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Treating thrombotic thrombocytopenic purpura without plasma exchange during the COVID-19 pandemic. A case report and a brief literature review

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ABSTRACT

We report the case of a patient diagnosed with a clinical relapse of acquired immune-mediated thrombotic thrombocytopenic purpura (TTP) who was successfully treated with low-dose rituximab plus corticosteroids without the use of plasma exchange (PEx), which was unavailable at the time due to the COVID-19 pandemic. Rituximab 100 mg weekly for 4 weeks was administered, combined with 1 mg/kg of prednisone, obtaining a complete hematological response in 6 weeks. This case suggests that PEx may be unnecessary for a subset of patients with relapsed TTP who are clinically stable without significant end-organ damage. A brief literature review regarding TTP patients treated without plasma exchange is also included.

1. Introduction

There are two main types of thrombotic thrombocytopenic purpura (TTP): congenital and acquired, with the latter being the most common. Congenital TTP is caused by a deficiency of metalloprotease thrombospondin type 1 motif 13 (ADAMTS13), which has a proteolytic activity towards von Willebrand factor (VWF). In its acquired immune-mediated form, autoantibodies inhibit the cleaving activity of ADAMTS13 triggering ultra-large VWF multimers that circulate freely and spontaneously bind to platelets. These multimers cause microangiopathic hemolytic anemia (MAHA) that results in tissue ischemia, end-organ damage, thrombocytopenia, and therefore, risk of bleeding. Diagnosis is made by combining clinical and laboratory features. The most common laboratory findings are thrombocytopenia and microangiopathic hemolytic anemia, schistocytes in the peripheral blood smear, a high reticulocyte count, elevated lactate dehydrogenase (LDH), and low haptoglobin. Creatinine levels might be elevated, and proteinuria or hematuria may be present if kidney injury occurs. The diagnosis of immune-mediated TTP is confirmed with a reduced plasma ADAMTS-13 activity (<10 %) in the presence of ADAMTS-13 antibodies [1]. The clinical findings include pallor, petechiae, fatigue, and neurological symptoms, among others [2]. Plasma exchange (PEx) in addition to corticosteroids are first-line treatment. Rituximab has been included as adjuvant therapy in both first-line therapy or relapsed disease [3]. In this report, we present the case of a patient diagnosed with a TTP relapse, treated exclusively with prednisone and low-dose rituximab during the COVID-19 pandemic, we also performed a brief literature review on this topic.

2. Case presentation

A previously healthy 20-year-old woman was diagnosed with immune-mediated TTP, after presenting with MAHA, kidney injury, and neurological symptoms. She was treated with eight PEx sessions. One year later, she relapsed and underwent splenectomy, gaining a complete response, and remained in yearly clinical surveillance without further relapses. Ten years after the first relapse, she presented with a headache, nausea, and disseminated ecchymoses on both legs. She was stable with an otherwise unremarkable physical examination. No triggering factors such as infection, pregnancy, alcohol, or drug use were detected. Baseline laboratory findings are shown in Table 1. Elevated reticulocytes (15.5 %) and schistocytes were observed in the blood smear. Creatinine and troponins were normal. ADAMTS13 activity was not detected, and the ADAMTS13 IgG antibody level was 25.51 U/mL (positive activity threshold of >15 U/mL) confirming a second relapse of acquired immune-mediated TTP without clinically apparent end organ-damage.

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Table 1
Laboratory findings before and after rituximab administration in a patient with a clinical thrombotic thrombocytopenic purpura relapse treated without plasma exchange.

	Hemoglobin (g/dl)	Leukocytes ($x10^9$/L)	Platelets ($x10^9$/L)	LDH (UI/L)
Baseline	8.7	23.1	28	988
Day 7	9	22	30	938
Day 14	7.8	17.5	47	–
Day 21	10.1	14.3	195	–
Day 28	11	8.89	462	251
Day 42	13	12	420	–
Day 80	13	12.5	400	182
Day 215			350	133

LDH, lactic dehydrogenase.
*LDH upper limit of normal: 180 UI/L.

Considering the absence of neurological symptoms and the lack of resources, brain imaging was omitted. We recommended she be immediately hospitalized to receive PEx and corticosteroids. However, due to the lack of availability during the current COVID-19 pandemic, facing significant bureaucratic economical, insurance-related issues, and lacking available beds, PEx was not a viable option. After a detailed explanation considering the lack of PEx, the patient gave her informed consent for an alternative therapy. Consequently, a therapy with prednisone and rituximab was chosen. The schema consisted of rituximab 100 mg weekly for 4 doses in combination with prednisone 1 mg/kg PO [4]. The patient had clinical improvement after her first rituximab administration with symptom resolution but persisted with laboratory parameters compatible with MAHA (Table 1); elevated schistocytes, LDH 938 UI/L, and an indirect bilirubin level of 1.7 mg/dl. She remained clinically stable and completed 4 doses of rituximab without complications. Her laboratory findings revealed hemoglobin 11 g/dL, platelets 462,000/μL, and LDH 251 IU/L. Prednisone was tapered over 4 weeks. She remained asymptomatic, and laboratory findings showed a complete response at day 42 (Fig. 1) including a small increase in ADAMST13 activity. The patient is currently living a normal life without PEx and undergoing clinical surveillance without anemia, thrombocytopenia, hemolysis (bilirubin and LDH in normal range), or renal injury (serum creatinine 0.6 mg/dl). Remarkably, the latest ADAMTS13 activity level at the 6-month follow-up visit showed 3% activity (range 3–68 %), the IgG anti-ADAMTS13 level was 77.35 U/mL (positive activity threshold is >15U/mL), with no sign of anemia, thrombocytopenia, or acute hemolysis. She is currently receiving pre-emptive rituximab.

3. Discussion

TTP treatment is based on counteracting the microthrombotic stimulus and acute end-organ damage to avoid the high mortality associated with untreated disease. The frontline approach includes PEx which replenishes functional ADAMTS13 and removes von Willebrand factor and its autoantibodies, combined with immunosuppressive therapy to counter ADAMTS13 antibody activity [3]. In this case, the unavailability of PEx or plasma infusions to treat a clinical TTP relapse represented a clinical challenge. Leukocytes were elevated at baseline without infection and were attributed to the splenectomy history as no trigger was documented. The patient was treated safely with rituximab and prednisone only, and to our knowledge, represents the first case treated with this management strategy. She did not experience significant adverse events and obtained a complete response. Recently a case of severe TTP was reported, in which the patient achieved complete remission after therapy with steroids plus rituximab but without PEx. However, it is important to note that plasma extraction was performed and replaced with human albumin solution [5]. Similar cases of TTP in Jehova's Witnesses treated without PEx using corticosteroids, rituximab, and albumin as a replacement fluid in combination with different drugs have also been reported (Table 2) [5–12]. In this scenario, it is difficult to evaluate the contribution of plasma extraction or fluid replacement alone versus the use of rituximab and corticosteroids on the good response obtained by those patients.

Corticosteroids are considered a useful standard adjunct to PEx [3]. It was recognized as beneficial for patients even before PEx emerged as the standard of care, but currently, it is uncertain if an additional benefit is obtained by adding steroids to PEx [13]. Rituximab is frequently utilized as a first-line or relapsed disease adjuvant, usually at a dose of 375 mg/m^2 administrated for 4 weeks, resulting in an 83–100 % complete remission rate [14,15] potentially decreasing the time to response and delaying subsequent relapses [16]. Also, its pre-emptive use in asymptomatic patients who experience a drop in ADAMTS13 levels has emerged as a promising strategy [17]. We and other authors have previously shown that low-dose rituximab (100 mg weekly) has been an efficacious adjuvant therapy for patients in acute episodes [4,18,19] and our initial observations were recently confirmed [20]. Low-dose rituximab has also been used in other hematological immune-mediated disorders, being a natural addition to patients with TTP [18,21]. Rituximab efficiently depletes B-cells in TTP patients in 24 h, decreasing plasma

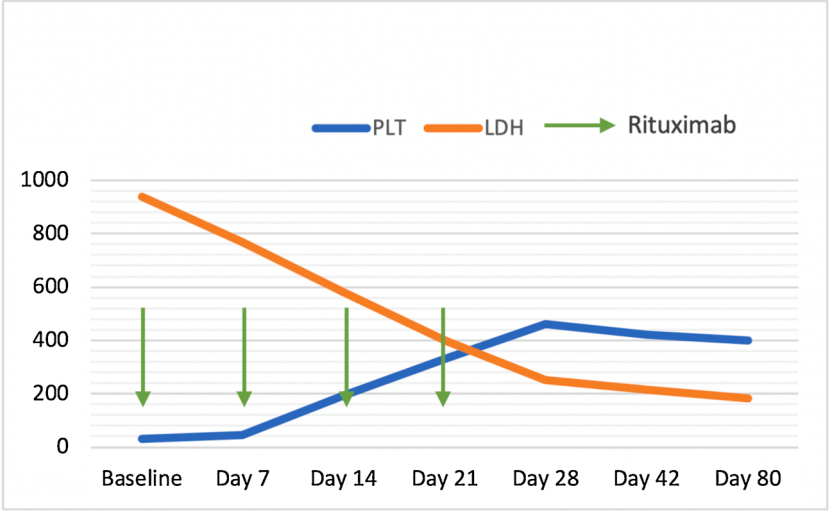

Fig. 1. Platelet (PLT) and lactic dehydrogenase (LDH) concentration before and after rituximab administration in a patient with a clinical thrombotic thrombocytopenic purpura relapse treated without plasma exchange.

Table 2
Management in Jehova's whitenesses with thrombotic thrombocytopenic purpura.

No.	Year	Author	Treatment
1	2000	Drummond	Corticosteroids, prostacyclin, apheresis with a gelatin-based plasma substitute
2	2007	Dabak	Corticosteroids, vincristine
3	2011	Walla	Corticosteroids, vincristine, aminocaproic acid, erythropoietin
4	2015	Chai	Corticosteroids, vincristine, intravenous immunoglobulin (IVIG), rituximab, apheresis with albumin replacement
5	2017	Sam	Corticosteroids, apheresis with albumin replacement, erythropoietin, folic acid, IVIG, rituximab, pegylated bovine carboxyhemoglobin.
6	2017	George	Corticosteroids, rituximab, apheresis with albumin replacement, erythropoietin, IVIG, IV iron, Factor VIII.
7	2019	Lim	Corticosteroids, rituximab, apheresis with albumin replacement, apheresis with cryosupernatant replacement, erythropoietin, folic acid, IV iron, IVIG, Factor VIII.
8	2019	Baseri	Corticosteroids, rituximab, albumin, cryoprecipitate, Factor VIII, plasma-derived clotting factors, apheresis.
9	2019	Chander	Corticosteroids, rituximab (375 mg/m2), prednisone. Factor VIII that also contains ADAMTS13, 9 U/mL. The dose was 5000 IU of factor VIII (50 mL) and approximately 450 U of ADAMTS13

ADAMTS13 inhibitor levels [22]. Therefore, this capacity could partly explain the good clinical response observed in our patient. Her clinical presentation was not severe, probably the most important factor associated with a favorable response to immunosuppressive therapy alone. Our patient had previously undergone splenectomy, nonetheless, relapses occur in about 35 % of splenectomized patients [23]. It is unclear whether she was favorably affected by this procedure, as the role of the spleen in TTP pathogenesis is still a matter of debate. It is the major source of autoantibody production and antibody-antigen complex clearance and its removal may decrease the risk of relapse [24]. Caplacizumab, a humanized nano-body that targets the A1 domain of von Willebrand factor, preventing interaction with the platelet glycoprotein Ib-IX-V receptor, is a novel treatment used in combination with PEx. This therapy has been shown to achieve earlier responses, fewer PEx sessions, and fewer relapses compared to placebo [25]. However, it is not available in our country and is highly expensive. Furthermore, it has been recently reported in a German retrospective study that patients could be treated with caplacizumab without PEx depending on their clinical presentation and evolution, rapidly reestablishing platelet levels and achieving clinical responses [26]. Moreover, a Jehovah's Witness patient with severe TTP received prednisone, rituximab, caplacizumab, and factor VIII, without PEx or plasma extraction and recovered rapidly [12]. Nevertheless, the cost of this drug is a limiting factor for low-middle income countries, such as Mexico.

In our patient, ADAMTS13 activity remains low, therefore a congenital TTP should be considered. Congenital TTP usually presents during early infancy, or late infancy with life-threatening thrombosis, although some patients can remain asymptomatic for decades until a triggering factor appears, usually leading to organ damage [29]. It is difficult to differentiate an acquired TTP from an inherited TTP; however, the presence of ADAMTS13 antibodies, the absence of renal and brain damage, and the absence of a triggering factor suggest acquired TTP [30]. Our patient recently tested positive for ADAMTS13 antibodies; interestingly, she has not presented clinical exacerbation or new symptoms. Also, this laboratory finding helped to ensure the acquired form of TTP. Moreover, the ADAMTS13 activity level fluctuation has been reported in the follow-up of asymptomatic TTP patients. In some cases, this represents a predictor of relapse [31].

4. Conclusion

To the best of our knowledge, this is the first patient that has been treated with corticosteroids plus low dose rituximab without PEx. Can we identify a subset of patients with TTP that can be treated without PEx successfully? Only a handful of patients have been successfully treated without plasma exchange. Since this is a single case experience, reporting bias cannot be excluded and therefore, our findings must be interpreted cautiously. The patient is asymptomatic but still undergoing treatment due to the low levels of ADAMTS-13. We acknowledge that PEx is the current gold standard in the treatment of TTP. However, our approach could be another effective method to handle specific presentations in selected uncomplicated patients suffering from TTP relapses in similar settings.

CRediT authorship contribution statement

César David Galindo-Calvillo: Writing - original draft, Methodology, Investigation, Writing - review & editing. **Carlos Saúl Rodríguez-Roque:** Writing - original draft, Methodology, Investigation, Writing - review & editing. **Andrés Gómez-De León:** Supervision, Visualization. **Luz Tarín-Arzaga:** Supervision, Writing - review & editing. **David Gómez-Almaguer:** Conceptualization, Visualization, Project administration, Validation.

Declaration of Competing Interest

The authors declare that they have no conflicts of interests.

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