Clin. Lab. 2022;68:XXX-XXX

CASE REPORT

Successful Treatment of Thrombotic Thrombocytopenic Purpura in a Patient with Mixed Connective Tissue Disease

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SUMMARY

Background: **Although the survival rate of thrombocytopenic purpura (TTP) has increased significantly due to the introduction of therapeutic plasma exchange (TPE). TTP in patients with mixed connective tissue disease (MCTD) has a very high mortality rate and a very small number of reported cases. In TTP, daily TPE is administered until a treatment response is achieved; however, in practice, TPE is often not performed for such long durations.**
Methods: **We report a case of TTP with MCTD in a female patient. She had developed thrombocytopenia and hemolytic anemia 9 months after delivery. She had status epilepticus and lapsed into a coma.**
Results: **The patient was successfully treated with extended sessions of TPE with corticosteroids and rituximab.**
Conclusions: **Although the TTP regimen has not yet been established and remains controversial, this report demonstrates the importance of continuing daily TPE until achieving a treatment response.**
(Clin. Lab. 2022;68:xx-xx. DOI: 10.7754/Clin.Lab.2021.210930)

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Case Report accepted October 25, 2021

KEY WORDS

TTP, MCTD, TPE, tapering, rituximab

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a disease characterized by microangiopathic hemolytic anemia, consumptive thrombocytopenia, and organ failure. TTP is caused by severe deficiency of the plasma enzyme ADAMTS13, a von Willebrand factor (vWF)-cleaving protease. Inherited TTP is rare and acquired TTP is more common. Acquired TTP is caused by polyclonal autoantibodies against ADAMTS13 and is divided into idiopathic and secondary TTP. Secondary TTP is associated with malignancy, infection, drugs, pregnancy, bone marrow transplantation, and connective tissue diseases [1-3]. TTP is a medical emergency that requires rapid diagnosis and treatment. The first-line therapy for TTP is daily therapeutic plasma exchange (TPE). Although several therapies for TTP have emerged over the past decades, including corticosteroids, TPE, and more recently, rituximab and the anti-vWF antibody caplacizumab, the mortality rate remains at 10 - 20% [4]. Cases of TTP in mixed connective tissue dis-

ease (MCTD) have been reported very rarely and have been described as having higher mortality. Herein, we report a case of a postpartum patient who successfully recovered from TTP secondary to MCTD following the administration of extended TPE sessions along with methylprednisolone and rituximab and present a brief review of the literature.

CASE PRESENTATION

A 31-year-old woman was admitted to the emergency department with headache, nausea, and vomiting that had lasted for 3 days. She had a medical history of MCTD for 5 years. The patient showed mild leukopenia and Raynaud's phenomenon upon MCTD diagnosis. Laboratory studies showed positivity for antinuclear antibody (ANA) (1:640 with a speckled pattern), anti-U1-RNP, and anti-SS-A antibodies. The patient had had her first pregnancy 17 months prior. In the third trimester, she complained of more severe dyspnea and nausea than typical pregnant women and had also developed mild thrombocytopenia.

On admission, the patient had a fever. Initial complete blood cell count revealed a white blood cell count of 7,200/mm^3, a hemoglobin level of 6.8 g/dL, and a platelet (PLT) level of 6,000/mm^3. Her reticulocyte count was 7.85%.

The patient was admitted immediately. The next evening, she had an abrupt change in mental status with seizure-like activity. A peripheral blood smear demonstrated anisocytosis, polychromasia, and poikilocytosis with spherocytes and schistocytes. Biochemical analysis revealed elevated levels of serum lactate hydrogenase (LDH) (1,884 U/L) and bilirubin (total 3.1 mg/dL). The direct Coombs test was negative and the prothrombin time (PT) and activated partial thromboplastin time (aPTT) were normal. TTP was clinically suspected owing to the patient's nonimmune hemolytic anemia along with red cell fragmentation, thrombocytopenia, and altered level of consciousness; thus, TPE was immediately planned. She was transferred to the intensive care unit (ICU). Eighteen TPE sessions with a plasma volume of 5,000 mL of fresh frozen plasma were performed for 3 weeks. She was administered intravenous methylprednisolone (500 mg/day) for 3 days, followed by 90 mg/day. Rituximab was administered immediately after the first and ninth TPE sessions. The patient was diagnosed with status epilepticus on day 8. On day 19, after the 13th TPE session, she showed a platelet count of > 50,000 for the first time after admission (Figure 1). A peripheral blood smear showed a reduction of schistocytes to < 2%.

Her ADAMTS13 activity was low (< b 0.5%) before TPE treatment and increased to 14% and after the sixth TPE session to 32.5%, which was close to the reference value (≥ 40%), after the 17th session (Figure 1). After the 18th session, two TPEs were added for 1 week by tapering before stopping treatment. The patient was transferred to the rheumatology ward on the 34th day of ICU admission and was mentally alert. After 90 days of hospitalization, she was discharged with improvement in laboratory tests and a good clinical outcome.

DISCUSSION

While the exact prevalence of MCTD is not known, it is reportedly 4 - 5-fold lower than that in patients with systemic lupus erythematosus [5]. When first described, MCTD was believed to be characterized by a good prognosis. However, after longer follow-up studies, this opinion has been revised to the view that the prognosis of MCTD is worse than that in lupus [6]. Raynaud's phenomenon is the main clinical feature of MCTD. Patients usually use corticosteroids to control their symptoms. A study with a long follow-up period reported that, while it was rare for patients to have major internal organ involvement, including interstitial lung disease and renal disease at the time of diagnosis of MCTD, the cumulative incidence at 10 years tended to increase. Ungrasert et al. reported that none of the 50 patients with MCTD showed thrombocytopenia at diagnosis; however, the cumulative incidence was 5.8% [7]. Rare cases of TTP in MCTD have been reported. To date, 17 cases of TTP associated with MCTD have preceded the present case. In addition, although the overall mortality of patients with MCTD did not differ from that of the general population, analysis of previously. Considering the fact that the average survival rate from the first episode of TTP not related to MCTD is 80 - 90% with prompt treatment initiation, TTP associated with MCTD shows a very poor prognosis.

The first-line therapy for TTP is daily TPE. With the introduction of TPE, the mortality in TTP decreased from > 90% to < 20% [8]. TPE should be performed daily until features related to organ involvement have resolved, the platelet count has stabilized, and hemolysis has ceased. The autoimmune nature of TTP is a rationale for the use of steroids as an adjunctive treatment in acquired TTP. TPE with steroids and rituximab can be used for patients with a suboptimal response to conventional TTP treatment. Rituximab is a monoclonal antibody that targets CD20 antigen present in B lymphatic cells. Rituximab rapidly depletes circulating B lymphocytes, resulting in a reduction in ADAMTS13 antibody. Although several treatments have been introduced, even the optimal TPE regimen that is the cornerstone of treatment has not yet been accurately established. The Canadian Apheresis Trial and the British Committee on Standards in Haematology guidelines recommend 1.5 plasma volume exchanges for the first 3 days and 1 plasma volume thereafter; however, other guidelines recommend 1 plasma volume from the beginning [9,10]. Neither of these regimens was found to be superior; however, beyond 1.5 volume exchanges, the benefit of a single TPE session is limited, both in terms of ADAMTS13 supplement and in decreased anti-ADAMTS13 autoantibody concentration.

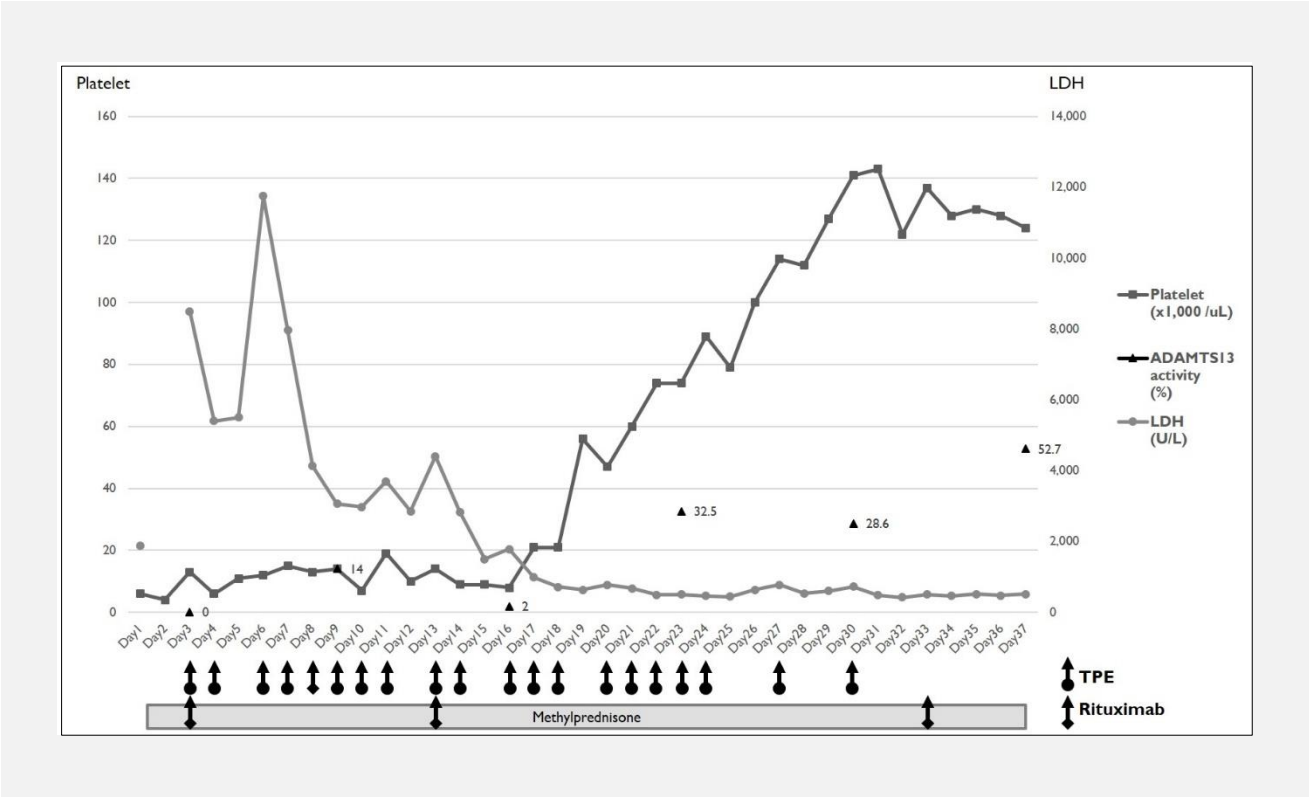

Figure 1. The course of the laboratory results with treatments.

LDH - lactate dehydrogenase, TPE - therapeutic plasma exchange.

The question arises regarding the discontinuation of TPE if the patient's condition worsens or if seizures continue despite TPE treatment. This is because the risks associated with TPE are not small. In this case, we proceeded with TPE safely in the ICU despite the patient's status epilepticus. Although there was a loss of blood cells due to TPE, the main cause of thrombocytopenia in patients was the consumption of platelets resulting from thrombus formation due to decreased ADAMTS13 activity. Seizures and mental changes are also caused by microthrombi generated due to decreased ADAMTS13 activity, blocking the terminal arterioles and capillaries of the cerebral cortex or brainstem. Therefore, ADMATS13 activity must be normalized by removing ADAMTS13 autoantibodies for fundamental patient treatment. Some reports suggested an average of 5 - 6 sessions of TPE treatment in patients with TTP [11,12]. The median time to hematologic remission was 15 days, while the median time to immunologic remission was 2 weeks [11]. Despite the recommendation to continue daily TPE until after achieving a treatment response, in the real world, there is no confidence in long-term daily TPE. Previously reported cases of TTP in MCTD showed that, although the exact cause was not described, cases occur in which daily TPE is performed only five times and the patient died after 1 - 2 months. Our case showed that even if the patient did not show immediate recovery during TTP, it could be effective in cases with continued TPE.

Another issue with the TPE regimen is the need for additional TPE procedures after achieving a treatment response. The effectiveness of TPE tapering remains controversial. Chae et al. reported that TPE tapering reduced the 30- and 180-day recurrence rates in TTP [13]. However, a previous study showed no significant difference in exacerbation rate and significantly increased treatment-related complications in the tapering group compared to the non-tapering group. In the present case, after daily TPE, TPE was stopped after performing two additional procedures once every 2 days for 1 week as tapering. The patient was discharged from the hospital on day 90 without TTP recurrence or exacerbation. At discharge, the laboratory results were as follows: platelet count 161 x 10^3/μL, no schistocytes on peripheral blood smear, and ADAMTS13 activity of 67.8%.

In summary, we report our experience with a patient with TTP successfully treated with 20 extended sessions of TPE, including tapering. The patient had two risk factors for secondary TTP: a history of connective tissue disease and postpartum status. In patients with these risk factors along with hemolytic anemia or thrombocytopenia, it is very important to quickly recognize TTP, proceed with ADAMTS13 activity-related tests, and start daily TPE for optimal patient prognosis. In particular, for TTP in MCTD,

although the prognosis is very poor, daily TPE until treatment response and the combination of glucocorticoid and rituximab helps the treatment.

Declaration of Interest:
The authors declare that they have no conflict of interest.

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