Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.6702-20
Intern Med 60: 2495-2497, 2021
http://internmed.jp

【 CASE REPORT 】

Age-related Epstein-Barr Virus-associated Lymphoproliferative Disorder Masquerading as Systemic Lupus Erythematosus

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Abstract:
Age-related Epstein-Barr virus (EBV)-positive B-cell lymphoproliferative disorder (LPD) occurs in elderly patients without immunodeficiency. An 81-year-old woman without any known immunodeficiency was examined for fever, rash, arthritis, thrombocytopenia, pleural and pericardial effusions, lymphadenopathy, and positive autoantibodies, which satisfied the classification criteria for systemic lupus erythematosus (SLE). However, a lymph node biopsy revealed EBV-LPD, and she was diagnosed with age-related EBV-LPD. In young individuals, EBV infection is a major differential diagnosis of SLE, but to our knowledge, this is the first reported case of age-related EBV-LPD mimicking SLE. We should therefore consider EBV-related disorders in the differential diagnosis of SLE even in elderly individuals.

Key words: Epstein-Barr virus, lymphoproliferative disorder, systemic lupus erythematosus

(Intern Med 60: 2495-2497, 2021)
(DOI: 10.2169/internalmedicine.6702-20)

Introduction

Systemic lupus erythematosus (SLE) can be mimicked by various disease conditions, including infection and malignancy (1). In teenagers and young adults, Epstein-Barr virus (EBV) infection is a major differential diagnosis of SLE because EBV-associated infectious mononucleosis and SLE are known to have similar symptoms and clinical manifestations (2). However, in elderly individuals, it is not easy to associate lupus-like manifestations with EBV-related disorders. Age-related EBV-associated B-cell lymphoproliferative disorder (LPD) occurs in elderly individuals without any known immunodeficiency. We herein describe a case of age-related EBV-LPD masquerading as SLE, which to our knowledge, has never been described in any previous reports. Our case highlights the importance of considering EBV-related disorders in the differential diagnosis of SLE, even in elderly individuals.

Case Report

An 81-year-old woman had been well until the day before admission, when fever (body temperature, >39.0℃) and general malaise developed. The next day, she visited the emergency department of our hospital and therefore was admitted.

On examination, her body temperature was 40.5℃. Patchy erythema was observed in the bilateral lower extremities. She had limb edema and swollen knees. Laboratory investigations revealed elevated levels of liver enzymes (aspartate aminotransferase, 122 U/L; alanine aminotransferase, 39 U/L; γ-glutamyl transpeptidase, 46 U/L), lactate dehydrogenase (743 IU/L), and C-reactive protein (87.3 mg/L), and hypocomplementemia (C3, 69.0 mg/dL; C4, 5.0 mg/dL). The anti-nuclear antibody test result was positive (80 folds, homogeneous pattern). Autoantibody tests revealed positivity for anti-DNA (9.6 IU/mL), anti-RNP (70.7 index), anti-cardiolipin immunoglobulin (Ig) G (52 U/mL), anti-

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Received: November 11, 2020; Accepted: December 23, 2020; Advance Publication by J-STAGE: February 15, 2021
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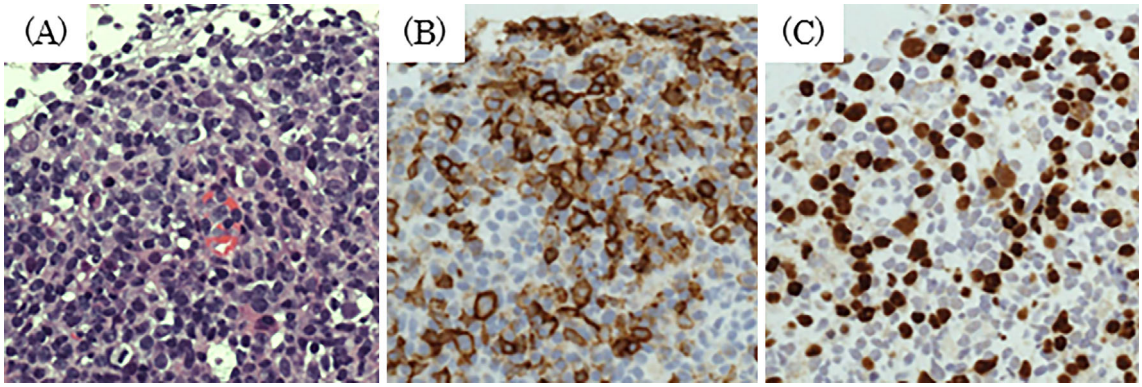

Figure. **Histological findings of the axillary lymph node biopsy. (A) Proliferation of heterogeneous cells, including lymphocytes and plasma cells, is observed in the interfollicular space (Hematoxylin and Eosin staining, ×400 magnification). (B) Diversely sized B cells are observed (CD20, ×400 magnification). (C) The proliferating cells tested positive for Epstein-Barr virus-encoding small RNA in situ hybridization (×400 magnification).**

cardiolipin IgM (8 U/mL), and anti-prothrombin antibodies (31 U/mL). The serum soluble interleukin-2 receptor level was also elevated (4,169 U/mL). Computed tomography revealed pericardial effusion, pleural effusion, ascites, axillary, mediastinal, periaortic and inguinal lymph node enlargements, and non-segmental pulmonary infiltrates suggestive of organizing pneumonia. The presentation of the patient was compatible with late-onset SLE and satisfied the classification criteria for SLE (3). She did not have a history of pregnancy complications or thrombosis, and thus did not meet the classification criteria for antiphospholipid syndrome. We performed a lymph node biopsy to rule out any mimickers of SLE, including malignancy and infection. Axillary lymph node biopsy showed proliferation of diversely sized CD20-positive B cells in the interfollicular space (Figure). The proliferating cells tested positive for EBV-encoding small RNA (EBER) in situ hybridization. A karyotype analysis did not show any chromosome abnormalities. The results of a flow cytometric analysis were as follows: CD2, 56%; CD3, 64%; CD4, 26%; CD8, 34%; CD5, 60%; CD19, 19%; CD20, 16%; kappa, 10%; rambda, 12%; negative for CD10, CD30, and CD56. These histological findings were compatible with those of EBV-LPD. EBV-positive diffuse large B-cell lymphoma (DLBCL) was considered unlikely because the general structure of the lymph node was well preserved and proliferating B cells were highly variable in their morphological appearance. According to the Ann Arbor staging classification and Lugano classification, the patient was classified as stage IIIB and stage III, respectively, although a bone marrow examination was not performed in this case. Antibodies to EBV in the patient's serum demonstrated a previous infection pattern, and EBV-DNA was detected in peripheral blood (6.8×10^3 copies/mL).

Considering the histological findings, we decided to follow-up the patient without any immunosuppressive treatment. Her skin rash, swollen knees, lymphadenopathy, pericardial effusion, pleural effusion, ascites, and elevated C-reactive protein level all resolved within three weeks after admission, and she was therefore discharged from the hospital. She was followed up in the outpatient office without any relapse. Her serum autoantibodies spontaneously decreased during follow-up (anti-DNA, from 9.6 to <2.0 IU/mL; anti-RNP index, from 70.7 to 26.6; anti-cardiolipin IgG, from 52 to 21 U/mL), and EBV-DNA in her peripheral blood also decreased (from 6.8×10^3 to 6.5×10^2 copies/mL). Her self-limiting clinical course was not suggestive of DLBCL, and it was compatible with EBV-LPD. As she had no known immunodeficiency, including acquired immunodeficiency syndrome (AIDS), transplantation, and immunosuppressive drugs, we confirmed the final diagnosis of age-related EBV-LPD.

Written informed consent was obtained from the patient for this case report.

Discussion

EBV-LPD has been reported in immunosuppressed patients with primary immune deficiency, AIDS, or iatrogenic immunosuppression (4). Recently, an increasing number of reports have also described EBV-LPD in elderly individuals, which is called age-related EBV-LPD (4-6). The neoplastic condition of this disease is now incorporated into the revised 4th edition of the 2017 World Health Organization Lymphoma Classification as EBV-positive diffuse large B-cell lymphoma, not otherwise specified (7). The postulated pathogenic mechanism of age-related EBV-LPD is immunosenescence. Age-related EBV-LPD shows a wide morphological variation and it includes both reactive and neoplastic conditions (4). Shimoyama et al. divided age-related EBV-LPD into three subtypes, i.e. 1) a polymorphous subtype, 2) a large cell lymphoma subtype, and 3) a reactive lymphoid hyperplasia (RLH) subtype (8, 9). The RLH subtype is characterized by the expansion of the interfollicular area with the diffuse infiltration of transformed lymphocytes and immunoblasts, together with varying numbers of plasma cells and plasmacytoid cells. EBV-harboring cells are dis-

tributed in hyperplastic germinal centers and interfollicular area. The RLH subtype is characterized by a self-limiting clinical course. The morphological findings and clinical courses of our case were thus quite compatible with the RLH subtype. To be precise, an analysis of immunoglobulin heavy chain (IGH) rearrangement should be considered to distinguish the RLH subtype from other subtypes. Since we did not perform an IGH rearrangement analysis, close monitoring is warranted to rule out the possibility of the other two types, which are associated with a worse prognosis.

Interestingly, it has been suggested that EBV infection might be an environmental trigger of SLE (10). Epidemiologically, almost all pediatric patients with SLE had EBV infection, while the prevalence of EBV infection in the control population was approximately 70% (2). In addition, patients with SLE are reported to have increased titers of anti-EBV antibodies, increased frequencies of EBV-infected peripheral B cells, high viral loads in the peripheral blood mononuclear cells, and increased frequencies of EBV-DNA elevation in serum (2, 11). The proposed mechanism by which EBV promotes SLE pathogenesis includes defective T cell responses to EBV infection in patients with SLE, molecular mimicry between the EBNA1 protein and the SmB and Ro60 proteins, and associations between the EBNA2 protein and SLE risk alleles (2, 10, 12). Considering the close association of EBV and SLE, it seems reasonable to assume that EBV-LPD can present with SLE-like manifestations.

Our case is associated with some limitations. First, a bone marrow examination was not performed in our case because the symptoms and laboratory abnormalities have already significantly improved at the diagnosis of EBV-LPD, which made us avoid invasive examinations and carefully follow up her clinical manifestations. Second, we did not examine the clonality of infiltrating B cells by an analysis of IGH rearrangement. In our institute, we make the diagnosis of EBV-LPD based chiefly on the morphological appearance, such as the preservation of the general lymph node structure and the heterogeneity and distribution of proliferating B cells, and thus, in the diagnosis of EBV-LPD, we do not routinely perform an analysis of IGH rearrangement to rule out EBV-positive DLBCL. As described above, however, an analysis of IGH rearrangement is helpful for determining the subtype of age-related EBV-LPD, and thus it should be considered in similar cases to better predict the prognosis.

In conclusion, age-related EBV-LPD is a great imitator of late-onset SLE. It should be noted that EBV-related disorders can present with lupus-like manifestations even in elderly individuals, because their clinical courses and treatment strategies are entirely different.

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

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