Rheumatol Ther (2022) 9:1213–1219
https://doi.org/10.1007/s40744-022-00469-2

CASE REPORT

Plasma Exchange in a Patient with Immune Thrombocytopenia Associated with Antiphospholipid Syndrome Hospitalized for COVID-19

Federico Boggio · Alessandro Ciavarella · Sara Arcudi · Roberta Gualtierotti · Raffaella Rossio · Francesco Tafuri · Andrea Artoni · Flora Peyvandi

Received: May 4, 2022 / Accepted: May 27, 2022 / Published online: June 15, 2022

ABSTRACT

Thrombocytopenia is a common feature of antiphospholipid syndrome (APS) and rarely requires treatment. Here we present the case of a 71-year-old man hospitalized for severe immune thrombocytopenia (ITP) secondary to APS and concomitant SARS-CoV-2 infection. The patient was successfully treated with systemic corticosteroids, intravenous immunoglobulins, and plasma exchange (PEX). Few data are published on the use of plasma exchange in the treatment of thrombocytopenia in non-catastrophic APS. In the setting of acute infection when immunosuppressive therapies might be contraindicated, plasma exchange may be considered an effective therapeutic option. SARS-CoV-2 infection may be a trigger for a relapse of immune thrombocytopenia.

Keywords: Plasma exchange; SARS-CoV-2; Lupus anticoagulant; Thrombocytopenia

Key Summary Points

SARS-CoV-2 infection may trigger a relapse of immune thrombocytopenia.

We describe the case of a patient with severe thrombocytopenia secondary to APS successfully treated with corticosteroids, intravenous immunoglobulins, and PEX.

PEX may be considered in cases of APS with severe thrombocytopenia unresponsive to standard treatments.

Few cases of thrombocytopenia secondary to APS treated successfully with PEX are reported in the literature.

F. Boggio (✉)
Università degli Studi di Milano, Milan, Italy
e-mail: federico.boggio2@gmail.com

A. Ciavarella
Department of Biomedical Sciences for Health, Università degli Studi di Milano, Milan, Italy

A. Ciavarella · S. Arcudi · R. Gualtierotti · R. Rossio · F. Tafuri · A. Artoni · F. Peyvandi
Angelo Bianchi Bonomi Hemophilia and Thrombosis Center, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan, Italy

S. Arcudi · R. Gualtierotti · F. Peyvandi
Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy

INTRODUCTION

Antiphospholipid syndrome (APS) is an autoimmune condition characterized by vascular thrombosis or pregnancy loss associated with antiphospholipid antibodies anticardiolipin antibody (aCL), anti-β_2 glycoprotein-I antibody (anti-β_2GPI), or lupus anticoagulant (LA) on two or more occasions at a minimum interval of 12 weeks between tests [1]. Patients with APS often present with other clinical and laboratory signs and symptoms not included in the classification criteria, such as heart valve disease, livedo reticularis, nephropathy, neurological manifestations, and thrombocytopenia. In particular, thrombocytopenia is reported in 20–50% of APS cases [2] and its presence is associated with significantly higher rates of other non-criteria manifestations such as cardiac valves thickening and disfunction, livedo reticularis, and skin ulcerations [3].

ITP can be idiopathic or secondary to other conditions, including chronic disorders and infectious diseases. Secondary ITP accounts for 20% of the total ITP cases and it is characterized by a variable natural history and response to therapy.

Here we present the case of a patient followed by our center for APS and secondary ITP who developed a severe thrombocytopenia resistant to multiple treatments associated with SARS-CoV-2 infection. Written informed consent was obtained from the patient for the publication of this case report.

CASE REPORT

A 71-year-old man with a history of recurrent deep vein thromboses in multiple sites dating from 1993 was diagnosed with triple-positive APS in 2006. Since then, the patient started antithrombotic prophylaxis with warfarin and acetylsalicylic acid (ASA). In 2013, he developed spontaneous ecchymoses and epistaxis with a platelet count of 6000/mm^3. Bone marrow biopsy excluded other hematologic disorders and a diagnosis of secondary ITP was made. The first episode of thrombocytopenia was managed with corticosteroid therapy. However, from that moment the patient had recurrent episodes of clinically relevant thrombocytopenia. Therefore, chronic administration of azathioprine was started to maintain normal platelet count. In 2019, the patient developed acute myocardial infarction complicated by cardiac arrest, which was treated with multiple stenting and dual antiplatelet (ASA and clopidogrel) therapy and warfarin until November 2019, when ASA was discontinued.

On April 9, 2021, the patient was admitted to the emergency department of our hospital for cough, fever, malaise, nausea, and dizziness. He tested positive for SARS-CoV-2 with a molecular nasopharyngeal swab and was hospitalized in our COVID-19 medical ward. At admission, the patient's physical examination was unremarkable except for the presence of crackles in the right pulmonary base. A chest X-ray was performed, revealing thickening of the peribronchovascular interstitium, while arterial blood gas test and ECG were normal. The patient did not present visible hemorrhages, petechiae, or hematomas, and he did not report melena. Blood tests showed severe thrombocytopenia (1000/mm^3), while the remaining blood tests were as follows: Hb 11.6 g/dl, WBC 5380/mm^3, INR 3.5, aPTT ratio 3.48, creatinine 1.26 mg/dl. The autoimmune screening showed a positive lupus anticoagulant test (although in the course of warfarin treatment) associated with the presence of anti-cardiolipin IgG and IgM, and anti-β2 glycoprotein 1 IgG and IgM. In addition, ANA with at the titer of 1/160 with fine speckled pattern, with positive Ab anti-Ro60 (89.4 U/ml) and anti-Ro52 (21.7 U/ml) were detected, whereas other anti-extractable nuclear antigens (ENA), anti-PF4 and anti-dsDNA were negative. C3 levels were low and C4 were within the lower normal range. A comparison of aPL antibodies and complement between baseline and the moment of admission is presented in Table 1. Systemic corticosteroids (prednisone 1 mg/kg) and sublingual vitamin K were started and clopidogrel was discontinued. In addition, therapy with intravenous immunoglobulins (IVIg) 500 mg/kg o.d. for the following 4 days was administered with a slight improvement of the platelet count to 7000 cells/mm^3. During the following days, the patient developed

Table 1 Baseline and admission comparison

	Baseline (04/2018)	Admission (04/2021)
C3 (mg/dl)	94	77
C4 (mg/dl)	23	14
Anticardiolipin IgM (UA)	69.5	129.5
Anticardiolipin IgG (UA)	483.1	197.2
Anti-β2 glycoprotein 1 IgM (UA)	30	269.8
Anti-β2 glycoprotein 1 IgG (UA)	236	816.9
dRVVT ratio	2.88	3.56
Silica clotting time ratio	5.61	3.2

gastrointestinal bleeding with blood in feces along with a gradual reduction in hemoglobin levels (8 g/dl on April 14). Hence, warfarin was discontinued, and four units of red cell transfusions were administered. A negative total body CT scan was carried out, while colonoscopy and esophagogastroduodenoscopy were initially not performed due to hemoglobin stabilization and respiratory worsening. Given the concurrent SARS-CoV-2 infection, immunosuppressive therapy with azathioprine was discontinued. On April 15, schistocytes in peripheral blood smear were detected, along with normal bilirubin levels (0.62 mg/dl), high LDH levels (305 U/l), normal renal function (creatinine 0.97 mg/dl), INR 2.31, aPTT ratio 2.18, fibrinogen 626 mg/dl and D-dimer 512 mcg/l. Furthermore, ADAMTS13 functional activity was within the normal range. A therapeutic trial with PEX (three sessions) was started, with the subsequent improvement of platelet count and hemoglobin levels, which reached, respectively, 153.000/mm^3 and Hb 10 g/dl on April 23. During hospitalization, the patient developed moderate respiratory failure (PaO_2/FiO_2 ratio nadir 193) secondary to COVID-19 pneumonia, requiring support with high flow nasal cannula. Except for oxygen supplementation and corticosteroids, the patient did not receive any specific treatment for COVID-19. Then, from April 22, patient's respiratory function improved and we progressively reduced oxygen supplementation, which was discontinued shortly after. On April 23, an esophagogastroduodenoscopy was performed, excluding upper gastrointestinal sources of bleeding, while in the colonoscopy a diverticulosis was found. The patient was discharged on May 3 and maintained a platelet count within the normal range during the following weeks (230,000/mm^3 in July). The blood count trend during hospitalization is shown in Fig. 1.

DISCUSSION

Only a few cases of thrombocytopenia secondary to APS treated successfully with PEX have been reported [4–6]. A patient with APS and systemic lupus erythematosus unresponsive to prednisone was treated with three sessions of PEX, observing reduction in antibody titer and increased platelet count. In another case, a man with Evans syndrome and APS was treated with steroids, cyclosporin A, cyclophosphamide, rituximab, and eventually with bortezomib and two sessions of PEX. In a recent case, in a woman with APS and aortic valve thrombus, PEX was started to lower antibodies titer and control thrombotic risk. The three cases are summarized in Table 2.

PEX is widely recognized as a therapeutic option in catastrophic antiphospholipid syndrome (CAPS) [7]. On the other hand, no international guidelines are available on the treatment of thrombocytopenia secondary to

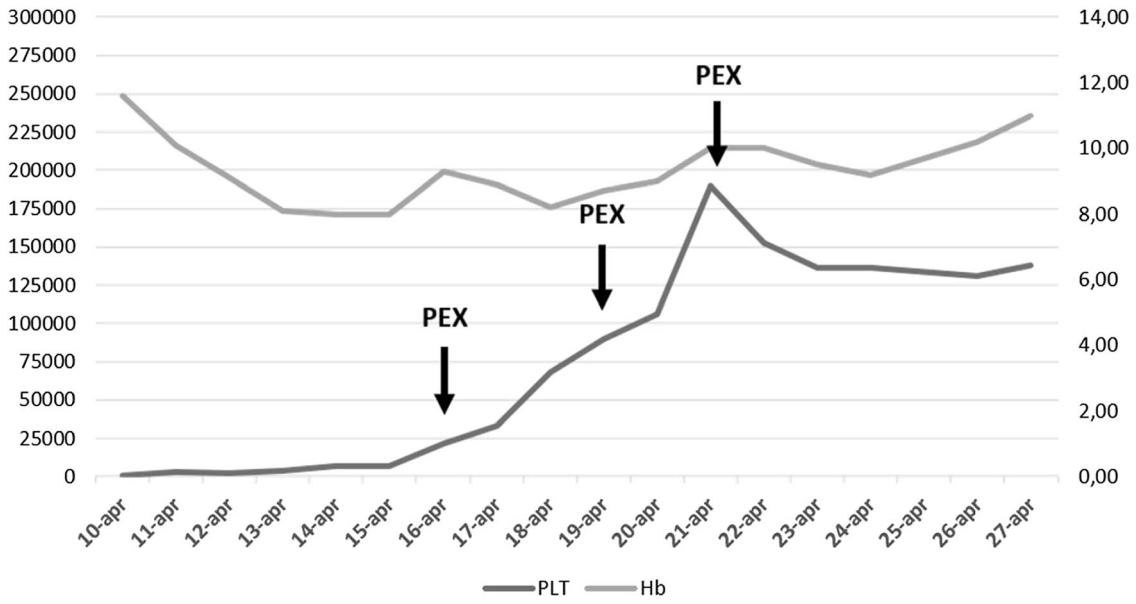

Fig. 1 Blood count trend

Table 2 Comparison between cases of PEX in APS thrombocytopenia

	1	2	3
Age	39	29	32
Gender	Male	Female	Male
Autoimmune disease	SLE with APS	APS	SLE with APS and Evans syndrome
PLTs before PEX	15.000	53.000	78.000
Bleeding at admission	Yes	No	Yes
Other therapies	Prednisolone	IGIV, steroids, rituximab	steroids, cyclosporin A, cyclophosphamide and rituximab
Sessions of PEX	3	NA	2

APS, where the clinical management does not differ from primary ITP. According to 2019 ASH guidelines for ITP [8], the first-line therapy of severe thrombocytopenia (< 20–30,000 platelets/mm^3) with or without major bleeding is corticosteroid with or without IVIg. In clinical practice, the administration of IVIg is reserved for patients resistant to steroid therapy or those who need a prompt increase of the platelet count because of acute bleeding or need for an urgent invasive procedure. However, it is still unclear whether IVIg therapy should be considered as first-line therapy in APS in view of the risk of thrombosis [9]. In recent years, the efficacy of rituximab as a steroid-sparing therapy has been confirmed in a small case series [10]. Other therapeutic strategies (splenectomy, immunosuppressive therapy) are considered second-line treatments in refractory cases. Thrombopoietin receptor agonists (TPO-Ras) in ITP patients have shown good efficacy, but because of their potential thrombotic risk in

patients with APS and SLE, their administration should be carefully evaluated.

Thrombocytopenia secondary to APS is frequently mild, and in most cases it does not require specific treatment. The development of severe thrombocytopenia has been described as a warning signal for disease activity and may represent a marker of early phase of CAPS with possible evolution towards thrombotic microangiopathy [11] and subsequent organ failure. In this case, the decision of beginning treatment with PEX was also induced by the detection of schistocytes in peripheral blood smear, in view of the risk of microangiopathic complications in case of development of CAPS, with the aim of obtaining a reduction in aPL autoantibody titer and accelerate platelet recovery. Immunosuppressive therapy with rituximab was unfeasible in our patient because of the concurrent SARS-CoV-2 infection, which also required the discontinuation of the patient's therapy with azathioprine.

Considering the rarity of the disease, the duration and the exact number of PEX sessions needed to maintain a normal platelet count in CAPS is unknown [12]. We based our choice to discontinue the treatment on aPL titer reduction, improvement of blood count and patient clinical stability. This decision was supported by some authors proposing to follow aPL antibody titer to monitor response to treatment [13]. Corticosteroids and IVIg without PEX might have presumably taken longer to prove effective as compared to what we observed.

In addition, recent insights on COVID-19 suggest the hypothesis that the treatment with PEX may have also affected the clinical course of our patient's pneumonia. Indeed, an antibody-dependent enhancement by antibodies directed against the receptor-binding domain of the SARS-CoV-2 spike protein has been demonstrated in severe cases of COVID-19 [14]. PEX may induce a titer reduction of such antibodies, thus improving COVID-19 clinical course.

An association between SARS-CoV-2 infection and APS flare has been proposed, but the mechanisms underlying such association are still unknown [15], although it is well established that infections can play a causative role in CAPS. COVID-19 causes a thromboinflammatory status that shows similarities with complement-mediated syndromes [16], possibly contributing to the development of a microangiopathy induced by endothelial injury.

CONCLUSIONS

Thrombocytopenia is the most common non-criteria manifestation of APS [3]. Nevertheless, in the absence of clinical trials addressing the treatment of such condition, its clinical management is still debated. In this case report, we described the efficacy of combination therapy of corticosteroids, IVIg, and PEX on severe thrombocytopenia in an APS patient ineligible for immunosuppressive therapy due to COVID-19. Although PEX is not recognized as a standard therapy for ITP, it should be considered a life-saving option in cases of APS with severe thrombocytopenia unresponsive to standard treatments. For example, PEX might be indicated in severe cases of thrombocytopenia secondary to APS to lower aPL antibodies titer, thus reducing the thrombotic and hemorrhagic risks associated with APS.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship.

Author Contributions. FB, AC, and AA wrote the manuscript. AA, FB, FT, and RR participated at the case management. RG, RR, SA, and FP critically reviewed and provided edits to the final manuscript. All authors read and approved the final manuscript.

Disclosures. Federico Boggio, Alessandro Ciavarella, Sara Arcudi, Roberta Gualtierotti, Raffaella Rossio, Francesco Tafuri, Andrea

Artoni and Flora Peyvandi have nothing to disclose.

Compliance with Ethics Guidelines. The authors declare that the tenets of the World Medical Association Declaration of Helsinki were followed. Written informed consent was obtained from the patient for the publication of this case report.

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