EBV-positive Reactive Hyperplasia Progressed into EBV-positive Diffuse Large B-cell Lymphoma of the Elderly over a 6-year Period

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Abstract:
A 70-year-old woman with lymphadenopathy was admitted to hospital in 2008. Lymph node biopsy showed reactive lymphoid hyperplasia (RH) with monoclonal proliferation of Epstein-Barr virus (EBV). Her lymphadenopathy regressed without treatment. In 2014, the patient presented with nasal obstruction because of a left nasal mass. She was diagnosed with EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly based on the examination of a biopsy specimen of the mass. The IgH rearrangement in the specimens from the 2008 and the 2014 revealed that they were genetically identical. This is the first report of RH progressing to DLBCL, and suggests that EBV-positive B-cells in RH lymph nodes predict the evolution to DLBCL.

Key words: EBV-positive reactive hyperplasia, EBV-positive diffuse large B-cell lymphoma, EBV-positive lymphoproliferative disorders

Introduction
Epstein-Barr virus (EBV) affects more than 90% of the adult population worldwide. Primary EBV infections in children are often asymptomatic, and EBV typically persists in an asymptomatic latent state in memory B-cells (1). Occasional reactivation from latency and virus production is triggered by environmental stimuli but tightly controlled by the immune system in healthy individuals. Suppression of the T-cell function by immunosuppressive agents or HIV infection, which usually plays a determinant role in controlling EBV-associated lymphoproliferative disorders (LPDs), increases the risk of EBV-positive B-cell LPDs (2-4). ‘EBV-positive diffuse large B-cell lymphoma (DLBCL) of the elderly’ is a provisional entity that was included in the 2008 World Health Organization classification of LPDs (5); the disease group is characterized by EBV-encoded small RNA-1 (EBER-1)-positive LPDs that occur in elderly individuals without predisposing immunodeficiency. It is also referred to by various other names, including “senile EBV-associated B-cell LPD”, “age-related EBV-associated B-cell LPD”, and “EBV-associated B-cell LPD of the elderly” (5-8). Dojcinov et al. (9) categorized age-related EBV-positive B-cell LPDs in a Western population as follows: (i) reactive lymphoid hyperplasia (RH), (ii) polymorphic extranodal, or (iii) polymorphic nodal LPD, and (iv) DLBCL; and reported the clinical features, histology, immunophenotype, EBER, and clonality of the T-cell receptor and immunoglobulin genes. Disease progression is rarely reported (9), but it may occur in stages of multi-step lymphomagenesis. We herein describe a case in which EBV-positive RH progressed to EBV-positive DLBCL of the elderly over a 6-year period.

Case Report
A 70-year-old woman with cervical lymphadenopathy was admitted to our hospital in 2008. A physical examination re-
revealed bilateral cervical and axillary lymphadenopathy. She had been healthy until the onset of disease. Laboratory findings revealed mild anemia (hemoglobin, 10.8 g/dL), and increased levels of soluble interleukin-2 receptor (sIL-2R; 1,854 IU/L); her lactate dehydrogenase (LDH) level was within the normal range (160 IU/L). The patient was HIV- antibody-negative. Her anti-EBV viral capsid antigen (VCA) IgG titer was elevated (1:2,560), and she was EBV nuclear antigen- positive (1:10), and anti-early antigen IgG- and EBV VCA IgM-negative. A biopsy of the right axillary lymph node revealed follicular hyperplasia with plasma cell infiltration. Tingible body macrophages were observed in the follicles, which were positive for CD20 and CD21, and negative for bcl-2. In situ hybridization revealed EBER-1-positive cells outside the follicles that were large and positive for CD20 and bcl-2, indicating that they were B cells. The plasma cells were considered polyclonal because no clear monotypic light-chain restriction for kappa protein was

Figure 1. The histological findings of the biopsy specimens from 2008 (right axillary lymph node) and in 2014 (left nasal mass). A: Biopsy of the right axillary lymph node. The biopsy specimen of the right axillary lymph node showed reactive patterns that included follicular hyperplasia [i: Hematoxylin and Eosin (H&E) staining; magnification: ×20]. Plasma cell infiltration and epithelioid granulomas were present in the paracortical area (ii: H&E staining; ×200). The cortex and paracortical area were positive for CD20 (iii: CD20-immunostaining; ×200), in situ hybridization revealed that the paracortical area was positive for Epstein-Barr virus-encoded RNA (EBER) (iv: ×200) and CD138 (v: CD138-immunostaining; ×200). B: Biopsy of the left nasal mass. The histopathological examination of the biopsy specimen of the left nasal mass showed the monomorphic and dense proliferation of large lymphoid cells accompanied by necrosis (i, ii: H&E staining; ×10, ×200). The large cells were positive for CD20 (iii: CD20-immunostaining; ×200). The expression of EBER was identified in the large cell nuclei (iv: ×200).
EBV is involved in the development of various types of lymphoproliferative disorders (LPDs), and then to monomorphic DLBCL. Other reports of these progressive states of EBV-positive LPDs are categorized into four different histological subtypes, the relationship among which is unclear. A previous report described one case of RH that progressed to EBV-positive classic Hodgkin lymphoma (9). This is the first case report of a patient with RH that progressed to EBV-positive classic Hodgkin lymphoma (9).

EBV-positive LPDs are categorized into four different histological subtypes, the relationship among which is unclear. A previous report described one case of RH that progressed to polymorphic nodal LPD, and two cases of RH that progressed to EBV-positive classic Hodgkin lymphoma (9). This is the first case report of a patient with RH that progressed to DLBCL. The progression was verified by a PCR to detect IgH rearrangement in both the axillary biopsy specimen from 2008 and the nasal mass biopsy specimen from 2014 using polymerase chain reaction (PCR) assays to confirm whether these two lesions were genetically identical. Both samples showed PCR products of identical size (single peak) (GeneScanning) (10) (Fig. 3).

**Discussion**

EBV-positive LPDs are categorized into four different histological subtypes, the relationship among which is unclear. A previous report described one case of RH that progressed to polymorphic nodal LPD, and two cases of RH that progressed to EBV-positive classic Hodgkin lymphoma (9). This is the first case report of a patient with RH that progressed to DLBCL. The progression was verified by a PCR to detect IgH rearrangement in both the axillary biopsy specimen from 2008 and the nasal mass biopsy specimen from 2014 using polymerase chain reaction (PCR) assays to confirm whether these two lesions were genetically identical. Both samples showed PCR products of identical size (single peak) (GeneScanning) (10) (Fig. 3).

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Phenomenon in EBV-positive LPDs. The findings of the present case suggest that further investigations might elucidate the mechanisms of multi-step lymphomagenesis in EBV-associated T/NK cells as well as B-cell lymphomagenesis. Our case provides evidence to support these hypothesized categories.

Age-related EBV-positive LPD is defined as an EBV-positive clonal lymphoproliferation that occurs in patients of >50 years of age with no known immunodeficiency (5, 12). Aging is thought to be a factor in immunosuppression. T-cell response dysregulation, the reduced output of new T-cells, the development of anergic memory cells, the loss of immunosurveillance, and deficient cytokine production, as well as limitations in the T-cell receptor repertoire are associated with immunosenescence (13). EBV-positive DLBCL was recently reported in young immunocompetent individuals (14, 15). Immune checkpoints of the programmed cell death 1/programmed cell death ligand-1 axis are dysregulated in young patients with EBV-positive DLBCL, similar to elderly patients (15, 16). These findings suggest that the downregulation of immune checkpoint receptors is one of the mechanisms of immunosenescence in these disorders. The findings of the present case suggest that further investigations might elucidate the mechanisms of multi-step lymphomagenesis in EBV-positive LPDs.

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

References


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