J Clin Exp Hematop
Vol. 55, No. 3, Dec 2015

Case Study

Spontaneous Regression of Intravascular Large B-Cell Lymphoma and Apoptosis of Lymphoma Cells: A Case Report

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A 61-year-old Japanese woman presented with hemophagocytic syndrome (HPS) and suffered from intravascular large B-cell lymphoma (IVLBCL). After a few days of supportive care, her condition improved without any anti-cancer drugs or steroids. She experienced recurrences of HPS at 15 mon and 21 mon after first presentation, but lymphoma cells were not observed. Relapse of IVLBCL with pulmonary involvement occurred 27 mon after first presentation. She underwent R-CHOP therapy followed by autologous stem cell transplantation. She is currently alive and without lymphoma. Immunostaining by anti-ssDNA suggested that spontaneous regression may have been due to apoptosis of the lymphoma cells. 〔*J Clin Exp Hematop 55(3) : 151-156, 2015*〕

Keywords: spontaneous regression, intravascular large B-cell lymphoma, apoptosis

INTRODUCTION

Spontaneous regression (SR) of malignant neoplasms has been defined as the complete or partial disappearance of a malignant tumor in the absence of any cancer treatment, or in the presence of therapy that is considered inadequate to exert a significant influence on neoplastic disease.[1] SR of aggressive lymphoma is a rare phenomenon. While the precise mechanism of SR remains unknown, apoptosis may be associated with its process.[2]

Secondary hemophagocytic syndrome (HPS) is induced by several causes, including malignant tumor, infection, drugs, and collagen diseases. In adults with HPS, it has been reported that 44% of cases are caused by lymphoma.[3] Half of these lymphoma patients have B-cell lymphoma, Epstein-Barr virus (EBV)-related B-cell lymphoma, or intravascular large B-cell lymphoma (IVLBCL). IVLBCL with HPS has been proposed as an Asian variant of IVLBCL.[4] We present a patient with the Asian variant of IVLBCL who experienced SR, with evidence suggesting that the lymphoma cells underwent apoptosis.

Received: September 1, 2014
Revised : October 11, 2014
Accepted: October 13, 2014

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CASE REPORT

A 61-year-old Japanese woman was admitted with a fever of 38.6℃ and appetite loss. She had been treated with amoxicillin for palmoplantar pustulosis 5 years previously. Computed tomography (CT) scan showed hepatosplenomegaly and no enlarged lymph nodes. Other than hepatosplenomegaly, physical examination showed no particular findings, such as skin lesions or neurological problems. Laboratory examination showed leukocytopenia ($2.24 \times 10^3/\mu L$), thrombocytopenia ($4.9 \times 10^4/\mu L$), and increased serum levels of aspartate aminotransferase (AST) (374 IU/L; normal range 10-38), alanine aminotransferase (ALT) (315 IU/L; normal range 5-40), lactate dehydrogenase (LDH) (2,535 IU/L; normal range 100-200), alkaline phosphatase (1,037 IU/L; normal range 100-200), and C-reactive protein (2.9 mg/dL). Serum levels of immunoglobulins G, A, and M were within normal range. The ratio of CD4/CD8 was normal. Anti-human immunodeficien9cy virus antibodies and anti-human T-cell lymphotropic virus type-1 antibodies were negative. The serum titers of anti-EBV antibodies showed viral capsid antigen-IgG ×80 (normal range < ×10), EBV-associated anti-

gen ×10 (normal range < ×10), and viral capsid antigen-IgM < ×10 (normal range < ×10). A bone marrow smear (1st bone marrow examination) showed infiltration of abnormal lymphocytes and proliferation of immature monocytes with hemophagocytosis (Fig. 1). Invasion of lymphoma cells associated with HPS was suspected, but diagnosis of lymphoma with HPS was unable to be confirmed because of the lack of further examinations due to the New Year's holiday. Her performance status was 1 and general condition was not serious. We carefully monitored her condition with supportive care, including oral administration of acetaminophen for fever and intravenous infusion of saline for dehydration. On the 3rd day after admission, her symptoms disappeared and laboratory data returned to normal. A bone marrow clot specimen at admission (1st bone marrow examination), showed a growth of abnormal lymphocytes within the lumina of the vessels. IVLBCL was subsequently diagnosed (Fig. 2). However, re-examination of bone marrow (2nd bone marrow examination), including a histologic examination and flow cytometry, showed no evidence of abnormal cells two weeks after admission. We carefully monitored her condition and she presented with the same condition as first presentation, exhibiting thrombocytopenia and elevated AST, ALT, and LDH levels, at 15 mon after admission (Episode 1 in Fig. 3). CT scan showed hepatosplenomegaly without enlarged lymph nodes or tumor formation. A bone marrow biopsy (3rd bone marrow examination) showed hemophagocytosis, but no abnormal lymphocytes at that time. After a week of supportive care without anti-cancer therapy, her condition recovered. Her condition remained stable for the following 6 mon. However, she presented again with a similar condition as first presentation at 21 mon (Episode 2 in Fig. 3). The 4th bone marrow examination showed hemophagocytosis without lymphoma cells. However, her condition did not improve with supportive care. She received oral prednisolone (10 mg/body) for two mon, and her condition improved. Her thrombocytopenia and AST, ALT, and LDH serum levels tentatively improved, but worsened during the tapering off of prednisolone. She complained of fever, dry cough, and dyspnea at 27 mon after first presentation (Episode 3 in Fig. 3). CT scan showed bilateral pulmonary infiltration, suggesting interstitial pneumonia. Biopsy specimens of the lung and bone marrow (5th bone marrow examination) showed infiltration of large B-cell lymphoma cells in the vessels, and relapsed lymphoma was diagnosed. She received eight courses of R-CHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisolone) and achieved complete remission (CR). Her symptoms disappeared, and thrombocyte count and serum levels of LDH, AST, and ALT normalized. One year after the start of R-CHOP, she complained of general fatigue and appetite loss, and thrombocytopenia and elevated LDH level reappeared. CT scan showed only splenomegaly with neither lung infiltration nor tumor formation, but a bone marrow examination (6th bone marrow examination) confirmed a diagnosis of relapsed IVLBCL. She received two courses of CHASER therapy (cyclophosphamide, high dose of cytarabine, dexamethasone, etoposide, and rituximab),[5] but did not achieve CR. She then received two courses of R-ICE therapy (rituximab, ifosphamide, carboplatin, and etoposide) and reached CR. Thereafter, she received high-dose chemotherapy (MCEC: ranimustine, carboplatin, etoposide, and cyclophosphamide)[6] followed by an autologous peripheral blood stem cell transplantation in CR. She was alive without lymphoma or serious complications six years after first presentation.

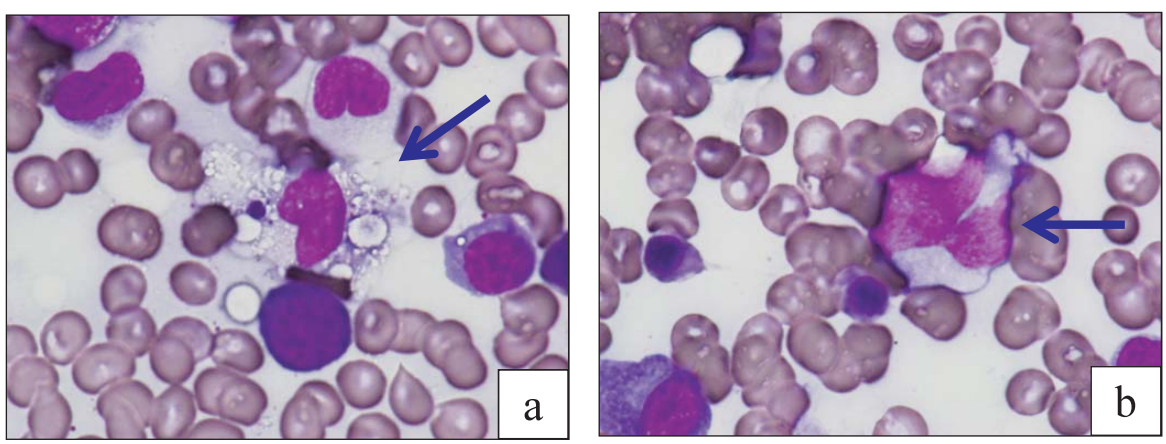

Fig. 1. Microscopic appearance of the bone marrow smear at first presentation. (***1a***) Macrophage phagocytizing blood cells are observed. *Allow* shows a hemophagocytic cell. May-Giemsa stain, ×1,000. (***1b***) A large lymphoid cell with an atypical nucleus is observed in the bone marrow. *Allow* shows a large lymphoid cell. Atypical cells with large irregular nuclei and large, slightly basophilic, cytoplasm without azurophilic granules. May-Giemsa stain, ×1,000.

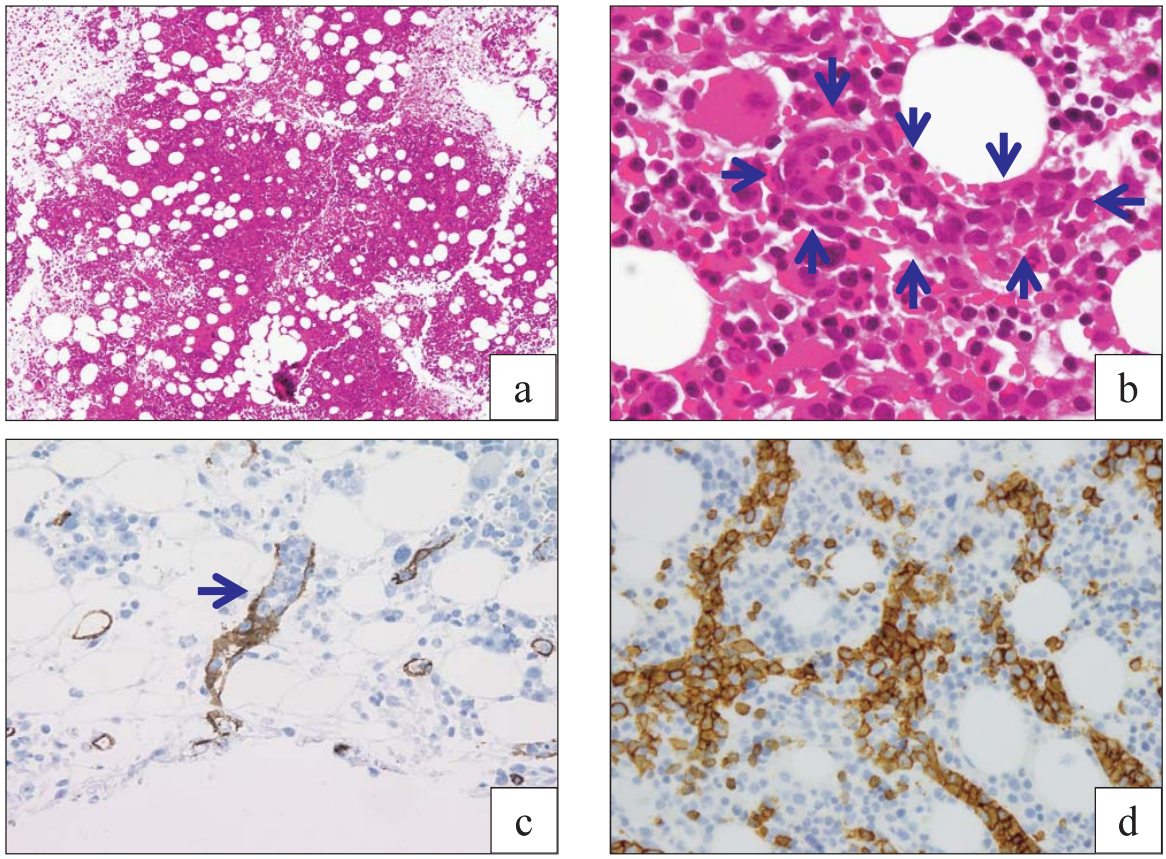

Fig. 2. Microscopic appearance of the bone marrow clot at first presentation. (***2a***) The bone marrow shows hypercellularity (70%) with three series of hematopoietic cells. H&E stain, ×100. (***2b***) Large atypical lymphoid cells are present in the lumina of the vessels. *Allows* show the vessel in which lymphoid cells are present. H&E stain, ×400. (***2c***) The endothelial cells of the vessels are positive for CD34, and infiltrating lymphoma cells in the lumina of vessels can be clearly observed. *Allow* shows the vessel in which lymphoid cells are present. ×400. (***2d***) Lymphoma cells in the vessels are positive for CD20. ×200.

PATHOLOGICAL FINDINGS

The 1st bone marrow examination showed hypercellularity (70%) and large atypical lymphoid cells within the lumina of the vessels, with hemophagocytosis. Immunohistochemical staining showed that the abnormal lymphoid cells within the lumina were positive for CD5 (Roche Diagnostics Japan, Tokyo), CD20 (DAKO Japan Inc., Kyoto), Bcl-2 (DAKO Japan Inc.), and MUM-1 (DAKO Japan Inc.), but negative for CD10 (Roche Diagnostics Japan) (Fig. 2). We diagnosed the patient with IVLBCL with hemophagocytosis. However, the 2nd to 4th bone marrow examinations, performed within 27 mon of the first presentation, showed no lymphoma cells. The lung biopsy at 27 mon after first presentation showed growth of large lymphoma cells in the capillary vessels of the alveolus and pleura. Simultaneously, the 5th bone marrow biopsy showed lymphoma cells in the vessels. Immunohistochemical staining revealed that the lymphoma cells at relapse had the same phenotypes as those of the lymphoma cells at first presentation. The MIB-1 labeling index of the lymphoma cells was 80% in the 1st and 5th bone marrow examination specimens. G-banding chromosomal analysis of the lymphoma cells in the lung tissue showed the following abnormal findings: 49,XX,−1,+3,del(6)(q?),+9,+add(12)(p11.2),add(12)(q13),−13,−19,−19,−20,+rl,+mar1,+mar2,+mar3,+mar4,+mar5 in 15 of the 20 cells examined. Chromosomal analysis of the bone marrow could not be performed at the 1st bone marrow examination. At the recurrences of HPS (15 and 21 mon after first presentation), chromosomal analyses of the 3rd and 4th bone marrow specimens showed normal karyotypes. Apoptosis of the lymphoma cells was assessed by immunostaining with a polyclonal antibody (rabbit anti-single-stranded DNA, DAKO Japan Inc., Kyoto) that recognizes single-strand DNA (ssDNA). The immuno staining by anti-ssDNA showed positive lymphoma cells at first presentation, but negative cells 27 mon later (Fig. 4). The lymphoma cells in the bone marrow at 27 mon after first presentation were negative for EBER by *in situ* hybridization.

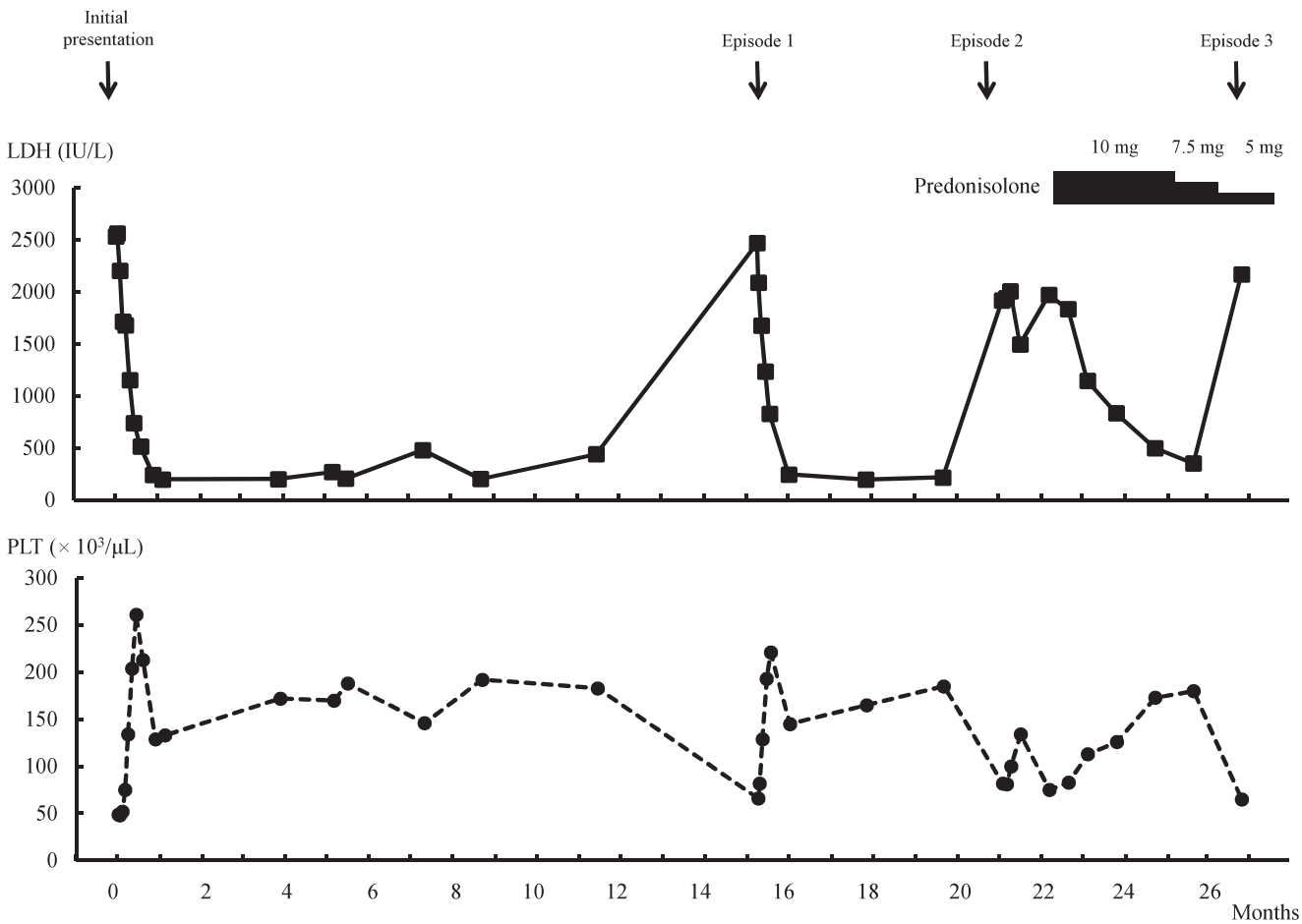

Fig. 3. Clinical course of the patient. Remarkable elevation of serum lactate dehydrogenase level and decrease of platelet count were observed at the occurrence of hemophagocytic syndrome. At Episode 1 and 2, bone marrow examination showed no lymphoma cells. LDH, lactate dehydrogenase; PLT, platelet count

Unfortunately, we unable to confirm whether the lymphoma cells at initial presentation and relapse were the same clone by polymerase chain reaction, due to insufficient amount of DNA in the samples.

DISCUSSION

We presented a patient with the Asian variant of IVLBCL with spontaneous regression for 27 mon. IVLBCL has two major patterns of clinical presentation. One is the Western form, characterized by symptoms related to the main organ involved, predominantly neurological or cutaneous, and the other is the Asian variant, in which the patients present with multiorgan failure, hepatosplenomegaly, pancytopenia, or HPS.[4] IVLBCL usually presents an aggressive clinical course and patients have a poor prognosis. However, it has been recently reported that prognosis can be improved by using immunochemotherapy.[7] In the present case, lymphoma cells initially appeared in the bone marrow with HPS. However, the lymphoma cells disappeared as HPS subsided with only supportive care. Lymphoma relapse did not occur until 27 mon after first presentation, without anti-lymphoma treatment. These findings suggested that the present case demonstrated SR of the Asian variant of IVLBCL.

It is well known that SR rarely occurs in malignant neoplasms, yet more frequently in leukemia and lymphoma than in other tumors.[2] SR of patients with low-grade lymphoma has been reported to occur in 10 to 23% of patients.[8-10] However, aggressive non-Hodgkin's lymphoma (NHL) cases with SR seem to be rare.[11-13] Gattiker *et al*. reported 2 of 69 cases with diffuse-type NHL showing SR.[8] Abe *et al*. reviewed 15 cases of SR in NHL and reported that three cases involved DLBCL.[13] To the best of our knowledge, only two patients with IVLBCL showing SR have been reported.[14,15] The remission duration of these patients was much shorter (one and five mon) than that of the present case, and these cases were the Western form of IVLBCL.

The mechanism of SR is not clear, but some hypotheses

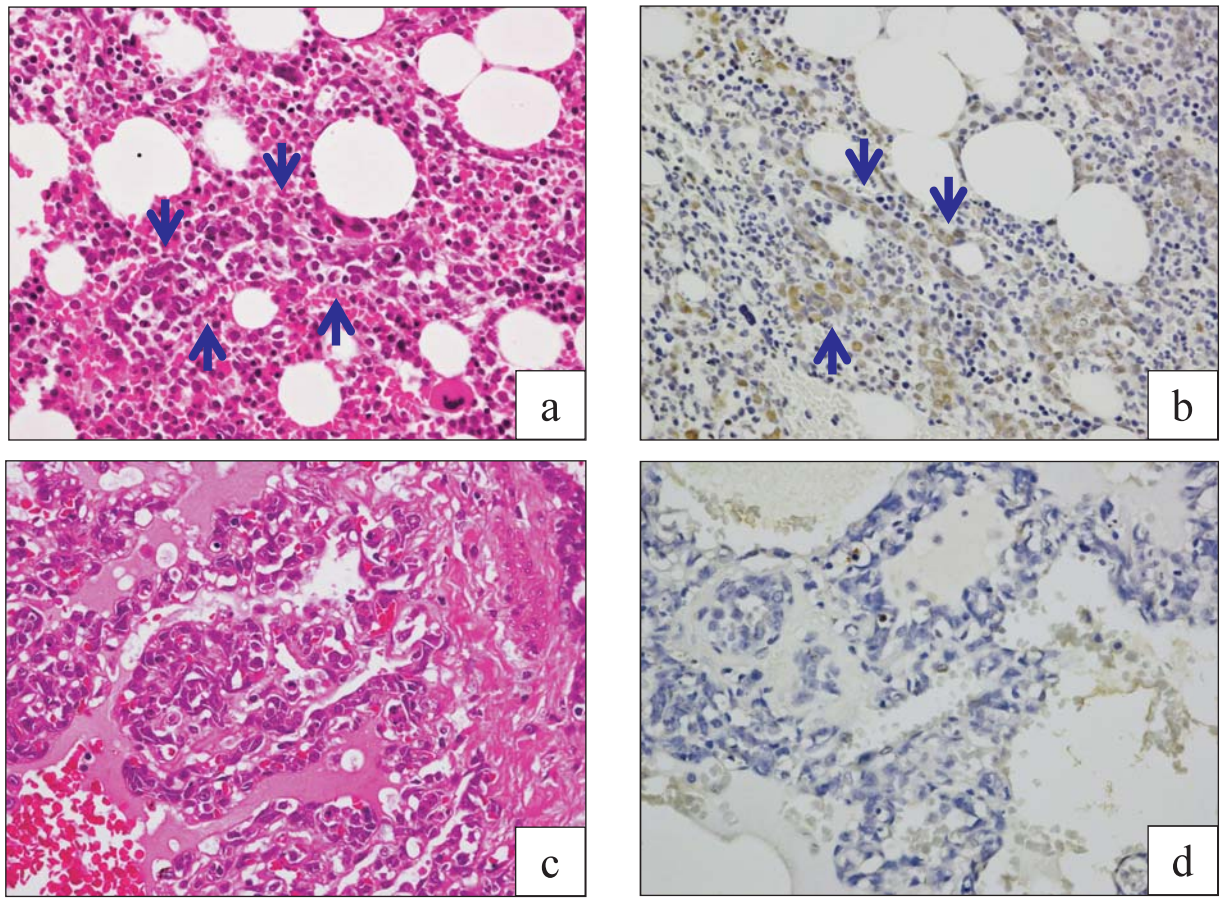

Fig. 4. Single-strand DNA (ss-DNA) staining. (***4a***) Bone marrow clot specimen at first presentation. *Allows* show the vessel in which lymphoma cells are present. H&E stain, ×400. (***4b***) Bone marrow clot specimen at first presentation. Lymphoma cells are positive for ssDNA. *Allows* show the vessel in which lymphoma cells are present. Lymphoma cells at this time may have been undergoing apoptosis. Anti-ssDNA staining, ×400. (***4c***) Lung biopsy specimen at 27 mon after first presentation. Lymphoma cells are present in the vessel. H&E stain, ×400. (***4c***) Lung biopsy specimen at 27 mon after first presentation. Distinct from the lymphoma cells at first presentation, lymphoma cells at this time are negative for ssDNA, and may not have been undergoing apoptosis. Anti-ssDNA staining, ×400.

have been proposed. SR may depend on apoptosis and immune system activity, as well as the conditions of the tumor microenvironment.[2] Immunodeficiency-associated lymphoproliferative disorders, such as post-transplant and methotrexate-related lymphoproliferative disorder, can regress after stopping immunosuppressive agents.[16,17] This suggests that the activity of the host immune system is related to the development of lymphoma in these diseases. However, the lymphoma cells of the present case were negative for EBER by *in situ* hybridization. This suggests that the SR of lymphoma was not related to immune system activity in the present case.

The process of apoptosis plays an important role in cases of SR, and is linked to a high percentage of cases with the presence of hormone receptors. It is well known that advanced-stage neuroblastoma often presents SR.[18] A recent study showed that apoptosis-related genes were overexpressed in neuroblastoma.[19] In the present case, we have no data on the overexpression of apoptosis-related genes. Lymphoma cells at first presentation were positive for ssDNA, but those at relapse became negative; the presence of ssDNA is a marker of cells undergoing apoptosis.[20] These findings suggest that SR in the present case may have been due to apoptosis of the lymphoma cells.

CONFLICT OF INTEREST: The authors declare no conflicts of interest.

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