HIV-associated Peripheral T-cell Lymphoma with a Cytotoxic Phenotype

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Abstract

Most human immunodeficiency virus (HIV)-related lymphomas are of B-cell origin, and the T-cell type is very rare. We experienced a Japanese case of HIV-associated peripheral T-cell lymphoma (HIV-PTCL). Sudden intestinal hemorrhage necessitated emergent surgical resection of the small intestine, in which an ulcerative lesion was detected. A histopathological examination revealed large tumor cells in the base of the ulcer, which were immunohistochemically CD30+, CD56+, granzyme B+, CD3+ (focally), CD4-, CD8- and EBER+. A diagnosis of PTCL, not otherwise specified, was therefore made. The differential diagnosis and significance of Epstein-Barr virus infection are also herein discussed.

Key words: human immunodeficiency virus (HIV), acquired immune deficiency syndrome (AIDS), AIDS-related lymphoma, peripheral T-cell lymphoma (PTCL)

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Introduction

Lymphoma is the most common disease in patients with acquired immune deficiency syndrome (AIDS)-defining malignancy (1, 2), and the incidence of non-Hodgkin lymphoma (NHL) is 60-200 times higher in human immunodeficiency virus (HIV)-positive patients (3). The majority of HIV-associated lymphomas have a B-cell phenotype, including Burkitt’s lymphoma and diffuse large B-cell lymphoma, as well as Hodgkin lymphoma (3). Since the introduction of highly active anti-retroviral therapy (HAART), the risk of developing B-cell lymphoma has decreased dramatically in patients with AIDS. In contrast, cases of HIV-associated T-cell lymphoma have been reported less frequently (4, 5). Epidemiological studies have shown the rate of T-cell lymphoma in patients with HIV-associated non-Hodgkin lymphoma to be 1.4-3% (6, 7).

We herein present a rare Japanese HIV-positive case of peripheral T-cell lymphoma—not otherwise specified (PTCL-NOS) with a cytotoxic phenotype. There was some difficulty in determining the lymphoma subtype due to the presence of atypical pathological findings, which may have been related to dysregulation of the lymphoid immune system by HIV infection. The patient’s clinical course was very aggressive, and he died within two months of clinical onset.

Case Report

A 50-year-old Japanese man presented at our hospital with a high-grade fever and abdominal pain. His past history was unremarkable, although his sexual behavior was unknown. A physical examination revealed redness on the left back and tenderness in the left upper abdomen. Neither the liver nor spleen were palpable, and no peripheral lymph nodes were palpable. Laboratory data showed elevated levels of serum AST (71 U/L), ALT (122 U/L), LDH (524 U/L), CRP (3.18 mg/dL), ferritin (2,367.1 ng/dL) and soluble interleukin-2 receptor (1,100 U/mL). HIV-1 antibodies were positive, and HIV-1 infection was later confirmed on Western blotting. The HIV viral load was 100,000 copies/mm³ and the CD4 cell count was 135 cells/mm³. The patient was subsequently diagnosed with AIDS due to the existence of esophageal candidiasis detected at another hospital. A computed tomography (CT) scan showed splenomegaly measuring 140 mm in the largest dimension, as well as a left adre-
We experienced a rare Japanese case of HIV-associated PTCL-NOS. Lymphoma is one of the most common AIDS-defining illnesses, and NHL remains one of the initial manifestations of AIDS (2). Most AIDS-related lymphomas are high- or intermediate-grade B-cell lymphomas. In contrast, cases of HIV-associated T-cell lymphoma have been reported less frequently (4, 5). However, the relative risk of peripheral T-cell lymphoma in the HIV population has been shown to be 24-fold higher than that observed in the general population (6). According to reviews of HIV-PTCL, there is a male predominance (approximately 80%), with a median age at diagnosis of approximately 38 years. In addition, the median CD4 cell count is approximately 150 cells/mm³, and the average HIV viral load is approximately 300,000 copies/mm³. With regard to subtypes, PTCL-NOS is most frequently reported, followed by anaplastic large cell lymphoma (ALCL), NK/T-cell lymphoma and angioimmunoblastic T-cell lymphoma (AITL) (4). We ultimately diagnosed the present case as PTCL-NOS with a cytotoxic phenotype. The lesion in the small intestine was interpreted to be a typical tumor lesion formed in the intestinal wall in patients with PTCL-NOS. Three days after the operation, the patient died due to shock and respiratory distress. A needle necropsy confirmed tumor invasion of the spleen.

Discussion

We experienced a rare Japanese case of HIV-associated PTCL-NOS. Lymphoma is one of the most common AIDS-defining illnesses, and NHL remains one of the initial manifestations of AIDS (2). Most AIDS-related lymphomas are high- or intermediate-grade B-cell lymphomas. In contrast, cases of HIV-associated T-cell lymphoma have been reported less frequently (4, 5). However, the relative risk of peripheral T-cell lymphoma in the HIV population has been shown to be 24-fold higher than that observed in the general population (6). According to reviews of HIV-PTCL, there is a male predominance (approximately 80%), with a median age at diagnosis of approximately 38 years. In addition, the median CD4 cell count is approximately 150 cells/mm³, and the average HIV viral load is approximately 300,000 copies/mm³. With regard to subtypes, PTCL-NOS is most frequently reported, followed by anaplastic large cell lymphoma (ALCL), NK/T-cell lymphoma and angioimmuno-
blastic T-cell lymphoma (AITL). One case of enteropathy-associated T-cell lymphoma (EATL) has been reported. Approximately 70% of patients exhibit extranodal involvement, including that of the bone marrow, head and neck, lungs and/or gastrointestinal tract. TCR gene rearrangement is detected in half of cases, and the median survival is six to 12 months (4, 5).

It is noteworthy that the present patient with PTCL demonstrated a cytotoxic phenotype and EBV positivity. A cytotoxic granule expression and EBV infection have been proposed to be poor prognostic factors of PTCL-NOS (8, 9). Three cases of HIV-PTCL with a cytotoxic phenotype have been previously reported. In all three cases, the neoplastic cells were positive for CD3 and CD8 and negative for CD30 and EBER, different from that observed in the present case (10). EBV has been reported to be present in approximately 40% of HIV-related lymphomas and 78% of lesions of HIV-PTCL, including cutaneous T-cell lymphomas (3, 5). However, the role of the EBV status as a prognostic factor and its implications for lymphomagenesis in patients with HIV-PTCL have not been clarified (4, 5).

Making the differential diagnosis of peripheral T-cell lymphoma subtypes is sometimes difficult, even for experts, as exemplified in the present case. In HIV-positive cases, atypical findings can be observed, which makes the diagnostic process even more difficult. Immune dysregulation and dysfunction due to HIV infection may account for the histological modifications noted in such cases. In the present case, we were particularly careful regarding the differential diagnosis among the possibilities of PTCL-NOS, ALCL, EATL, Hodgkin lymphoma and NK-cell lymphoma. Differentiating the present case from ALCL was difficult, as the phenotypes were nearly identical to those of ALCL. Typically, tumor cells in patients with ALCL show a solid and cohesive growth pattern and are consistently negative for EBV (11). We finally ruled out ALCL according to the sporadic and diffuse spread of the tumor and positivity for EBER. Perez et al. reported that 33% of HIV-associated ALCL cases are EBER-positive, suggesting that there are some ambiguities in the HIV-PTCL classification (12). Differentiating the lesion in the present case from EATL was also difficult. However, the lack of atypical intraepithelial cells in the mucosal tissue adjacent to the lesion and the overall rarity of tumor cells in the mucosal tissue, with confinement of the tumor cells to the ulcer base, did not support a diagnosis of EATL (13). The existence of systemic tumor lesions in multiple sites other than the small intestine also may have had a negative impact on categorizing the present case into this subtype. Conducting flow cytometric analyses of CD103 is important for diagnosing EATL. However, the limits of the

Figure 2. Immunohistochemical features of the tumor. The tumor cells were positive for CD30 (A), granzyme B (B) and EBER (C), partially positive for CD3 (D) and negative for CD8 (E) and CD4 (F).
Figure 3. Evaluation of the TCR-β gene rearrangement between Vβ and Jβ2 based on a PCR analysis. Upper row: Positive control. Middle row: Bone marrow sample of the patient. Lower row: Negative control. The arrow indicates a monoclonal peak for the rearranged TCR-β gene.

sampling method prevented us from performing flow cytometry. In contrast, differentiating from NK-cell lymphoma was possible given the phenotypes observed in the present case. Furthermore, Hodgkin’s lymphoma was ruled out based on the negativity for PAX5 and positivity for granzyme B.

The prevalence of HIV/AIDS in Japan has been estimated to be approximately 0.02%, which is much lower than that observed in the US (0.4%). However, the cumulative number of HIV/AIDS cases is certainly increasing, and the diagnosis and management of HIV-associated lymphoma, including the rare variant of HIV-PTCL, will be among the critical problems to be resolved in Japan in the near future (2). The present case and previous reports suggest that patients with HIV-PTCL display a highly aggressive clinical course (4, 5). Although we were unable to administer chemotherapy or anti-viral therapy in the present case due to the patient’s serious general condition, these treatments may improve the prognosis of HIV-PTCL. Further studies are needed to establish a strategy for treating this characteristic lymphoma.

The authors state that they have no Conflict of Interest (COI).

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References