Elderly-onset systemic Epstein–Barr virus-positive T-cell lymphoma of childhood

To the Editor,

Systemic Epstein–Barr virus (EBV)-positive T-cell lymphoma of childhood (STCLC) is a life-threatening disease in children and young adults. It is characterized by the clonal proliferation of EBV-infected T cells with an activated cytotoxic phenotype, and it is prevalent in East Asia and Latin America. It can occur shortly after primary acute EBV infection or in chronic active EBV infection (CAEBV). It has rapid progression, with multiorgan failure, sepsis, and death, usually within days to weeks. Neoplastic cells typically lack atypia and have CD2+, CD3+, CD56−, and EBER+ phenotypes, with the expression of cytotoxic molecules. Most secondary to acute primary EBV infection cases are of the CD8+ phenotype. Herein, we report a case of a 68-year-old woman with highly aggressive mature T-cell lymphoma, which possessed clinical features of STCLC.

A 68-year-old Japanese woman had a fever, sore throat, and general malaise over several weeks. These symptoms had resolved once but deteriorated later and led her to admission. She had no previous episodes of hydroa vacciniforme-like syndrome, hypersensitivity to mosquito bites, and persistent hepatitis or fever. Lymphadenopathy, hepatosplenomegaly, and rash were not observed. Laboratory findings showed anemia, thrombocytopenia, and elevated levels of liver enzymes, lactate dehydrogenase, and ferritin (Supporting Information: Table S1). On the peripheral blood smear, 10% abnormal lymphocytes were observed (Supporting Information: Figure S1), and this increased to 79% with marked leukocytosis 6 days after admission (Supporting Information: Table S1). Viral capsid antigen (VCA)-IgG, VCA-IgM, early antigen (EA)-IgG, and EA-IgA titers were 1280, <10, 10, and <10-fold, respectively. EBV nuclear antigen (EBNA)-IgG titer was 10-fold in the fluorescent antibody method and 2.8 in the enzyme immunoassay. The EBV-DNA load in the peripheral blood mononuclear cells fraction was 1.67 × 10⁶ copy/µg DNA. Computed tomography revealed mild hepatosplenomegaly, and cervical, axillary, liver hilar, and para-aortic lymph nodes were slightly swollen, but none were larger than 10 mm.

We tried an axillary lymph node biopsy and obtained the soft tissue around there. Pathological findings of that soft tissue and bone marrow revealed infiltration of abnormal cells, most of which were EBER+, LMP-1+, and EBNA-2−, and of CD3+, CD4−, CD8+, CD19−, CD56−, and perforin1+ phenotypes (Figure 1). The cells were positive for monoclonal rearrangement of the T-cell receptor (TCR) genes by polymerase chain reaction. In addition, flow cytometric in situ hybridization assay also showed that EBER+ mononuclear cells were positive for CD3, CD8, HLA-DR, and TCRγδ, and negative for CD4, CD16, CD20, CD56, and TCRαβ (Supporting Information: Figure S2). The DNA extracted from the bone marrow specimen was analyzed for targeted gene sequencing of 377 recurrently mutated genes in lymphoid neoplasms, but no significant somatic mutations were identified. In addition, we evaluated the integrity of the EBV genome of the bone marrow specimen using targeted-capture sequencing of the entire EBV genome, which showed substantial intragenic deletion of 157 490 bp in size (NC_007605:7835–165324).

Her clinical condition rapidly deteriorated despite receiving cyclophosphamide, doxorubicin hydrochloride (hydroxydaunorubicin), vincristine sulfate (Oncovin), and prednisone (CHOP) therapy, and she died on day 44 after admission due to lymphoma. Based on clinical, morphological, and immunophenotypic features, we diagnosed her with elderly-onset STCLC.

EBV plays an essential role in the oncogenesis of lymphomas. The revised 2016 World Health Organization (WHO) lymphoma classification recognizes the following EBV+ T-/NK-cell lymphomas: extranodal NK/T-cell lymphoma, nasal type (ENKTCL); aggressive NK-cell leukemia (ANKL); STCLC; and primary EBV-positive nodal T-/NK-cell lymphoma as a provisional entity. In addition, CAEBV is also included in the WHO classification.

Differentiating the present case from other EBV+ T-/NK-cell lymphomas was challenging. Considering the patient’s leukemic and fulminant presentation, ANKL is one of the most important differential diagnoses. However, neoplastic cells showed CD3+ and CD56− phenotypes in this case and monoclonal TCR gene...
rearrangements were positive. These results indicated that neoplastic cells were not derived from NK cells. Subsequently, we differentiated primary EBV+ nodal peripheral T-/NK-cell lymphomas. By definition, primary EBV+ nodal peripheral T-/NK-cell lymphomas show nodal presentation, and the neoplastic cells are pleomorphic large to medium-large cells with anaplastic morphology, which are different from those observed in the present case. In addition, the neoplastic cells lacked atypia, which is a morphological feature of STCLC. It is also difficult to differentiate STCLC from CAEBV based only on morphological features. Our case lacked a history of persistent infectious mononucleosis-like symptoms. In addition, cases developing in the setting of CAEBV revealed a CD4+ or a CD4+/CD8+ mixed phenotype, whereas the neoplastic cells in our case were positive for CD8. Based on these features, we excluded CAEBV and diagnosed her with elderly-onset STCLC.

The mechanism of STCLC development in the present case remains unclear. Previous case series have reported that patients similar to ours had serology results suggestive of prior infection and lacked apparent immunodeficiency, consistent with our case. They suspected that senility might play a role in STCLC occurrence. However, we examined the EBV latency patterns of neoplastic cells using immunohistochemical staining; the results showed a type-II latency pattern corresponding to that of a healthy virus carrier. This is different from a type-III latency pattern, which indicates severely impaired cellular immunity, seen in EBV+ diffuse large B-cell lymphoma (DLBCL), which is related to immunosenescence resulting from aging.

The genetic mechanism of STCLC is not well defined owing to the lack of comprehensive genomic studies. Okuno et al. reported recurrent mutations in 29% of CAEBV samples, and these genes were also mutated in ENKTCL. These results suggest a potential pathological relationship between CAEBV and ENKTCL. However, targeted gene sequencing of the DNA in the present case did not reveal any significant somatic mutations.

Targeted-capture sequencing of the entire EBV genome showed a massive intragenic deletion. Intragenic deletions in the BamHI A rightward transcript microRNA cluster region or essential lytic genes have been identified in CAEBV, ENKTCL, and EBV+ DLBCL, whereas no deletions in either IM or post-transplant lymphoproliferative disorder have been reported. The association between intragenic EBV deletions and EBV-associated neoplastic proliferation has been reported in a xenograft model.

In conclusion, we diagnosed this patient with an elderly-onset STCLC based on clinical, morphological, and immunophenotypical features, except old age. STCLC can develop in the elderly Asian population and should be considered a differential diagnosis of aggressive T-/NK-cell lymphoma. Prompt detection of EBV-infected CD8+ abnormal T cells without atypia can lead to early diagnosis and intervention for elderly-onset STCLC.

AUTHOR CONTRIBUTIONS
Masashi Nishikubo collected the data and wrote the manuscript. Nobuhiro Hiramoto supervised manuscript writing, editing, and review. Hiroharu Imoto provided the clinical information and comments. Daisuke Yamashita and Hironori Haga provided pathological information and comments. Yoshitaka Sato, Yusuke Okuno, and Hiroshi Kimura provided information on the genetic analysis of EBV and their comments. Yasuhi Nannya and Seishi Ogawa provided information on somatic mutations in lymphoma cells and their comments. Nobuhiro Hiramoto and Takayuki Ishikawa coordinated the project and edited the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTEREST
The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT
Not applicable.

FIGURE 1  Biopsy of the soft tissue around the left axillary lymph node: (a) Hematoxylin and eosin staining (×40) with diffuse lymphoid infiltration. (b–f) Immunohistochemistry staining (×40) showing that the tumor cells are of CD3+ (b), CD4– (c), CD8+ (d), EBER+ (e), and perforin1+ (f) phenotypes.
ETHICS STATEMENT
Performing a target sequence analysis of the patient's genome was approved by the institutional review board (IRB) in Kobe City Medical Center General Hospital (KCGH) and Graduate School of Medicine, Kyoto University. Performing a target sequence analysis of the infecting EBV was approved by the IRB in KCGH and Nagoya University Graduate School of Medicine. Informed consent was obtained from the patient.

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SUPPORTING INFORMATION
Additional supporting information can be found online in the Supporting Information section at the end of this article.