Successful Treatment of a Patient With Epstein-Barr Virus–Positive B-Cell Lymphoproliferative Disorder Resembling Post-Transplant Lymphoproliferative Disorder Using Single-Agent Rituximab

Introduction

Lymphoproliferative disorders that are associated with the Epstein-Barr virus (EBV) are most common after organ and allogeneic bone marrow or stem-cell transplantation. These disorders are rare but can be quite serious. Multiple treatment regimens have been attempted, including the anti-CD20 monoclonal antibody rituximab.¹ Nontransplantation-related EBV-positive lymphoproliferative disorders such as age-related EBV-positive diffuse large-cell lymphoma also occur, although less commonly. There is no standard management for these latter disorders.²

We herein describe an elderly patient with no prior history of transplantation or known immunodeficiency who developed a life-threatening lymphoproliferative disorder that was associated with a clonal immunoglobulin gene rearrangement secondary to EBV. The patient was treated successfully with single-agent rituximab.

Case Report

An 82-year-old man with diabetes and hypertension was referred because of anemia in October 2006. He had a history of a colorectal carcinoma 24 years prior that had been treated surgically. Five months prior to the referral, he underwent a tonsillectomy for markedly enlarged tonsils. Pathologic examination showed lymphoid hyperplasia and immunohistochemical studies revealed a heterogeneous population without aberrant marker expression, thus favoring a reactive process.

The physical examination in October 2006 was remarkable for a palpable right-sided 1×1.5 -cm cervical node. No other nodes were palpable and no hepatosplenomegaly was present. The hemoglobin was 12.6 gm/dL, WBC was 5,000/ μ L with 52% neutrophils, 34% lymphocytes, and 12% monocytes, and the platelet count was 98,000/ μ L. Sedimentation rate was 7 mm/h, antinuclear antibodies were negative, and blood chemistries and liver profile tests were normal. Serum protein electrophoresis showed a diffuse hypergammaglobulinemia with no monoclonal spike. A computed tomography scan of the neck showed several cervical adenopathies, one with a necrotic center. A cervical lymph node biopsy was performed that revealed reactive lymphoid hyperplasia; this was confirmed again by immunohistochemical studies that were similar to the original tonsillar pathology. A serum β 2-microglobulin level was 3.4 mg/L (normal range, 1 to 1.7 mg/L). A bone marrow aspiration and biopsy were nondiagnostic and immunophenotypic studies were negative for lymphoma.

In September 2008, the patient returned with upper GI complaints. An upper endoscopy confirmed *Helicobacter pylori*-associated gastritis and was treated. Subsequently, the patient experienced diar-

Fig 1.

rhea with a weight loss of 9 lbs. A 5-gm xylose absorption test was normal. A computed tomography scan of the abdomen and pelvic area was unremarkable.

In March 2009, the patient was referred because of difficulty swallowing and breathing; the cause of his symptoms was determined to be large, bilateral masses approximately 10×5 cm in size that were located at the base of his tongue. The serum β 2-microglobulin level was again obtained and had increased to a level of 5.4 mg/L. A biopsy of one of the masses was performed and was found to be similar to the previous tonsillar biopsy. Figure 1 shows the tongue with intact squamous epithelium and expansion of lymphoid tissue with reactive features ($\times 10$ magnification). Figure 2 shows the tongue lesion ($\times 40$

Fig 2.

Fig 3.

magnification) with a polymorphous lymphoid infiltrate that was composed of a mixture of B cells and T cells and marked plasmacytosis that was polyclonal for κ and λ stains (not shown). The specimen was referred to the Laboratory of Pathology of the National Institutes of Health/National Cancer Institute for consultation. The infiltrate was composed of a mixture of B and T cells. CD79 and MUM-1 highlighted plasma cells that were polyclonal for κ and λ . The preliminary diagnosis was considered to be lymphoid hyperplasia with polyclonal plasmacytosis. In situ hybridization for EBV using an EBV-encoded small RNA probe showed scattered positive cells of varying size (Fig 3). Bcl6 and CD10 highlighted germinal centers. Reactivation of EBV, possibly secondary to age-related immunologic deterioration, was considered to be the cause.^{3,4} Immunoglobulin heavy chain (*IgH*) gene polymerase chain reaction studies, using primers to both framework II and framework III and the Jh region of the *IgH* gene, revealed a significant clonal rearrangement that indicated the presence of a clonal B-cell population (not shown). T-cell receptor gamma (*TCRγ*) gene rearrangement studies showed an abnormal pattern that was suggestive of a significant clonal rearrangement. The latter was thought to be consistent with restricted responses that are occasionally associated with EBV infection. In view of the patient's age, mature B-cell proliferation, EBV-encoded RNA positivity, and lack of a predisposing immunodeficiency disorder, the final diagnosis was considered to be an EBV-positive B-cell lymphoproliferative disorder that resembled post-transplantation lymphoproliferative disease (PTLD).

Because of the patient's significant respiratory distress and the nature of the tumor, the decision was made to treat the patient with rituximab at a weekly dose of 375 mg/m² for 4 weeks. There was a prompt and dramatic improvement with complete resolution of the enlarged lymphoid tissue. Twenty months later, the patient remains asymptomatic with no evidence of the posterior tongue masses and no lymphadenopathy but with an elevated β 2-microglobulin of 4.25 mg/L.

Discussion

EBV was first identified in cultures from Burkitt's lymphoma tissue specimens in 1964.⁵ The virus has been shown to induce blast

transformation and proliferation of infected B lymphocytes.⁶ EBV is known to infect approximately 90% of the world population and to persist in the host for life. An increased understanding of this infection has led to the identification of EBV as the causative agent in some post-transplantation-associated malignancies including nasopharyngeal carcinoma. Among other diseases associated with EBV are Hodgkin's lymphoma, PTLD after allogeneic blood stem-cell transplantation, infectious mononucleosis, X-linked lymphoproliferative disease, chronic active EBV infection, and hypersensitivity to mosquito bites.⁶ Clonality of EBV-driven proliferations can be determined by examination of the terminal regions of EBV in both B cells and T/natural killer cells.⁷

The EBV-related PTLDs have been described primarily in association with liver transplantation but also with kidney, lung, heart, and bone marrow transplantations.^{8,9} PTLD occurs when immunosuppression allows reactivation of EBV, which spreads to other B cells that are then transformed. Initially these EBV-transformed cells are polyclonal, but gradually an oligoclonal and later a monoclonal population can emerge. The average frequency of EBV-infected cells is significantly increased during the early stages of PTLD. When patients with PTLD are treated with rituximab, a gradual decline in viral load is observed immediately. This striking rapid decrease in viral load after treatment with rituximab suggests that the localization of these viral genomes is in the peripheral blood B lymphocytes. Thus, early treatment before the occurrence of a well-established tumor that is characterized by a monoclonal population seems to be the most effective approach. For this reason, preemptive therapy with rituximab is being used when the viral load increases, even before there is evidence of PTLD. Although rituximab is more effective in the early stages of nonmonoclonal or oligoclonal PTLD, it has also been shown to have activity in monoclonal polymorphic post-transplantation lymphoma that resembles diffuse large-cell lymphoma.⁸

The term EBV-related B-cell lymphoproliferative disorder resembling PTLD is used to describe morphologically similar lymphoid proliferations without a history of iatrogenic immunosuppression. These lesions can be observed in the elderly and represent a spectrum of EBV-related lymphoproliferative disorders, ranging from EBV-associated lymphoid hyperplasia to EBV-positive large B-cell lymphoma in the elderly.¹⁰ In the patient described here, the polymorphous nature of the infiltrate and the range in cell size is similar to that seen in polymorphic PTLD.¹¹ In the elderly, these lesions are believed to be related to the deterioration of the immunologic system that occurs as part of the aging process; its pathophysiology is similar to that observed after immunosuppression that occurs after organ transplantation.¹² These lesions frequently present with extranodal involvement and commonly involve the oral cavity, lips, gingiva, tonsils, tongue, nasopharynx, skin, adrenals, and GI tract, similar to many cases of PTLD.¹⁰

In 1997, rituximab was the first monoclonal antibody approved by the US Food and Drug Administration for oncologic targeted therapy. The use of rituximab, which was originally intended for B-cell lymphomas, has been extended to many other neoplastic B-cell disorders as well as many nonmalignant immunologic disorders. There have been several reports of the use of rituximab in both adult and pediatric patients with clonal lymphoproliferative disorders after orthotopic liver transplantation.⁹ Several prospective studies have been performed. Choquet et al¹ reported on 46 patients with PTLD who were treated with rituximab after tapering immunosuppression. They received 375 mg/m² for 4 consecutive weeks. At 80 days, 86% of the patients were alive, and at 1 year, the overall survival was 67%.

In view of the similarities between PTLD and the histologic features in the patient presented, along with the successful use of rituximab in PTLD, we decided to use this drug for the treatment of our patient.¹ To our knowledge, this is the first report of a patient with age-related EBV-positive lymphoproliferative disorder who was successfully treated with single-agent rituximab. However, there are other reports of patients with lymphomatoid granulomatosis, another spontaneous clonal EBV-positive B-cell disorder, who were treated with rituximab.^{13,14} Furthermore, the successful use of rituximab in our patient justifies additional exploration of this well-tolerated drug for this disorder that is characterized by immunosuppression and, frequently, advanced age, both characteristics that severely limit the use of myelosuppressive cytotoxic agents.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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