

Epstein-Barr Virus-Infected Malignant T/NK-Cell Lymphoma in a Patient with Hypersensitivity to Mosquito Bites

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We report an autopsy case of Epstein-Barr virus (EBV)-infected malignant lymphoma in a young male who had hypersensitivity to mosquito bites. The autopsy revealed multiple confluent lymphoma lesions in the lungs, and on the right leg irregular-shaped skin ulcers were seen. The left pleural effusion also contained a large number of lymphoma cells. The lymphoma cells were determined as T/NK-cell type cells by immunohistochemistry. EBV DNA was detected most intensively in the lungs and EBV-encoded small RNAs-positive lymphoma cells were also observed in the lungs at a high frequency. EBV latent membrane protein-1 expression and a high Ki-67 labeling indices were noted in the lymphoma cells of the lung lesions. These findings indicate that the development of the malignant lymphoma was associated with the proliferation of EBV-infected lymphoma cells, and the cells that infiltrated the whole the body, especially the lungs, caused the patient's death. *Int J Surg Pathol* 12(3):265–272, 2004

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Epstein-Barr virus (EBV), a member of the herpes virus family, is associated with not only B-cell but also T-cell lymphoproliferative disorders (LPDs), including peripheral T-cell lymphoma [1–4]. Recently, it has been reported that EBV infection is associated with hypersensitivity to mosquito bites (HMB) and malignant complications [5,6]. However, EBV infection has not been satisfactorily characterized in malignant lymphoma development in patients with HMB. It is unclear how EBV is associated with the pathogenesis of lymphoma cells in patients with HMB.

HMB is characterized by intense local skin reactions including erythema, bulla, and ulcers and scars, with general symptoms such as high fever and lymphadenopathy following mosquito bites [7]. This disorder is relatively rare, and most of the reported cases have been from Asia, especially Japan [5,6,8–16]. Another important clinical feature is the high mortality rate due to complications such as hemophagocytic syndrome and LPDs [14,15]. To prevent complications and improve the survival rate, it is important to analyze the pathogenesis of the complications in patients with HMB retrospectively. However, autopsy reports of HMB are extremely rare, and only 3 reports are described in the English literature [14–16]. We characterized the autopsy of a patient with EBV-infected malignant lymphoma accompanied with HMB by using immunohistopathological methods.

Case Report

The Japanese male autopsied developed HMB with EBV-positive inflammatory cells when he was 17 years old, which has already been reported by Oh-sawa et al [9] in clinical viewpoints. At that time, he suffered from skin ulcers of the leg and fever after mosquito bites. During the course, he underwent a biopsy of an ulcer from the right leg, which showed nonatypical lymphoid cell infiltration in the dermis (Fig. 1a, b). He was also diagnosed with chronic active EBV infection with a high titer of EBV antibodies: anti-EBV associated nuclear antigen 1:1,280, anti-early antigen (IgG) 1:1,280, and antiviral capsid antigen 1:5,120 [9]. When he was 20 years old, he was again admitted for the treatment of a severe skin ulcer on the right leg and a high fever (38°C). Histopathology of the second biopsy from the skin ulcer lesion showed prominent atypical lymphoid cell infiltration with focal necrosis in the dermis and fat tissue (Fig. 1c, d). Radiographic examination of the chest showed several nodular shadows in the chest field (Fig. 2a). Peripheral blood data from 23 days after admission were as follows: leukocyte count $11.8 \times 10^3/\mu\text{L}$ (normal range: $3.3\text{--}8.8 \times 10^3/\mu\text{L}$) with 17% (normal range: 13–57%) lymphocytes (atypical lymphocytes were not detected), and 0% (normal range: <8%) eosinophils; erythrocytes $3.27 \times 10^6/\mu\text{L}$ (normal range: $4.00\text{--}5.70 \times 10^6$); hemoglobin 9.2 g/dL (normal range: 12.0–17.0); hematocrit 27.5% (normal range: 36.0–51.0%); aspartate aminotransferase 221 IU/L (normal range: 5–40); alanine aminotransferase 103 IU/L (normal range: 5–47); and lactate dehydrogenase 2,988 IU/L (normal range 100–225). Twenty-five days after admission, the patient died from severe respiratory dysfunction.

Materials and Methods

Immunohistochemistry

An avidin-biotin complex immunoperoxidase technique was performed for the paraffin-embedded tissue sections from the autopsy specimens. The primary antibodies used in this study are listed in Table 1. As pretreatment, microwave-based (CD3, CD8, Ki-67, EBNA2) or autoclave-based (CD4, CD56, CD79a, Granzyme B) antigen retrieval was performed in 10mM citrate buffer (pH 6.0).

The Ki-67 labeling index (KI) was determined in tumor areas showing the highest density of cells with positively stained nuclei, and was calculated under a 200-fold magnification. At least 5 areas were selected, and the KI was calculated as the number of Ki-67-positive cells per 1,000 cells.

EBV DNA was detected by polymerase chain reaction (PCR)-Southern analysis and *in situ* hybridization of EBV-encoded small RNAs (EBER).

Genomic DNA was extracted from formalin-fixed, paraffin-embedded autopsy sections according to the DEXPAT™ (TaKaRa Biochemicals Co., Ohtsu, Japan) method. The primers were designed to amplify a 129-base pair segment in the *Bam*HI-W region of the EBV genome, as previously described [17]. The procedure of the PCR-Southern hybridization was also performed according to a previous report [18]. The DNA extracted from an EBV-positive cell line, Raji, and distilled water, were used as the positive and negative controls, respectively.

In situ hybridization of EBER was carried out in paraffin-embedded sections of autopsy specimens using digoxigenin-labeled 30-base oligonucleotides complementary to a portion of the EBER-1 sequence. The sequence was 5'-AGA CAC CGT CCT CAC CAC CCG GCA CTT GTA-3', as previously described [9,19]. Briefly, deparaffinized sections were dehydrated and pretreated with pepsin, then hybridized with a digoxigenin-labeled probe and an alkaline phosphatase-conjugated antidigoxigenin. A color solution was prepared with 5-bromo-4-chloro-3-indolylphosphate and nitroblue tetrazolium chloride (Roche Diagnostics, Tokyo, Japan). The sections were counterstained with methyl-green. As a negative control, paraffin-embedded sections of lichen planus were used.

Pathological Findings

Macroscopic findings from the bilateral legs and arms showed many irregular-shaped ulcers, measuring a maximum of 23.5×10.0 cm on the right leg, until the skeletal muscle. A yellowish unclear left pleural effusion was deposited (700 mL). A va-

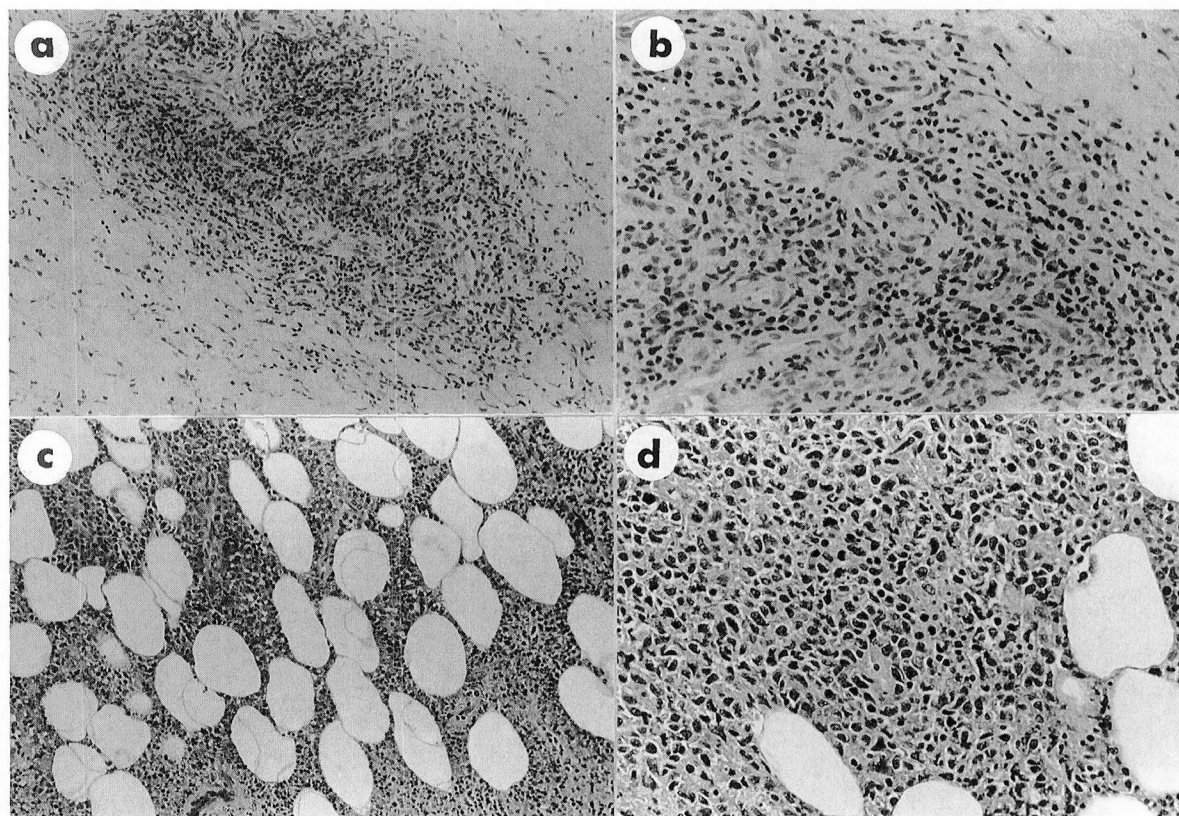


Fig. 1. Microscopic findings of the skin ulcer 3 years before the autopsy (**a, b**). Many lymphocytes, which exhibit no nuclear atypia, infiltrate the dermis. Microscopic findings of the skin ulcer 5 days before the autopsy (**c, d**). Severe atypical lymphoid cell infiltration with focal necrosis in the fat tissue is observed.

Table 1. List of Antibodies Used in This Study

Antibody	Source	Clone	Target Cell or Antigen	Dilution
LCA*	Nichirei	2B11+PD7/26	T and B lymphocytes	Prediluted
Leukocyte T cell	Bio-Science	MT1	T lymphocytes	1:50
CD45RO	DAKO	UCHL-1	T lymphocytes	1:50
CD3	Nichirei	PS1	Pan T lymphocytes	Prediluted
CD4	Nichirei	1F6	T helper cells, monocytes	Prediluted
CD8	DAKO	C8/144B	T suppressor lymphocytes	1:50
CD20	Nichirei	L26	B lymphocytes	Prediluted
CD79a	Nichirei	JCB117	B lymphocytes	Prediluted
CD56	Nichirei	1B6	NK cells	Prediluted
Granzyme B	Nichirei	GrB-7	granzyme B	Prediluted
Ki67	DAKO	MIB1	nuclear antigen	1:50
EBNA 2†	DAKO	PE2	EBNA2	1:25
LMP-1‡	DAKO	CS1-4	LMP-1	1:25

*LCA: leukocyte common antigen, †EBNA 2: EBV-encoded nuclear antigen 2, ‡LMP-1: latent membrane protein-1.

riety of large and small, elastic hard and soft, and whitish nodules in the bilateral lungs, alimentary tract, pancreas, and testes, as well as an enlargement of the lymph nodes, were observed. The bilateral lungs demonstrated large confluent nodules, measuring a maximum of 3.5×3.5 cm, which were larger than in the other organs (Fig. 2b). On the

other hand, there was no tumor formation in the liver (2,040 g) or spleen (400 g) in spite of hepatosplenomegaly. Formalin-fixed, paraffin-embedded tissue sections demonstrated that atypical lymphoid cells had diffusely proliferated with focal necrosis in these nodules. These cells had large-sized severely atypical nuclei, irregular nuclear

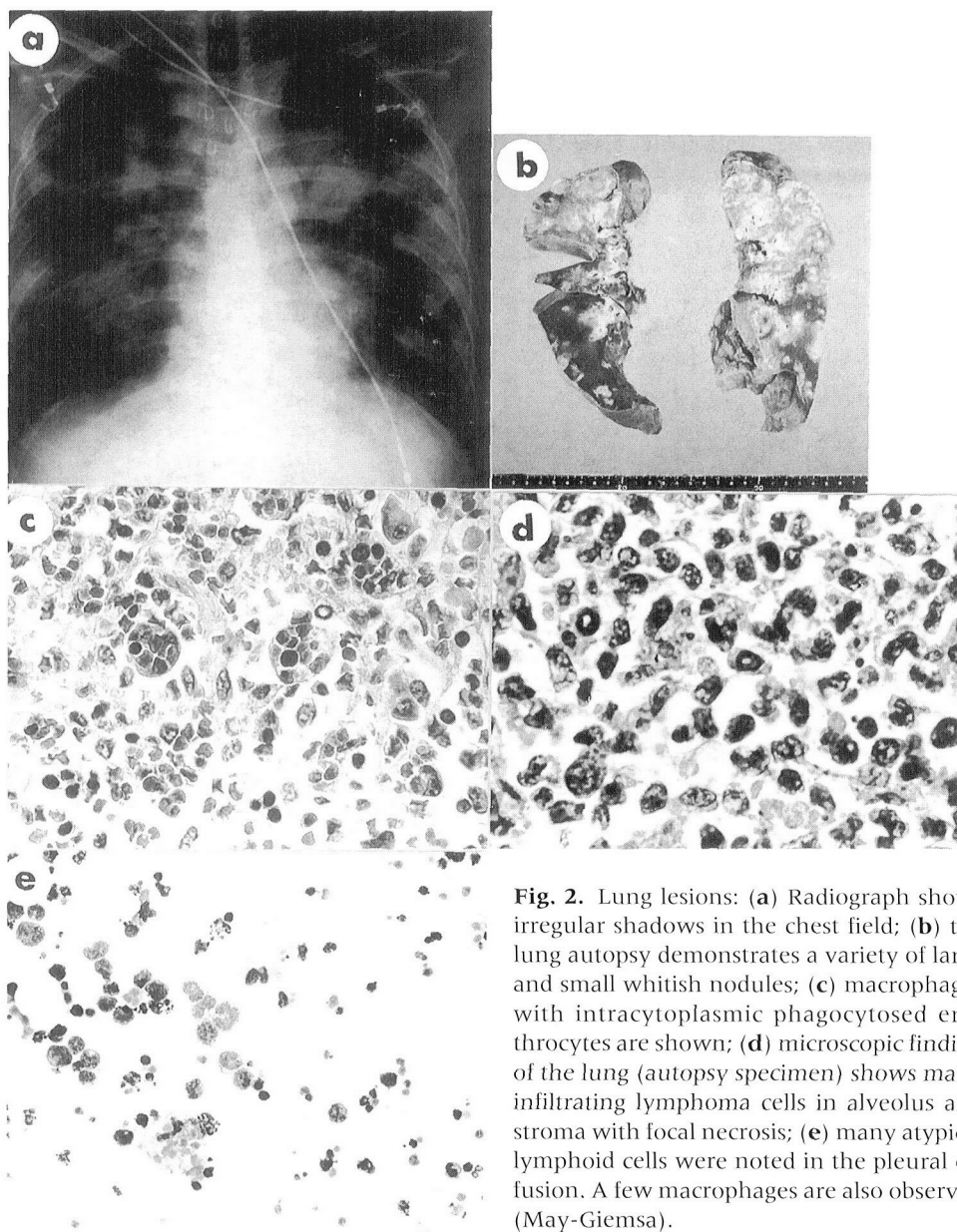


Fig. 2. Lung lesions: (a) Radiograph shows irregular shadows in the chest field; (b) the lung autopsy demonstrates a variety of large and small whitish nodules; (c) macrophages with intracytoplasmic phagocytosed erythrocytes are shown; (d) microscopic finding of the lung (autopsy specimen) shows many infiltrating lymphoma cells in alveolus and stroma with focal necrosis; (e) many atypical lymphoid cells were noted in the pleural effusion. A few macrophages are also observed (May-Giemsa).

Table 2. Correlation Between Degree of Lymphoma Cell Invasion; Detection of EBV DNA; Expression of EBER, LMP-1, EBNA2, and KI in the Lung, Skin Ulcer of the Right Leg, and the Supraclavicular Lymph Node

Organ	Invasion of Lymphoma Cells	EBV* DNA	EBER†	LMP-1‡	EBNA 2§	KI (%)**
Lung	++	++	++	++	—	23.1
Leg	+	+	+	+	—	14.3
Lymph node	+	+	+	+	—	10.0

EBV: Epstein-Barr virus, †EBER: EBV-encoded small RNAs, ‡LMP-1: latent membrane protein-1, §EBNA2: EBV nuclear antigen, **KI: Ki-67 labeling index.

—: not detected, +: mild positive, ++: strong positive.

edge, several mitoses, and small cytoplasm. Some atypical cells showed obvious nucleoli and irregular convoluted nuclei (Fig. 2c, d). Invasion of these atypical cells was most prominent in the lungs, followed by the skin of the right leg and the supraclavicular lymph node (Table 2). There were also many macrophages that displayed phagocytosis of the erythrocytes in the cytoplasm of the bone marrow, spleen, and in the other lesions (Fig. 2c). The liver and spleen showed extramedullary hematopoiesis without an infiltration of atypical cells. The cells in the left pleural fluid consisted of a large number of atypical lymphoid cells and some macrophages (Fig. 2e).

To identify the origin of lymphoma cell, we also analyzed the rearrangement of T-cell receptor on tumor cells by using DNA extracted from paraffin-embedded tumor specimens. However, we could not detect the rearrangement at all (data not shown). Many atypical lymphoid cells showed cytoplasmic immunoreactivity for leukocyte common antigen (LCA) (data not shown), CD45RO (Fig. 3a), CD56 (Fig. 3b) and leukocyte T-cells (data not shown). CD3 was partially positive (data not shown). In contrast, cells positive for CD4, CD8, CD20, CD79a, and granzyme B were not detected. Nuclear immunoreactivity for Ki-67 was observed in atypical lymphoid cells (Fig. 3c). The KI was higher in the lungs (23.1%) followed by the leg (14.3%) and the lymph nodes (10.0%) (Table 2). EBV latent membrane protein (LMP)-1 was detected on the cell membrane and cytoplasm of almost all atypical lymphoid cells (Fig. 3d). However, EBV nuclear antigen (EBNA) 2 was not detected in the cells (data not shown).

EBV DNA was detected most strongly in the lungs, and weakly in the leg and lymph nodes, by PCR-Southern analysis (Fig. 4a). EBER positive cells were detected in the lymphoid cells of the lung lesions (Fig. 4b). A large number of EBER-positive atypical cells were observed in the lung lesions compared with the leg and lymph node lesions. The results from the EBV DNA, EBER, latent proteins, and KI for each organ are summarized in Table 2.

Discussion

We diagnosed the patient as having EBV-infected T/NK-cell lymphoma in this autopsy case by morphologic and immunohistochemical analyses. Invasion of the lymphoma cells was most prominent in the lungs. It is extremely rare for EBV-infected malignant lymphoma to develop in the lungs of pa-

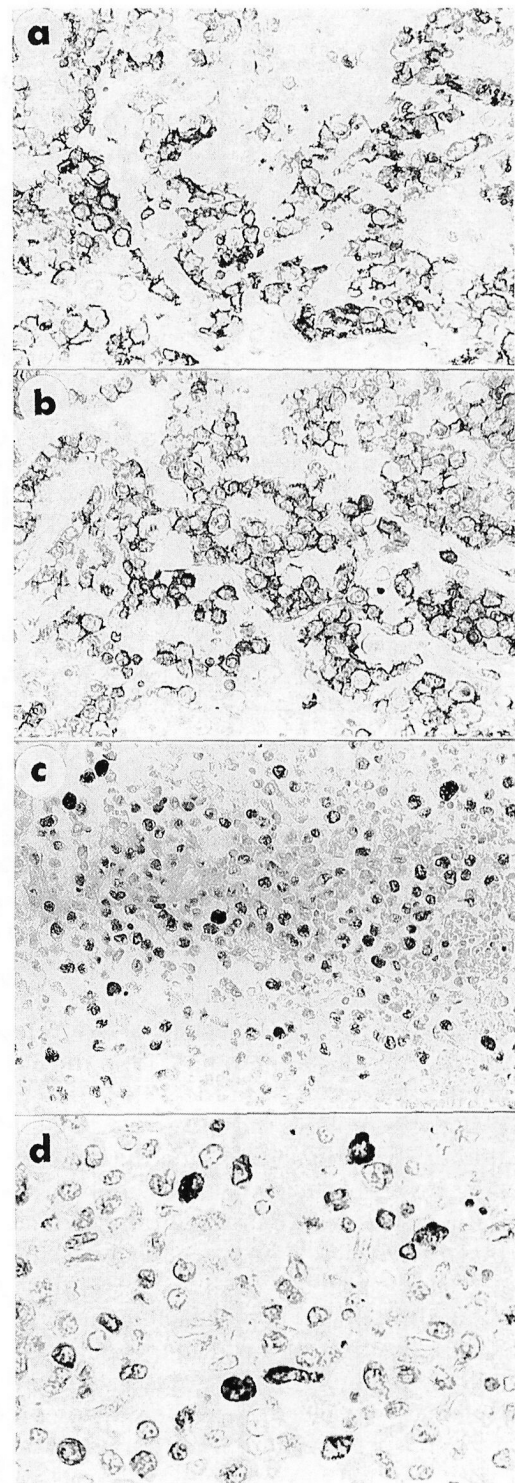


Fig. 3. Immunohistochemistry for CD45RO, CD56, Ki-67, and LMP-1 in the lymphoma cells of the autopsy specimens. (a, b) Immunoreactivity for CD45RO (a) and CD56 (b) are noted in cell membrane. (c) Many lymphoma cells express Ki-67 in nuclei. (d) LMP-1 is mainly expressed on the cell membrane and in the cytoplasm of the lymphoma cells in the lung.

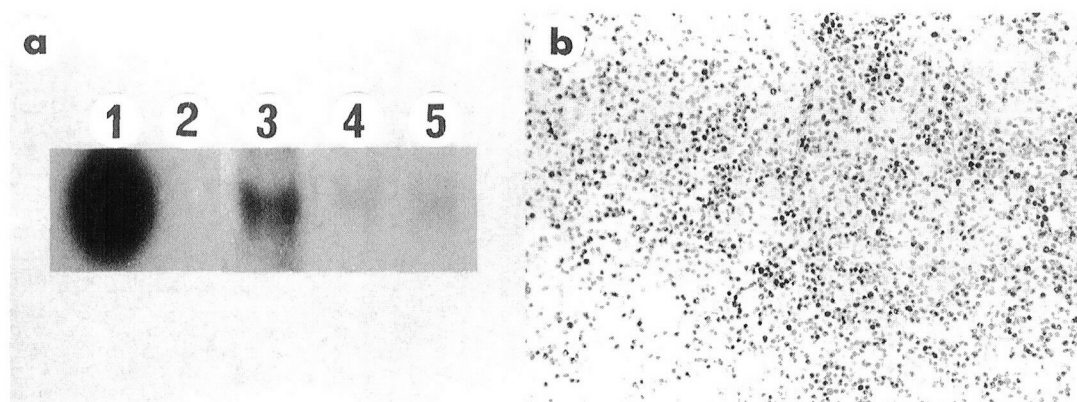


Fig. 4. Detection of EBV DNA and the expression of EBER in the autopsy specimens. (a) EBV DNA. lane 1: Raji cells as EBV DNA positive control; lane 2: distilled water as EBV DNA negative control; lane 3: lung; lane 4: leg; and lane 5: lymph node. (b) Detection of EBER-positive cells. EBER-positive cells are detected in the lymphoma cells of the lung.

tients with HMB. Only 1 case has previously been reported; a young female with HMB who died from the prominent invasion of natural killer cell-derived large granular lymphocyte lymphoma to the lung [20]. Hypercytokinemia, such as soluble Fas ligand, interleukin-10, and interferon γ , in the pleural effusion, was observed in the report. In our case, the left pleural effusion contained a large number of lymphoma cells, which might reflect on the prominent development in the lungs, and correlate with the cytokines described previously.

We analyzed the EBV infection in 3 organs, the lung, a leg, and the lymph nodes, from the autopsy specimens. The results from the PCR-Southern and EBER analyses indicate that EBV was certainly detected in the lymphoma cells, and the pathogenesis and progression of the malignant lymphomas were associated with the EBV infection. There might have been a correlation between the degree of lymphoma cell invasion and the positive signal of EBV DNA and EBER expression in each organ.

Autopsy findings showed many macrophages with intracytoplasmic phagocytosed erythrocytes in the bone marrow, spleen, and other organs, indicating hemophagocytic syndrome (HPS). HPS is associated with lymphomas and leukemias, as well as EBV, which is a virus-associated HPS [21]. In this case, we confirmed HPS with EBV-infected T/NK-cell lymphoma, but not B-cell.

The correlation between the proliferation activity of lymphoma cells and EBV infected cells has not been sufficiently characterized. We examined KI in the lymphoma cells using immunohistochemistry and compared EBV DNA and EBER expression. The

KI was higher in the lungs, followed by the leg and the lymph nodes. The results of the KIs were also correlated with the detection of EBV DNA and the number of positive cells of EBER (Table 2). Thus, the lymphoma cells in the lungs showed the highest proliferation activity, and this strongly suggests that the death of this patient had been caused by lymphoma development in the lungs. Taken together, EBV-positive lymphoma cells correlated with a high proliferation activity, indicating that the development of the lung lymphomas resulted from the proliferation of EBV-positive lymphoma cells in this case.

EBV mainly displays a latency program of infection with a restricted pattern of gene expression, which can be classified into 3 types [22]. Latency type I, where only EBNA 1 is expressed, is found in Burkitt's lymphoma. Coexpression of EBNA 1 and LMPs is characteristic of latency type II, found in nasopharyngeal carcinoma, Hodgkin's disease, and T-cell lymphomas. Latency type III, with expression of the 5 EBNAs and 3 LMPs, is found in lymphomas of immunodeficient patients. EBNA 2 and LMP-1 correlate with the immortalization of lymphocytes and tumorigenesis [23,24]. To determine EBNA 2 and LMP-1 expression in the lymphoma cells in the patient, we examined the autopsy specimens by immunohistochemistry with specific monoclonal antibodies. The lymphoma cells were positive for LMP-1, but not EBNA 2, suggesting that EBV latency was type II in this case. LMP-1 acts on the cell proliferation in some cell types with the type II latency [22]. Thus, our data suggest that the expression of LMP-1 may have played an important role in

the proliferation and pathogenesis of the malignant lymphoma in the patient. Recently, adoptive immunotherapy with allogeneic EBV-specific cytotoxic T lymphocytes was attempted for patients with EBV-related lymphoma, and some effects have been confirmed [25]. Successful anti-EBV therapy might have suppressed tumorigenesis and the proliferation of lymphoma cells in this patient.

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