



Bone Marrow Involvement of Epstein-Barr Virus-Positive Large B-Cell Lymphoma in a Patient with Angioimmunoblastic T-Cell Lymphoma

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Dear Editor,

Angioimmunoblastic T-cell lymphoma (AITL) is the second most common subtype of peripheral T-cell lymphoma, accounting for approximately 15–20% of the cases [1]. It is a systemic lymphoproliferative disorder that typically presents with constitutional symptoms, generalized lymphadenopathy, hepatosplenomegaly, skin rash, and immunological disturbances [2]. AITL may be accompanied by either polyclonal or clonal proliferation of B lymphocytes, which seems to be triggered by Epstein-Barr virus (EBV) infection [3].

Although AITL accompanying B-cell proliferation is not rare, the occurrence of large B-cell lymphoma in AITL patients has rarely been reported [2]. Here, we describe bone marrow (BM) involvement of EBV-positive large B-cell lymphoma in a patient who was diagnosed as having AITL. Informed consent was obtained from the patient for this study, and ethical approval was waived by the institutional review board.

In December 2016, a 73-year-old man presented with a one-month history of enlarged cervical lymph nodes, fever, and general weakness. Enlargement of multiple lymph nodes and hepatomegaly were detected by physical examination and computed tomography. A biopsy of the left cervical lymph node (level V)

was performed, and the patient was diagnosed as having AITL. Immunohistochemical (IHC) stain results showed small to medium-sized lymphocytes positive for CD3 and CD4 and negative for CD8 and CD20 (Fig. 1).

Complete blood count parameters were as follows: hemoglobin, 10.7 g/dL; platelets, $64 \times 10^9/L$; and white blood cells, $18.6 \times 10^9/L$, with 2% myelocytes, 1% metamyelocytes, 3% band neutrophils, 61% segmented neutrophils, 17% lymphocytes, 4% monocytes, 1% eosinophils, and 11% atypical lymphoid cells (Fig. 2A). BM aspiration failed owing to extensive fibrosis. BM biopsy showed hypercellular BM with about 95% cellularity, which was mostly comprised of large neoplastic lymphoid cells. The neoplastic lymphoid cells were diffusely infiltrated in an interstitial pattern with extensive fibrosis (Fig. 2B). IHC analysis revealed that the large neoplastic lymphoid cells were mostly positive for CD20 but not for CD3, CD4, or CD8 (Fig. 2C and 2D). *In situ* hybridization for EBV-encoded RNA (EBER) showed nuclear positivity in the large neoplastic B lymphoid cells, although only less than 10% were positive. The final BM diagnosis was BM involvement of large B-cell lymphoma, and the patient was subsequently treated with a CHOP (cyclophosphamide, hydroxyl doxorubicin, vincristine, and prednisone) regimen.

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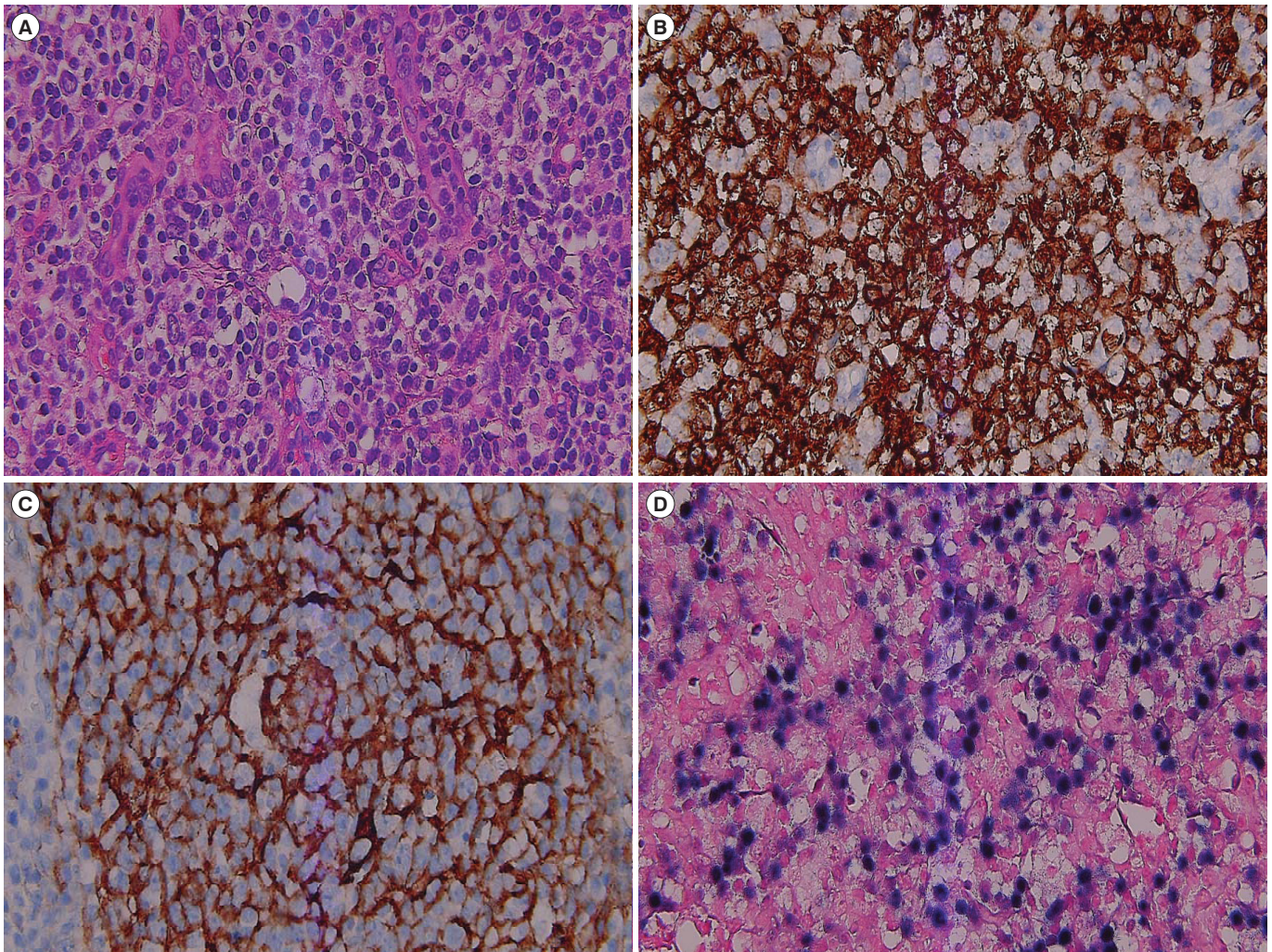


Fig. 1. Pathological findings of cervical lymph node biopsy. (A) Polymorphic infiltrate of small- to medium-sized lymphocytes with clear cytoplasm, distinct cell membrane, and mild cytological atypia, and increased high endothelial venules (H&E stain, $\times 400$). (B) Positivity for CD4 in small- to medium-sized lymphocytes and (C) for CD21 in irregularly expanded meshwork of follicular dendritic cells (IHC stain, $\times 400$). (D) Strong positivity of Epstein-Barr Virus (EBV) in the nuclei of immunoblasts (EBV *in situ* hybridization, $\times 400$).

BM is commonly involved in AITL, with an incidence of more than 50% of AITL cases [4]. The composition of the BM infiltrate is usually similar to that in involved lymph nodes, consisting of perivascular collections of medium- to large-sized T lymphocytes, with either clear or pale cytoplasm, and increased number of B lymphocytes of variable sizes [5]. However, clonal B-cell proliferation, such as large B-cell lymphoma or plasma cell myeloma, is a rare event in AITL. Previously, only lymph nodal [6], tonsillar [7], cutaneous [2], upper leg [2], or cerebellar [8] involvement of large B-cell lymphoma accompanying AITL has been reported. To the best of our knowledge, this is the first report of diffuse BM infiltration in large B-cell lymphoma with AITL.

EBV latent membrane protein 1 or EBER is detected in cases

of large B-cell lymphoma with AITL; therefore, EBV is considered to play a role in the pathogenesis of large B-cell lymphoma in patients with AITL [2]. In our case, EBER was detected in both lymph node and BM.

The discrepancy between lymph node biopsy findings and pathological features of BM can pose a diagnostic challenge. Although there are various clinical features of AITL and large B-cell lymphoma, AITL typically presents as advanced-stage disease and severe immunodeficiency; however, most patients with large B-cell lymphoma, especially diffuse large B-cell lymphoma (DLBCL), are asymptomatic [1]. When DLBCL is first diagnosed but the clinical symptoms are not correlated with DLBCL, caution must be exercised because AITL could be the original cause.

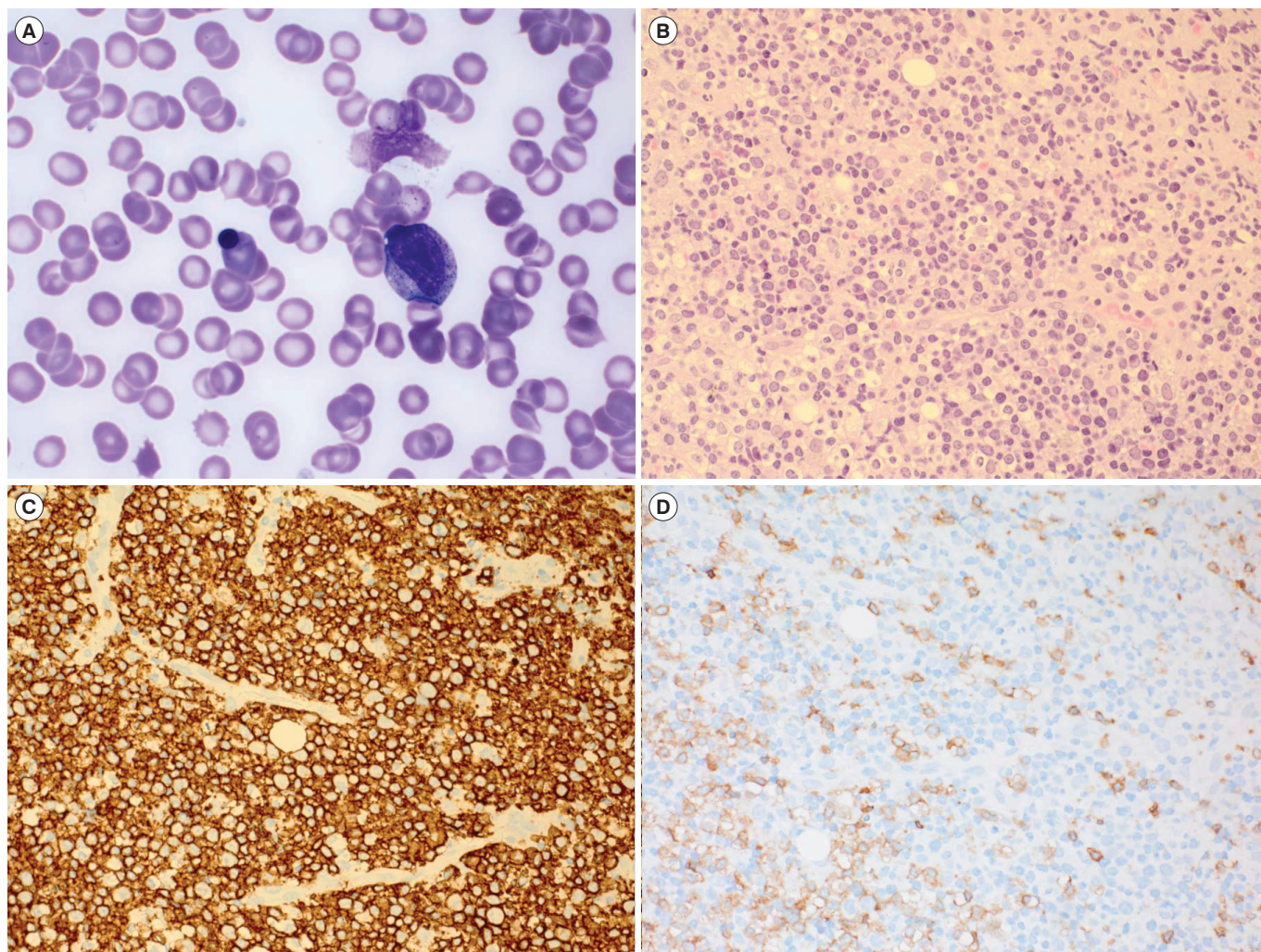


Fig. 2. Peripheral blood and bone marrow findings. (A) Leukoerythroblastic reaction (Wright stain, $\times 1,000$). (B) Interstitial infiltration of large lymphoid cells with background fibrosis (H&E stain, $\times 400$). (C) Large neoplastic lymphoid cells with CD20 positivity and (D) CD3 negativity (IHC stain, $\times 400$).

Although some studies have reported that rituximab can suppress EBV-positive B-immunoblasts in AITL and improve the prognosis when combined with a standard CHOP regimen [9], a recent study revealed no clear benefit of rituximab in targeting intratumoral B-cells in AITL [10]. Although the effect of rituximab on clonal B-cells in AITL remains controversial, it is important to determine the presence of clonal B-cells in patients with AITL because this can indicate treatment with an R-CHOP (rituximab and CHOP) regimen. Therefore, BM examination should be considered in patients with AITL to determine the possibility of BM involvement of clonal B-cell proliferation.

In conclusion, BM involvement of AITL should be diagnosed with caution because of the possibility of clonal B-cell proliferation despite T-cell malignancy.

Authors' Disclosure of Potential Conflict of Interest

No potential conflicts of interest relevant to this article are reported.

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