

Case Report

Systemic Epstein-Barr virus-positive T/natural killer-cell lymphoproliferative disorder: a case report and review of literature

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Abstract: Systemic Epstein-Barr virus-positive T/natural killer-cell lymphoproliferative disorder (EBV + LPD) has predominantly been observed among pediatric patients as a life-threatening condition. The present study presents a rare case of EBV + LPD in an adult with good outcome. This patient's history is more than 2 years and her condition was stable. She received 6 cycles of chemotherapy cyclophosphamide/doxorubicin/vincristine/prednisolone (CHOP). The evaluation was complete remission. The low levels of EBV-DNA in the peripheral blood may have potential benefit factor for the sensitivity to the chemotherapy and good outcome.

Keywords: Epstein-Barr virus, T/natural killer-cell, lymphoproliferative disorder

Introduction

Epstein-Barr virus (EBV) is a linear, double-stranded DNA virus that can cause both acute and chronic active infections. The primary infection generally occurs at an early age and is usually asymptomatic [1]. But infection in adolescents evokes a striking immune response such as infectious mononucleosis. Rare adults infected with EBV develop a life-threatening condition termed systemic EBV-positive lymphoproliferative disease (EBV + LPD) [2]. Affected patients usually have high levels of EBV DNA in the peripheral blood, or proliferation of EBV-encoded small RNA in tissues. Herein, we report an adult case of EBV + T/NK LPD characterized by extensive lymphadenopathy in head and neck and facial symptoms may with good outcome.

Clinical history

A 49-year-old female was admitted with rhinostegnosis for 2 years, swelling of eyes for more than 1 year, earplug and hoarseness for 9 months, right parotid was found enlarged for 3 months, and a mass of right lacteal gland was found 2 months ago.

On admission, her temperature was 36.3°C. Physical examination revealed swelling of blepharas with brown pigmentation, both parotids were enlarged, the right side was 4 × 3 cm. Leukocyte count was $3.7 \times 10^9/L$ (segmented neutrophils 75.10%, lymphocytes 12.60%), hemoglobin was 100 g/L, and platelet count was $174 \times 10^9/L$. The serologic tests for EBV showed EBV viral capsid antigen (VCA)-IgA (+/-), EBV VCA-IgM (-), EBV VCA-IgG (-). EBV - DNA < 5000 copies/ml. The test of EBV - DNA < 5000 copies/ml in peripheral blood was unavailable. The flow cytometry showed in the peripheral blood 80.33% was CD3 expression, 28.49% was CD4 expression and 54.19% was CD8 expression, which is abnormal lymphocyte expression and conform to the Immunohistochemical (IHC) studies. A bone marrow biopsy did not show involvement. Magnetic resonance imaging (MRI) demonstrated multiple cervical lymphadenopathy, nasopharyngeal and paranasal sinus mucosa were thick (**Figure 1**), both parotids were enlarged (**Figure 2**), both blepharas and extraocular muscles were thickening (**Figure 3**), both mastoids had abnormal signals. The computer tomography (CT) showed interstitial pneumonitis and splenomegaly (**Figures 4 and 5**). After received 6 cycles of

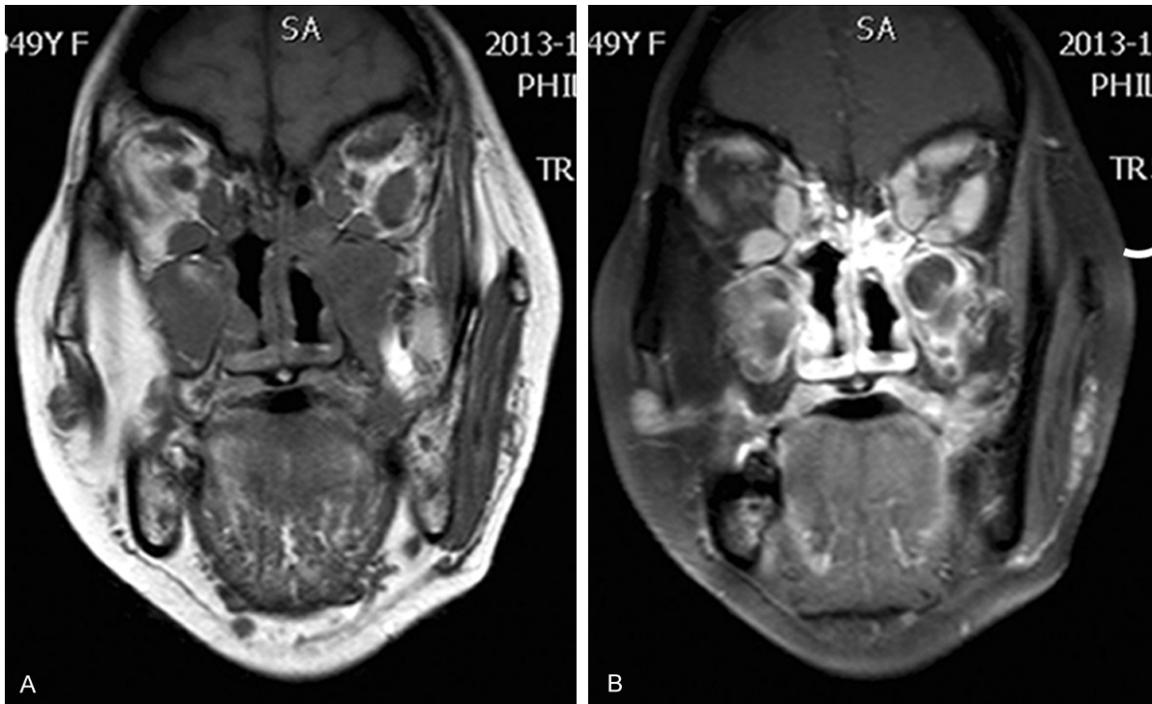


Figure 1. A. (T1W1), B. (Contrast-enhanced, T1W1): Extraocular muscles, nasal mucosal hypertrophy maxillary sinus mucosal hypertrophy with exudative lesions.



Figure 2. A. (T2W1), B. (Contrast-enhanced, T1W1): Both parotid glands enlargement, lymphadenopathy in retropharyngeal space and submandibular space.

chemotherapy cyclophosphamide/doxorubicin/vincristine/prednisolone (CHOP). Her symp-

toms and signs had resolved, and her PET (positron emission tomography)-CT showed normal.

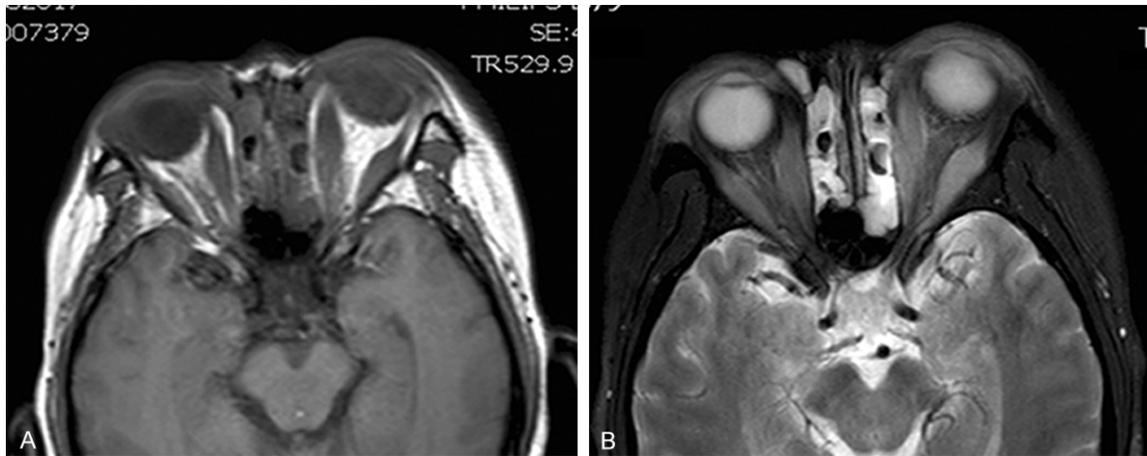


Figure 3. A. (T1W1), B. (T2W1): Both blepharals, extraocular muscles are thickening.



Figure 4. CT: Interstitial pneumonitis.



Figure 5. CT (Contrast-enhanced): Splenomegaly.

The evaluation was complete remission. She discharged from the hospital. On regular bases the patient has been followed and still there is no clinical nor laboratory evidence of relapse.

Pathological findings

Right lacteal gland was taken 2 strips, measuring 0.8×0.1 cm and 1.0×0.1 cm. Microscopically (Figure 6A), the interstitial substance showed prominent lymphoid infiltration with rare heterocysts and no necrosis. Immunohistochemical (IHC) studies showed the infiltrated lymphocytes were composed predominantly of T-cell lineage, with CD3 ϵ (+) (Figure 6B), CD56 (-). Staining for CD4 and CD8 showed that the infiltrate was CD4 (-), CD8 (+) (Figure 6C), the infiltrated lymphocytes expressed cytotoxic molecules, such as TIA-1 (Figure 6D). In situ hybridization (ISH) for EBV using the EBV-encoded RNA-1 (EBER1) probe showed up moderate number of positive cells (Figure 6E). These EBER (+) cells were mostly small, and

were scattered instead of forming clusters. The patient had left inferior turbinate biopsy 17 months ago and laryngeal biopsy 6 months ago. They showed the same results. The histological appearance was diagnostic of systemic EBV-positive T/natural killer-cell lymphoproliferative disorder.

Discussion

EBV+ T/NK-LPD is characterized by fever, lymphadenopathy, hepatitis, vasculitis, interstitial pneumonitis, uveitis or tubulointerstitial nephritis [3-5]. EBV is intimately associated with the pathogenesis. The central to these syndromes is a clonal systemic proliferation of EBV-infected cytotoxic T or NK cells. It is seen more in younger children and Asian [6]. This disease can be evolving into a more aggressive neoplasm or as a benign or borderline condition with a high risk of evolution into a cytotoxic

EBV+ T/natural killer-cell lymphoproliferative disorder

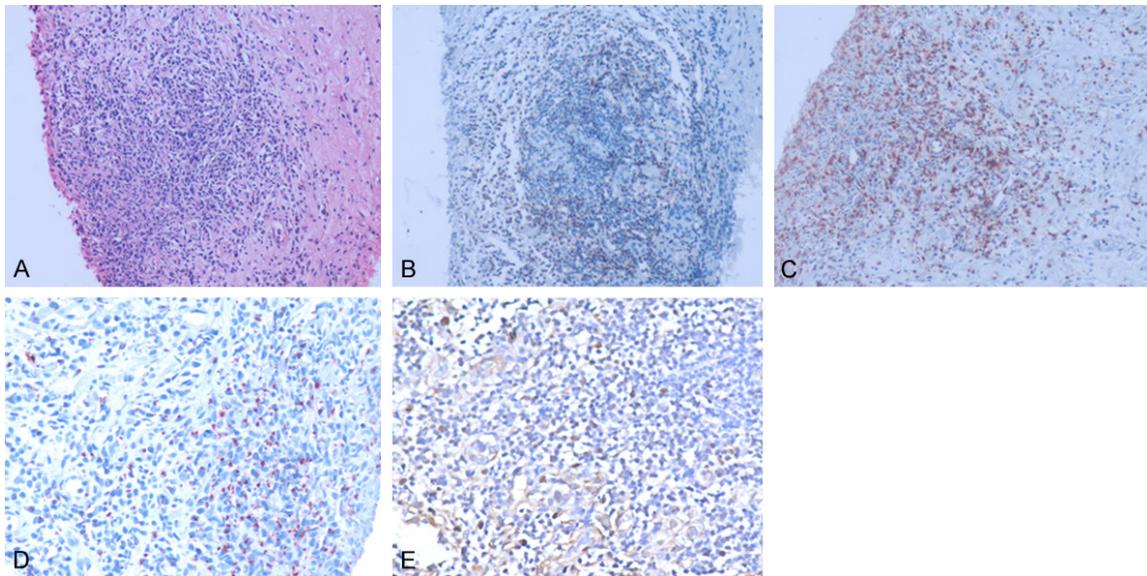


Figure 6. The interstitial substance showed prominent lymphoid infiltration with rare heterocysts and no necrosis (A, hematoxylin and eosin, $\times 40$). The infiltrated lymphocytes of lacteal gland are predominantly CD3 + (B, immunohistochemistry, $\times 40$) and CD8 + (C, immunohistochemistry, $\times 40$). Some lymphocytes are positive for TIA (D, immunohistochemistry, $\times 100$) and EBER (E, in situ hybridization, $\times 100$).

T-cell or NK-cell lymphoma. EBV-associated T and NK-cell LPD was first incorporated into the 4th World Health organization (WHO) classification of tumors of hematopoietic and lymphoid tissues, in which systemic EBV + T-cell LPD of childhood and hydroa vacciniforme-like lymphoma are proposed as distinct entities [7]. In 2008 acute and chronic EBV syndromes of T cells and NK cells were clarified to have a broad spectrum, in which hydroa vacciniforme (HV), HV-like lymphoma, severe mosquito bite allergy, and systemic EBV + T-LPD under an umbrella term of chronic active EBV disease (CAEBV) of T/NK-cell type. The treatments include chemotherapy and hematopoietic stem cell transplantation (HSCT). Although allo-HCT has been recognized as a promising strategy to eradicate residual disease and prevent relapse in pediatric CAEBV, treatment-related death is a problem [8, 9]. As mentioned by Kawa et al. [9], transplant survivors tended to receive non-myeloablative transplants. The therapeutic advantage has not been shown in adult cases.

Most patients with CAEBV have defective EBV-specific cytotoxic T cells, NK cells, and lymphokine-activated killer activity, which involve the defective production of several cytokines, such as interferon gamma and interleukin-1 [10]. The etiology of CAEBV remains unclear. The

exact role of EBV in the pathogenesis is still hypothetical, however, it is possible that defective EBV replication in T/NK cells and aberrant EBV-infected T/NK cell proliferation are major factors in the development of CAEBV. In our case, the patient's EBV-DNA in peripheral blood is low, but her several biopsies showed EBER (+) in the tissues. So, the low levels of EBV-DNA in the peripheral blood maybe a benefit factor to the outcome. The majority previously reported studies' eligibility criteria including high EBV load detected in peripheral blood at diagnosis, which may missed EBV-associated T/NK-LPD if EBV-infected cells failed to migrate into the peripheral blood. Therefore, prospective analysis with large samples involving this kind of patients is needed.

To the best of our knowledge no case reported the disease with extensive lymphadenopathy in head and neck and characterized by facial symptoms. The long term outcome in the majority of the previously reported patients was poor, and the disease followed a relatively refractory chemotherapy responsive course [11]. Compared to the other case reports, our patient's history is long and progress slowly. She was taken a "watch and wait" strategy for 2 years and remained well. She was sensitive to glucocorticoid. Kimura's [12] study showed that sex

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(female), onset age (≥ 8 years), liver dysfunction, splenomegaly, anemia and thrombocytopenia were significantly associated with mortality. Our patient, a mid-aged woman, who has anemia, splenomegaly and lymphadenopathy in head and neck, but she has low levels of EBV DNA in the peripheral blood and normal liver function, which may bring benefits to her outcome. She may have good outcome.

Disclosure of conflict of interest

None.

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