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Detection of Epstein-Barr virus in a pyothorax-associated lymphoma with T-cell phenotype

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Pyothorax-associated lymphoma (PAL), a rare type of extranodal lymphoma, is known to arise from the pleural cavity of long-standing pyothorax.[1] Most patients with PAL have a medical history of artificial pneumothorax performed for the treatment of pulmonary tuberculosis or tuberculous pleuritis, and are Japanese.[2] The majority of PAL patients have a pathological diagnosis of diffuse large cell lymphoma.[2] In addition, such lymphoma cells often have a B-cell phenotype[2] and contain EB virus genomes.[3,4] In this report, we describe for the first time a case of PAL exhibiting a pure T-cell phenotype with detectable EB virus in the lymphoma cells.

A 74-year-old Japanese woman was referred to our hospital because of a subcutaneous mass in the left chest. At the age of 28 years she had suffered from pulmonary tuberculosis and received artificial pneumothorax therapy. Physical examination on admission revealed no lymphadenopathy, splenomegaly or hepatomegaly. A whole-body CT scan confirmed only a soft-tissue mass arising from a pyothorax cavity and invading the adjacent chest wall. ^{67}Ga scintigraphy revealed intense uptake localized in this tumor. Bone marrow biopsy showed no evidence of lymphoma cell infiltration. A complete blood count revealed no particular changes, with a normal differential leukocyte count. Increased levels of serum lactic dehydrogenase (904 IU/L), and soluble interleukin-2 receptor (821 U/mL: normal, 145-519) were noted. Histopathological examination of a biopsy specimen obtained from the mass showed diffuse proliferation of large lymphoid cells (Figure 1a).

Immunohistochemistry and flow cytometry revealed that the neoplastic cells were positive for CD3 (Figure 1B), CD7, CD8dim, CD25dim and CD45RO, but not for CD2, CD5, CD16, CD19, CD20 (Figure 1C), CD30, CD56 (Figure 1D) and CD57. According to the revised European-American classification of lymphoid neoplasms, these findings were compatible with peripheral T-cell lymphoma, unspecified type. Therefore, we had diagnosed the patient as having PAL with T-cell phenotype. The patient received combined modality treatment including 6 cycles of chemotherapy (a combination of cyclophosphamide, pirarubicin, vincristine, sobuzoxane, and prednisolone) and involved field irradiation of 40 Gy. Following this therapy, ^{67}Ga accumulation in the tumor disappeared, and serum levels of lactic dehydrogenase and soluble interleukin-2 receptor normalized.

Detection of Epstein-Barr (EB) virus RNA was performed using fluorescein isothiocyanate-labeled peptic nucleic acid (PNA) probes against EB virus-encoded samll RNAs (EBER) (code Y5200; Dako patts, Glostrup, Denmark) on the biopsy tissue specimen. PNA *in situ* hybridization (ISH) detection kit (code K5201; Dako patts) was used according to the manufacturer's instruction to visualize the site of hybridization. As a result, the signals of EBER were located in the nuclei of the neoplastic cells (Figure 2). Moreover, real time polymerase chain reaction showed the EB virus genome level of $2x10^5$ copies/mg DNA in this sample. Serum anti-EB virus capsid antigen (VCA)-IgG antibody was significantly elevated to a titer of 1:1280. The titer of anti-EB nuclear antigen (EBNA) antibody was 1:20. However, infectious mononucleosis-like symptoms were not evident.

EB virus has marked tropism for B-cells as in cases of infectious mononucleosis, because the CD21 on B-cells acts as a receptor for this virus.[5] Therefore, it is not surprising that EB virus can play a tumorigenic role in some B-cell malignancies such as Burkitt's lymphoma,

acquired immunodeficiency syndrome lymphoproliferative disorder, and PAL of the B-cell type.[5] However, recent studies have revealed that EB virus can also cause some peripheral T-cell lymphomas.[6] On the other hand, T-cell-derived PAL (T-PAL) is particularly rare.[2,7] For instance, based on a nationwide study of PAL in Japan, only one out of 33 cases was T-cell lymphoma.[2] Previously, some patients with T-PAL have been reported in the Japanese literature.[7] However, as yet, there have been few attempts to analyze the association of EB virus in these cases. Two cases of PAL showing unusual phenotypes have been described recently.[8,9] One had a biphenotypic feature of both T (CD3+, and CD4+) and B cells (CD19+, and CD20+).[8] The other was an anaplastic large cell lymphoma (CD3+, CD4+, and CD30+) with co-expression of CD20.[9] In spite of these findings, both cases also revealed latent infection of EB virus in the lymphoma cells. In contrast, the neoplastic cells in the present case were characterized by the expression of several kinds of T-cell antigens, and lack of B- and natural killer-cell antigens, and CD30. Thus, except for those unique cases, our observations primarily suggest that EB virus may be involved in the pathogenesis of T-PAL as well. In conclusion, an etiologic relationship appears to exist between PALs and EB virus, irrespective of phenotypic differences in the neoplastic cells.

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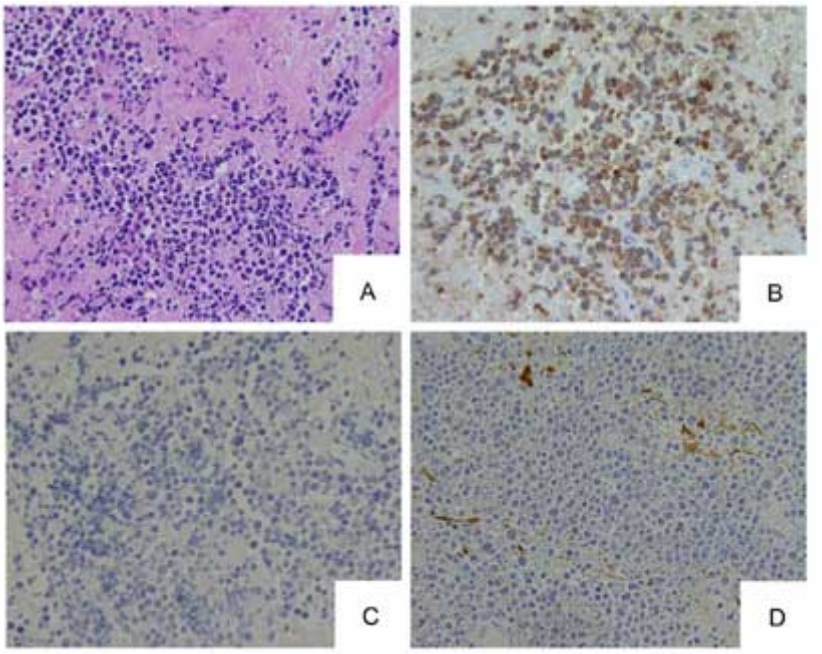

Figure 1. Histopathology and immunohistochemical staining for CD3, CD20, and CD56 in the biopsy specimen. (A) The tumor shows diffuse proliferation of large lymphoid cells (hematoxylin and eosin stain, original magnification x200). (B, C, D) These lymphoma cells were positive for CD3 (B), but not for CD20 (C) and CD56 (D) (immunoperoxidase with hematoxylin counterstain, original magnification x200).

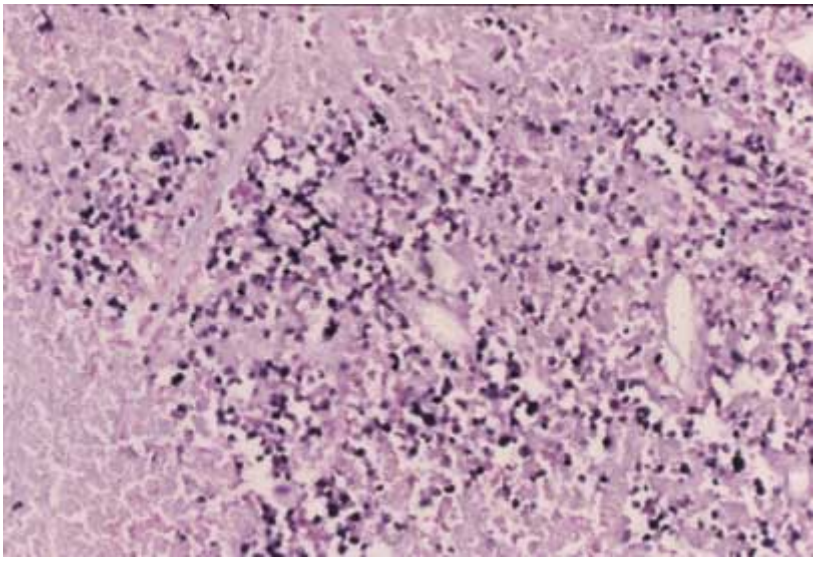

Figure 2. In situ hybridization reveals the signals of EBER in the nuclei of the neoplastic cells.