

**[ CASE REPORT ]**

# **Treatment with Rituximab in the Acute Phase of Relapsing Remitting Multiple Sclerosis: A Case Report.**

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**Abstract:**

There have been a few reports on the administration of rituximab for relapsing-remitting multiple sclerosis (RRMS) in the acute phase. We report the case of a 62-year-old woman with an acute lesion of RRMS. Although corticosteroid therapy and plasmapheresis were not effective, the lesion improved with the administration of rituximab. We believe that the B cells were promptly depleted after the infusion of rituximab, and that the inflammatory reactions related to the B cells were suppressed. We suggest that the administration of rituximab can be considered as a treatment option for acute-phase RRMS when conventional therapies are not effective.

**Key words:** Relapsing remitting multiple sclerosis, Rituximab, Treatment

(Intern Med Advance Publication)

(DOI: 10.2169/internalmedicine.3408-19)

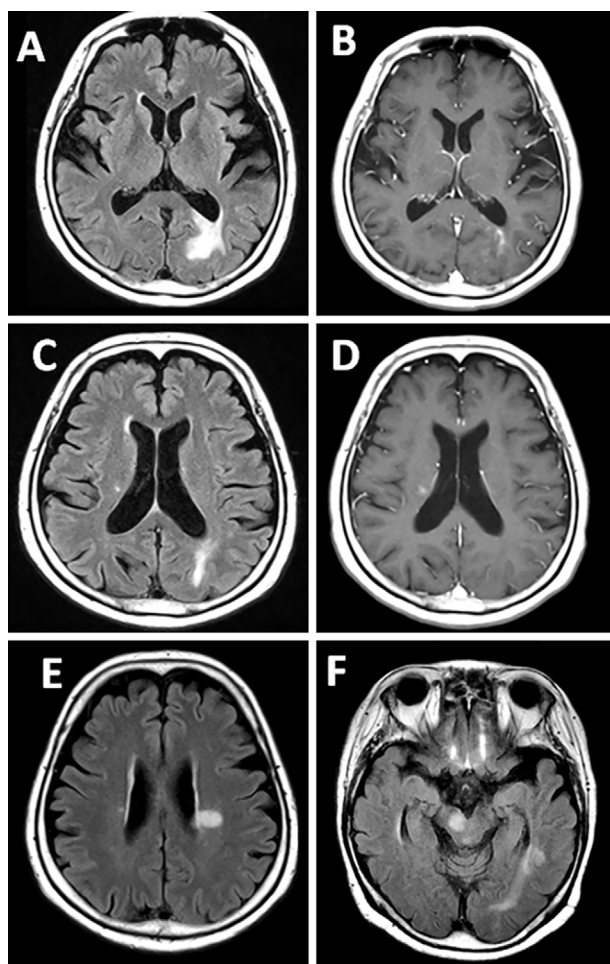
## **Introduction**

Rituximab, a monoclonal antibody against CD20 surface antigen on B cells, can reduce disease activity in patients with relapsing-remitting multiple sclerosis (RRMS). The administration of rituximab can also reduce the number of relapses when used as a disease-modifying therapy (1-3). There have been a few reports on the administration of rituximab for acute-phase RRMS. We herein report a case involving a patient with an acute lesion of RRMS that was resistant to the first-line and second-line therapies, which improved with the administration of rituximab.

## **Case Report**

A 62-year-old woman without any significant medical history presented with right homonymous hemianopsia and progressive left hemiparesis. Magnetic resonance imaging (MRI) of the brain revealed areas of hyperintensity in the white matter of the left occipital and temporal lobes and the right corona radiata on T2-weighted imaging (T2WI) and fluid-attenuated inversion recovery (FLAIR) with heterogeneous enhancement after the administration of gadolinium (Fig. 1A, B, C and D). An enzyme-linked immunosorbent

assay (ELISA) and cell-based assay (CBA) were negative for serum anti-aquaporin 4 (AQP4) antibodies. A CBA for anti-myelin oligodendrocyte glycoprotein antibodies was also negative. The patient's serum was also negative for antinuclear antibodies and antibodies for collagen diseases. The concentrations of serum soluble interleukin-2 receptor (sIL-2R) and beta-2-microglobulin ( $\beta$ 2-MG) were normal. A cerebrospinal fluid (CSF) analysis revealed normal concentrations of protein and glucose without pleocytosis. The myelin basic protein (MBP) concentration was elevated (256.0 pg/mL, normal <102 pg/mL), although the immunoglobulin G (IgG) index (0.53) and the concentrations of sIL-2R and  $\beta$ 2-MG were normal. Neither oligoclonal bands (OCB) nor malignant cells were found in the CSF. Blood and the CSF cultures were negative. A biopsy of the left occipital lobe lesion showed inflammatory demyelination, focal demyelination, numerous CD68 foamy macrophages and reactive astrocytes, and perivascular and parenchymal lymphocytic infiltration with predominant CD4+ T cells and a smaller population of CD8+ T cells and CD20+ B cells. The findings were consistent with those observed in multiple sclerosis (MS) (Fig. 2). The patient was treated with intravenous methylprednisolone (IVMP, 1,000 mg/day for 3 days) and with a tapering course of oral prednisolone. The symptoms and lesions on MRI showed improvement after the



**Figure 1.** Magnetic resonance imaging (MRI) of the brain at the time of the first attack (A-D), the second attack (E) and the third attack (F). Axial fluid-attenuated inversion recovery (FLAIR) images revealed areas of hyperintensity in the white matter of the left occipital lobe (A), right corona radiata, and left occipital lobe (C), with heterogeneous enhancement on post-gadolinium T1-weighted images (T1WI) (B and D). FLAIR images showed hyperintense lesions in the left corona radiata (E) and the right cerebral peduncle (F).

treatment.

At five months after the first attack, the patient experienced recurrence with an asymptomatic lesion in the left corona radiata (Fig. 1E). The diagnosis of RRMS was made in accordance with the revised McDonald's criteria (4). The patient was treated with IVMP, which resulted in the improvement of the lesion. Interferon- $\beta$  was initiated after the second attack. At two months after the second attack (7 months after the first attack), the patient experienced recurrence again, with weakness of the left lower limb and MRI revealing an area of hyperintensity in the right cerebral peduncle on T2WI and FLAIR (Fig. 1F). Improvement was observed after treatment with IVMP.

At ten months after the first attack, the patient presented with a sensory disturbance on the left side of the face, weakness of the left upper and lower extremities, and dysarthria. A neurological examination revealed sensory distur-

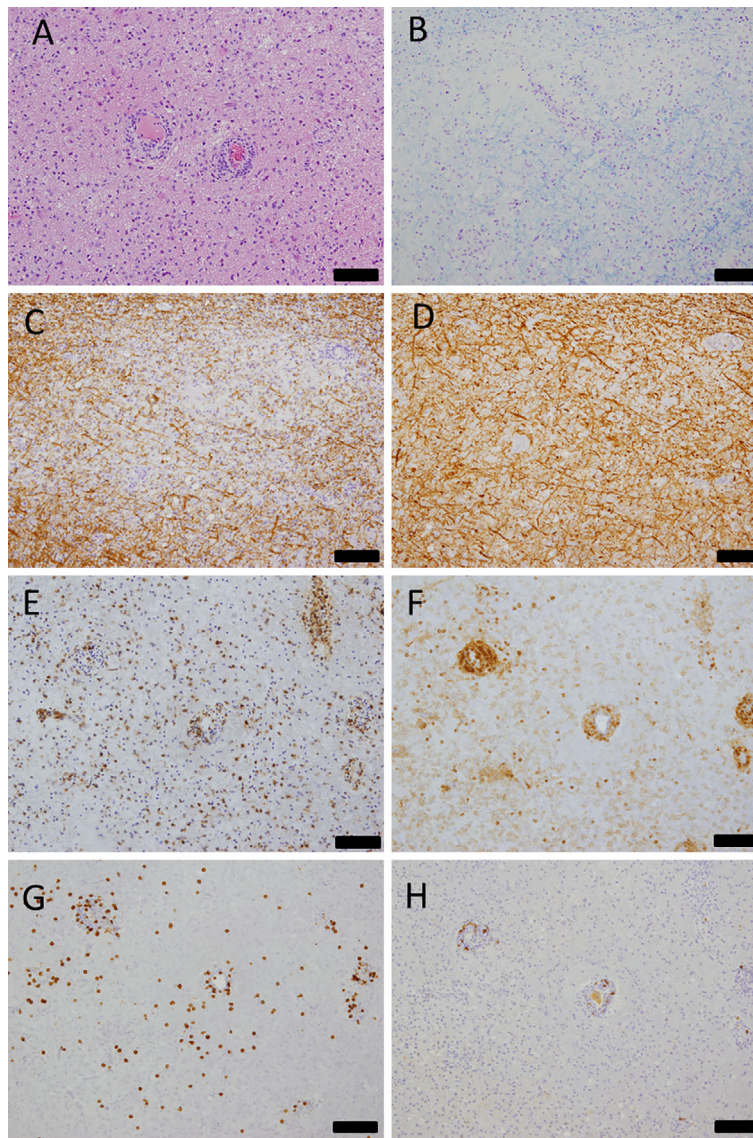
bance on the left side of the face, dysarthria, left hemiparesis, hyperreflexia of the left lower limb, and limb ataxia. MRI showed a hyperintense edematous lesion extending from the right mesencephalic tegmentum to the crus cerebri on T2WI and FLAIR with heterogeneous enhancement after gadolinium administration (Fig. 3A, B, C and D). Laboratory investigations, including the serum levels of sIL-2R and  $\beta$ 2-MG, were normal. An ELISA to detect serum anti-AQP4 antibodies was negative. The patient's serum was also negative for antinuclear antibodies and antibodies for collagen diseases. CSF analyses for MBP, IgG index (0.63), sIL-2R, and  $\beta$ 2-MG were normal and neither OCB nor malignant cells were found in the CSF. Interferon- $\beta$  was discontinued, and the patient was treated with two courses of IVMP, three courses of immunoadsorption plasmapheresis (IAPP), and three courses of plasma exchange. However, her symptoms deteriorated. She developed ophthalmoplegia, could not eat due to dysphagia, and required assistance while walking. Brain MRI revealed that the brainstem lesion extended to the pons (Fig. 3E, F, G and H). The patient was treated with intravenous immunoglobulin (IVIg), but her condition deteriorated further, and she became drowsy. She was treated with rituximab (1,000 mg/day on days 1 and 15) after the institutional committee for the evaluation of highly difficult new medical technologies approved the treatment, and after obtaining written consent from the patient's family. Her symptoms started to improve immediately after the administration of rituximab, and the peripheral blood B cell count dropped rapidly to undetectable levels. At one month after the administration of rituximab, the patient could eat, and brain MRI showed a reduction in the size of the brainstem lesion without enhancement (Fig. 3I, J, K and L). The patient could walk by herself and was discharged from our hospital three months after the administration of rituximab without any complications. At ten months after the administration of rituximab, her B cell count recovered to over 800/mm<sup>3</sup>, and dimethyl fumarate was initiated. There has been no recurrence for approximately 23 months since the administration of rituximab.

## Discussion

We believe that the present case report is the first to describe the clinical course of a patient with RRMS who was treated with rituximab in the acute phase of the disease.

In the present case, the lesion biopsied at the time of the first attack showed pathological findings consistent with those of acute-phase lesions of RRMS. The lesions on brain MRI and the symptoms of the first 3 attacks improved immediately after the administration of IVMP. However, the latest attack was resistant to immunotherapy with corticosteroids, plasmapheresis, and IVIg, with rituximab being the only effective treatment. These findings suggest that the mechanism underlying the last recurrence differed from that of the first 3 attacks.

According to previous case reports, 5 patients with clini-



**Figure 2.** A histological examination of the left occipital lobe lesion of the first attack. Hematoxylin and Eosin staining (A) revealed perivascular and parenchymal lymphocytic infiltrates. Klüver-Barera staining (B) and immunohistochemical staining of myelin basic protein (C) showed demyelination. Axons were preserved on immunohistochemistry with an antibody against phosphorylated neurofilament (SMI-31) (D). Immunohistochemical studies showed numerous CD68+ foamy macrophages (E), parenchymal and perivascular infiltration of CD4+ T cells (F) and a smaller population of CD8+ T cells (G), and a few perivascular CD20+ B cells (H). All scale bars =100  $\mu$ m.

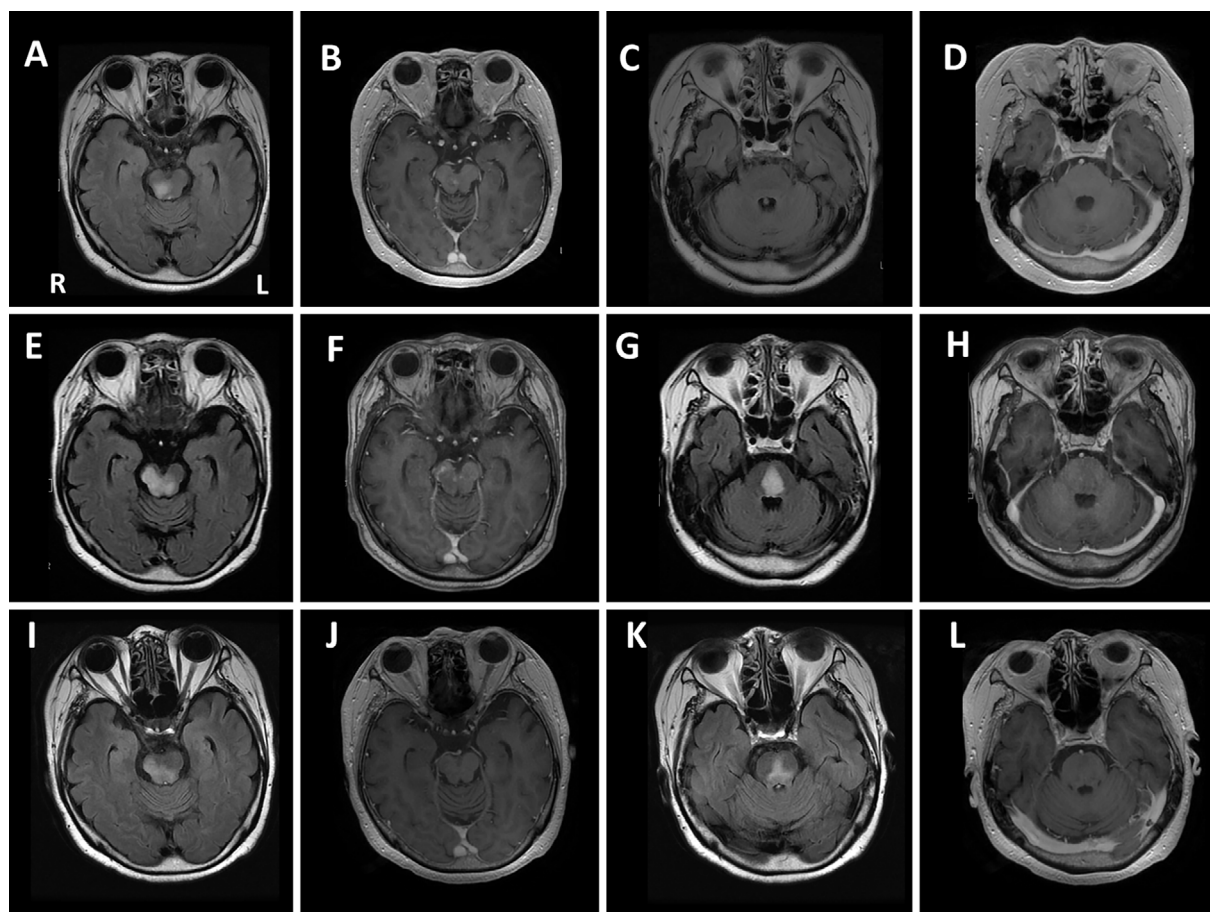
cally isolated syndrome (CIS) or MS are reported to have been treated with rituximab in the acute phase of the disease, and 4 the 5 patients showed improvement after the administration of rituximab (5-7). The detailed clinical course was reported in 2 of these cases. Both patients had CIS and improved soon after the first administration of rituximab (6, 7). Similarly, the symptoms of the patient in the current case report started to improve promptly after the administration of rituximab. We believe that the B cells were promptly depleted after the infusion of rituximab, and that inflammatory reactions related to B cells might have been suppressed due to the loss of the B cell functions, such as antigen-presentation, activation of T cells, and cytokine production (8).

Because the present patient had atypical features of MS, such as late onset, edematous and relatively large lesions on brain MRI, no OCB in CSF, and resistance to the conventional immunotherapies, we could not exclude the possibility that the disease of this patient differed from typical RRMS. We believe that rituximab could be effective in the acute phase of RRMS, especially for the patients who show no improvement with conventional therapies.

## Conclusion

Our findings suggest that the administration of rituximab can be considered as a treatment option for acute-phase RRMS when conventional therapies are not effective.





**Figure 3.** Serial MRI scans of the brain at ten months after the first episode before treatment (A-D), after treatment with corticosteroids, plasmapheresis, and intravenous immunoglobulin (E-H), and after the administration of rituximab (I-L). Axial fluid-attenuated inversion recovery (FLAIR) images showed a hyperintense lesion extending from the right mesencephalic tegmentum to the crus cerebri (A and C), with heterogeneous enhancement on post-gadolinium T1-weighted images (T1WI) (B and D). FLAIR images revealed that the brainstem lesion extended to the pons (E and G) with enhancement on post-gadolinium T1WI (F and H). FLAIR images showed a reduction in the size of brainstem lesion (I and K) without enhancement on post-gadolinium T1WI (J and L) after the administration of rituximab.

The authors state that they have no Conflict of Interest (COI).

## References

- Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. *N Engl J Med* **358**: 676-688, 2008.
- Bar-Or A, Calabresi PA, Arnold D, et al. Rituximab in relapsing-remitting multiple sclerosis: a 72-week, open-label, phase I trial. *Ann Neurol* **63**: 359-400, 2008.
- Naismith RT, Piccio L, Lyons JA, et al. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis: a 52-week phase II trial. *Neurology* **74**: 1860-1867, 2010.
- Polman CH, Reingold SC, Banwell B, et al. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. *Ann Neurol* **69**: 292-302, 2011.
- Sánchez P, Meca-Lallana V, Barbosa A, et al. Tumefactive demyelinating lesions of 15 patients: Clinico-radiological features, management and review of the literature. *J Neurol Sci* **381**: 32-38, 2017.
- Fan X, Mahta A, Jaqer PLDe, Kesari S. Rituximab for tumefactive inflammatory demyelination: a case report. *Clin Neurol Neurosurg* **114**: 1326-1328, 2012.
- Sempere AP, Feliu-Rey E, Sanchez-Perez R, Nieto-Navarro J. Neurological picture. Rituximab for tumefactive demyelination refractory to corticosteroids and plasma exchange. *J Neurol Neurosurg Psychiatry* **84**: 1338-1339, 2013.
- Sospedra M. B cells in multiple sclerosis. *Curr Opin Neurol* **31**: 256-262, 2018.

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