

## Successful Treatment with Rituximab in a Patient with Stiff-Person Syndrome Complicated by Dysthyroid Ophthalmopathy

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### Abstract

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We report a patient with stiff-person syndrome and insulin-dependent diabetes mellitus with anti-glutamic acid decarboxylase (GAD) antibody, who suddenly complained of diplopia due to dysthyroid ophthalmopathy. Therapeutic efficacy of plasmapheresis and high-dose intravenous immunoglobulin was transient. After starting administration of rituximab, the patient showed obvious improvement of muscle spasms due to stiff-person syndrome and ophthalmoplegia following quick depletion of CD20-positive cells in peripheral blood. The anti-GAD and anti-thyroid antibodies decreased slowly. This drug might be a potent therapeutic option for refractory patients with stiff-person syndrome, particularly in those associated with dysthyroid ophthalmopathy.

**Key words:** stiff-person syndrome, dysthyroid ophthalmopathy, anti-glutamic acid decarboxylase (GAD) antibody, rituximab

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### Introduction

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Stiff-person syndrome (SPS) is a rare intractable disorder characterized clinically by progressive rigidity and episodic sudden-onset muscle spasms with frequent association of insulin-dependent diabetes mellitus (DM) and chronic thyroid disorders (1). The anti-glutamic acid decarboxylase (GAD) antibody plays an important role in the pathogenesis by affecting the synaptic transmission of inhibitory neurons, and SPS has come to be recognized as a B-cell-mediated autoimmune disorder of the central nervous system (1-3). To ameliorate clinical symptoms due to SPS, therefore, immunomodulatory therapies targeting the anti-GAD antibody, such as plasmapheresis and high-dose intravenous immunoglobulin (IVIg), are often employed for treatment (4). Here, we report a patient with SPS complicated by dysthyroid ophthalmopathy, who received intermittent administrations of rituximab. The patient showed obvious improvement of both SPS and dysthyroid ophthalmopathy after starting this treatment, and we focus upon the usefulness of rituximab in

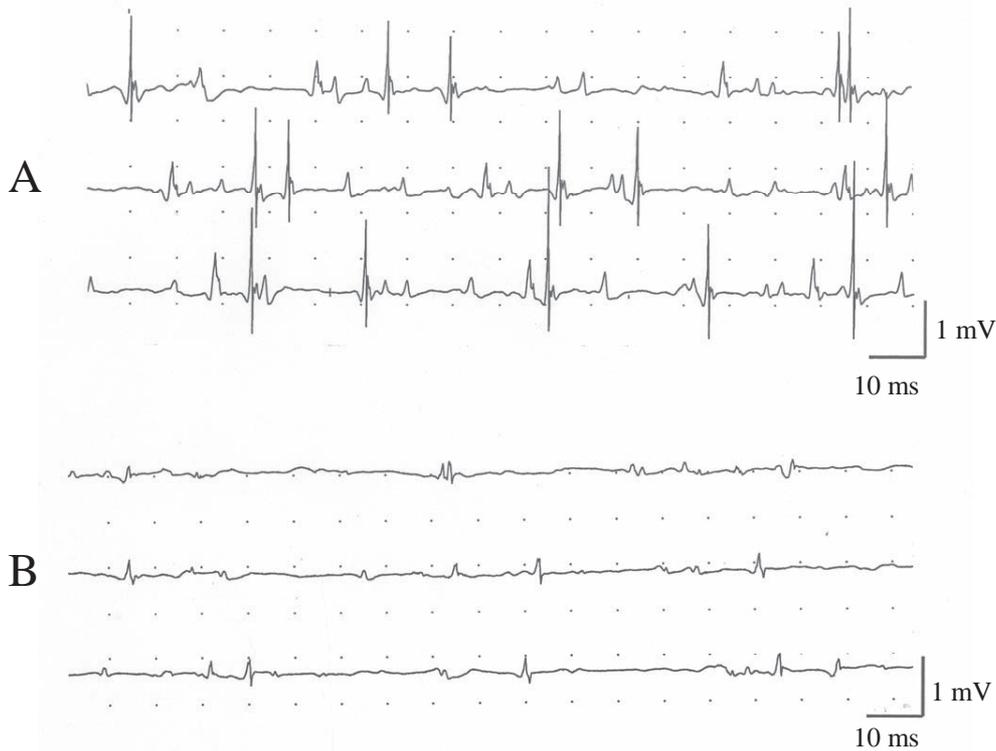
both disorders with regard to clinical efficacy and safety.

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### Case Report

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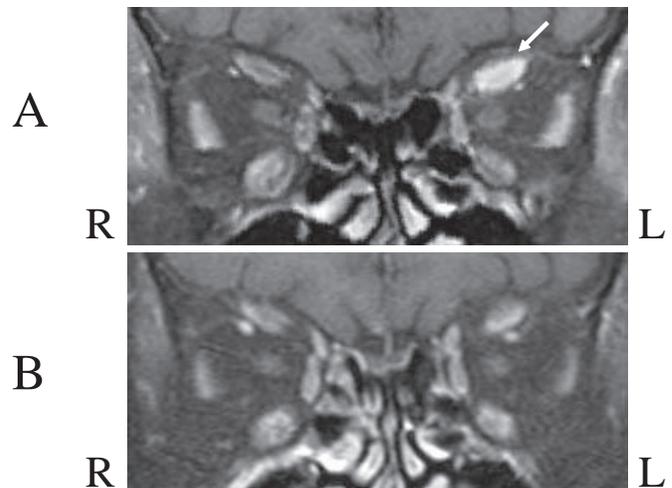
A 59-year-old woman noticed muscle stiffness with sudden-onset spasms mainly in lower extremities with no precipitating cause or significant family history while being treated for Graves' disease in a neighboring hospital. At age 62 she started to use insulin for treatment of DM with the anti-GAD antibody. She gradually became unable to walk because of frequent muscle spasms in her lower extremities. At age 66 she suddenly complained of diplopia, and was referred to our hospital. On admission physical examination showed diffuse goiter, bilateral mild exophthalmos, limited downward movement in the left eye and marked rigidity in the abdomen, lower back and both legs. Muscle power and deep tendon reflexes were normal with no fasciculation, and pathological reflexes were negative. The muscle stiffness score of SPS (4) and clinical activity score of dysthyroid ophthalmopathy (5) were 3 and 1, respectively. Sudden-onset muscle spasms lasting approximately 5 minutes



**Figure 1.** Spontaneous motor unit activity recorded from the right quadriceps at rest showed involuntary muscle contraction (A), which disappeared after intravenous administration of diazepam at a dose of 5 mg (B).

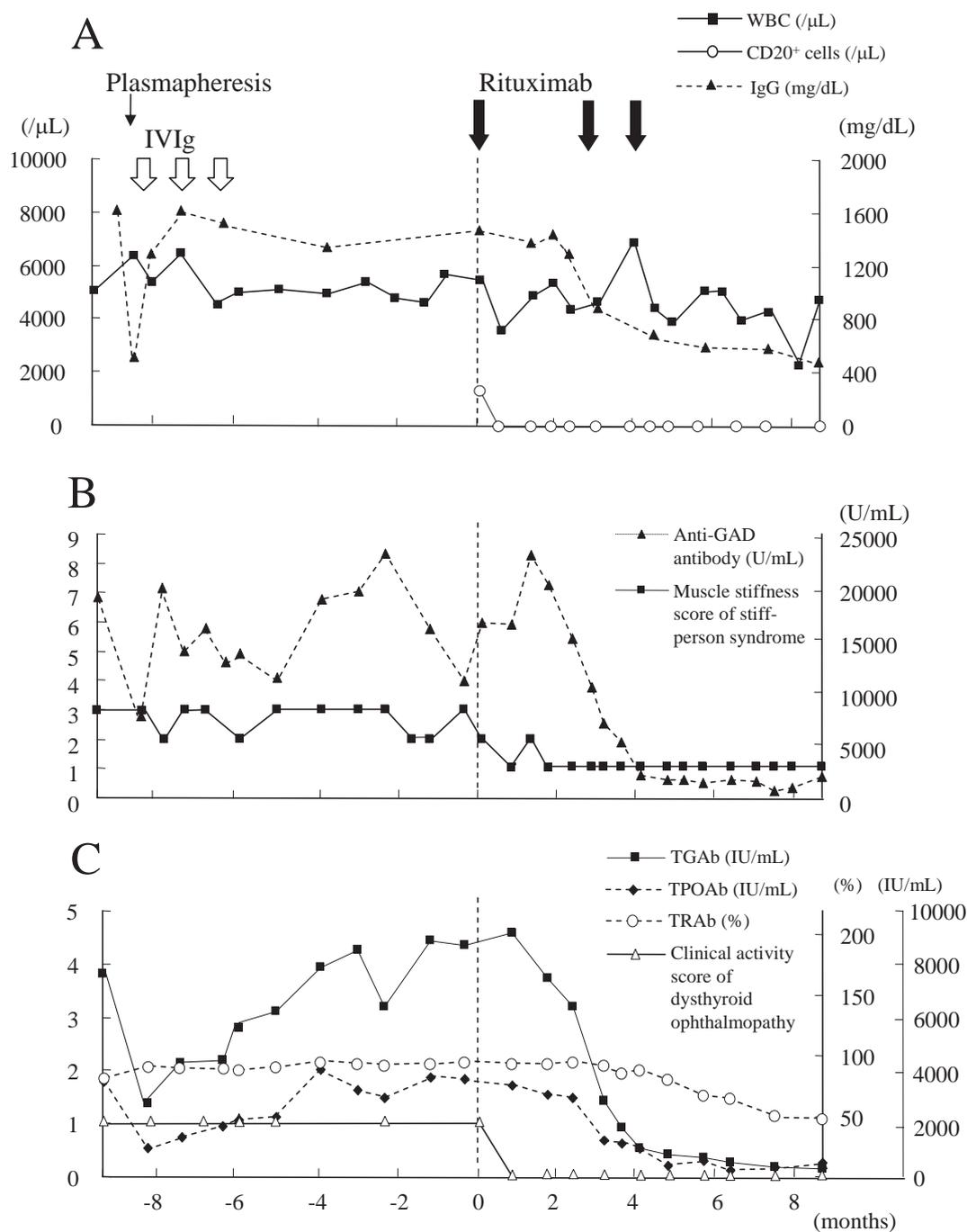
mainly in both legs appeared several times a day, particularly on emotional stress. She could not perform routine daily activities by herself because of anxiety-triggered spasms and frequent falls. There were no abnormal findings in routine laboratory data, including urinalysis, hematology, renal and hepatic indices, and electrolytes except for hemoglobin A1c (6.8%, normal 4.3-5.8%). Free T3 and T4 were 4.56 pg/mL (normal 2.3-4.0 pg/mL) and 1.54 ng/dL (normal 1.0-2.0 ng/dL), respectively, and thyroid function was well controlled by levothyroxine and thiamazole. Marked elevation was seen in the anti-thyroglobulin antibody (TGA<sub>b</sub>, 7,842 IU/mL, normal  $\leq 10.0$ ), anti-thyroid peroxidase antibody (TPOAb, 3,942 IU/mL, normal  $\leq 10.0$ ), anti-thyroid stimulating hormone receptor antibody (TRAb, 87.8%, normal  $\leq 15$ ), thyroid-stimulating antibody (TSAb, 3,850%, normal  $<180\%$ ) and anti-GAD antibody (19,900 U/mL, normal  $<1.5$  U/mL). Electromyography demonstrated spontaneous motor unit activities, which transiently disappeared right after intravenous administration of diazepam (Fig. 1). Magnetic resonance imaging (MRI) demonstrated hypertrophy with gadolinium enhancement in ocular muscles, particularly in the left eye (Fig. 2A).

To ameliorate sudden-onset spasms and diplopia, the patient was treated with IVIg (0.4 g/kg/day for 5 days) repeated 3 times at an interval of 1 month after plasmapheresis in addition to conventional muscle relaxants, including diazepam, baclofen, and alprazolam. Gait disturbance due to muscle spasms improved slightly in conjunction with a de-



**Figure 2.** MRI demonstrated hypertrophy with enhancement effects in ocular muscles, particularly in the left superior rectus (arrow), before treatment (A, T1-weighted image with gadolinium enhancement, TR/TE=600/9.4). These abnormal findings markedly improved 3 months after the rituximab therapy (B, T1-weighted image with gadolinium enhancement, TR/TE=600/9.4).

crease in the anti-GAD antibody, but the efficacy did not continue for longer than 6 weeks. No improvement was seen in diplopia. Six months later the anti-CD20 monoclonal antibody, rituximab, was administered intravenously at a dose



**Figure 3.** Clinical profiles of the patient. After starting administration of rituximab, the patient showed obvious decreases in the muscle stiffness score of SPS (B) and clinical activity score of dysthyroid ophthalmopathy (C) following quick complete depletion of CD20-positive cells in peripheral blood (A). The anti-GAD and anti-thyroid antibodies decreased slowly (B and C).

of 375 mg/m<sup>2</sup> after obtaining informed consent. The Local Ethical Committee approved rituximab for use in this patient. After starting administration of rituximab, the patient showed obvious decreases in the muscle stiffness score of SPS (Fig. 3B) and clinical activity score of dysthyroid ophthalmopathy (Fig. 3C) following quick complete depletion of CD20-positive cells in peripheral blood (Fig. 3A). The anti-GAD antibody, TGAb and TPOAb decreased from approximately 6 weeks after the administration of rituximab (Figs. 3B, 3C), while the TRAb showed no obvious change.

MRI demonstrated reduction in size of ocular muscles with disappearance of gadolinium enhancement (Fig. 2B). Three months later rituximab was additionally given at the same dose as the first administration 2 times at an interval of 1 month because of a slight increase in the frequency of muscle spasms. The anti-GAD antibody, TGAb and TPOAb remained at low levels, and TRAb also decreased gradually. Five months after the third administration of rituximab muscle spasms almost completely disappeared, and the stiffness score of SPS and clinical activity score of dysthyroid oph-

thalmopathy were 1 and 0, respectively. She became able to walk by herself again. No improvement was seen in insulin-dependent DM. There were no serious adverse events other than mild pneumonia due to *Pneumocystis jiroveci* infection, which immediately recovered in response to sulfamethoxazole/trimethoprim. She has remained in good neurological condition with low levels of autoantibodies for 8 months since the third administration of rituximab. The total follow-up period from referral to our hospital is 23 months.

## Discussion

The present patient was diagnosed as having SPS based on muscle stiffness with sudden-onset systemic spasms, spontaneous motor unit activities on electromyography, and strongly positive results for the anti-GAD antibody in serum (1). SPS sometimes develops as a paraneoplastic syndrome (6-8), but there was no evidence suggestive of associated malignancies in the present patient despite intensive systemic survey. Insulin-dependent DM and diplopia due to limited downward movement in the left eye appeared 3 and 7 years after onset of SPS, respectively. Considering that the present patient had hypertrophy of ocular muscles on MRI and Graves' disease with some anti-thyroid autoantibodies, such as TGAb and TRAb, dysthyroid ophthalmopathy was considered to be the cause of diplopia.

Both SPS and dysthyroid ophthalmopathy are usually treated with immunomodulatory therapies, including corticosteroid and plasmapheresis. In the present patient, however, corticosteroid was inadequate because of associated insulin-dependent DM, and the clinical efficacy of plasmapheresis and IVIg was transient. As B-lymphocytes play an important role in the pathogenesis of SPS and dysthyroid ophthalmopathy with regard to production of autoantibodies (1, 4, 9), we decided to use rituximab for treatment of the present patient. This drug is a humanized chimeric anti-CD20 monoclonal antibody capable of killing CD20-positive cells by complement-mediated cytotoxicity, antibody-dependent cellular cytotoxicity and direct induction of apoptosis (10, 11). CD20 is expressed on the surface of pre-B- and mature B-lymphocytes (12), and rituximab shows no direct effects on plasma cells producing immunoglobulins. This drug has been reported to show a favorable outcome in the treatment of malignant lymphoma and autoimmune diseases, including SPS and dysthyroid ophthalmopathy (9, 13-17). In the present patient also, intermittent administrations of rituximab produced obvious improvement of both SPS and dysthyroid ophthalmopathy with a persistent decrease in the anti-GAD and anti-thyroid antibodies. According to the recommended therapeutic protocol for autoimmune disorders, including dysthyroid ophthalmopathy, rituximab is usually given twice at an interval of 2 weeks (13, 14), but in the present patient a single administration was performed at her request. As the frequency of muscle spasms slightly increased 3 months later, rituximab was given again. The interval of approximately 6 weeks be-

tween disappearance of CD20-positive cells from peripheral blood and a decrease in the serum autoantibodies may be due to the lack of direct effects of rituximab on plasma cells. No serious adverse events occurred during and after the treatment in the present patient except for mild pneumonia due to *Pneumocystis jiroveci*, although rituximab has been recently reported to occasionally induce a fatal disease due to infection, such as progressive multifocal leukoencephalopathy (18, 19). We plan to readminister this drug if the frequency of muscle spasms increases again.

There are 2 notable points in the present patient. One is that rituximab failed to ameliorate insulin-dependent DM, in which autoimmune mechanisms play a central role in the pathogenesis as seen in SPS. Decreased production of  $\gamma$ -aminobutyric acid by the anti-GAD antibody causes reversible impairment in function of inhibitory neurons mainly in the spinal cord, leading to spontaneous activities of the motor unit in SPS (2, 3). In contrast to that, insulin-dependent DM has been reported to histopathologically show approximately 80% loss of islet cells in the pancreas, particularly  $\beta$ -cells, at onset of hyperglycemia (20). The discrepancy in response to the rituximab therapy between SPS and insulin-dependent DM may be due to these different pathogenetic mechanisms. The other notable point is that the anti-GAD and anti-thyroid antibodies are not necessarily correlated with disease activity of SPS and dysthyroid ophthalmopathy, respectively. Particularly in SPS in the present case, sudden-onset spasms obviously improved soon after administration of rituximab, although the anti-GAD antibody still remained at a high serum level. These findings suggest that the clinical effectiveness of rituximab in SPS and dysthyroid ophthalmopathy may be not only due to decreased concentrations of autoantibodies but also to other immune-mediated mechanisms, such as inhibition of antigen presentation and cytokine production by B cells. Several recent reports showing a lack of correlation between clinical activity of dysthyroid ophthalmopathy and autoantibodies in serum after rituximab therapy also support this hypothesis (13, 14). The remaining autoantibodies after rituximab therapy in the present patient probably have no significant pathogenicity as long as the titer stays at a low serum level.

In summary, rituximab might be useful in the treatment of SPS with regard to efficacy and safety, although the precise mechanisms remain unclear. This drug should be considered as a potent therapeutic option in refractory patients with SPS, particularly when concurrent with associated disorders, such as dysthyroid ophthalmopathy.

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## References

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1. Espay AJ, Chen R. Rigidity and spasms from autoimmune encephalomyelopathies: stiff-person syndrome. *Muscle Nerve* **34**: 677-690, 2006.
2. Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of  $\gamma$ -aminobutyric acid. *Ann Intern Med* **131**: 522-530, 1999.
3. Levy LM, Levy-Reis I, Fujii M, Dalakas MC. Brain  $\gamma$ -aminobutyric acid changes in stiff-person syndrome. *Arch Neurol* **62**: 970-974, 2005.
4. Dalakas MC, Fujii M, Li M, Lutfi B, Kyhos J, McElroy B. High-dose intravenous immune globulin for stiff-person syndrome. *N Engl J Med* **345**: 1870-1876, 2001.
5. Mourits MP, Prummel MF, Wiersinga WM, Koorneef L. Clinical activity score as a guide in the management of patients with Graves' ophthalmopathy. *Clin Endocrinol* **47**: 9-14, 1997.
6. De Camilli P, Thomas A, Cofell R, et al. The synaptic vesicle-associated protein amphiphysin is the 128-kD autoantigen of stiff-man syndrome with breast cancer. *J Exp Med* **178**: 2219-2223, 1993.
7. Butler MH, Hayashi A, Ohkoshi N, et al. Autoimmunity to gephyrin in Stiff-Man syndrome. *Neuron* **26**: 307-312, 2000.
8. McCabe DJ, Turner NC, Chao D, et al. Paraneoplastic "stiff person syndrome" with metastatic adenocarcinoma and anti-Ri antibodies. *Neurology* **62**: 1402-1404, 2004.
9. Baker MR, Das M, Isaacs J, Fawcett PR, Bates D. Treatment of stiff person syndrome with rituximab. *J Neurol Neurosurg Psychiatry* **76**: 999-1001, 2005.
10. Demidem A, Lam T, Alas S, Hariharan K, Hanna N, Bonavida B. Chimeric anti-CD20 (IDEC-C2B8) monoclonal antibody sensitizes a B cell lymphoma cell line to cell killing by cytotoxic drugs. *Cancer Biother Radiopharm* **12**: 177-186, 1997.
11. Reff ME, Carner K, Chambers KS, et al. Depletion of B cells in vivo by a chimeric mouse human monoclonal antibody to CD20. *Blood* **83**: 435-445, 1994.
12. Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. *Am J Transplant* **6**: 859-866, 2006.
13. Salvi M, Vannucchi G, Campi I, et al. Treatment of Graves' disease and associated ophthalmopathy with the anti-CD20 monoclonal antibody rituximab: an open study. *Eur J Endocrinol* **156**: 33-40, 2007.
14. Bonara P, Vannucchi G, Campi I, et al. Rituximab induces distinct intraorbital and intrathyroidal effects in one patient satisfactorily treated for Graves' ophthalmopathy. *Clin Rev Allergy Immunol* **34**: 118-123, 2008.
15. Salvi M, Vannucchi G, Campi I, Curro N, Beck-Peccoz P. New immunomodulators in the treatment of Graves' ophthalmopathy. *Ann Endocrinol (Paris)* **69**: 153-156, 2008.
16. McLaughlin P, Grillo-López AJ, Link BK, et al. Rituximab chimeric anti-CD20 monoclonal antibody therapy for relapsed indolent lymphoma: half of patients respond to a four-dose treatment program. *J Clin Oncol* **16**: 2825-2833, 1998.
17. Silverman GJ, Weisman S. Rituximab therapy and autoimmune disorders: prospects for anti-B cell therapy. *Arthritis Rheum* **48**: 1484-1492, 2003.
18. Molloy ES, Calabrese LH. Progressive multifocal leukoencephalopathy in patients with rheumatic diseases: are patients with systemic lupus erythematosus at particular risk? *Autoimmun Rev* **8**: 144-146, 2008.
19. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood* **113**: 4834-4840, 2009.
20. Klöppel G, Löhr M, Habich K, Oberholzer M, Heitz PU. Islet pathology and the pathogenesis of type 1 and type 2 diabetes mellitus revisited. *Surv Synth Pathol Res* **4**: 110-125, 1985.