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【 CASE REPORT 】

Thrombotic Thrombocytopenic Purpura Treated with Rituximab Associated with Primary Sjögren's Syndrome and Primary Hypothyroidism

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Abstract:

A 47-year-old man was admitted to our hospital because of thrombocytopenia and consciousness disturbance. As his laboratory data showed undetectable activity of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) and the presence of ADAMTS13 inhibitor, he was diagnosed with acquired thrombotic thrombocytopenic purpura (TTP). Asymptomatic primary Sjögren's syndrome (SS) and primary hypothyroidism were incidentally diagnosed on screening. After initial plasma exchange therapy and pulse corticosteroid therapy, the patient received rituximab therapy for refractory TTP with "inhibitor boosting" and recovered. TTP secondary to primary SS is rare but can trigger refractory TTP. Treatment with rituximab, which is considered "inhibitor boosting," should be considered when re-exacerbation occurs.

Key words: thrombotic thrombocytopenic purpura, ADAMTS13, rituximab, Sjögren's syndrome, primary hypothyroidism

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Introduction

Thrombotic microangiopathy (TMA) is a pathological condition characterized by generalized microvascular occlusion by platelet thrombi, thrombocytopenia, and microangiopathic hemolytic anemia (1). It is potentially a life-threatening multisystem disorder. Thrombocytopenic purpura (TTP) is a representative disease included in TMA and can be classified as either congenital or acquired TTP. If the activity of a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13 (ADAMTS13) is less than 10%, the patient is diagnosed as having TTP. If a patient is positive for anti-ADAMTS13 autoantibodies, a diagnosis of acquired TTP is made (2). Observations supporting the diagnosis include the presence of schistocytes in peripheral blood smears, an increase in lactic dehydrogenase (LDH) levels, normal coagulation test results, and negative Coombs test results.

The pathogenesis of TTP is mainly due to a deficiency in von Willebrand factor (vWF) cleaving protease activity. ADAMTS13 physiologically cleaves large vWF multimers in plasma. Deficiency of ADAMTS13 activity subsequently causes the aggregation of platelets and extensive microvascular thrombosis. This condition can be caused by malignancy, infection, connective tissue disease, transplantation, pregnancy, and drugs. Several cases of acquired TTP associated with connective tissue disease have been reported, with causes typically attributed to systemic lupus erythematosus (SLE).

In contrast, TTP secondary to primary Sjögren's syndrome (SS) is rare despite its prevalence. Furthermore, primary hypothyroidism is occasionally associated with primary SS, but whether or not primary hypothyroidism can

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Table. Laboratory Data on Admission to Our Hospital.

WBC	5.58 $\times 10^3$ /μL	PT	11.4 sec
RBC	2.20 $\times 10^6$ /μL	APTT	24.0 sec
Ret	18.1 $\times 10^4$ /μL	FIBG	311.0 mg/dL
Schistocyte	3.6 %	D-dimer	2.7 μg/mL
Hb	6.7 g/dL		
Plt	0.9 $\times 10^4$ /μL	FT-3	1.56 pg/mL
		FT-4	0.86 ng/dL
TP	6.5 g/dL	TSH	16.36 μIU/mL
Alb	3.7 g/dL		
AST	51 U/L	FANA	×160
ALT	35 U/L	anti-ds-DNA antibodies	3.0 IU/mL
T-Bil	3.47 mg/dL	anti-RNP antibodies	<2.0 U/mL
D-Bil	0.68 mg/dL	anti-Sm antibodies	<1.0 U/mL
I-Bil	2.79 mg/dL	anti-SSA antibodies	1,200.0 U/mL
ALP	208 U/L	anti-SSB antibodies	2.5 U/mL
γGT	24 U/L	RF	19 U/mL
LD	745 U/L	anti-TG antibodies	94.7 IU/mL
BUN	29.6 mg/dL	anti-TPO antibodies	42.3 IU/mL
Cre	1.20 mg/dL		
Na	140 mmol/L	ADAMTS13	<0.01 IU/mL
K	3.7 mmol/L	ADAMTS13 inhibitor	2.0 BU/mL
Cl	105 mmol/L		
CRP	0.38 mg/dL		
Haptoglobin	<5 mg/dL		

Ret: reticulocyte, T-Bil: total bilirubin, D-Bil: direct bilirubin, I-Bil: indirect bilirubin, FIBG: fibrinogen, FT3: free triiodothyronine, FT4: free thyroxine, TSH: thyroid stimulating hormone, FANA: fluorescent antinuclear antibody, TG: thyroglobulin, TPO: thyroid peroxidase, ADAMTS13: a disintegrin-like and metalloproteinase with thrombospondin type 1 motifs 13

manifest in combination with TTP is unclear.

TTP associated with primary SS and primary hypothyroidism is exceedingly rare, and there have been no such cases treated with rituximab. We encountered the first case of TTP associated with primary SS and primary hypothyroidism that was successfully treated with rituximab in addition to plasma exchange (PE) and pulse corticosteroid therapy. We herein report the clinical course along with a brief review of the relevant literature.

Case Report

A 47-year-old man visited a hospital with a main complaint of hematuria. He had a history of minimal change nephrotic syndrome (MCNS) that had developed 17 years earlier and been treated with steroids and cyclosporin therapy. He had been in complete remission from nephrotic syndrome without medication for five years. Although he showed anti-SSA antibody positivity during an examination for MCNS, he did not meet the diagnostic criteria for SS at that time.

To examine the cause of hematuria, a blood sample was collected. Laboratory examination results showed marked thrombocytopenia (10,000/μL). Although platelet transfusion was performed, his platelet level did not increase. In addition, treatment with prednisolone (60 mg daily, orally) was initiated under the suspicion of immunogenic thrombocytopenia. After 7 days of treatment, his platelet count did not improve, and consciousness disturbance appeared.

He was referred and transported to our hospital for further diagnosis and therapy. A physical examination at admission revealed a fever of 38.5℃, a yellow ocular conjunctiva, palpebral conjunctival anemia, and scattered purpura on the upper limbs. His consciousness level was E4 V4M6 per the Glasgow Coma Scale (GCS). The laboratory findings at our hospital are shown in Table. He showed marked anemia and thrombocytopenia. His haptoglobin level was undetectable, and his peripheral blood smears revealed 3.6% fragmented red cells. These findings indicated intravascular hemolysis. His ADAMTS13 activity was undetectable, and ADAMTS13 inhibitor (2.0 BU/mL) was also detected. Based on these findings, we diagnosed the patient with acquired TTP. Blood culture, other cultures, serological tests, an endoscopic examination, and computed tomography (CT) did not reveal any signs of infectious diseases or malignancy.

Endocrine examinations revealed low FT4, high thyroid-stimulating hormone (TSH), and positive anti-thyroglobulin (TG) and anti-thyroid peroxidase (TPO) levels. These findings indicated primary hypothyroidism, although he did not have symptoms or obvious goiter thyroid enlargement.

Autoantibody screening was performed, and the significant findings were the presence of a speckled pattern of

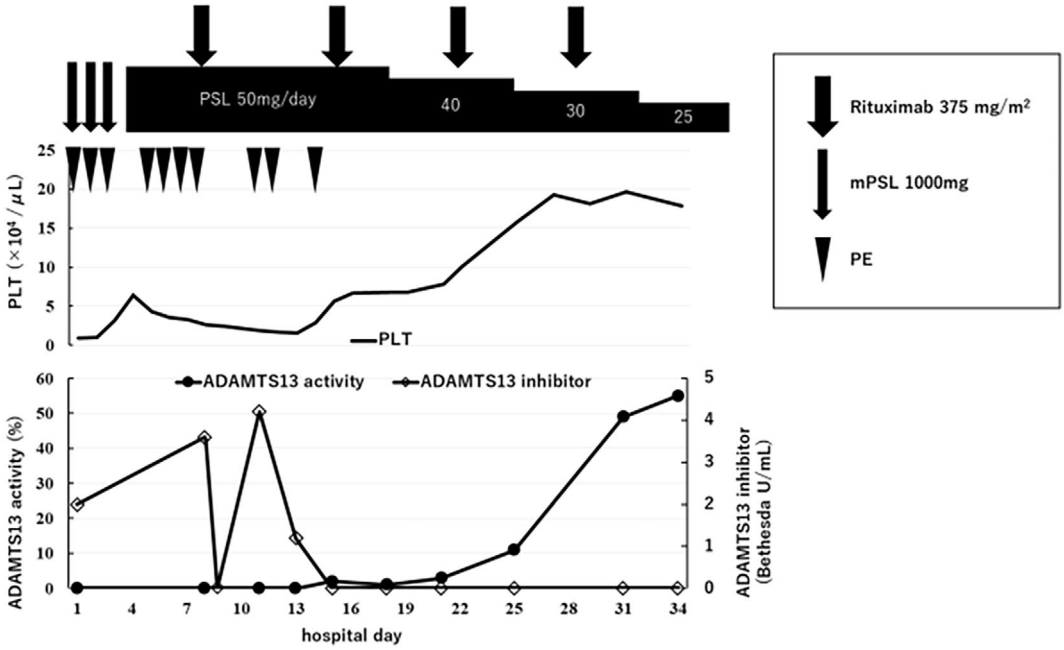

Figure. **The change in the platelet count, ADAMTS13 activity, and ADAMTS13 inhibitor level as well as the treatment interventions during the hospital course. On day 8, the ADAMTS13 inhibitor level detected before PE was markedly decreased to an undetectable value after PE. However, this level increased to a value more than that on day 8 just before starting the next PE session. PLT: platelet, PE: plasma exchange therapy, mPSL: methylprednisolone**

anti-nuclear antibody (ANA) and a positive anti-SSA level. Therefore, this patient was diagnosed with acquired TTP associated with asymptomatic SS and hypothyroidism. He was initially treated with daily PE and pulse corticosteroid therapy (intravenous methylprednisolone 1,000 mg/day for 3 days), which was switched to oral prednisolone therapy (50 mg/day). PE was performed using nafamostat mesylate for anticoagulation and a blood-access catheter for vascular access. Fresh-frozen plasma of 1.2 plasma volumes was used as a replacement solution. We used the OP-08W filter (Asahikasei Medical, Tokyo, Japan) and ACH-Σ (Asahikasei Medical) for single-filtration plasmapheresis.

No adverse events associated with the initial treatment occurred, his consciousness level improved to normal, and his platelet count began to increase. Treatment with PE and steroids was continued, but his platelet count began to decrease again on day 5 of hospitalization. His platelet count continued to decrease subsequently despite treatment with PE and steroids. It was suspected that the initial treatment had not controlled his disease condition. It was observed later that his ADAMTS13 inhibitor levels had increased to 3.6 BU/mL before PE on day 8 despite antibody removal by PE according to a post-therapy comparison. On the same day, treatment with rituximab (375 mg/m^2, once a week for 4 weeks) was started under suspicion of refractory TTP. Five days after starting the treatment with rituximab, his platelet count began to increase again. In addition, his hemolytic anemia was improved, and his fragmented red cell count was decreased. ADAMTS13 inhibitor was no longer detected on day 15, and we stopped PE on the same day. The ADAMTS13 activity showed a recovering trend and reached 55% on day 36. The time course of changes in the platelet count, ADAMTS13 inhibitor level, and ADAMTS13 activity is shown in Figure. This time course shows that his platelet count improved temporarily after starting PE but decreased again subsequently. It seems that the ADAMTS13 inhibitor level increased after starting PE but was ameliorated by treatment with rituximab, and then TTP was improved following the disappearance of the inhibitor.

After the amelioration of TTP, he started to receive levothyroxine treatment (25 μg/day via oral) for primary hypothyroidism. His thyroid function improved following this treatment. The positive anti-SSA antibody presence led to suspicion of SS. The lacrimal gland function was normal, including on Schirmer's test and ocular staining. Salivary scintigraphy showed a decreased salivary function, and the chewing gum test showed a decreased salivary secretion. Based on the above findings, the diagnosis of primary SS was made according to the revised Japanese Ministry of Health criteria for the diagnosis of SS (1999) (3).

He was asymptomatic at the diagnosis and did not need any treatment at that time. He was discharged from the hospital on day 40, as his examination values had completely recovered to normal levels, and he was prescribed treatment with 25 mg/day prednisolone orally. Following discharge, no signs of TTP relapse were observed, and his platelet count has subsequently remained stable. However, he complained of mouth dryness despite being asymptomatic before discharge. This was considered to be a symptom of SS, and he has received symptomatic treatment with pilocarpine.

Discussion

We reported a case of acquired TTP associated with primary SS and primary hypothyroidism treated with rituximab in addition to standard therapies. We believe that our case is clinically instructive in several aspects, particularly concerning the diagnosis and treatment of TTP.

Acquired TTP is caused by various conditions, such as connective tissue diseases, malignant tumors, infections, drugs, and pregnancy, among others (4). There have been several reports on TTP secondary to connective tissue diseases, such as to SLE, mixed connective tissue disease, rheumatoid arthritis, scleroderma, and dermatomyositis. Fujimura examined 422 TTP cases with ADAMTS13 inhibitor positivity, among whom 108 (25.6%) had connective tissue disease or associated diseases (5). Among connective tissue diseases, SLE accounted for the largest percentage, at 41.6%.

Compared to SLE, SS combined with TTP is quite rare. In our patient, there were no other predisposing factors for TTP, such as other autoimmune disease, malignant tumor, or infectious disease. Therefore, the causes of TTP in our patient were considered to be related to primary SS and primary hypothyroidism. To our knowledge, only 4 cases of TTP with positive ADAMTS13 inhibitor combined with SS have been reported in the past 20 years, and none of them were associated with primary hypothyroidism (6-8). It should be noted that none of those cases had been diagnosed with SS previously, as in our case.

In the present patient, dry mouth appeared as an initial symptom of SS after the onset of TTP, although the patient was asymptomatic at the time of the TTP diagnosis. Furthermore, there were no symptoms of primary hypothyroidism at the diagnosis, but the patient required supplementation of thyroid hormone for hypothyroidism. Roriz et al. reported that some patients developed an autoimmune disorder after the onset of TTP (9). In addition, Jonsson et al. reported that autoantibodies (ANA, rheumatoid factor, anti-SSA, anti-SSB) presented before the symptom onset in primary SS (10). There are asymptomatic SS patients who have antibody positivity. It is thought that symptoms of autoimmune disease, such as SS, may be triggered by the onset of TTP, and autoimmune disease requiring treatment, such as primary hypothyroidism, can be diagnosed by screening for TTP. If asymptomatic SS can be diagnosed in advance, it can be treated promptly when symptoms appear. If patients with connective tissue disease develop thrombocytopenia, we should consider the possibility of TTP and check the ADAMTS13 inhibitor level. However, if the diagnosis of secondary TTP is made, it is important to screen for collagen diseases, including SS, even if the patient is asymptomatic.

It is also noteworthy that our patient was resistant to initial PE and pulse corticosteroid therapy but responded to rituximab. PE is the established treatment for acquired TTP (11), but a proportion of TTP cases is resistant to PE, as in our case. In these cases, rituximab can be an effective alternative treatment. Rituximab is an anti-CD20 monoclonal antibody that has been successfully used mainly in B-cell lymphoma treatment. Its efficacy in various autoimmune diseases has also been investigated in recent years. It is being used increasingly frequently in clinical practice for patients resistant to PE in the acute phase of TTP (12, 13). Rituximab is thought to resolve TTP by depleting the B cells producing ADAMTS13 inhibitor, and its effectiveness against TTP is now well known. Rituximab has a recommendation grade of 1B in the 2017 diagnostic and treatment guidelines for TTP in Japan (4). While we did not decide to use rituximab to treat the TTP in the present case, it has been the accepted treatment for refractory relapsing TTP for reimbursement through the public health insurance system in Japan since August 2019. However, it is impractical to use rituximab for all TTP patients due to the costs and adverse events accompanying treatment. Therefore, it is important to determine the patient group most urgently needing rituximab to treat TTP refractory to PE.

In the present case, ADAMTS13 inhibitor was removed by PE based on a post-treatment comparison. However, the ADAMTS13 inhibitor level before each PE session continued to be increased. This phenomenon is known as "inhibitor boosting" (14). Although the exact mechanism underlying "inhibitor boosting" is unclear, it is thought that an immunologic response induces an increase in ADAMTS13 inhibitor production because the exogenous ADAMTS13 epitopes supplied by fresh-frozen plasma during PE are recognized as antigens (15). "Inhibitor boosting" is considered to be a phenomenon observed in refractory TTP cases and is suggested to be a kind of anamnestic response. Anamnestic responses are defined as the renewed rapid production of an antibody following a subsequent contact with related antigens. Therefore, the occurrence of "inhibitor boosting" may depend on the antibody-producing capability. Anamnestic responses may be more likely to occur in patients with autoimmune diseases, as they tend to have a high antibody-producing capability and hypergammaglobulinemia. For example, patients with SS tend to have several types of autoantibodies, such as rheumatoid factor (RF), ANA, anti-SS-A, and anti-SS-B (16). Thus, "inhibitor boosting" may more likely occur in patients with autoimmune diseases than in those without such diseases, although research concerning this subject has not yet been conducted.

In addition, the present patient had a history of recurrent MCNS and was diagnosed with autoimmune thyroiditis on admission. One of the pathogeneses of MCNS is T cell dysfunction, and he already had several antibodies. Therefore, it is possible that his immune tolerance system was malfunctioning, and the risk of autoantibody production-including ADAMTS13 inhibitor-was elevated.

Isonishi et al. noted that high ADAMTS13 inhibitor titers measured prior to PE were a good indicator for predicting refractory TTP (14). Fujimura examined 108 cases of TTP

with ADAMTS13 inhibitor positivity secondary to connective tissue diseases, of whom only 28 (26%) exhibited high levels of ADAMTS13 inhibitor (2.0 BU/mL) (5); the ADAMTS13 inhibitor titer in our case was 2.0 BU/mL. This finding suggests that the antibody production capacity in such cases, including our own, may be high. Therefore, it is important to observe the clinical course, including the transition of ADAMTS13 inhibitor levels, carefully during PE in cases of TTP with ADAMTS13 inhibitor positivity and/or immunological disorders.

Several reports have stated rituximab to be effective against TTP with "inhibitor boosting," as in our case (17, 18). While there is no consensus concerning the timing of initiating rituximab therapy, it should be administered when "inhibitor boosting" is suspected. Therefore, even if the standard treatments, including PE, generate responses initially, rituximab treatment should be considered promptly when the therapeutic effects with the initial treatment worsen and re-exacerbation is observed, such as platelet re-reduction or an increasing trend in ADAMTS13 inhibitor.

Conclusions

In conclusion, we described the first case of TTP treated with rituximab therapy associated with SS and primary hypothyroidism. Autoantibody screening in the workup of secondary TTP is important in order to avoid missing a diagnosis and to enact prompt treatment of autoimmune diseases, such as primary SS or primary hypothyroidism. In addition, treatment with rituximab should be considered without delay when re-exacerbation that is considered to involve "inhibitor boosting" is observed.

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

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