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【 CASE REPORT 】

# Successful Rituximab Treatment in Thrombotic Thrombocytopenic Purpura Patients Complicated by Other Autoimmune Disorders: Two Case Reports

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**Abstract:**
We herein report two cases of thrombotic thrombocytopenic purpura (TTP) complicated by other autoimmune disorders, autoimmune hepatitis and immune thrombocytopenia, respectively. In both cases, corticosteroids were continuously administered for the treatment of preceding autoimmune disorders. However, a sufficient objective response for TTP was not obtained by plasma exchange and corticosteroid treatment. Once a week rituximab (375 mg/m$^2$) treatment for 4 times was initiated within 2 weeks from the diagnosis. Both patients achieved a sufficient response, and have never had any recurrence as of the last follow-up dates. The early introduction of rituximab could be an effective treatment option in TTP patients complicated with other autoimmune disorders.

**Key words:** thrombotic thrombocytopenic purpura, autoimmune hepatitis, immune thrombocytopenia, rituximab, ADAMTS13

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## Introduction

Thrombotic thrombocytopenic purpura (TTP) is a rare but severe clinical condition characterized by thrombocytopenia, hemolytic anemia, and damage of vital organs, including the kidneys and central nervous system. The pathological condition of TTP is based on thrombotic microangiopathy owing to a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13 (ADAMTS13) deficiency. In most cases, acquired autoantibody against ADAMTS13 plays a central role in TTP development (1). Plasma exchange (PE) with corticosteroids is a standard treatment procedure for acquired TTP. TTP is occasionally complicated by other autoimmune disorders such as systemic lupus erythematosus (2). We experienced two TTP cases complicated by other autoimmune disorders, autoimmune hepatitis and immune thrombocytopenia, respectively. Both patients achieved a sufficient and sustained response after being treated with rituximab.

## Case Reports

### Case 1

A 65-year-old man with autoimmune hepatitis (AIH) was admitted to our hospital because of consciousness disturbance with severe thrombocytopenia. Five years prior to admission, he had undergone comprehensive examinations because of elevated serum aspartate aminotransferase and alanine aminotransferase (ALT) levels, elevated serum IgG level, and positive reaction for antinuclear antibody (ANA) without any evidence of hepatitis B and C virus infection. A histopathological analysis of liver tissue specimens indicated chronic hepatitis with lymphoid cell aggregation in the portal vein area. Eventually, a diagnosis of AIH was made.

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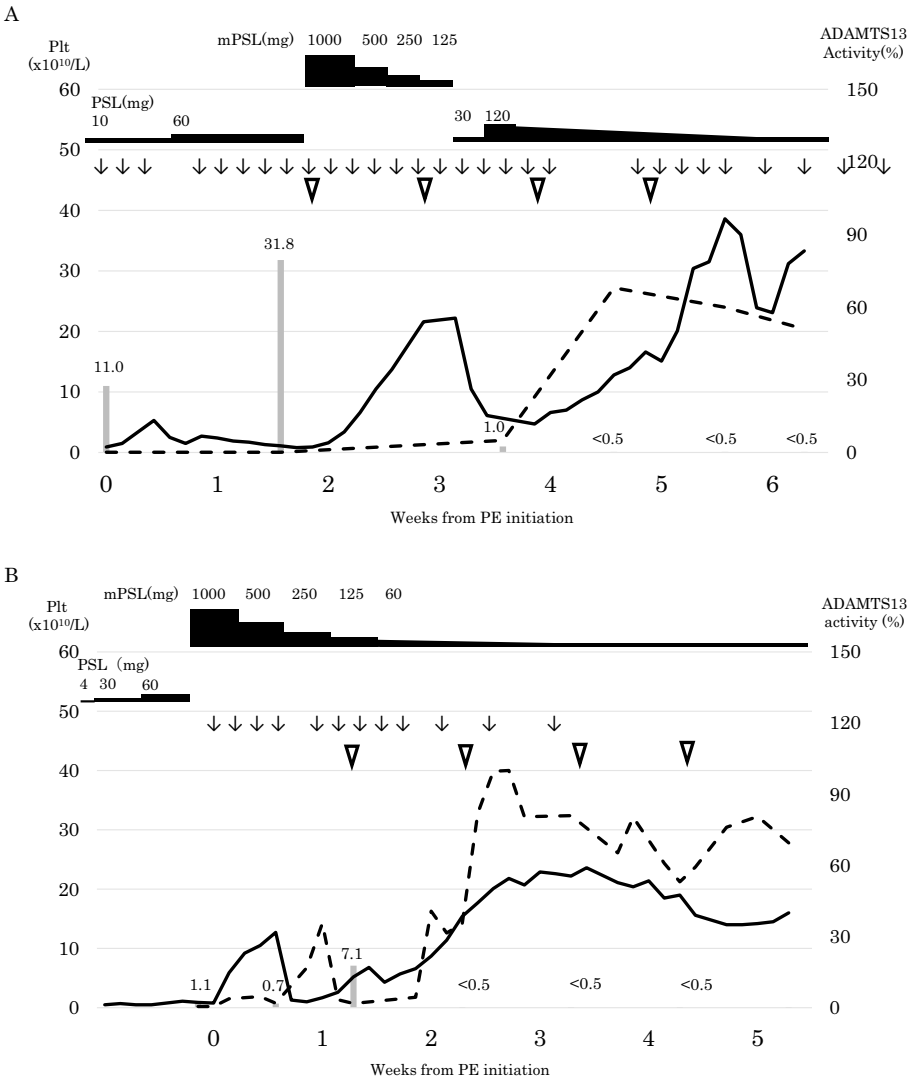


**Figure. Clinical courses of Case 1 (A) and Case 2 (B) after the initiation of plasma exchange (PE). The solid line shows the platelet count (×10¹⁰ /L). The dotted line shows the serum ADAMTS13 activity (%). The vertical bars in graphs show the titers of inhibitor for ADAMTS13 (BU/mL). The inverted triangles show rituximab (375 mg/m²). The arrows show PE. Plt: platelet, PSL: prednisolone, mPSL: methylprednisolone**

Prednisolone (PSL) of 30 mg/day was initiated, and his liver function improved. The dose of PSL was gradually decreased, and subsequently, a maintenance dose (10 mg/day) was continuously administered until admission.

At admission, laboratory data demonstrated severe thrombocytopenia (9×10⁹/L), anemia (Hb 6.7 g/dL), high serum lactate dehydrogenase (LDH) (2,041 U/L, normal range, 119-229 U/L), increased total bilirubin (3.5 mg/dL) and indirect bilirubin (3.0 mg/dL), and undetectable serum haptoglobin with appearance of red cell fragmentation on the blood film, indicating thrombotic microangiopathy. The disease status of AIH was considered to be stable because the ALT level was in the normal range (30 U/L). The serum IgG level was almost normal (1,719 mg/dL, normal range, 870-1,700 mg/dL), and the titer of ANA was increased (1: 160). The immature platelet fraction (IPF) was 5.3%. Disseminated intravascular coagulation (DIC) was ruled out because of findings of coagulation tests of PT (12.0 sec, control 11.2 sec), APTT (28.6 sec, control 32.5 sec), fibrinogen (441 mg/dL) and FDP (10.5 μg/mL). Renal insufficiency and fever were observed, leading to the clinical diagnosis of TTP. PE was initiated immediately with a maintenance dose of PSL (10 mg/day) for AIH (Figure A). The diagnosis of TTP was then confirmed according to decreased serum ADAMTS13 activity (<1%) with a high titer of inhibitor for ADAMTS13 (11.0 BU/mL). The platelet count increased to 50×10⁹/L on day 3 from PE initiation. The PSL dose was not increased, because an objective response was obtained. However, an interruption of PE on day 4 resulted in a decreased platelet count to 25×10⁹/L again on day 5. Although we reinitiated PE every day with an increased dose of PSL of 60 mg/day (1 mg/kg/day), the platelet count did not increase. Therefore, high-dose methylprednisolone (1 g/day) was administered for 3 days. In addition, rituximab (375

mg/m$^2$) was administered once a week for 4 times from day 14. Before rituximab treatment, off-label rituximab use for TTP was approved by the institutional committee for the evaluation of unapproved, contraindicated, and off-label drug use. Written informed consent was obtained from the patient before rituximab use. The platelet count increased gradually and normalized on day 35. We continued PE every day until day 21, and then, on alternate days until day 40. The activity of ADAMTS13 recovered with a decreased inhibitor titer. The PSL dose was tapered gradually, and PSL of 10 mg/day was administered continuously. Corticosteroid, PE, and rituximab therapies were tolerable, and there were no significant toxicities resulting in any treatment interruption. The platelet count was still maintained within the normal range at the last follow-up date, 6 months after the TTP diagnosis. The disease status of AIH also remained stable without an elevation of ALT (23 U/L) under maintenance therapy of PSL (10 mg/day). The serum IgG level decreased to 937 mg/dL, and the ANA titer decreased to the normal range (1: 40).

### Case 2

A 33-year-old woman who had been diagnosed with immune thrombocytopenic purpura (ITP) at 13 years of age was admitted to our hospital because of the sudden appearance of severe purpura and worsening of thrombocytopenia with a platelet count of $5\times10^9$/L. When she was 13 years old, multiple petechia appeared on her legs, and a blood test revealed thrombocytopenia (platelet count $3\times10^9$/L). A diagnosis of ITP was made according to a bone marrow analysis of megakaryocytic hyperplasia without any dysplastic features and a high serum level of platelet-associated immunoglobulins (PAIgG) (42.4 ng/$10^7$cells, normal range, <27.6 ng/$10^7$cells) at another hospital, and PSL was initiated for ITP treatment. She first visited our hospital at 19 years of age. Treatment for ITP by PSL (4-30 mg/day) had been continued. Until 4 days before admission, her platelet count had been kept over $100\times10^9$/L with a maintenance dose of PSL (4 mg/day).

At admission, she had slight anemia (Hb 11.4 g/dL), an increase of total bilirubin (2.4 mg/dL), indirect bilirubin (2.4 mg/dL) and serum LDH (838 U/L) with normal serum ALT (18 U/L) and creatinine (0.43 mg/dL). IPF increased (14.1%) and the reticulocyte count was in the normal range ($8\times10^{10}$/L). The PSL dose was increased to 60 mg/day, since an exacerbation of ITP was suspected. However, no objective response was obtained. On the 6th hospital day, she had fever, and the laboratory data showed anemia (Hb 5.4 g/dL), an elevated serum LDH level (1,140 U/L), total bilirubin (2.4 mg/dL), and indirect bilirubin (2.3 mg/dL), and an undetectable serum haptoglobin level with the appearance of red cell fragmentation on peripheral blood film, indicating thrombotic microangiopathy. Therefore, a clinical diagnosis of TTP was made. Blood coagulation tests, including PT (10.7 sec, control 11.0 sec), APTT (20.9 sec, control 33.7), fibrinogen (276 mg/dL), and FDP (10.9 μg/mL), showed no definite evidence of DIC. PE was initiated with high-dose methylprednisolone of 1 g/day for 3 days followed by 500 mg/day for 3 days, and tapered doses, and then, her platelet count increased gradually (Figure B). Later, the diagnosis of TTP was confirmed due to a decreased serum ADAMTS13 activity (<5%) with a high titer of inhibitor for ADAMTS13 (1.1 BU/mL). After the cessation of PE, her platelet count decreased again on day 6 from PE initiation. Therefore, we restarted PE and rituximab (375 mg/m$^2$) was introduced on day 10. Before rituximab treatment, off-label rituximab use for TTP was approved by the institutional committee for the evaluation of unapproved, contraindicated, and off-label drug use. Written informed consent was obtained from the patient before rituximab use. Rituximab was administered once a week for 4 times, and then, the platelet count and the ADAMTS13 activity increased, while the inhibitor concentration decreased. The serum haptoglobin increased to detectable level (95 mg/dL) on day 21. The platelet count was stable after PE cessation. The corticosteroid dose gradually decreased and eventually stopped at one year from TTP diagnosis. No significant adverse events which required treatment interruption. The platelet count has remained in the normal range for 6 years without any treatment including corticosteroids, thus suggesting that rituximab was effective for not only TTP, but also for ITP.

## Discussion

There are few reports describing TTP complicated by AIH or ITP (3, 4). It remains unclear whether there are differences in the clinical courses and outcomes between TTP patients with or without other autoimmune disorders. Letchumanan et al. (5) showed higher mortality rates and a longer time to achieve complete remission in TTP patients with SLE than those without SLE. Patients with autoimmune disorders often receive corticosteroid therapy. The optimal corticosteroid dose for treatment has yet to be established in TTP patients complicated by autoimmune disorders, especially those who already received corticosteroids at the time that TTP is first diagnosed.

A sufficient objective response was not achieved by PE and corticosteroids in the two patients described in the present report. In addition, the titer of ADAMTS13 inhibitor increased during PE and corticosteroid treatment. Rituximab, a humanized anti-CD20 monoclonal antibody, could be effective for TTP via different mechanisms from corticosteroid and/or PE. Rituximab may reduce autoantibody production by decreasing the number of B-lymphocytes, similar to other autoantibody-mediated disorders such as ITP. In the present two cases, the ADAMTS13 inhibitor decreased after rituximab administration. Rituximab is effective for the treatment of TTP refractory to PE and corticosteroid therapy (6) and also effective for the treatment of TTP associated with SLE refractory to them (7). The frontline use of rituximab for TTP remains controversial. In certain conditions, including cases complicated by autoimmune disorders, the early or

frontline introduction of rituximab for TTP treatment may improve the clinical outcomes of such patients.

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

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