13 to 33), alanine-aminotransferase 60 IU/L (normal 8 to 42), C-reactive protein 2.88 mg/dL (normal <0.30), soluble interleukin 2 receptor 460 U/mL (normal 220 to 530), leukocyte count 4000×10^9/L (normal 3900 to 9800), absolute lymphocyte count 840×10^9/L without abnormal lymphoid cells, hemoglobin 14.4 g/dL (normal 13.5 to 17.6), and platelet count 31.3×10^9/L (normal 13.1 to 36.2). Serum test results were negative for hepatitis B virus, hepatitis C virus, HIV, and human T-cell lymphotropic virus type I. Serostatus for EBV was previously infected pattern. Serum Ig levels were as follows; IgG 987 mg/dL (normal 870 to 1700), IgA 297 mg/dL (normal 110 to 410), and IgM 94.7 mg/dL (normal 35 to 220) without monoclonal gammopathy. Peripheral blood mononuclear cell (PBMNC) subsets were as follows; CD3 27%, CD4 15%, CD8 12%, CD20 31% and CD56 29%. The absolute $CD4^+$ lymphocyte count was 126×10^9/L (normal >400). Bone marrow aspiration demonstrated normocellularity without neoplastic cell infiltration. Computed tomographic scan of the chest and abdomen showed left pleural and pericardial effusion but no mass was detected. The cytological study of the drained pericardial effusion showed a lot of large-sized lymphoid cells that had abnormal nuclei and cytoplasmic vacuoles (Figure 1). Pericardial fluid culture for bacteria and mycobacterium were negative. Flow cytometric analysis of the pericardial effusion showed that the neoplastic cells were positive for B-cell markers (CD19, CD20, CD22), surface Ig M, IgD, Igλ, and activation markers (HLA-DR), but negative for CD10, CD56, and T-cell markers (CD3, CD4, CD5, CD8). Cytogenetic analysis of the pericardial effusion showed complicated abnormalities including add 3q27. Polymerase chain reaction (PCR) analysis was performed to determine whether HHV-8 genome and EBV genome were present in lymphoma cells, and findings were positive for EBV, but negative for HHV-8. By Southern blot and FISH analysis, the lymphoma cells were positive for BCL-6 gene rearrangement but negative for c-myc and Myc oncogene rearrangement (data not shown).

The patient was treated with rituximab, a chimeric anti-human CD20 monoclonal antibody, plus THP-COP (pirarubicin, cyclophosphamide, oncovine, predonisolone) regimen. With the chemotherapy, the patient achieved complete remission of PEL. At the time of this

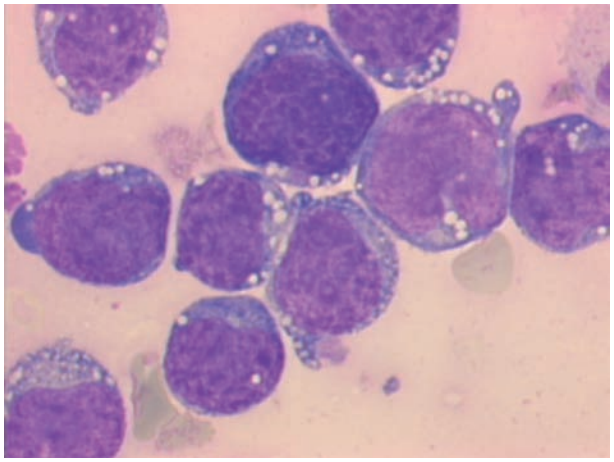

Figure 1. The cytological study of the drained pericardial effusion showed a lot of large-sized lymphoid cells that had abnormal nuclei and cytoplasmic vacuoles (Wright-Giemsa staining, original magnification x1000).

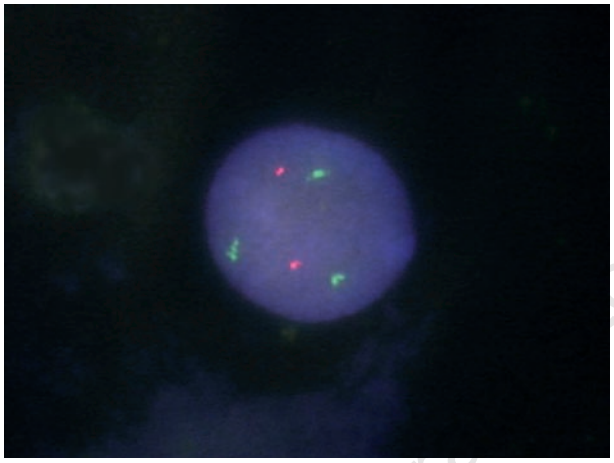

Figure 2. Translocation pattern of the split signals (*BCL6*) was observed in 96.5% of the tumor cells. The split signals (2 red and 2 green) are present. The probe used is the 5'/3' BCL6(3q27), dual-color probe (Vysis).

report, he had been free from PEL for more than 30 months after the chemotherapy. However, the low level of CD4 positive T lymphocytes has been continued (absolute $CD4^+$ and $CD8^+$ lymphocyte counts were 198 and 776×10^9/L, respectively).

Discussion

ICL was defined by the Centers for Disease Control and Prevention as including patients with depressed numbers of circulating CD4 T lymphocytes (<300 cells/μL or <20% of total T cells) on a minimum of two separate time points at least 6 weeks apart, with no laboratory evidence of infection with HIV-1 or HIV-2, and the absence of any defined immunodeficiency or therapy associated with depressed levels of CD4 T cells.[5] The CD4 T-lymphocyte count was decreased at onset, and during and after the entire course of treatment in this case. Although the etiology is unknown, ICL apart from AIDS is rarely associated with malignancy. There have been five previously reported patients with ICL who had NHL, all of which were B cell type.[10-14] This is the first PEL case developed in an ICL patient. Since three cases including the present case achieved durable remissions by chemotherapy, NHL associated with ICL appears to be not exclusively poor prognostic in contrast to AIDS-related NHL.

Although PEL was initially found only in HIV-positive patients with HHV8 infection,[1] there have been several reports of PEL occurring in HIV-negative patients.[2-4] Their lymphoma cells were usually negative for HHV8 infection and c-myc rearrangement.[3] The origin of PEL is speculated as activated B cell but not germinal center derived B cells because the lymphoma cell showed a high frequency of somatic hypermutation of *BCL6* gene.[15] However, rearrangement of *BCL6*, which is the most frequent abnormality in nodal DLBCL,[16] has been reported rare in PEL.[17] The present case is peculiar as PEL because of *BCL6* gene rearrangement, expression of surface Ig and lack of HHV8 infection. HHV8-negative PEL in HIV-negative patients have been reported especially from Japan and a few other countries.[2-4] Therefore, further investigations in more cases are warranted to clarify the pathogenesis, epidemiology and clinical features of PEL.

In conclusion, this is the first case of PEL developed in a patient with ICL. In contrast to PEL associated with HIV infection, the lymphoma cells were negative for HHV8 infection but positive for *BCL6* rearrangement and Ig expression, and successfully treated with rituximab-combined chemotherapy.

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