Relapsed/refractory acquired thrombotic thrombocytopenic purpura in a patient with Sjögren syndrome

Case report and review of the literature

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Abstract
Rationale: Thrombotic thrombocytopenic purpura (TTP) is a rare, fatal disorder which could be caused by autoimmune diseases. However, TTP secondary to Sjögren syndrome (SS) is extremely rare.

Patient concerns: A 47-year-old woman with an 8-year history of SS was admitted due to skin ecchymosis and bleeding gums. Then she gradually developed fever and headache.

Diagnoses: Laboratory investigations suggested anemia, thrombocytopenia, increased lactic dehydrogenase, and a disintegrin-like metalloproteinase with thrombospondin motif type 1 member 13 (ADAMTS13) activity deficiency with high inhibitor titers. Acquired TTP was thus diagnosed.

Interventions: Plasma exchange (PE) was the first choice for treatment, while glucocorticoid, cyclosporine A (CSA), rituximab, and intravenous immunoglobulin (IVIG) were used simultaneously. Bortezomib, a selective proteasome inhibitor and thereby inducing apoptosis in both B-cells and plasma cells, was added.

Outcomes: She was discharged from the hospital and then treated with prednisone of 40 mg/d and hydroxychloroquine. The patient remained in full remission.

Lessons: We conclude that bortezomib should be considered for patients with TTP refractory to PE, steroids, and rituximab due to its efficacy and relatively favorable side effect profile.

Abbreviations: CSA = cyclosporine A, IVIG = intravenous immunoglobulin, PE = plasma exchange, SS = Sjögren syndrome, TTP = thrombotic thrombocytopenic purpura.

Keywords: ADAMTS13, bortezomib, Sjögren syndrome, thrombotic thrombocytopenic purpura

1. Introduction
As a critical disease with low incidence, thrombotic thrombocytopenic purpura (TTP) is commonly characterized by 5 typical symptoms, including fever, thrombocytopenia, microangiopathic hemolytic anemia, neurological symptoms, and renal damage.[1] Its pathogenesis is mainly due to deficiency of von Willebrand factor lyase (ADAMTS13) activity, which cannot cleave large von Willebrand factor (vWF) multimers in plasma, causing massive platelet (PLT) aggregation and extensive microvascular thrombosis. Plasma exchange (PE) is the most fundamental and optimal treatment for such a disorder, which can achieve an overall survival rate of 80% to 85%.[2] However, 40% of TTP patients still have early recurrence, and some refractory/recurrent TTP patients are facing death.[3] TTP can be secondary to a variety of autoimmunity diseases. TTP secondary to Sjögren syndrome (SS) is not common, and refractory/recurrent manifestations are particularly rare. In the present study, we described and analyzed a case of refractory/recurrent TTP secondary to SS.

2. Case report
The study was approved by the Ethics Committee of the Soochow University. Informed written consent was obtained from the patient for publication of this case report and accompanying images. The medical records of the patient were anonymous. This was a 47-year-old woman with an 8-year history of SS. At diagnosis, she had a recurrent sensation of dry eyes, dry mouth, musculoskeletal pain, Raynaud phenomenon, and cough. The autoimmunity panel revealed the presence of nRNP, SSA/Ro, Ro52, and Ro60, and her antinuclear antibody titer reached 1/320. Ophthalmological examinations showed positive Bengal stain in each eye and shortened tear break-up time (both 2 s/5 min). Salivary gland biopsy indicated lymphocytic infiltration in salivary glands (a number of lymphocytic foci contained more than 50 lymphocytes) and fibrous tissue proliferation. She was treated with prednisone (30 mg/d) and hydroxychloroquine. Within her long-term follow-up, prednisone dose was gradually...
tapered at a dose of 5 mg/d, in addition to immunosuppressive mycophenolate mofetil of 1.5 g/d. After a 3-day treatment with cefixime and ibuprofen for toothache, she was admitted to our department on October 23, 2017 due to skin ecchymosis and bleeding gums. Her temperature and blood pressure were normal. She was further examined by laboratory tests. The counts of white blood cells were normal, while the PLT count was reduced to 2 × 10^5/L, and hemoglobin (HGB) content was 6.2 g/dL. Urinalysis revealed large amounts of urinary proteins and red blood cells. The titer of 24-hours urinary protein excretion was 0.60 g/d. The serum glutamic pyruvic transaminase, glutamic oxaloacetic transaminase, and total bilirubin levels were normal, whereas the lactic dehydrogenase (LDH) level was obviously increased to 624 U/L. The titer of C-reactive protein was 19.9 mg/L. Serum immunoglobulin G (IgG) and immunoglobulin A levels were slightly increased. Activated partial thromboplastin time was slightly prolonged. Prothrombin time, thrombin time, and fibrinogen remained unchanged. Moreover, results were negative for antidouble stranded DNA, antineutrophil antibody, anti-PLT antibody, and Comb test. The reticulocyte percentage was significantly increased. Bone marrow examination indicated iron-deficiency anemia, megalakaryocyte dysmaturity, and thrombocytopenia.

The patient was immediately treated with methylprednisolone (MP) at a dose of 80 mg/d and intravenous immunoglobulin (IVIG) of 20 g/d for 5 consecutive days. The PLT count was decreased to 1 × 10^5/L. Therefore, MP pulse therapy (500 mg/d for 3 days) was given on hospital day 6. Intravenous steroids were also given (80 mg of MP daily except for the days of pulse therapy). Mycophenolate mofetil was changed to cyclosporine A (CSA) of 100 mg/d, in addition to IVIG (20 g/d for 5 days). The patient had a fever of 39°C and headache after 2 units of PLT transfusion. There were no obvious symptoms of infection. The head CT scan demonstrated lacunar infarction and right maxillary sinus inflammation. There was rare red cell debris in her peripheral blood smears. The diagnosis of TTP was confirmed based on a severe deficiency of ADAMTS13 activity as well as the presence of inhibitors. On hospital day 6, PE therapy (twice a day, each treatment contained 3000 mL plasma for a total of 17 times) and steroids were prescribed. The fever and headache were relieved significantly. PLT count was elevated from 90 to 180 × 10^3/L, and HGB was 98.0 g/L. LDH returned to normal range. However, her ADAMTS13 activity was 0%. The PLT function examination and lymphoma immunophenotyping were normal. The next-generation sequencing of the coagulation was used to detect heterozygous missense mutations in genes of ADAMTS13, vWF, and ITGA2B.

After another 55 times of PE, her PLT count still kept decreasing, finally reaching 21 × 10^5/L. On December 17, 2017, she received rituximab (375 mg/m², once a week for 4 weeks), but she remained severely thrombocytopenic. On January 23, 2018, she received 2 circles of infusion of bortezomib (1.3 mg/m², days 1, 4, 8, 11 on a 21-day cycle). She also received pulse MP (500 mg/d for 3 days and then reduced to 40 mg/d). On March 19, 2018, her ADAMTS13 activity returned to the normal level. The PLT count was increased to 66 × 10^5/L, HGB was increased to 91.0 g/L.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** The changes of HGB, PLT and LDH, and treatment interventions during hospital course. HGB = hemoglobin, LDH = lactic dehydrogenase, MP = methylprednisolone, PE = plasma exchange, PLT = platelet.
L, and LDH returned to 384 U/L. She was discharged from the hospital and then treated with prednisone of 40 mg/d (Fig. 1) and hydroxychloroquine. The patient remained in full remission.

### 3. Discussion

The cases of TTP associated with connective tissue disease are seldom reported. The spectrum of connective tissue disease causing acquired TTP includes systemic lupus erythematosus, mixed connective tissue disease, rheumatoid arthritis, systemic scleroderma, dermatomyositis, and antiphospholipid antibody syndrome. However, TTP secondary to SS is exceedingly rare. Only 11 cases of TTP complicating with SS have been reported in literatures in the past 40 years.[3] About half of these patients have not been diagnosed as SS previously. They also show variability in the severity of classic triad or pentad symptoms of TTP. Besides the damage to exocrine glands, SS can destroy the hematological system, with an incidence rate ranging from 34% to 44%. Its common clinical manifestations are thrombocytopenic purpura and immune-mediated hemolytic anemia. SS and TTP have nearly the same clinical manifestations in hematological system, leading to difficulty in distinguishing them. Our patient did not present with classic triad or pentad symptoms of TTP. There were no fragmented red cells in her peripheral blood smear. Her bone marrow examination indicated megakaryocyte dysmaturity and thrombocytopenia. The Coombs test was negative. All these information brought infrequent difficulties to differential diagnosis of anemia and thrombocytopenia. As our patient had a history of SS, we treated her with MP pulse. The immunosuppressive therapy was ineffective, and then the following PLT transfusion was administrated. Our SS patient complained of headache and fever. Finally, we confirmed the diagnosis of TTP according to decreased ADAMTS13 activity and positive anti-ADAMTS13 antibodies. As a result, the SS patients with hematological abnormalities, without classic TTP symptoms, are misdiagnosed and never diagnosed easily.

The pathogenesis of TTP secondary to SS still remains unclear. There are many autoantibodies in the serum of SS patients. Therefore, we speculated that the patient might have ADAMTS13 antibody in peripheral blood. Recent studies have shown that this antibody is a subtype of IgG. This anti-ADAMTS13 IgG usually inhibits the proteolytic activity of ADAMTS13 on VWF, resulting in the deposition of ULvWF on vascular wall, injury of endothelium, and activation and monitoring progression.[6] The persistently decreased ADAMTS13 activity and monitoring progression.[6] The persistently decreased ADAMTS13 activity and presence of inhibitor lead to a greater risk of relapse.[5] Our patient with severe ADAMTS13 deficiency (0%) became refractory and dependent on PE and steroids.

There is limited information or consensus on treatment of relapsed/refractory acquired TTP. In the management and treatment of refractory/refrapsed TTP, PE (1.5 × plasma volume exchange for the first procedure) should be started at the early stage of TTP. PE can be performed even twice daily.[12] In general, standard-dose prednisone (1 mg/kg/d) can be used together with PE in patients with newly diagnosed TTP.[8] High-dose MP (10 mg/kg/d for 3 days) may be efficacious in refractory/refrapsed TTP patients who do not respond to initial treatment of PE and low-dose steroids.[9] Other treatments include rituximab, vincristine, cyclophosphamide, CSA, and splenectomy.[10–13] Our case was treated with PE twice a day, 2 circles of high-dose MP pulse (500 mg/d for 3 days and then 80 mg/d), immunomodulators (CSA) and IVIG (20 g/d for 5 days), but the PLT count continued to fall below 30 × 10⁹/L. Hemolysis did not cease such reduction, and severe ADAMTS13 deficiency (<10%) persisted.

Rituximab, a human-mouse chimeric monoclonal antibody binding to CD20, can kill normal B lymphocytes by complement-dependent cytotoxicity and antibody-dependent cytotoxicity, and deplete B-cell clones producing anti-ADAMTS13 antibodies. Therefore, rituximab has become a new and promising therapeutic approach for TTP,[14] which is currently recommended as a substitute of routine treatment for patients without significant effect of PE in the acute phase of TTP. In a multicenter, prospective, historical phase 2 clinical trial in the United Kingdom, rituximab in combination with PE is taken as a first-line treatment.[15] Bresin et al have reported that prophylactic infusion of rituximab given to patients at the remission phase with ADAMTS13 deficiency (activity <10%) can prevent the relapse of TTP.[16] Treating refractory/refrapsed TTP with rituximab can improve remission rate of TTP, especially in patients with a severe ADAMTS13 deficiency and positive inhibitors.[17–19] A case meta-analysis has shown that the complete remission rate of rituximab in treating those refractory patients is up to 88%. In relapsed TTP, all patients achieve complete remission.[18] The optimal dose of rituximab has not been standardized. A recent article [20] published in Hematology, has suggested that low-dose (100 mg, once a week for 4 weeks) of rituximab is equally effective as the standard-dose (375 mg/m² once a week for 4 weeks) in TTP patients. Unfortunately, our patient did not respond to standard PE, steroids, CSA, IVIG, and rituximab. Though additional alternative therapies for refractory TTP, including cyclophosphamide, vincristine, and splenectomy, have been reported with variable success, considering the severity and specificity of this case, we selected bortezomib instead, a proteasome inhibitor.

The proteasome is an enzyme that degrades ubiquitous proteins in cells. Selective proteasome inhibitor bortezomib leads to cell cycle arrest and apoptosis. Bortezomib has been found to significantly reduce circulating autoantibody levels by inducing apoptosis of B and plasma cells,[21] which is of particular interest of autoimmune disease therapy. B cells form part of the physiopathology of SS. There have been reports of an increase in the number of plasma cells, which partly are Ro-52 or Ro-60 specific. Plasma cells without expression of CD20 are also important in the maintenance of the inflammatory response in SS. As an alternative treatment of SS, rituximab (anti-CD20 antibody) is not effective in targeting these plasma cells, which to a large extent may be responsible for the production of autoantibodies.[22–27] However, the ability of bortezomib to target plasma cells has been well documented in plasma cell dyscrasia.[28] In patients with refractory liver and kidney transplant treated with rituximab, bortezomib has been shown to significantly reduce pathological antibody titers and promote long-term survival of organs.[19,29,30] It has been reported[19] that bortezomib can effectively ameliorate experimental SS in mice by inhibiting the Th17 response, which is helpful for the development of a novel therapeutic strategy for SS. Furthermore, Jakez-Ocampo et al[32] have reported a case of a severe SS patient refractory to conventional treatment in response to bortezomib. Bortezomib is a proteasome inhibitor which can inhibit the Th17 response and reduce pathological antibodies.
We believed that active treatment of the primary SS greatly contributed to improved curative effect of TTP.

Recently, bortezomib has been used to treat refractory/refractory TTP,[33–41] which can eliminate residual anti-ADAMTS13 antibodies produced by plasma cells refractory to conventional immunosuppressive therapy.[33,34] There is an argument that auto-reactive B cells and plasma cells may produce ADAMTS13 antibodies, resulting in ongoing sequelae of PLT consumption in refractory TTP patients. Additional autoantibodies are thought to be synthesized from plasma cells. Bortezomib is administered to eradicate the autoantibody-producing plasma cells. In addition, bortezomib can induce apoptosis of immature dendritic cells, which is required for CD4+ T-cell activation and responsible for autoantibody production.[42] In a study, 5 relapsed TTP patients treated with bortezomib achieve complete remission, and 1 died of cardiac arrest with underlying cause.[39]

In the past 10 years, 15 patients with relapsed/refractory TTP have received bortezomib treatment. Moreover, 14 patients have survived and maintained remission during the acute attack (Table 1). Bortezomib directly exerts influence on plasma cells and significant inhibitory effect within 48 hours. This is why the refractory/refractory TTP patients respond rapidly to bortezomib treatment.

The source of IgG autoantibodies contains mature B cells and plasma cells. Rituximab, an effective treatment for TTP, can target against nor CD20-negative plasma cells but CD20-positive B cells. Therefore, anti-ADAMTS13 autoantibodies levels in TTP patients treated with standard rituximab may decrease, and the increase of ADAMTS13 activity due to continuous production of antibodies by plasma cells may delay. Our patient still showed an increase of ADAMTS13 activity due to continuous production of antibodies. Thus, we assumed that active treatment of the primary SS greatly contributed to improved curative effect of TTP.

We concluded that bortezomib was an option for the treatment of refractory/refractory TTP since it showed a therapeutic effect and acceptable adverse effect. Considering other limited treatments and their significant side effects, such as cyclophosphamide, vincristine and splenectomy, bortezomib was particularly effective for TTP compared with PE, steroids, and rituximab. However, prospective studies of bortezomib in TTP would be cumulatively difficult due to the low incidence of relapsed/refractory TTP. It is important to register and analyze a large-scale retrospective case review of TTP treated with bortezomib. In the next few years, the therapeutic field in TTP should pass the original treatment strategy derived from clinical experience and broaden the evaluation of currently administrated promising new drugs, including acetylcysteine, recombinant ADAMTS13, and caplacizumab (glycoprotein-Ib/IX-vWF axis inhibition agent) by large international clinical trials.

**Author contributions**

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**Table 1**

Published cases with relapsed/refractory TTP who received bortezomib.

| Authors, year of publication, reference | N | Age | F/M | Primary disease | ADAMTS13 activity(%) | Inhibitor titre | Therapy Prior to bortezomib | Therapy during bortezomib | C | Side effect | Prognosis |
|----------------------------------------|---|-----|-----|-----------------|---------------------|-----------------|---------------------------|---------------------------|---|------------|-----------|
| Shott et al, 2013 [33]                 | 1 | 53  | 1/0 | NR             | ‘3/2.2              | PEP/PE/MP/CY/RTX/NAC | PE/RTX/NAC                | 4 | NR         | Alive     |
| Yates et al, 2014 [34]                | 1 | 48  | 1/0 | None           | ‘5/0.4-6           | PEP/PE/MP/CY/RTX     | PE                        | 13 | Pulmonary toxicity | Alive     |
| Mazzei et al, 2014 [34]              | 1 | 51  | 1/0 | None           | ‘3/0               | PEP/RTX/PLV/MMF      | PE/PE/MP/CFY               | 8  | NR         | Alive     |
| van Balen et al, 2014 [34]           | 1 | 16  | 1/0 | None           | ‘1/+              | PEP/PE/RTX/NAC      | PE/RTX                    | 4  | NR         | Alive     |
| Patel et al, 2016 [35]               | 1 | 22  | 1/0 | FVL           | ‘5/2.4             | PE/MP/RTX            | PE                        | 4  | Peripheral neuropathy | Alive     |
| Acedillo et al, 2016 [36]            | 1 | 56  | 1/0 | None           | ‘1/48             | PEP/PE/MP/CY/SSA     | SPL/MP/NAC/CY/RTX         | 8  | Infection | Alive     |
| Patruin et al, 2016 [37]             | 6 | 52.5 (27–76) | 3/0 | None           | ‘9/10             | PEP/MP/RTX/MM/MPF    | PE/RTX                    | 2  | Cardiac toxicity 5 Alive | 1 dead |
| Rathnam et al, 2016 [38]            | 2 | 48/53 | 2/0 | NR            | ‘3/2.0–19.2        | PEP/MP/RTX/NAC       | PE/MP/RTX                 | 2  | NR         | Alive     |
| Pandey et al, 2017 [41]              | 1 | 33  | 1/0 | None           | ‘5/8              | PEP/PE/RTX            | PE/MP                    | 3  | NR         | Alive     |
| This case                            | 1 | 47  | 1/0 | SS             | ‘1/+              | PEP/MP/CF/SA/RTX     | PE/PE/MP                  | 2  | None       | Alive     |

CSA = cyclosporine A, CY = cyclophosphamide, F = female, FFP = fresh frozen plasma, FVL = factor V Leiden mutation, M = male, MMF = mycophenolate mofetil, MF = methylprednisolon, N = number of patients treated, NAC = n-acetylcyst, NR = not reported, PE = plasma exchange, PRE = prednisone, SPL = splenectomy, SS = Sjögren syndrome, VCR = vincristine. C = circles of bortezomib.
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