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OPSOCLONUS-MYOCLONUS SYNDROME DURING RITUXIMAB TREATMENT FOR AUTOIMMUNE AUTONOMIC GANGLIONOPATHY

OPEN

Adult-onset opsoclonus-myoclonus syndrome (OMS) is an autoimmune disorder with paraneoplastic, parainfectious, or idiopathic etiologies.[1] Nonparaneoplastic cases are generally immunotherapy responsive.[1] Although previously described accompanying encephalopathy in NMDA receptor (NMDA-R) encephalitis,[2] OMS occurring as an isolated CNS finding in an NMDA-R antibody–positive patient appears to be unusual, particularly among patients with preexisting α3AChR antibody–associated dysautonomia. We describe a patient in whom an autoimmune CNS disorder isolated to OMS arose in the context of rituximab treatment administered for refractory autoimmune dysautonomia.

A 61-year-old woman with a history of prior gastric sleeve procedure to treat morbid obesity presented with profound orthostatic hypotension and recurrent syncopal episodes. She was diagnosed with severe global autonomic failure involving postganglionic sympathetic sudomotor, cardiovagal, and cardiovascular adrenergic systems. The serum α3AChR antibody was positive (value, 1.30 nmol/L; normal, ≤0.02). CSF studies were not pursued at that time. IV immunoglobulin, mycophenolate mofetil, plasma exchange, and symptomatic therapy provided modest or transient benefit. Because of suboptimal treatment response, rituximab was initiated (1,000 mg, 2 infusions, 2 weeks apart, with diphenhydramine and acetaminophen as premedication). Within 2 weeks of the first infusion, the patient developed progressive vertigo, oscillopsia, gait instability, and diffuse body tremulousness. Symptoms worsened after the second rituximab infusion. Despite this, autonomic symptomatology had improved, and no behavioral or mood changes were encountered. Neurologic examination 1.5 weeks after the second rituximab infusion revealed opsoclonus, myoclonic limb movements, and truncal ataxia. Contrast-enhanced brain MRI was unrevealing. Chest, abdomen and pelvis CT, mammography, and whole-body PET/CT did not identify underlying malignancy. CSF evaluation revealed 119 nucleated cells/μL (normal less than 5) with lymphocytic predominance (91%), absent red blood cells, normal glucose (55 mg/dL), and mildly elevated protein (63 mg/dL, normal range 14–45). There were no supernumerary CSF oligoclonal bands. Flow cytometry, cytology, and detailed serum and CSF infectious studies for fungal, bacterial, mycobacterial, spirochetes, and viral pathogens were negative. Comprehensive serum and CSF autoantibody testing demonstrated NMDA-R antibody in the CSF only (at a low titer by cell-based assay [1:2]; indirect immunofluorescence assay using a composite of mouse tissues, including brain, was negative [<1:120]), and α3AChR antibody in serum (titer, 0.69 nmol/L). OMS improved significantly within 1 week of initiation of IV methylprednisolone treatment (1 g daily for 5 days). The patient was discharged to a skilled nursing facility with plan for a 12-week course of pulse methylprednisolone: 1 g of methylprednisolone once weekly for 5 more weeks, followed by once every other week dosing for 6 weeks.

Despite improved recognition of OMS in adults and advancements in antibody diagnostics, the pathogenesis of many cases remains incompletely understood.[1] Unusual aspects of this report include NMDA-R autoimmunity occurring in the context of OMS without NMDA-R-typical encephalopathy or neuropsychiatric symptoms and the occurrence of this clinical-serological constellation in the context of rituximab treatment of another autoimmune disorder. OMS has been previously reported in patients with NMDA-R autoimmunity, where the clinical course was otherwise typical for that disorder, and encephalitic symptoms were prominent.[2]

The mechanism by which the patient paradoxically developed OMS after the initiation of rituximab is unclear. Rituximab appears to be an effective off-label therapy in many cases for autoimmune encephalitis.[3] In neuromyelitis optica, relapses of optic neuritis and transverse myelitis have been reported to occur within 2 weeks of rituximab treatment.[4] It has been hypothesized that rituximab-induced B-lymphocyte depletion leads to transient increases in serum B-cell activating factor, which in turn induces a paradoxical upregulation of aquaporin-4 autoimmunity.[5] Similarly, paradoxical and abrupt elevations in serum IgM levels after rituximab therapy

initiation have been described in Waldenstrom macroglobulinemia.[6] Biological factors specific to rituximab in contrast to other novel anti-CD20 monoclonal antibodies[7] may play a role in pathogenesis, such as differences in core epitope sequences and binding conformations, although precise mechanisms have yet to be elucidated. It is possible that NMDA-R autoimmunity was triggered by a similar mechanism in our patient, although α3AChR antibody titer did not rise and autonomic symptomatology remained stable. Coadministration of methylprednisolone will be considered for future rituximab treatment epochs in our patient. Similarly, coadministration of "prophylactic" corticosteroids with initial rituximab infusions might be warranted in the management of other autoimmune disorders.

Previous studies have demonstrated that rituximab may paradoxically promote autoantibody production through a poorly understood mechanism.[5] The risk of new or recurrent immune-mediated neurologic disorders arising as a result of rituximab therapy mandates close posttreatment monitoring, particularly at the present time when the use of B-cell depletion therapy for the treatment of autoimmune neurologic diseases is increasing.

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