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ENTEROVIRAL T-CELL ENCEPHALITIS RELATED TO IMMUNOSUPPRESSIVE THERAPY INCLUDING RITUXIMAB

Enteroviruses are a common cause of aseptic meningitis and mild infections in childhood. However, in immunocompromised patients they may cause severe neurologic conditions such as encephalitis or polio-like paralysis.

Rituximab, a chimeric anti-CD20 mononuclear antibody, has revolutionized the treatment of hematologic and autoimmune conditions. Although it is considered a safe and effective treatment, some related infections include hepatitis B reactivation and progressive multifocal leukoencephalopathy. We present the case of a patient with a chronic meningoencephalitis caused by enterovirus, likely related to rituximab therapy.

Case report. A 66-year-old man had been successfully treated with R-CHOP therapy for Waldenstrom macroglobulinemia 6 years previously. After 4 years remission, he relapsed and was treated with corticosteroids, cyclophosphamide, and rituximab, achieving a complete response. His maintenance therapy was rituximab 375 mg/m² every 2 months.

The patient presented with drowsiness and fever. Neurologic examination showed mild encephalopathy with no focal signs. Laboratory workup disclosed moderate lymphopenia with B-lymphocytes depletion. Serial brain MRIs showed corticosubcortical atrophy and mild nonobstructive hydrocephalus in the last MRIs, without contrast enhancement or other signs of inflammation. CSF examination revealed mononuclear pleocytosis (20 lymphocytes/ μ L) and hyperproteinorrachia (0.71 g/L) with normal glucose levels. Viruses' real-time PCR, including enterovirus, bacterial, and fungal cultures on CSF, were all negative.

The diagnosis was a subacute meningoencephalitis, and infectious, inflammatory, and neoplastic etiologies were considered.

As no etiologic agent was identified, an immune-mediated condition was suspected and methylprednisolone 1,000 mg/d (5 days) and IV immunoglobulin (IVIg) (2 g/kg every 2 months) were started, without improvement. In order to rule out a treatable disorder, a right temporal lobe biopsy was performed (figure).

The histologic features included astrogliosis and meningeal and parenchymal infiltration with T cells, with no B cells present. Microglial nodules and neuronophagia were also identified. There was no evidence supporting demyelinating, vasculitic, or myeloproliferative disease. Enterovirus detection by RT-PCR was positive on brain tissue.

The patient was treated again with IVIg, experiencing a transient improvement, but his condition deteriorated. He finally died of pneumonia, 7 months after the meningoencephalitis debut.

Discussion. Enteroviruses cause around 90% of acute aseptic meningitis cases in children and account for 70% of overall meningitis cases. They also represent 5% of encephalitis cases, having a more benign course than those caused by herpes simplex or arbovirus.¹ Nevertheless, in patients with humoral immunodeficiency, congenital or acquired, these viruses can behave more aggressively. Since the first case of rituximab enterovirus encephalitis was reported in 2003, only 10 more cases have been published.²

The majority of these patients have similarities with our case, including an oncohematologic condition, inflammatory CSF, and lymphopenia with B-cell depletion. Our patient received cyclophosphamide 6 months before encephalitis onset, and it may have contributed to overall immunosuppression, but the relation between severe enteroviral infections and B-cell or humoral deficiency suggests that rituximab was the main risk factor. Clinical presentation, CSF, and MRI in this condition are nonspecific. MRI can be normal³ or show T2 cortical, basal ganglia,⁴ or white matter abnormalities.² Contrast enhancement is possible, but seems to be rare.²

An interesting feature of our case is the T-cell encephalitis related to enterovirus infection. Previous publications include clinical reports in absence of brain biopsy (enterovirus PCR was positive in CSF) or a more varied histopathologic spectrum (including B and T cells).^{3,4} We consider that this striking inflammatory pattern is possibly related to the B-cell depletion induced by rituximab, rather than something specific to enterovirus pathology. In this regard, enterovirus encephalitis in other immunosuppressed or immunocompetent patients shows a predominance of T cells,⁵ but an absence of B cells is very rare.

(A) Hematoxylin & eosin (×100). Moderate infiltration of the meninges and parenchyma with lymphocytes, compatible with inflammation. Inset ×200. (B) Hematoxylin & eosin (×400). Microglial nodule within the brain parenchyma. (C) CD3 immunostaining (×100). Numerous T lymphocytes infiltrate brain parenchyma and meninges. Inset ×200. (D) CD20 immunostaining (×100). Total absence of B lymphocytes on the sample. Inset ×200.

It is interesting that CSF enterovirus PCR was negative, being that cerebral biopsy is the key for diagnosis, as in one of the patients previously reported.⁶ Despite a clinician's best effort, the exact etiology for a substantial number of patients with chronic meningoencephalitis remains undiagnosed, rendering a brain biopsy necessary.⁷ Enterovirus meningoencephalitis has also been reported in immunocompromised patients other than those under anti-CD20 therapies.¹ The number of cases is scarce, and there is no proven therapy for enteroviral encephalitis. Early withdrawal of immunosuppressive drugs,

administration of IVIg, or the antiviral agent pleconaril have been used in some surviving patients,² but the latter is no longer available. Despite being a very rare complication of rituximab, enteroviral infection should be considered in the differential diagnosis of patients with meningoencephalitis and previous exposure to anti-CD20 therapies.

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Author contributions: Drs. Villarejo-Galende, Vila-Bedmar, and Garzo-Caldas: study concept and design, drafting the manuscript. Drs. Villarejo-Galende, Garzo-Caldas, Vila-Bedmar, Ruiz-Sainz, Folgueira-López, Hernández-Lain, Llamas-Velasco, and Ruiz-Morales: acquisition of data. Drs. Villarejo-Galende, Garzo-Caldas, Vila-Bedmar, Ruiz-Sainz, Folgueira-López, Hernández-Lain, Llamas-Velasco, and Ruiz-Morales: critical revision of the manuscript for important intellectual content.

Acknowledgment: The authors thank the patient and his family.

Study funding: No targeted funding reported.

Disclosure: The authors report no disclosures relevant to the manuscript. Go to Neurology.org for full disclosures.

Received October 27, 2016. Accepted in final form April 19, 2017.

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