Orbital Epstein-Barr Virus-Positive Polymorphic B-Cell Lymphoproliferative Disorder in an Apparently Immunocompetent Woman

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Established Facts

- Epstein-Barr virus (EBV) infection is ubiquitous and results in latent gene expression in memory B-cells.
- Latent EBV gene expression can cause changes in oncogenes and transcription pathways, forming the basis for the development of EBV-associated lymphoproliferative disorders (EBV-LPDs).
- Four patterns of latent EBV gene expression have been described: types III, II, I, and 0.
- Type I and type II latency-associated EBV-LPDs can arise in anyone, but type III latency-associated EBV-LPDs are rare in the absence of immunocompromise.

Novel Insights

- We report a rare case of type III latency-associated EBV-LPD involving the lacrimal gland of a young woman with no identifiable immunodeficiency. The lesion regressed with limited therapy and has not recurred for over 2 years.
- This patient may have an underlying immunodeficiency resulting from subtle changes in T-cell physiology. Alternatively, chronic EBV infection may have contributed to her immune dysfunction through an unclear mechanism, possibly by causing a pathogen-specific exhaustion of T-cell effector functions.

Keywords

Epstein-Barr virus · Lymphoproliferative disorder · Orbital lesion · Lacrimal gland · Immunocompetent woman

Abstract

We report a rare case of Epstein-Barr virus (EBV)-positive polymorphic B-cell lymphoproliferative disorder (LPD) involving the lacrimal gland of a 28-year-old, apparently im-

munocompetent woman. She presented with a chief complaint of orbital swelling and tenderness and was found to have a lesion involving the right lacrimal gland and distal superior and lateral rectus muscles. Histology of the lesion revealed histiocytes with pleomorphic nuclei, reactive lymphocytes, and scattered cells that resembled the Reed-Sternberg (R-S) cells of classical Hodgkin lymphoma. The R-S-like cells were positive for PAX5 and CD30 and negative for CD15, supporting a diagnosis of polymorphic B-cell LPD. In

situ hybridization for EBV-encoded RNA demonstrated the presence of EBV. Most EBV-positive polymorphic B-cell LPDs are associated with immunodeficiency. However, the patient described is HIV-negative and has no identifiable defects in immunoglobulin levels or cell-mediated immunity. This raises the question of whether she has an underlying immunodeficiency resulting from subtle changes in T-cell physiology, or whether chronic EBV infection contributed to her immune dysfunction through an unclear mechanism. The orbital mass partially regressed with chemotherapy, and the patient has done well clinically with no recurrence of this EBV-LPD for over 2 years.

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Introduction

Epstein-Barr virus (EBV) is a double-stranded DNA lymphotropic herpesvirus that has been associated with numerous human malignancies. Infection is ubiquitous; over 90% of adults worldwide are seropositive [1]. Primary infection typically occurs in childhood and is asymptomatic, while occurrence in adulthood results in infectious mononucleosis in roughly one-third of the cases [2]. Infection spreads through oral transmission and proceeds from a lytic (productive) infection of the oropharynx to a persistent latent infection of memory B-cells [2].

Four patterns of latent EBV gene expression have been described: types III, II, I, and 0 [2]. Type III latency refers to EBV-infected naïve B-cells that express all of the latent genes: 6 Epstein-Barr nuclear antigens (EBNA 1, 2, 3A, 3B, 3C, and LP); 3 latent membrane proteins (LMP 1, 2A, and 2B), and 2 Epstein-Barr-encoded RNAs (EBERs) [2]. These cells enter the germinal center (GC) and proliferate, increasing the pool of EBV-infected cells. The resulting GC cells show a restricted EBV gene expression pattern (EBNA 1, the LMPs, and the EBERs), referred to as type II latency [2]. These GC cells then differentiate into memory B-cells, which express only EBNA 1 and the EBERs (type I latency) or just the EBERs (type 0 latency) [2].

Latent gene expression results in a state of chronic infection that can cause changes in oncogenes and transcription pathways, forming the basis for the development of EBV-associated lymphoproliferative disorders (EBV-LPDs) that range from non-neoplastic polymorphic B-cell infiltrates to fully malignant lymphoma [1–4]. Type I and type II latency-associated EBV-LPDs can arise in anyone. Type III latency B-cells are quite immu-

Fig. 1. CT scan showing the right lacrimal gland mass involving the anterior orbit.

Fig. 2. Histopathology shows Reed-Sternberg-like cells (arrows) scattered through an infiltrate of histiocytes and reactive lymphocytes (H&E, ×400).

nogenic and therefore are suppressed in normal individuals by regulatory and EBV-specific cytotoxic T-cells. Accordingly, type III latency-associated EBV-LPDs are rare in the absence of immunocompromise.

The following case report describes an EBV-positive polymorphic B-cell LPD, a lesion often associated with type III latency and immunocompromise, that arose in the orbit of an apparently immunocompetent woman.

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Fig. 3. The Reed-Sternberg (R-S)-like cells stain positive (brown) for B-cell markers PAX5 (**a**) and CD30 (**b**) by immunohistochemistry ($\times 400$). **c** The R-S-like cells (arrows) are CD15-negative, unlike true R-S cells in most classical Hodgkin lymphomas ($\times 400$). These findings are typical of polymorphic B-cell lymphoproliferative disorders associated with EBV. **d** In situ hybridization for Epstein Barr-encoded RNA (blue) demonstrating the presence of EBV ($\times 400$).

Case Report

A 28-year-old female presented with an 8-month history of swelling and tenderness in the right orbit. She had been diagnosed at an outside hospital with an EBV-LPD involving the right lacrimal gland and hard palate. The palate lesion was resolving with chemotherapy, but the orbital lesion persisted. During this time, she developed and recovered from an episode of pneumocystis pneumonia. Her clinical history also included 2 episodes of meningitis and several episodes of bronchitis during childhood. She was HIV-negative, her serum immunoglobulin levels were normal, and T-, B-, and NK-cell subset analysis revealed no defects in cell-mediated immunity. In addition, she had no history of transplantation, systemic malignancy, or treatment with immunosuppressive drugs.

On examination, there was a firm, tender, ovoid lesion in the superotemporal aspect of the anterior right orbit that was causing mechanical ptosis and reactive conjunctivitis. The remainder of the examination was unremarkable. Computed tomography demonstrated an enhancing soft-tissue mass in the right lacrimal gland

that involved the distal superior and lateral rectus muscles (Fig. 1). The mass was biopsied to exclude infection or malignant lymphoma.

Histology of this biopsy tissue revealed histiocytes with pleomorphic nuclei, reactive lymphocytes, and scattered cells that resembled the Reed-Sternberg (R-S) cells of classical Hodgkin lymphoma (Fig. 2). The R-S-like cells had an atypical B-cell pattern by immunohistochemistry, positive for PAX5 and CD30 and negative for CD15 and CD20 (Fig. 3a–c). In situ hybridization demonstrated that these R-S-like cells were uniformly positive for EBER, confirming the presence of EBV (Fig. 3d). These findings support a diagnosis of non-neoplastic, EBV-positive polymorphic B-cell LPD. The outside hospital's slides from the hard palate and lacrimal gland lesions were reviewed and showed similar morphology and staining patterns.

In follow-up, the patient received 4 doses of rituximab after this biopsy. The orbital mass regressed and there was no evidence of systemic involvement, so treatment was discontinued. The patient has done well clinically since then with no additional tumor-directed therapy or recurrence of EBV-LPD for over 2 years.

Discussion

Several EBV-LPDs may affect the eye. Neoplastic examples include primary intraocular lymphoma and various periocular lymphomas, such as extranodal marginal zone lymphoma (MALT lymphoma), diffuse large B-cell lymphoma, Burkitt lymphoma, NK/T-cell lymphoma, and lymphomatoid granulomatosis [1, 2, 4–8]. Non-neoplastic examples include the conjunctival and lacrimal gland lesions of infectious mononucleosis and polymorphic B-cell LPD, which sometimes include R-S-like cells [9–11]. The R-S-like cells in polymorphic B-cell LPD are often positive for CD20 (a B-cell marker) and CD30 but importantly are negative for CD15 (unlike true R-S cells in most classical Hodgkin lymphomas) [9]. This patient's R-S-like cells matched this pattern except for CD20, which likely was negative due to prior treatment with rituximab, a monoclonal antibody that targets CD20. However, the R-S-like cells were positive for PAX5, another B-cell marker.

Most EBV-LPDs are associated with immunodeficiency resulting from HIV infection, primary (congenital) immune disorders, iatrogenic causes, and age-related immune dysregulation [9]. The most common EBV-LPDs in HIV-positive patients are diffuse large B-cell lymphoma, Burkitt lymphoma, and Hodgkin lymphoma. Polymorphic B-cell LPD is less common in this population [9]. The complete range of non-neoplastic and lymphomatous EBV-LPDs can arise in patients with primary immune disorders, such as ataxia-telangiectasia, Wiskott-Aldrich syndrome, and common variable immunodeficiency [9]. In 1 report, a patient with acute lymphoblastic leukemia developed an EBV-LPD. This case highlights the loss of immune function that can be associated with primary neoplastic transformation of lymphocytes that normally serve as immune effector cells [12].

Iatrogenic immunosuppression from solid organ, bone marrow, or stem cell transplantation can lead to post-transplant LPD. The manifestations of EBV-LPD in these patients range from polymorphic B-cell LPD to B-cell lymphomas and, less commonly, NK/T-cell lymphomas [3, 9]. Other forms of iatrogenic immunosuppression include treatment of systemic autoimmune diseases. The immunosuppressive drugs most commonly associated with LPDs are methotrexate and TNF- α antagonists (e.g., infliximab, adalimumab, and etanercept) [9, 13].

This young patient is HIV-negative, has normal serum immunoglobulin levels and lymphocyte subset

analysis, and has no history of transplantation, systemic malignancy, or treatment with immunosuppressive drugs. Based on these studies and this history, the development of EBV-positive polymorphic B-cell LPD is surprising. However, given the patient's recent history of pneumocystis pneumonia and childhood history of infection, it is possible that she has a subtle defect in cell-mediated immunity that was not identified by standard screening. This report and recent research on the nature of the immune response to EBV indicate that our understanding of systemic immunodeficiency is in evolution, and that various and sometimes subtle molecular defects in T-cell function can contribute to a relative lack of immune response in patients who develop EBV-LPDs [14, 15]. Moreover, clinical and animal studies have indicated that chronic infection, as occurs with EBV, can lead to pathogen-specific exhaustion of T-cell effector functions [15]. Increasingly sophisticated methods of EBV detection and immunological testing will facilitate further investigation of these LPDs in apparently immunocompetent patients.

Treatment and prognosis for EBV-LPDs are variable. For malignant lymphomas, treatment and prognosis depend on histology, stage, and patient condition. Non-neoplastic polymorphic B-cell LPD, as seen in this patient, may evolve into a progressive disorder that requires therapy with rituximab, lymphoma-like chemotherapeutic regimens, or both [3, 9]. However, a proportion of polymorphic B-cell LPDs will regress, as was ultimately the case with this patient, typically with a reduction in immunosuppression, after rituximab, or with limited chemotherapy [3, 9]. Antiviral agents can also play a role in management and even prophylaxis in high-risk patients [3, 9].

Statement of Ethics

The patient gave informed consent, and the study protocol was approved by the institute's committee on human research. Animal experiments conformed to institutional standards.

Disclosure Statement

The authors have no conflicts of interest to disclose.

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