Case Report

Systemic Epstein-Barr virus-positive T-cell lymphoma in an adult patient with chronic myeloid leukemia receiving a tyrosine kinase inhibitor

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Systemic Epstein-Barr virus (EBV)-positive T-cell lymphoma (TCL) of childhood rarely develops in adults. The first case of systemic EBV-positive TCL, which occurred in an adult patient with chronic myeloid leukemia who was treated with a tyrosine kinase inhibitor (TKI), is reported. The patient was treated with nilotinib (TKI) for two years. He presented with a two-month history of cervical lymphadenopathy, common cold symptoms and had high titers of EBV in peripheral blood. A lymph node biopsy showed CD8-positive atypical T cells with EBV infection. Because of the pathological finding of EBV-positive T-cell lymphoma and status of EBV reactivation, we diagnosed him with systemic EBV-positive TCL. Conventional chemotherapy followed by hematopoietic stem cell transplantation was a valuable therapeutic option for this patient. TKIs are likely to inhibit T-cell activation and proliferation, and might be involved in the onset of systemic EBV-positive TCL.

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Introduction

Most Epstein-Barr virus (EBV)-associated lymphoproliferative disorders are of B-cell origin and occur in the presence of immunosuppression following organ transplant or bone marrow transplant, although EBV may also infect T lymphocytes in healthy individuals[1)]. In the WHO classification of 2017, EBV-related T-cell lymphoproliferative disorder includes two major groups: chronic active EBV infection (CAEBV) and systemic EBV-positive T-cell lymphoma (TCL) of childhood. Both occur mainly in Asians and Native Americans from Central and South America and Mexico[2)]. Systemic EBV-positive TCL of childhood was previously named EBV-positive T-cell lymphoproliferative disorder of childhood in the WHO classification of 2008, and it is a life-threatening illness of children and young adults, characterized by clonal proliferation of EBV-infected T cells. It can occur shortly after primary acute EBV infection (infectious mononucleosis) or during the course of CAEBV. Because primary EBV infection occurs most often in childhood, most patients with systemic EBV-positive TCL of childhood are children and young adults[3-5)], and it is a rare disorder in middle-aged or older adults[6-9)].

The first case of systemic EBV-positive TCL with EBV reactivation in a patient with chronic myeloid leukemia (CML) treated with a second-generation tyrosine kinase inhibitor (TKI) is reported.

Case presentation

A 58-year-old Japanese man was diagnosed with CML in the chronic phase and treated with second-generation TKI (nilotinib), 300 mg twice daily for two years, resulting in an optimal response (*BCR-ABL1* ≦ 0.1%), and finally achieved major molecular response. He presented with a two-month history of bilateral cervical soft painful lymphadenopathy,

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pharyngeal pain, cough, and a two-week history of high fever resistant to conventional therapies. The patient had no history of immunological abnormalities prior to these symptoms, such as hypersensitivity to mosquito bites and hydroa vacciniforme-like eruptions. On admission, a physical examination showed jaundice of the skin and conjunctiva and bilateral soft lymphadenopathy of the cervical, axillary, and inguinal regions. The liver was not palpable, but the spleen was felt 2 cm below the costal margin. He showed pancytopenia (WBC 1,900/μL (Neu 85%, Lym 10%, Atypical 5%), Hb 11.3 g/dL, Plt 32,000/μL), high LDH level (1,005 U/L), liver dysfunction (total bilirubin 4.3 mg/dL, direct bilirubin 2.0 mg/dL, AST 115 U/L, ALT 153 U/L, ALP 939 U/L, and γ-GTP 636 U/L), an inflammatory response (C-reactive protein 10.0 mg/dL), and elevated soluble interleukin-2 receptor (9,753 U/mL). Bone marrow biopsy indicated no evidence of malignancy or slight hemophagocytosis. There was no finding of Disseminated Intravascular Coagulation. Computed tomography of the cervico-abdominal area showed systemic lymphadenopathy, hepatosplenomegaly, ascites, and bilateral pleural effusions (Figure 1). Results of EBV-specific antibody pattern analysis showed that he had a past infection with EBV (EBV anti-VCA-IgM was negative, and EBV anti-VCA-IgG and anti-EBNA antibodies were positive). However, he had high levels of EBV polymerase chain reaction (PCR) quantitation, with 52,000 nucleic acid copies/μg DNA (peripheral blood mononuclear cells).

The cervical lymph node was resected for pathological examination. Histopathological findings showed that the lymph node structure was destroyed and diffuse infiltration of medium-to-large atypical cells was observed. Immunohistochemical findings showed that the atypical cells were positive for CD2, CD3, CD5, CD7, CD8, and cytotoxic molecules including TIA-1, Granzyme B, and perforin, and negative for CD4, CD20, and CD56. Moreover, the atypical cells were positive for EBV-encoded RNA (EBER) *in situ* hybridization (ISH) and LMP-1 but negative for Epstein-Barr nuclear antigen 2 (EBNA2) (Figure 2). Thus, the atypical cells revealed CD8-positive cytotoxic T cell lymphoma with EBV infection in latency II. Cytogenetic analysis of the lymphoma cells showed a normal karyotype, and *major/minor BCR-ABL1* was not detected by PCR. In addition, PCR analysis of the T-cell receptor-β gene rearrangement showed a monoclonal pattern (Figure 3). Taken together, a diagnosis of systemic EBV-positive T-cell lymphoma was made. Cessation of TKI, and subsequent chemotherapy with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) was administered for 2 cycles, resulting in an improvement in overall lymph node swelling (partial response) and marked reduction of the EBV viral load (300 nucleic acid copies/μg DNA).

As the patient obtained control of the disease and maintained a good condition, he finally underwent HLA-matched related donor hematopoietic stem cell transplantation (HSCT) with a reduced-intensity conditioning regimen (Fludarabine 125 mg/m^2, Melphalan 80 mg/m^2, Total body irradiation 4 Gy). Finally, he achieved complete remission.

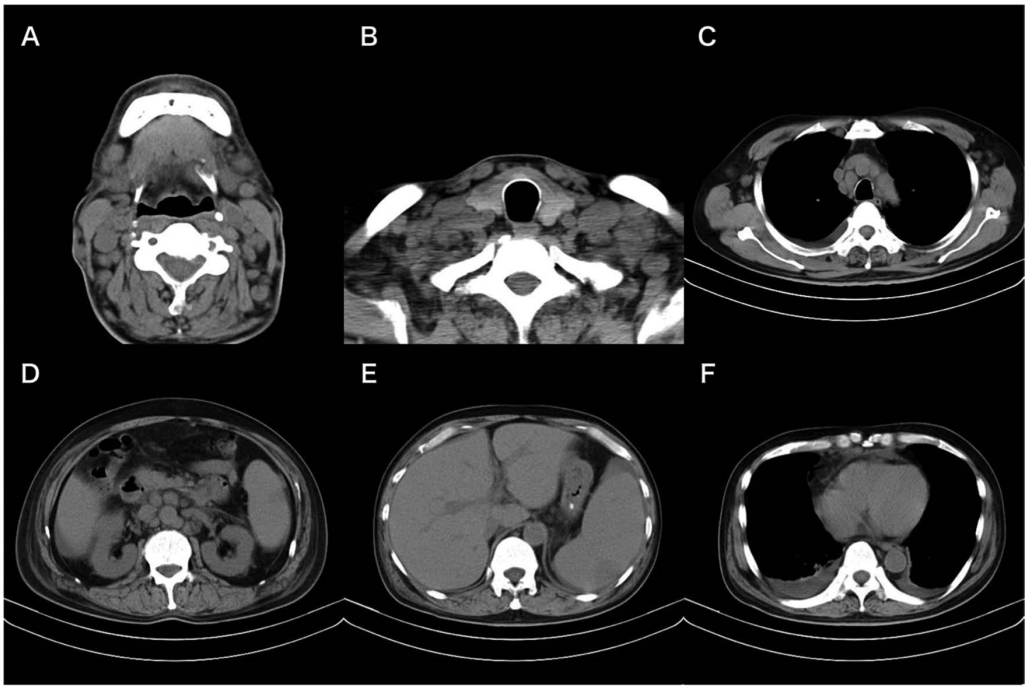

Fig. 1. Computed tomography images upon admission. Image shows systemic lymphadenopathy (A-D), hepatosplenomegaly, ascites (E), and bilateral pleural effusions (F).

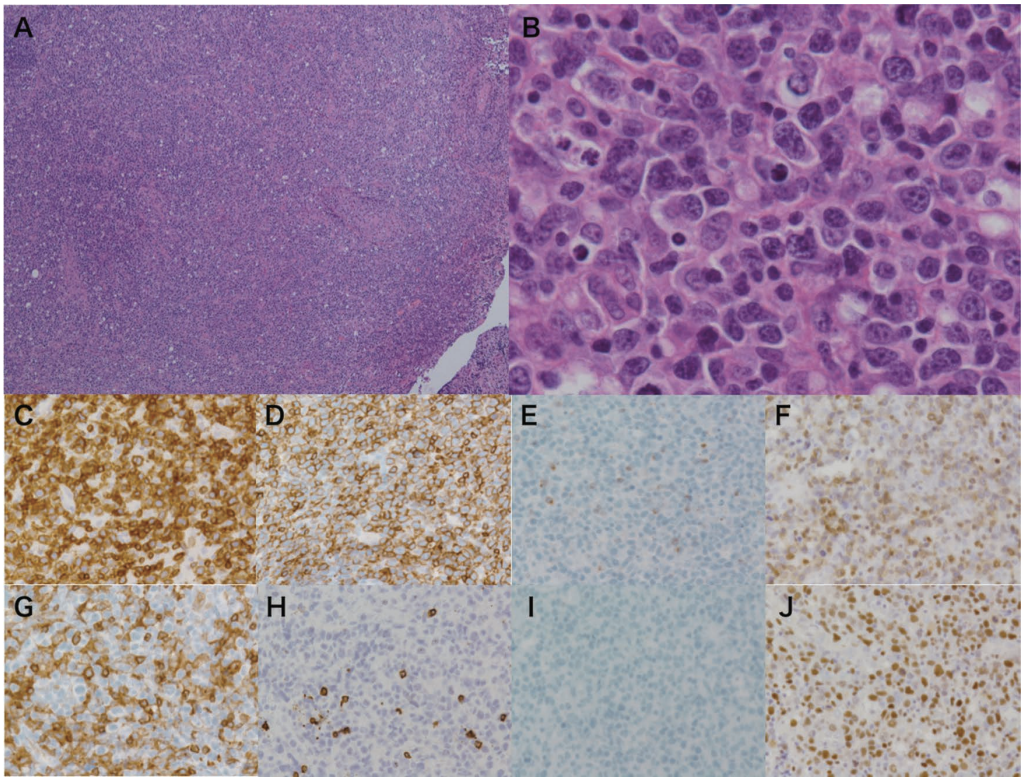

Fig. 2. Morphological and immunohistochemical findings. Light microscopic images of a present case. Lower magnification of the lymph node biopsy showed destroyed lymph-node architecture with diffuse infiltration of atypical cells (A). Higher magnification showed medium-to-large sized atypical lymphoid cells infiltration (B). (Hematoxylin-eosin stain, ×40 [A] and ×400 [B]). Immunohistochemical findings showed the atypical cells were positive for CD3 (C), CD8 (D), TIA-1 (E) and Granzyme B (F), and negative for CD4 (G), CD20 (H) and CD56 (I). EBER-ISH (J) revealed positivity for the atypical cells (C-J, ×400).

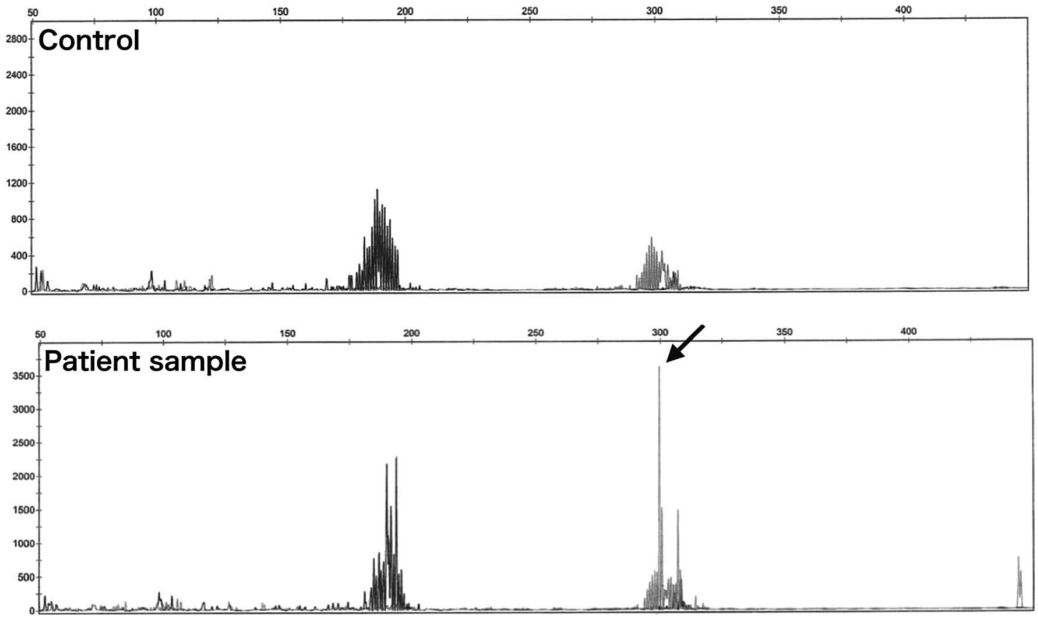

Fig. 3. To confirm T-cell receptor (TCR)-β gene rearrangement, we performed polymerase chain reaction. Analysis of TCR-β gene rearrangement shows a clonal.

Discussion

This is the first report of systemic EBV-positive TCL that occurred in an adult patient who was treated with a second-generation TKI (nilotinib). The cause of systemic EBV-positive TCL in childhood is thought to be EBV infection of T cells and lack of sufficient EBV-specific T cells, which could lead to inadequate elimination of EBV, resulting in virus per-

sistence in T cells [10]. Since most primary EBV infections occur in childhood, the median age of systemic EBV-positive TCL of childhood cases is 12.7 (±10.6) years [5]; which substantiates the fact that occurrence in an adult patient (>20 years old) is rare. However, the present patient was old, similar to previous adult cases of systemic EBV-positive TCL[6-9].

Middle aged or older adult cases of systemic EBV-positive TCL and EBV-positive nodal peripheral TCL should be differentially diagnosed[11-14], because the clinical features at diagnosis and pathological characteristics are similar to those of systemic EBV-positive TCL in childhood. Therefore, it is difficult to distinguish from systemic EBV-positive TCL of childhood in a clinical setting. Retrospective studies of EBV-positive nodal TCL have not investigated sufficient anti-EBV antibody patterns and EBV viral load in peripheral blood; some of these cases should be nominated as systemic EBV-positive TCL, not EBV-positive nodal TCL.

In the present case, the patient had a past history of EBV infection, but a high EBV viral load was observed at diagnosis, and the lymphoma cells expressed cytotoxic molecules. From these clinical and pathological findings, the diagnosis of systemic EBV-positive TCL is more plausible in this case.

The mechanism of EBV infection of T cells in patients with CAEBV or systemic EBV-positive TCL in childhood remains unclear. However, there are several hypotheses. For instance, the TGF-β1 codon 10 C allele plays a role in the development of EBV-related diseases, and the IL-1α −889 C allele may be involved in EBV-related disease[15]. In addition, an especially important hypothesis has reported that the T cells infected by EBV could constantly reproduce (first mechanism), and most EBV-infected T cells are excluded by their host immune mechanism, but some of them escape (second mechanism), and CAEBV or systemic EBV-positive TCL of childhood finally develops (third mechanism)[10]. The second mechanism is thought to be due to congenital factors. However, in the present case, the patient was too old at onset of systemic EBV-positive TCL to have congenital factors. The possibility of involvement of acquired factors is higher in this case. In addition, CML was treated with a TKI (nilotinib) for two years. Studies have shown that TKIs act as immunosuppressive agents[16,17], and several studies have shown hepatitis B reactivation in CML patients receiving TKIs because of the inhibition of T-cell activation and proliferation by TKIs[18]. In a similar fashion, in the present case, there might have been inhibition of T-cell activation and proliferation by the TKI (nilotinib), which led to a lack of sufficient T-cells specifically inhibiting EBV, reactivation of EBV, production of EBV-infected T cells (first mechanism), and insufficient elimination (second mechanism), resulting in systemic EBV-positive TCL (third mechanism).

The development of EBV-positive lymphoma has been described in a patient with chronic phase CML[19,20]. EBV-positive T-cell malignancies should be considered if CML patients exhibit fever and multiple lymphadenopathy during TKI treatment.

Conclusion

Although systemic EBV-positive TCL of childhood has been thought to develop only in childhood, the present report describes a case of middle-aged or older adult. A TKI might have been involved in the middle-aged or older adult onset of systemic EBV-positive TCL as an immunosuppressive agent. HSCT seems to be a valuable treatment option for middle-aged or older adult onset of systemic EBV-positive TCL.

Further studies are needed to address the relationship between TKI treatment and EBV reactivation regarding the pathogenesis of systemic EBV-positive TCL.

Conflicts of Interest

The authors declare that there are no conflicts of interest associated with this report.

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チロシンキナーゼ阻害薬で治療中の慢性骨髄性白血病患者に発症した Systemic Epstein-Barr virus-positive T-cell lymphoma

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Systemic Epstein-Barr virus（EBV）-positive T-cell lymphoma（TCL）は小児期に多いが，稀に成人でも発症する．今回，成人慢性白血病（CML）に対しチロシンキナーゼ阻害薬（TKI）で加療中の患者に発症した EBV-positive TCL を経験した．CML に対しニロチニブ（TKI）で 2 年間加療が行われ，分子生物学的寛解の状態であった．入院 2ヶ月前より頸部リンパ節腫脹，感冒様症状がみられ，末梢血の単核球中に EBV の高い増殖を認めた．リンパ節生検で，CD8 陽性の異型リンパ球に EBV の感染が確認された．全身での EBV の再活性化，EBV 陽性 T 細胞性リンパ腫の所見から，systemic EBV-positive TCL と診断した．化学療法後の造血幹細胞移植が本症例において有効であった．TKI は T 細胞の免疫応答を阻害する報告があり，本症例で systemic EBV-positive TCL の発症に関与した可能性がある．

