Enteroviral Meningoencephalitis after Anti-CD20 (Rituximab) Treatment

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Treatment with the chimeric anti-CD20 monoclonal antibody rituximab induces rapid and long-lasting depletion of circulating B cells. We report the occurrence of enteroviral meningoencephalitis following rituximab therapy in 1 child with immune thrombocytopenia and in 1 adult patient with relapsed B cell lymphoma.

The chimeric anti-CD20 monoclonal antibody rituximab is increasingly being used for the treatment of primary B cell lymphoma, posttransplantation B cell lymphoproliferative disorder, and, more recently, refractory autoimmune cytopenia [1–4]. Rituximab induces a long-lasting depletion of the peripheral B cell pool, which leads to hypogammaglobulinemia [4]. However, the safety profile of this drug is generally assumed to be good [1–2]. We report the occurrence of enteroviral meningoencephalitis following rituximab therapy in 2 patients.

Case reports. Patient 1 had been treated for severe autoimmune thrombocytopenia from 4 through 10 years of age, at which time rituximab therapy was initiated. Several immunosuppressive treatments were sequentially provided that had no, or only transient, effect on platelet counts, including intensive immunosuppressive therapy followed by autologous hematopoietic stem-cell transplantation (HSCT) administered when the patient was 8 years old. When rituximab treatment was initiated (20 months after HSCT), T cell immunity was normal, as assessed by T cell counts as well as mitogen- and antigen-induced T cell proliferation assays in vitro. Serum immunoglobulin levels were normal, with the exception of the IgG2 level, which, at 0.27 g/L, was at the lower end of the normal range for the patient’s age. Ongoing treatment consisted of orally administered prednisone (0.4 mg/kg per day) and dapsone (Disulone; Adventis Pharma) (3 mg/kg per day). After a course of 4 rituximab infusions (375 mg/m² per week), platelet counts reached normal values within 3 weeks of the first infusion. However, a relapse occurred 6 months later, when the prednisone dosage was 0.15 mg/kg per day. A second course of 4 rituximab infusions was then administered, which resulted in long-lasting resolution of the thrombocytopenia.

Eighteen months after the first series of rituximab infusions and 11 months after the second series, the patient was admitted to the hospital with a progressive alteration in cognitive functions associated with aphasia and sensorimotor deafness that developed over a period of 9 months. He also presented with mild fever and a marked extrapyramidal syndrome. By this time, long-lasting B cell deficiency had developed, as well as undetectable levels of CD19+ and CD20+ circulating B cells, low serum IgG levels (3.2 g/L; normal range for the patient’s age, 5.4–16.1 g/L), and low anti–varicella-zoster virus, poliovirus, and tetanus toxoid antibody levels. Epstein-Barr virus, viral capsid antigen, Epstein-Barr nuclear antigen IgG, and antibody to cytomegalovirus were, however, present at high levels. MRI of the brain revealed diffuse white matter abnormalities (figure 1). Enteroviral RNA was detected by PCR in 2 plasma and 2 CSF samples obtained at 1-week intervals and sent to 2 different laboratories. CSF analysis revealed 27–33 leukocytes/mm³ (100% lymphocytes) and increased protein levels (0.34–0.94 g/L).

Viral cultures of CSF, blood, and feces samples and a throat swab failed to isolate the virus. In view of these results, combination treatment consisting of high-dose intravenous immunoglobulin (IVIG) and the antipicornaviral agent pleconaril was initiated. This led to marked and continued clinical improvement. Dapsone therapy was discontinued, and low-dose oral prednisone was continued during subsequent months. Seven months after the initiation of IVIG therapy, the patient was well oriented and able to read and write, but learning disabilities and behavioral problems persisted. No motor dysfunction was observed, and the patient’s deafness had completely resolved. There were still no detectable circulating B lymphocytes. Cytologic analysis of bone marrow revealed 2%...
Figure 1. Patient 1: T2-weighted MRI revealing white matter abnormalities.

CD19⁺ and 0.4% CD20⁺ B cells. CSF analysis revealed 13 lymphocytes/mm³ and a protein concentration of 0.52 g/L, but no enteroviral RNA was detected by PCR. MRI findings were unchanged.

Patient 2 had stage IIIA (Ann Arbor classification) follicular lymphoma diagnosed at the age of 53 years. Initially, the patient was treated with 12 courses of low-dose chemotherapy, which consisted of cyclophosphamide, adriamycin, teniposide, and prednisone in association with IFN-α. Complete remission was achieved. A nodal relapse occurred 28 months after the initial diagnosis. Four rituximab infusions (375 mg/m² per week) induced a second complete remission within 3 months after this therapy was initiated. However, 6 months after the rituximab course was completed, fever, headaches, diffuse paresthesia, concentration difficulties, sensorimotor deafness, diplopia, a pyramidal syndrome, and ataxia developed. At this time, serum immunoglobulin levels were low (IgG, 5.5 g/L; IgA, 0.69 g/L; and IgM, 0.15 g/L). An MRI revealed evidence of myelitis at the level of the fourth thoracic vertebra and an asymmetrical signal enhancement of the right parietal meninges after gadolinium injection. CSF analyses revealed as many as 300 lymphocytes/mm³ and protein concentrations as great as 1.2 g/L, but cytologic analysis and immunophenotyping revealed only 2% malignant B cells. Cultures of 3 successive CSF samples obtained at 4-week intervals isolated echovirus 13. Cultures of throat swabs and fecal samples showed no growth. Atypical circulating lymphocytes were detected, and a CT scan of the abdomen revealed thickening of the duodenal wall.

Histological and immunologic analyses of duodenal biopsy samples led to the diagnosis of a second lymphoma relapse. Before we considered enteroviral meningoencephalitis as the diagnosis for this second relapse, the patient was treated with high-dose corticosteroid therapy and salvage polychemotherapy and underwent HSCT, and a third complete remission was achieved. The patient’s neurological symptoms partially improved. Nevertheless, 2 months after undergoing HSCT, the patient experienced a recurrence of mild fever, severe sensorimotor deafness, and neurological symptoms identical to those experienced during the second relapse. An MRI performed at this time revealed nothing abnormal. CSF pleocytosis was still present (leukocyte count, 300 cells/mm³ [monocytes, 6%; lymphocytes, 92%; CD3⁺, 89%; CD4⁺, 28%; CD8⁺, 59%; CD3⁺ CD56⁺, 5.6%; and no malignant B cells]), as were elevated protein levels (1.07 g/L). CSF cultures showed no growth, but PCR analysis of CSF samples, performed in 2 different laboratories 8 months after the first isolate was obtained, still detected enterovirus. There were almost no detectable circulating B cells, and marked hypogammaglobulinemia had developed. High-dose IVIG and pleconaril were then administered. During the next 4 months, marked and continued clinical improvement was observed, although deafness, a mild pyramidal syndrome, and CSF cytologic and biochemical abnormalities persisted. Results of PCR analyses of CSF samples obtained 3 and 9 weeks after the initiation of high-dose IVIG and pleconaril therapy were negative.

Discussion. We describe 2 patients who developed enteroviral meningoencephalitis following treatment with rituximab. The diagnosis was established in both cases by detection of enterovirus in CSF by PCR or culture. In addition, for patient 2, the identification of echovirus 13 followed an outbreak of 174 cases of enteroviral meningitis within the administrative district, which included 35 cases from which echovirus 13 was isolated [5]. Moreover, the clinical improvements achieved by means of the combination of intensive IVIG therapy with pleconaril therapy are consistent with the diagnosis of enteroviral meningoencephalitis and with the experience of the treatment of this illness in hypogammaglobulinemic patients [6–8].

Rituximab administration has been associated with profound and long-lasting, albeit transient, antibody deficiency of usually 6–12 months’ duration, in our experience [6]. Severe enterovirus disease is well described in patients with inherited B cell defects [7]. Hence, although one cannot exclude the role of previous immunosuppressive treatments in the 2 cases we describe, one must consider the possibility that rituximab played a role in the severe enteroviral illness. However, to date, persistent enteroviral infection has not been reported following rituximab treatment. Thus, the diagnosis of enteroviral infec-
tion was not immediately considered for our 2 patients. In patient 2, the symptoms were initially attributed to the relapsing lymphoma. The transient improvement observed during corticosteroid therapy and chemotherapy may well have been the result of a nonspecific anti-inflammatory effect of this treatment.

MRI of the brain of patient 1 revealed marked diffuse white matter abnormalities, whereas MRI findings for patient 2 were consistent with the diagnosis of myelitis. Although no direct insight into the pathogenesis of these abnormalities was possible, perivasculitis secondary to enteroviral infection and disruption of the blood-brain barrier are likely explanations. Intraparenchymatous cellular infiltration of the brain and glial cell activation have been reported in patients with primary agammaglobulinemia and chronic enteroviral infection. The type of cells that harbor the virus in these patients has not been well characterized. However, endothelial cell lesions and neuronal cell death have been reported [9].

Rituximab is usually well tolerated [1–2]. Nevertheless, life-threatening infections have been described in recent case reports of patients treated with rituximab combined with chemotherapy or immunosuppressive regimens [10–13]. Parvovirus B19–induced pure RBC aplasia has been reported in 1 patient [11]. For this virus, as for enterovirus, an adequate antibody response is of major importance. Hence, we would recommend close medical follow-up after rituximab therapy, particularly for patients treated with a combination of rituximab and immunosuppressive or cytotoxic drugs, and prophylactic IVIG substitution should be considered for some of these patients. In addition, the fact that one of our patients received 2 series of rituximab infusions and had profound B cell deficiency that persisted 24 months after the last infusion may caution against the repeated use of monoclonal anti-CD20 antibodies.

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References