CD3- and CD4-Positive Plasmablastic Lymphoma: A Literature Review of Japanese Plasmablastic Lymphoma Cases

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Abstract

Plasmablastic lymphoma (PBL) is a very rare and recently-described subtype of diffuse large B-cell lymphoma. A maxillary tumor in an 84-year-old HIV-negative Japanese man was referred. The biopsied specimen showed a diffuse proliferation of mature plasma cells, expressing CD3 (+), CD4 (+), CD20 (-), CD138 (+) and EBER (+) by immunohistochemistry. He was diagnosed as a plasmablastic lymphoma; radiation therapy (RT) was started, but the response to the RT was only a partial response. To our knowledge, this is the first report of a patient with PBL expressing CD3 and CD4.

Key words: plasmablastic lymphoma, Japanese, CD3

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Introduction

Plasmablastic lymphoma (PBL) is a recently-described subtype of diffuse large B-cell lymphoma. It has its highest incidence in HIV-positive individuals, predominantly males. PBL may also be associated with other immunodeficiency states, including advanced age and post-transplant lymphoproliferative disorders (1-6).

PBL is characterized by diffuse growth of large tumor cells with a high MIB-1 proliferation index, the presence of immunoglobulin heavy (IgH)-chain gene rearrangement, and expression of the plasma cell-associated antigens CD38 and CD138. Typically, PBL lacks expression of leukocyte common antigen, CD19, and CD20. Positivity for Epstein-Barr virus (EBV)-encoded RNA (EBER) is frequently observed (1).

We describe the case of PBL, which interestingly expressed CD3 and CD4, and review the literature of Japanese cases.

Case Report

An 84-year-old Japanese man was referred to our hospital in 2008 due to a two-month history of left face pain and inadaptation of a denture. On physical examination, the left parasnasal area of his face was swollen and his left upper gingiva was partially swollen with a tumor. His peripheral blood count was within normal range. Biochemical analysis revealed the following: C-reactive protein 2.70 mg/dL, lactate dehydrogenase 167 IU/L, BUN 41 mg/dL, and creatinine 2.33 mg/dL. Hypergammopathy and monoclonal gammopathy were detected neither in urine nor in serum. The patient was HIV negative. Even though the tumor cells...
expressed the T cell markers, CD3 and CD4 by IHC, results of IgH rearrangement indicated B cell lymphoma, and the diagnosis of PBL was established.

Computed tomography (CT) showed a soft tissue mass that infiltrated the left nasal cavity and upper oral cavity (Fig. 1). Bone marrow aspiration and biopsy were negative for infiltration of lymphoma cells by light microscopy and flow cytometry. He was Stage IIA and the international prognostic index was low-intermediate. After informed consent, the patient chose to receive involved-field radiation therapy (RT) of 30 Gy/20 fractions and limited local field RT of 20 Gy/10 fractions (total 50 Gy) and had a partial response to the RT. Three months after the completion of RT, a right chest wall tumor was newly found, suggesting lymphoma infiltration.

**Histopathology, immunohistology, in situ hybridization, and flow cytometry**

Histopathological analysis revealed diffuse proliferation of mature plasma cells having a round nucleus, intermingled with large-sized cells with higher nuclear to cytoplasmic (N/C) ratio were intermingled (Fig. 2a, b). On immunohistochemistry (IHC), the tumor cells were negative for B cell markers including CD10, CD20 (Fig. 2e), CD38, CD79a, and PAX-5, but were positive for the T cell markers, CD3 (Fig. 2c) and CD4 (Fig. 2d). They were also positive for plasma cell markers, CD138 (Fig. 2f) and MUM-1. As other markers that are often used for IHC to diagnose lymphoma, Bcl-2, CD56, and TdT were negative, but Bcl-6 was positive. The MIB-1 labeling index was high, and the tumor cells were strongly positive on in situ hybridization with an EBER probe (Fig. 2g). The flow cytometric study of the biopsied specimen did not reflect the actual lymphoma cells.

**PCR**

At first, clonality analysis of IgH chain was performed with primer recognizing not only FR2 but also FR3 region; semi-nested PCR using FR3A and LJH for the first PCR and FR3A and VLJH for the second PCR, as described previously (7, 8). To analyze clonality of T cell receptor β chain, multiplex PCR assays were performed, as described previously (9).

PCR of the IgH chain showed a discrete band, indicating IgH rearrangement (Fig. 3), but PCR of T cell receptor (TCR) beta (V beta/J beta 1, 2, V beta/J beta 2, D beta/J beta) showed no amplification, indicating no rearrangement.

**Discussion**

We reported the first Japanese patient with PBL, and it expressed CD3 and CD4, and it arose in an 84-year-old, HIV-negative Japanese patient. Interestingly, this case heterotropically expressed CD3 and CD4. The pathological findings of the present case seemed to resemble pyothorax-associated lymphoma (PAL), which usually arises from chronic inflammation (10, 11). PAL is often associated with EBV infection, and it also frequently expresses T-cell antigen. However, the present patient did not have a medical history of chronic inflammation of sinusoids. Heterotropic expression of T-cell antigen in B-cell lymphoma is frequently associated with EBV infection with or without chronic inflammation.

Our case was interesting and difficult to diagnose because it expressed pan-T cell antigens, CD3 and CD4, as detected by IHC. And this case is the first report of CD3 and CD4 positive PBL. CD3 positivity by IHC is used as a pan-T marker, namely, CD3-positive lymphoma generally means T-cell lymphoma. The monoclonal antibody for CD3, clone F7.2.38 (DAKO), which we use, recognizes the cytoplasmic domain of the epsilon chain, and stained at least membrane and cytoplasm of lymphoma cells in this case.

Several studies on aggressive CD3-positive B-cell lymphoma were reported (11, 13-18). PAL has peculiar clinicopathological features, and some cases express CD3 and other T cell antigens (11). Aggressive CD3-positive B cell lymphoma cases are often EBER-positive (11, 16, 17) as in the present case. EBV may interfere with the PAX-5 gene,
Figure 2. Histological and immunohistochemical photographs of the biopsied tumor. a. Hematoxylin and Eosin staining, original magnification×100. b. Hematoxylin and Eosin staining, original magnification×400. c. Anti-CD3 (original magnification×400). d. Anti-CD4 (original magnification×400). e. Anti-CD20 (original magnification×400). f. Anti-CD138 (original magnification×400). g. EBER (original magnification×400). Photographs show diffuse proliferation of large cells that are positive for CD3, CD4 (weak), CD138, and EBER and negative for CD20, which indicates a plasmablastic lymphoma. In figure 1-c, d, arrows indicate epithelial cells(→) and normal T cells(⇒), CD3 and CD4 are stained in the serial section, and CD3 and CD4 coexist on the same lymphoma cells. Compared to the normal T cells, positivities for CD3 and CD4 of lymphoma cells are weaker than normal T cells. And epithelial cells are negative for CD3 and CD4.
which is the master gene throughout B cell development from pro-B to the mature B cell stage. PAX-5 expression was negative in our case. Loss of PAX-5 may cause de-differentiation to the immature lymphoid cell and lead to the development of lymphoid malignancy (19, 20).

The possibility of extraosseous plasmacytoma (21) was also considered. As a differential diagnosis, plasmacytoma is the most difficult to distinguish from our case. EBV is not normally harbored in normal plasma cells and neoplastic plasma cells in immunocompetent individuals (22). Thus, plasmacytomas do not express EBER, and therefore plasma cytoma was ruled out in this case. However, recently, EBER-positive plasmacytoma was reported (22). The definition of PBL is still confusing. The clinical course of the present case followed the typical clinical course of lymphoma, but not plasmacytoma.

From the results of a literature review, we found 9 Japanese cases with PBL among the studies published in Japanese (23-31) (Table 1). Considering these patients along with the present patient, their ages ranged from 33 to 84 years (median, 59 years) with male dominance. As to the background disease of PBL, only one patient (10%) was HIV-positive. However, in Western countries the majority (81%) of cases arise in the setting of HIV infection (6).

Prognoses were also reported in nine cases; three cases were alive with complete response (CR) and the other six died or had refractory cases. PBL is considered to be a highly aggressive lymphoma and the prevalence of disease-related death was 59.6% over a mean period of 10.4 months from diagnosis (6, 32). Interestingly, case 9 underwent surgery only but has survived without recurrence for more than two years. The clinical course of PBL varies and standard therapies for PBL have not yet been developed.

We reported CD3- and CD4-positive PBL arising in an HIV-negative patient. Its clinicopathological features were very unique. To our knowledge, this is the first report of patient with PBL expressing CD3 and CD4. We hope that, with the accumulation of clinicopathologic data of PBL cases, we will be able to elucidate the mechanism(s) involved in the development of PBL, to confirm the most suitable treatment.

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References


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