Rituximab as a Second-Line Treatment for Lymphocytic Vasculitis of the Central Nervous System

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KEY WORDS: primary central nervous system angiitis, lymphocytic vasculitis, rituximab

IMAJ 2016; 18: 630–632

Lymphocytic vasculitis of the central nervous system (CNS) is an uncommon subtype of primary angiitis of the CNS (PACNS), which is a male-predominant inflammatory disorder that affects brain parenchymal and leptomeningeal vasculature. Small vessels are mostly involved and may cause ischemia and infarction to surrounding brain tissues. Glucocorticoids and cyclophosphamide are the current first-line therapy for this condition, although a selected group of patients respond poorly to this regimen. We describe here an unusual presentation of this rare disease and discuss an alternative pharmacotherapy for treatment-resistant cases.

PATIENT DESCRIPTION

A 64 year old man, a music teacher, presented to our department with a 5 day history of left monocular visual blurring and painful eye movements. He had lost 10 kg over the previous 6 months and began to suffer from nausea and diarrhea 2 months before arrival at the emergency department, where a routine gastrointestinal workup was unrevealing. Vital signs, general physical examination and routine blood work were unremarkable.

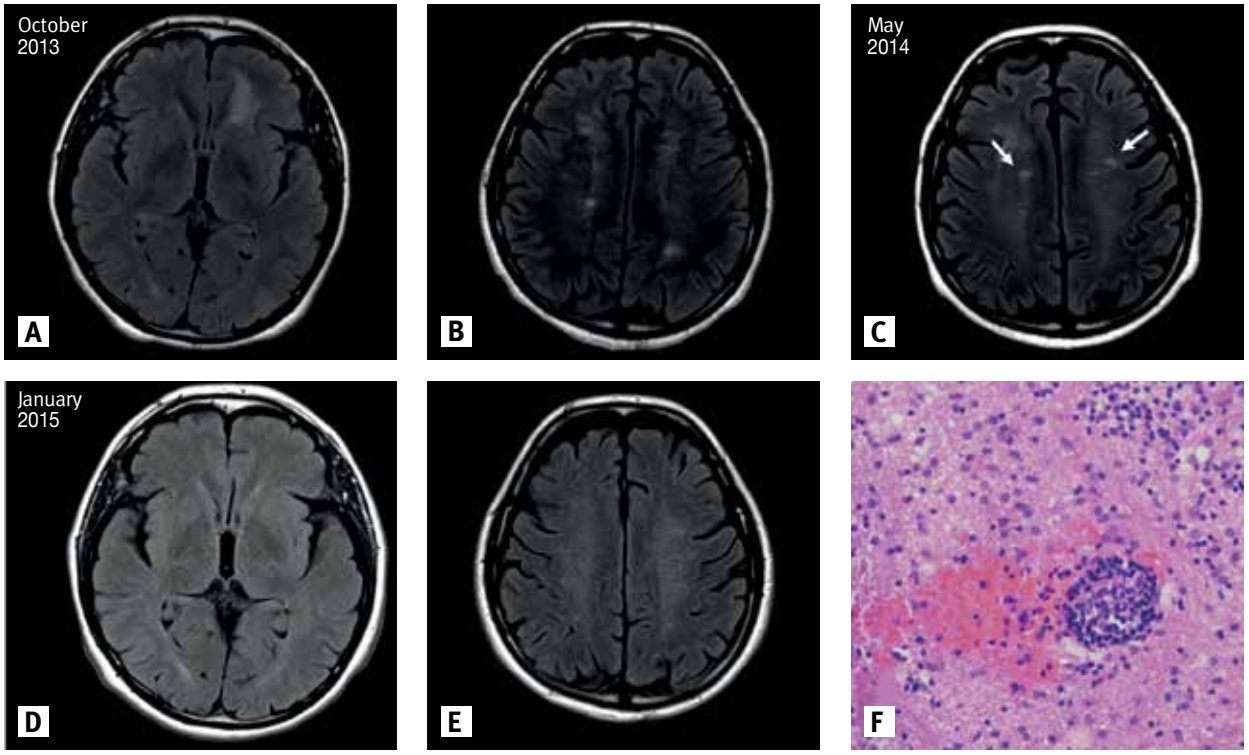
Neurological examination showed decreased visual acuity (right 20/25, left 20/30), a left afferent pupillary defect, bilateral optic disk edema (left>right) and an enlarged left blind spot. Head computed tomography (CT) and CT venography were unremarkable. Optic neuritis was highly suspected. Lumbar puncture showed normal opening pressure, clear cerebrospinal fluid (CSF), 35 white blood cells (WBC) with lymphocytic predominance, elevated protein 82 mg/dl, and normal glucose. CSF flow cytometry, serum rheumatologic screen, hepatitis serology and syphilis panel were negative. Inflammatory markers (C-reactive protein, erythrocyte sedimentation rate and angiotensin-converting enzyme) were within normal limits. Brain magnetic resonance imaging (MRI) showed abnormal signals in the periventricular white matter and the base of the left frontal lobe on T2 FLAIR sequences [Figure 1 A & B]. Stereotactic right frontal lobe brain biopsy revealed fragments of brain tissue with T and B lymphocytic infiltration in the white matter and blood vessel walls [Figure 1F]. There was no evidence of fibrinoid necrosis but hemorrhage and extravasation of erythrocytes were present. Myelin basic protein (MBP), neurofilament (NF) and glial fibrillary acidic protein (GFAP) staining showed no significant changes. Immunoperoxidase staining for P53, cytomegalovirus and herpes were negative. Periodic acid-Schiff (PAS) staining was negative for fungi. CD4 and CD8 were positive in T4 and T8 lymphocytes, and CD138 was positive in a few isolated plasma cells.

A diagnosis of isolated lymphocytic vasculitis of the CNS was made. The treatment regimen included pulse intravenous methylprednisolone (1000 mg/day for 5 days) followed by oral prednisone (1 mg/kg weight) and monthly intravenous cyclophosphamide (at a dose adjusted to his body surface area and kidney function, e.g., 900 mg/month) for 6 consecutive months. At neuro-ophthalmic follow-up there was resolution of papilledema with a trace of relative afferent pupillary defect on the left. Follow-up MRI after the sixth dose of cyclophosphamide revealed two new enhancing left frontal lobe lesions [Figure 1 C, white arrows] and a new right periventricular lesion. In lieu of the apparent sub-therapeutic response to first-line therapy, a trial of rituximab (1 g bimonthly) in combination with prednisone was initiated. After 2 months there was symptomatic improvement and the patient returned to his activities of daily life. Furthermore, his chronic fatigue and nausea subsided and he resumed his profession of teaching music. The 6 month follow-up MRI demonstrated reduced periventricular and frontal lobe lesions [Figure 1 D & E] and no new contrast enhancement. Following resolution of symptoms, the patient received a second course of rituximab 9 months after the first administration and continues in follow-up.

COMMENT

The treatment strategy for primary CNS angiitis is currently a matter of debate as there are no randomized controlled trials investigating this rare disorder. The presentation of blurred vision, painful eye movements, bilateral papilledema and visual field loss is typical of optic neuritis but atypical as the presenting manifesta-

Figure 1. Brain MRI findings at diagnosis (October 2013), following the sixth injection of cyclophosphamide (May 2014), and 6 months following rituximab treatment initiation (January 2015). **[A & B]** T2 FLAIR sequences showing abnormal signal in the periventricular white matter and base of the left frontal lobe. **[C]** T2 FLAIR sequences showing two new hyperintense frontal lesions (white arrows). **[D & E]** T2 FLAIR showing reduction in hyperintense periventricular, centrum semiovale and frontal lesions. **[F]** Pathology of stereotactic frontal lobe biopsy showing lymphocytic perivascular and white matter infiltration with extravasation of blood cells



tion of primary CNS angiitis, though it has been previously described [1]. Past combination treatment strategies have included adjunct immunosuppression to steroids such as cyclophosphamide or mycophenolate mofetil.

In the above case, this approach failed to stabilize the patient's disease. Rituximab, however, yielded both clinical and MRI improvement. The pathogenesis of primary CNS vasculitis is suggested to result from an antigen-specific immune response to ill-characterized arterial epitopes [2] and manifests as an infiltration of T cells and occasional plasma cells in and around small vessels. Rituximab, a chimeric monoclonal antibody directed against B lymphocyte cell-surface protein CD20, is known to mediate the destruction of B lymphocytes through a variety of mechanisms such as antibody-dependent cellular cytotoxicity, complement-dependent cytotoxicity and apoptosis. Interestingly, the large molecular weight of rituximab (146 kDa) renders it theoretically impermeable to the blood-brain barrier. Tokunaga et al. [3] measured serum and CSF rituximab concentrations in a patient with lupus cerebritis 24 hours after induction treatment and found low but detectable rituximab concentration in the CSF. The assumption is that rituximab indirectly affects the CNS by eliminating peripheral B cells, thereby limiting interactions between B cells and activated T cells. This effect reduces pro-inflammatory cytokine production, inhibits complement activation and therefore limits lymphocytic infiltration into the brain. Alternatively, we propose a hypothetical direct mechanism of action where damage to the CNS vasculature resulting from lymphocytic mediated endothelial damage allows for adequate permeability of rituximab into the CNS.

Further investigation of this hypothesis with the use of gas or liquid chromatography and or spectroscopy could further substantiate this claim and is a line of research that is currently underway. To date, treating isolated CNS vasculitis with rituximab is still experimental. There have been three prior successful reports of this treatment modality [4,5] and this is the fourth. Since optic neuritis is a rare but previously described presenting symptom of PACNS, further investigation may identify this heralding symptom as a potential biomarker and/or predictor of positive response to rituximab treatment. Further investigations along these lines are of paramount importance.

Acknowledgments

The authors wish to thank Esther Eshkol MA (Tel Aviv Medical Center) and Jacob Hascalovici MD PhD (Montefiore Medical Center, Bronx, NY, USA) for editorial assistance

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