Epstein-Barr Virus-positive Diffuse Large B-cell Lymphoma of the Elderly Complicated by the Onset of Acute Myeloid Leukemia

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Abstract

We herein describe the case of a 62-year-old woman who presented with anemia and an 8-month history of weight loss. Bone marrow aspiration showed increased myeloblasts. The histopathology findings of biopsy specimens of the right cervical lymph node and intestinal mass indicated B-lymphoproliferative disorder (B-LPD) with Hodgkin lymphoma-like morphologic features and polymorphous diffuse large B-cell lymphoma (DLBCL), respectively. In addition, both types of lymphoma cells were positive for Epstein-Barr virus (EBV)-encoded small RNA-1. The patient was diagnosed with EBV-associated B-LPD and simultaneous acute myeloid leukemia (AML). This is the first case of a patient diagnosed with simultaneous EBV-positive DLBCL of the elderly and AML.

Key words: Epstein-Barr virus (EBV), EBV-positive diffuse large B-cell lymphoma of the elderly, acute myeloid leukemia

Introduction

Epstein-Barr virus (EBV) infection commonly occurs in early childhood, with EBV persisting in a small proportion of B-cells (1, 2). A spectrum of EBV-driven B-cell lymphoproliferative disorders (B-LPDs) occurs in immunosuppressed patients with primary immune deficiency, human immunodeficiency virus infection or iatrogenic posttransplantation immunosuppression and patients receiving other treatments, including methotrexate and tumor necrosis factor-α antagonists (3). It was recently recognized that defective immune surveillance for EBV may result in the development of EBV-positive B-LPDs in older individuals with no apparent immune deficiency (4), and this condition is now a provisional entity in the 2008 World Health Organization (WHO) classification: EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly (3). Host immunosuppression is determined by the patient’s clinical history, laboratory data and medication history. EBV-positive DLBCL of the elderly is a nosologic term based on the hypothesis that the pathogenesis of these two conditions is closely associated with immunologic deterioration or senescence caused by the aging process (5, 6). T-cell responses seem to be the most profoundly affected, and there is an accumulation of clonal CD8-positive T-cells with mature, memory cell phenotypes with diminished functionality (7).

Acute myeloid leukemia (AML), a heterogeneous clonal disorder of hematopoietic progenitor cells, is the most common malignant myeloid disorder in adults. The median age at presentation for patients with AML is 70 years. Genetic reprogramming of AML blasts renders them ineffective for generating mature red cells, neutrophils, monocytes and platelets. The principal sign of marrow failure is infection, one of the primary clinical features of AML, and is referred to as an immunocompromised state (8). Whether AML is an

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underlying disease of EBV-positive DLBCL in individuals with otherwise no apparent immune deficiency, however, is unknown.

We herein report the case of a patient with EBV-positive DLBCL simultaneously occurring with AML, in whom chemotherapy led to a remission of the AML, while the DLBCL continued.

Case Report

In November 2009, a 62-year-old woman complained of weight loss to her family doctor. She was diagnosed with a duodenal ulcer after undergoing a gastrointestinal endoscopic examination. At that time, the laboratory findings indicated mild anemia (hemoglobin, 11.3 g/dL) without other abnormalities. Her ulcer improved following the administration of a proton-pump inhibitor; however, it recurred after the medication was changed to an H2 blocker. Despite receiving these medications, the patient continued to lose weight, and the anemia did not improve. In July 2010, her blood cell count indicated normocytic anemia with white blood cell (WBC) and platelet counts within the normal ranges (hemoglobin: 8.8 g/dL, mean corpuscular volume: 97.2, WBC: 7.6×10^9/L with 42.7% neutrophils without blasts and platelet count: 215×10^9/L). In August, she was referred to the Japanese Red Cross Society Wakayama Medical Center due to the anemia and 8-month history of weight loss. She had been healthy until the onset of disease and had not received any immunosuppressant medications. She had no record of lymphadenopathy or WBC smear abnormalities before being admitted to our hospital. She had no antibodies for human T-cell leukemia virus type 1 or human immunodeficiency virus. The laboratory findings indicated anemia (hemoglobin, 9.6 g/dL), mild leukocytosis (WBC, 9.2×10^9/L with 38% neutrophils and 16% blasts), mild thrombocytopenia (platelet count, 109×10^9/L) and slightly elevated levels of lactate dehydrogenase (LDH, 286 IU/L) and soluble interleukin-2 receptor (3,212 IU/L). A smear preparation of the bone marrow revealed excessive blasts (56%) with maturation of the myeloid lineage without dysplasia. The patient’s leukemic cells were positive for myeloperoxidase staining, and a flow cytometric analysis revealed that the cells were also positive for CD13, CD33, CD10, CD15, CD21, CD34, CD56, CD246, and Granzyme B in a background of small lymphocytes that comprised a mixture of T- and B-lymphocytes with CD3-positive cells predominating over CD20-positive cells. An in situ hybridization analysis revealed that the RS-like cells were positive for EBER-1 (Fig. 1b). Southern blotting of lymph node cell-derived DNA probed with the terminal repeats of EBV showed monoclonal bands. A cyto genetic examination of a lymph node cell suspension showed the following: 52, XX, -5, -8, +11, add (12)(p11.2), -13, -15, -21, -22, +11mar[1]/46,XX[19]. Quantitative polymerase chain reaction (PCR) for EBV DNA was not very high (50 copies/10^6 cells) in the peripheral blood lymphocytes (PBL). The anti-EBV anti-viral capsid antigen IgG (×320) and anti-early antigen IgG (×20) titers were elevated. Because the two different histological findings had surface antigen CD20 and CD79a and negative for CD3, CD5, CD10, CD19, Bcl-6 and LMP-1 in common, and polymorphism is a morphologic characteristic of EBV-related B-LPD, we considered a diagnosis of EBV-related B-LPD.

Following treatment with a standard dose of cytarabine (100 mg/m^2×7 days) combined with daunorubicin (50 mg/m^2×1-5 days) (8), the patient achieved a complete remission (CR) (Fig. 2). She underwent high-dose cytarabine chemotherapy (9) as postremission therapy. Because a repeat CT scan showed a persistent ileocecal mass, she was treated with R-CHOP (rituximab [R], cyclophosphamide [CY], doxorubicin [ADR], vincristine [VCR] and prednisolone [PSL]) chemotherapy for B-LPD. The pancytopenia period was prolonged after R-CHOPE chemotherapy; thus, we performed bone marrow aspiration. The smear findings of the bone marrow aspiration revealed that there was hemophagocytic lymphohistiocytosis and that the AML was in CR. Although quantitative PCR for EBV DNA was low (<20 copies/10^6 cells) in the PBL, the ileocecal mass persisted with elevated levels of soluble interleukin-2 receptor (1,585 IU/L) and ferritin (2,127 ng/mL). Based on these findings, the pancytopenia was assumed to be caused by lymphoma-associated hemophagocytic lymphohistiocytosis. Chemotherapy with R-CHOPE [R-CHOP and etoposide (ETP)] was promptly initiated for EBV-related B-LPD and hemophagocytic lymphohistiocytosis (10) in January 2011. After the first cycle of R-CHOPE therapy, the level of bone marrow histiocytes decreased and the pancytopenia improved; however, EBV-related B-LPD remained evident on CT and 18F-FDG PET/CT. The patient refused to undergo allogeneic stem cell transplantation (allo-SCT) for AML and EBV-related B-LPD, and the chemotherapy was continued. The
Figure 1. Histological findings of the biopsy specimens of the right cervical lymph node and ileocecal mass. a. Biopsy of the ileocecal mass. A, The histopathology of the biopsy specimen of the ileocecal mass showed monomorphic and dense proliferation of lymphoid cells with medium- to large-sized nuclei [Hematoxylin and Eosin (H&E) staining]. B, Immunohistochemical staining with anti-CD20 monoclonal antibodies. C. In situ hybridization for Epstein-Barr virus-encoded RNA (EBER). The EBER expression was identified in the lymphoid cell nuclei. b. Biopsy of the right cervical lymph node. A, A biopsy of the ileocecal mass showed scattered mononuclear or binuclear giant cells with abundant cytoplasm in a background of small lymphocytes (H&E staining). B, Giant cells were CD20-positive (immunohistochemical staining with anti-CD20 monoclonal antibodies). C. The EBER expression was identified in the giant cell nuclei.

The ileocecal mass continued to be detected on CT following the administration of induction therapy and consolidation therapy for AML, one cycle of R-CHOP therapy and four cycles of R-CHOPE therapy, and the patient was therefore treated with one cycle of R-EPOCH [ETP, PSL, VCR, ADR and CY (11)] as salvage therapy (Fig. 2). An 18F-FDG PET/CT scan performed after these therapies revealed significant regression of the lymph nodes and duodenal mass with a weak effect on the ileocecal mass, and the EBV-related B-LPD was determined to be in partial remission. She refused additional chemotherapy and showed no relapse of AML or progression of the EBV-related B-LPD for 11 months. The
iliococcal mass gradually enlarged, however, and colonic perforation occurred in May 2012. The patient underwent emergency exploratory surgery, which revealed ileocolic perforation with disseminated intravascular coagulation in July 2012. At the time of her death, the AML was still in CR.

Figure 2. Clinical course of the patient with EBV-positive diffuse large B-cell lymphoma of the elderly with acute myeloid leukemia. The time course of the intravenous infusion of DNR-AraC (cytarabine [Ara-C], daunorubicin [DNR], gray bar), high-dose AraC (black blank bar), rituximab (black arrow), CHOP (cyclophosphamide [CY], doxorubicin [ADR], vincristine [VCR], prednisolone [PSL]; black bold arrow) chemotherapy, CHOP-E (CY, ADR, VCR, PSL and etoposide [ETP]; gray bold arrow) chemotherapy and EPOCH (ETP, PSL, VCR, ADR, CY; black bar) surgery for perforation (gray arrow) is shown. WBC: white blood cells, LDH: lactate dehydrogenase, sIL2R: soluble interleukin-2 receptor. The EBV titers were based on a folic acid assay, except in a). Abbreviations: EBV VCA IgG: EBV viral capsid antigen immunoglobulin G, EBV EA IgG: anti-early antigen IgG against EBV. *The EBV titers were based on an enzyme-linked immunosorbent assay.

Discussion

We herein reported a case of EBV-positive B-LPD that simultaneously occurred with AML. A relationship between B-LPD and AML was considered in this case. The patient had no history of immune deficiency or immunosuppressant medications at disease onset, and we considered that the B-LPD had gone undiagnosed until the onset of AML. Furthermore, the EBV-related B-LPD remained after the CR of AML was obtained. This clinical history allowed us to conclude that the onset of AML was independent of the B-LPD and an exacerbating factor of the B-LPD. The AML may have made the latent B-LPD more obvious. Therefore, we considered that the B-LPD was EBV-positive DLBCL of the elderly based on the 2008 WHO classification.

EBV-positive DLBCL of the elderly is a disease group characterized by EBV-associated large B-cell lymphoma in the elderly without predisposing immunodeficiency. It is referred to by various other names in the literature, including “senile EBV-associated B-cell LPD,” “age-related EBV-associated B-cell LPD” and “EBV-associated B-cell LPD of the elderly” (1-6). Clinically, the disease may present with lymphadenopathy and is often extranodal, frequently involving the skin, gastrointestinal tract or lungs. These patients have a worse prognosis than those with EBV-negative DLBCL or EBV-positive classical Hodgkin’s lymphoma (CHL). More than half of patients with EBV-positive DLBCL of the elderly have a high or high-intermediate International Prognostic Index score. Disease onset usually occurs after 50 years of age; the median patient age is 71 years (range: 45-92 years), and the incidence increases with age. EBV-driven B-cell lymphoma is thought to be related to immunological deterioration or senescence in immunity, which is a part of the aging process (3, 5, 6). The details of the definition of predisposing immunodeficiency and the EBV reactivation mechanisms of the aging process remain unclear; however, a reduction in the T-cell repertoire is
thought to contribute to decreased immune surveillance. This appears to be the result of a decline in the capacity to generate a pool of new, naïve T-cells, which is compensated for by proliferation within the mature senescent memory cell pool. This results in a prevalence of oligoclonal T-cell populations in elderly subjects that are markedly restricted and deficient in their epitope-specific repertoire, rendering the host vulnerable (7, 12, 13). On the other hand, myeloid leukemic cells can be induced to differentiate into leukemia-derived dendritic cells (DCleu), regaining the stimulatory capacity of professional DCs while presenting the leukemic antigen repertoire. Stimulation with the DC/DCleu cell fraction favors the expansion of CD4-T cells, whereas stimulation with leukemic blasts predominantly gives rise to the expansion of CD8-T cells (14). In our case, the patient first suffered from EBV-positive DLBCL of the elderly, then from AML, which would be an additional load for the immune response under immunodeficient conditions. This is how the two diseases may be actualized. This case will help to elucidate the mechanisms of immunodeficiency in patients with EBV-positive DLBCL of the elderly.

Pathologically, EBV-positive DLBCL of the elderly is characterized by the proliferation of atypical large B-cells, including Hodgkin- or RS-like cells, and there is morphologic and metachromatic overlap with CHL and DLBCL (3, 5, 6). Dojcinov et al. reported the clinical features, histology, immunophenotype, EBER and clonality on PCR of the T-cell receptor gamma and immunoglobulin genes categorized in age-related EBV-positive B-cell lymphoproliferation in a Western population as follows: (1) reactive lymphoid hyperplasia, (2) polymorphic extranodal or (3) polymorphic nodal LPD and (4) DLBCL. They also postulated that the pathogenetic mechanism is immunosenescence, a complex spectrum of regressive changes that affect the immune system with aging, and T-cell clonal selection may occur locally as a result of a reaction to LPD (13). In our case, the biopsy results of the right cervical lymph node and intestinal mass revealed diagnoses of polymorphic nodal LPD with RS-like cells and DLBCL, respectively. Although the reasons for the different histologic findings among organs are unclear because there are no similar reports, there may be varying degrees of immunosenescence depending on the T-cells in the organ.

The current treatment for EBV-positive DLBCL of the elderly includes conventional chemotherapy, radiotherapy or both, with an overall response rate of 66% and a median survival of two years (6). The quantification of EBV-DNA in the plasma and peripheral blood mononuclear cells is a good indicator of both the response to treatment and overall survival in patients with EBV-associated diseases, such as Hodgkin lymphoma, hemophagocytic lymphohistiocytosis and extranodal NK/T-cell lymphoma, nasal type (15-17). We have not yet obtained data regarding the viral load and prognosis in patients with EBV-positive DLBCL; however, in our case, there may have been a relationship between the slow progression of the patient’s clinical course and the low viral load. Patients in a previous study received comparable treatment; however, due to the consultation nature of the series, the conclusions were limited regarding treatment efficacy. Because the presumed underlying pathogenetic mechanism of this disease is immunosenescence, possible management approaches include the restoration of immunologic control over EBV (13). In order to eliminate immunosenescence and reconstruct the immune system, as in other EBV-related lymphoproliferative disorders (18-20), we proposed allo-SCT as a therapeutic option for AML and EBV-positive DLBCL of the elderly to our patient. She refused treatment with allo-SCT, however, and we therefore continued the chemotherapy, although allo-SCT was a promising option for curing both diseases.

We herein reported a case of EBV-positive DLBCL of the elderly occurring simultaneously with AML. To our knowledge, this is the first report of a patient having both diseases simultaneously, and the case of EBV-positive DLBCL of the elderly exhibited two different histologic findings at onset. This case provides information regarding the underlying mechanisms of EBV-positive DLBCL of the elderly.

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

References

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