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Therapeutic plasma exchange for anticoagulant-refractory antiphospholipid syndrome with severe ischemic and necrotic skin lesions: A case series

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ABSTRACT

Antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by clinical findings including thrombosis and/or obstetric complication and laboratory findings, e.g. ≥1 positive antiphospholipid antibodies (aPL) (lupus anticoagulant, anticardiolipin IgG/IgM and/or anti-β2-glycoprotein IgG/IgM). A rare APS clinical entity is severe necrosis which is difficult to treat and often does not respond to anticoagulant therapy. Three consecutive patients with primary or secondary APS who presented with necrotic skin lesions secondary to APS were treated with therapeutic plasma exchange (TPE), glucocorticoids and low-molecular-weight heparin. All patients had a rapid-onset, either full or significant recovery of their APS-related necrotic lesions.

Upon treatment, one patients showed resolution of lupus anticoagulant. Two patients had a decrease of at least 88 % in aPL titers after the initial treatment, and were kept on TPE maintenance every 5–6 weeks. None of the patients experienced significant side effects of the TPE. This is the first case series showing the clinical benefits of TPE in patients with ischemic and necrotic skin lesions due to severe anticoagulant-refractory vascular APS.

1. Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disease defined by the occurrence of venous and/or arterial thrombotic events and/or pregnancy-related morbidity, combined with the presence of circulating antiphospholipid antibodies (aPL) and/ or a lupus anticoagulant (LAC) [1]. In this manuscript the term "aPL" refers to both LAC and the aPL antibodies anticardiolipin (ACL) IgM/IgG and/or anti--β2-glycoprotein IgM/IgG. Clinical manifestations of APS vary widely [2]. Necrotic skin ulceration is a severe complication of APS which was observed in 5.5 % of APS patients and were the presenting sign in approximately 4% [3]. The cornerstone of treatment is anticoagulant therapy to prevent and/or treat thrombotic complications [2]. Still in APS patients with anticoagulant therapy the recurrence rate of thrombosis is 24–37 % within 5 years [4,5]. The most severe variant, the catastrophic APS (CAPS), is classified as multiple (≥3) organ thromboses and microthrombotic involvement of at least one organ, developing within 7 days in a patient with persistently positive aPL [6]. Only in this case therapeutic plasma exchange (TPE) combined with immunosuppressive and anticoagulant therapy is recommended (ASFA guidelines category 1, grade 2C evidence) [7]. Currently, no specific treatment for vascular necrosis is available. Treatment can be difficult as skin necrosis might be a direct consequence of CAPS. Patients might need more than anticoagulant treatment alone, such as a full CAPS treatment strategy. We describe 3 consecutive patients with severe anticoagulant-refractory APS who presented with skin necrosis, and were treated as CAPS with TPE, glucocorticoids and low-molecular-weight heparin (LMWH).

2. Case 1

A 53-year-old female with primary APS since 2001 presented in 2017 with necrotic lesions at the upper and lower right leg and foot. Despite adequate treatment with vitamin K antagonist (VKA) fenprocoumon (target INR 2.0–3.0) her lesions progressed (Fig. 1A). At presentation she had triple-positive aPL with high titers of ACL IgG and anti-β2-GPI IgG (Table 1). Because of the severity and extensiveness of the necrotic wounds she was treated with daily TPE for 7 days, glucocorticoids and LMWH leading to normalization of LAC and an 88 % decrease in ACL IgG and anti-β2-GPI IgG (Table 1). Four weeks after the last TPE (and after amputation of the tip of her toe) she had full recovery of all her wounds

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(Fig. 1A). Despite consecutive additional immunosuppressive therapies, including Rituximab (4 times 375 mg/m2 once a week), followed by cyclophosphamide (1250 mg intravenously 3 times once a month), followed by mycophenolate mofetil (1000 mg twice daily for 2 months) followed by hydroxychloroquine (400 mg once daily for 3 months) and 5 times TPE (7 days each time), her lesions progressed and her aPL titers increased every time. As it seemed she was only responding to TPE, she started with 1 TPE every 6 weeks leading to more stable aPL titers and full control of the wounds (Fig. 1D).

3. Case 2

The second case is a 73-year-old male with a history of peripheral atherosclerosis with several surgical interventions since 1999. In 2017 he was diagnosed with a deep venous thrombosis from the right leg. Despite adequate anticoagulation with therapeutic LMWH he developed necrotic lesions requiring amputation of the lower leg left. One day post-surgery he was diagnosed with symptomatic bilateral pulmonary embolism and progressive severe cyanosis of the fingertips of the left hand (Fig. 1B). aPL were triple-positive with high titers of ACL IgG and anti-β2-GPI IgG (Table 1). He was diagnosed with primary APS and treated

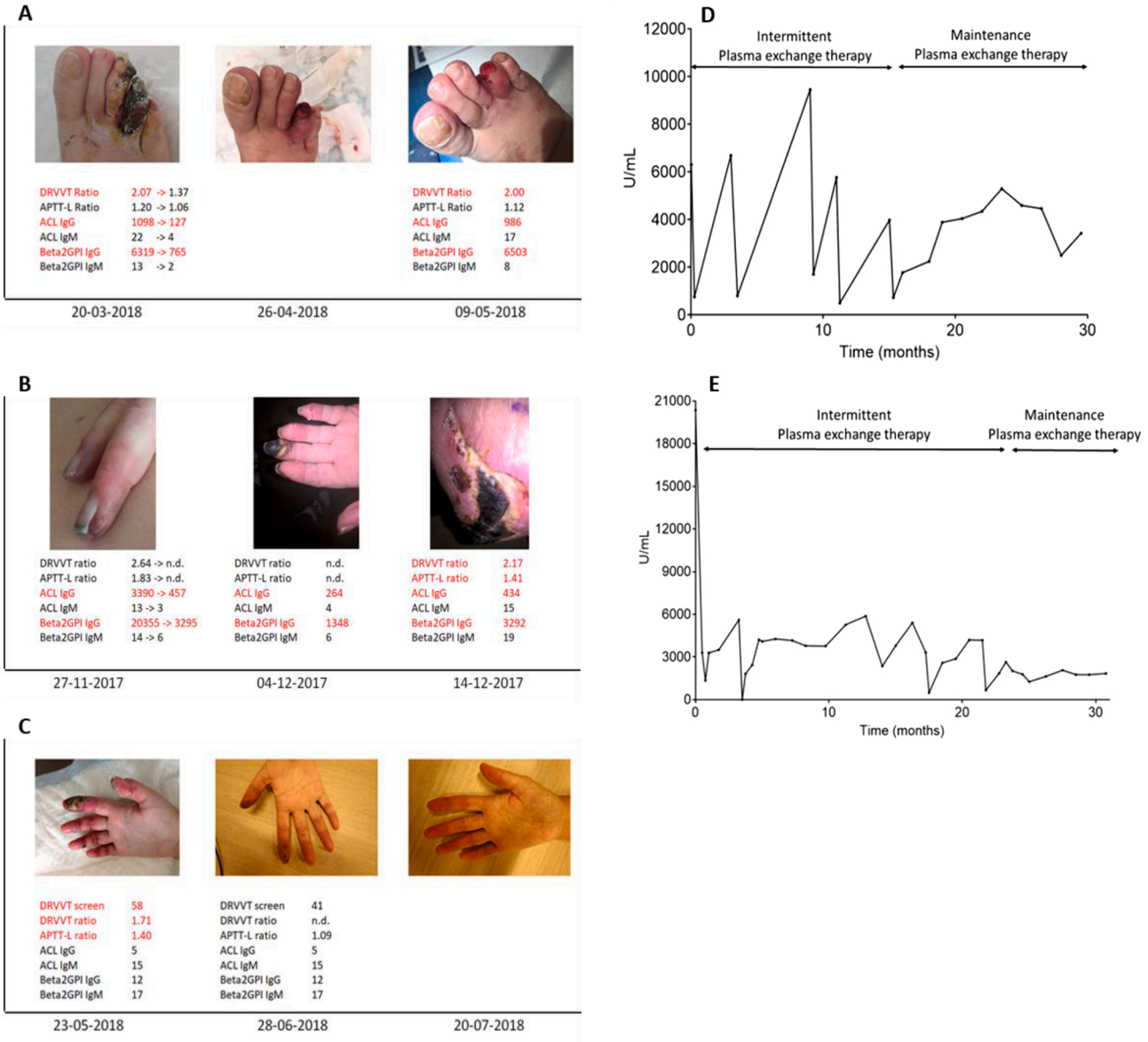

Fig. 1. A-C: Clinical symptoms and aPL titers of patient 1 (A), patient 2 (B) and patient 3 (C) before and after treatment with therapeutic plasma exchange, glucocorticoids and low-molecular-weight heparin. Numbers in red are increased (Normal values are DRVVT Ratio <1.66, APTT-L ratio <1.31, ACL IgG <20U/mL, ACL IgM <20U/mL, anti-β2-GPI IgG <60 U/mL, anti-β2-GPI IgM <20U/mL). Patient 2 (B) and 3 (C) had full recovery of their lesions and patient 1 (A) also after amputation of the tip of her toe. D-E: Blood was drawn before each cycle of TPE according to routine clinical practice. Titers of anti-β2-GPI IgG (U/mL) of patient 1 (D) and patient 2 (E) during treatment with intermittent and maintenance TPE. Illustrated are the levels of anti-β2-GPI IgG in the period of 30 months after first TPE. Patient 1 (D) received 5 cycles of TPE, therapeutic LMWH and glucocorticoids, together with several consecutive immunosuppressive therapies including rituximab (4 times 375 mg/m2 once a week), followed by cyclofosfamide (1250 mg intravenously 3 times once a month), followed mycophenolate mofetil (1000 mg twice daily for 2 months) and hydroxychloroquine (400 mg once daily for 3 months) during the period of intermittent TPE therapy. Patient 2 (**E**) received during this period 4 cycles TPE, therapeutic LMWH and glucocorticoids, together with Rituximab (twice, 1000 mg once weekly) and hydroxychloroquine (6 months, 400 mg once daily). After approximately 16 months both patients started with TPE maintenance every 5-6 weeks, without immunosuppressive therapy leading to more stable aPL titers without clinical symptoms (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).

Table 1
Patient characteristics.

Case	1	2	3
Age (Years)	53	73	46
Sex	Female	Male	Female
Duration of APS (Years)	17	0	0
APS category	Primary	Primary	Secondary
Obstetrical medical history	1 miscarriages (27wks) 2 premature deliveries	N.A.	N.A.
Recurrent thrombosis	iCVA	VTE	iCVA
aPL before plasma exchange (ref)			
dRVVT ratio (<1.66)	1.99	2.64	1.71
APTT ratio (<1.31)	1.20	1.83	1.40
anti-β2-GPI IgG (<60 U/mL)	6166	20,355	12
anti-β2-GPI IgM (<20U/mL)	13	14	17
ACL IgG (<20 U/mL)	1020	3390	5
ACL IgM (<20 U/mL)	21	13	15
aPL after 7d plasma exchange (ref)			
DRVVT ratio (<1.66)	1.37	Unknown	Negative
APTT ratio (<1.31)	1.20	Unknown	1.09
anti-β2-GPI IgG (<60 U/mL)	765	1348	<6
anti-β2-GPI IgM (<20U/mL)	2	6	8
ACL IgG (<20 U/mL)	127	264	<3
ACL IgM (<20 U/mL)	4	15	7

Abbreviations: APS = antiphospholipid syndrome, N.A. = not applicable, iCVA = ischemic cerebro-vascular accident; VTE = venous thrombotic event; dRVVT = Dilute Russel Viper Venom Test; anti-β2-GPI = anti-β2-glycoprotein; ACL = anticardiolipin. ref = reference values.

with the combination treatment TPE, glucocorticoids and LMWH. His lesions recovered completely after 7 days TPE, with a 93 % and 88 % reduction of anti-β2-GPI IgG and ACL IgG respectively. Similar to the first patient he had multiple progressions of his lesions and headache parallel with the increase in aPL titers (Fig. 1B). In all these instances only treatment with TPE was successfully, despite several consecutive immunosuppressive therapies, including Rituximab (twice, 1000 mg once weekly) and hydroxychloroquine (6 months 400 mg once daily) and 4 times TPE (7 days each time). Since treatment with 1 TPE every 5–6 weeks he had more stable aPL titers and clinical symptoms (Fig. 1E).

4. Case 3

The third patient is a 46-year-old female with ankylosing spondylitis, with several treatments in the past, including adalimumab, sulfasalazine, methotrexate, leflunomide and dexamethasone. With clopidogrel 75 mg once daily, and without immunosuppressive therapy, she presented in May 2018 with necrosis of the fingertips (Fig. 1C) and tested positive for LAC. Although not completely fulfilling the revised Sapporo criteria with only one positive aPL measurement (deferral of diagnosis for re-testing after 3 months was deemed unwise) she was diagnosed with secondary APS. She was treated with methylprednisone, TPE and LMWH for 7 days leading to disappearance of LAC and full recovery of her necrotic lesions within 2 months (Fig. 1C).

5. Therapeutic plasma exchange

Considering the severity of the clinical presentation, all patients started initial treatment with methylprednisolone 1 g/day for 3 days and therapeutic LMWH. With a recommended duration of TPE for at least 3–5 days, in our center patients receive TPE once daily for 7 days [7]. TPE was performed using Optia Spectra version 11 (TerumoBCT, Lakewood, CO, USA). Volume of TPE was 50 mL/kg fresh frozen plasma (FFP). TPE maintenance was performed for patient 1 with a 5% albumin solution and for patient 2 with gelofusine. Anticoagulant citrate dextrose solution with a 1:12 ratio was used during TPE. Calcium was added 1375 mg per hour during the procedure.

6. aPL testing

For LAC measurement the dRVVT (Screening reagent LA1 and LA2 (Siemens, reagents number OQGP17) and the APTT-Lupus with Actin FSL and Actin FS sensitive for LAC (Siemens) on the Sysmex CS5100 were used. dRVVT reagent contained heparin inhibitor. In patients on vitamin K antagonist (VKA), the anticoagulant intensity at the time of testing for LAC was measured using the INR. Diagnostic tests were mixed with normal pooled plasma to correct for anticoagulant therapy with vitamin K antagonist (VKA) (INR 1.5–3). In addition, in case of heparin use, LAC testing was performed after incubation of plasma with heparinase. aPL antibodies were determined using the HemosIL™ AcuStar aCL IgG and IgM and HemoSIL AcuStar anti-β2GPI IgG and IgM assays were determined using chemiluminescence in human citrated plasma and serum on the ACL AcuStar (Werfen). Cutoff values were determined based on the 99th percentile according to the International Society on Thrombosis and Haemostasis Scientific and Standardization Subcomittee (ISTH-SSC) guidelines [8].

7. Discussion

This is the first case series describing the success of TPE and TPE maintenance in patients with severe necrosis due to anticoagulant refractory APS. It is a safe and effective treatment option with a good response on aPL titers and wound healing.

Current treatment of APS is mainly focused on prevention and/or treatment of thrombotic complications with anticoagulation therapy. Management of APS patients who are refractory to anticoagulant therapy is challenging [8,9]. For these patients mostly empirical treatment options are described, including vitamin D, statins, hydroxychloroquine, intravenous immunoglobulin, B-cell inhibition and complement inhibition (e.g. eculizumab). The pathophysiological mechanism of the occurrence of thrombosis in patients with APS may be multifactorial: due to a pro-inflammatory response with monocyte, leucocyte and complement activation and a pro-coagulant response with increased coagulation factors and platelet activation after production and binding of the aPL [10]. For many autoimmune diseases TPE is a common treatment modality to remove potential pathogenic factors like autoantibodies [7]. Although a positive effect of TPE in combination with immunosuppressive therapy has been described in 1 patient with purpura fulminans [11] we could show the beneficial effects of TPE alone. Maintenance TPE may be better in cases with soon recidivism of symptoms.

TPE is a relatively safe procedure. In general 1–1.5 plasma volumes are exchanged per TPE, leading to removal of approximately 60–70 % of the substances, including antibodies [7]. In patients with CAPS TPE with FFP for minimum 3–5 days is recommended to remove aPL [7]. Our patients were treated with 7 days TPE initially due to the severity of the clinical presentation. Our patients had approximately 90 % reduction of aPL titers after 7 days of TPE and/or normalization of LAC. Additionally, patients 1 and 2 received TPE maintenance therapy, with excellent clinical results.

In this manuscript we describe the first case series of 3 patients with primary or secondary APS and severe necrosis in whom treatment with TPE was rapidly successful, even limb saving, without new thrombotic complications. TPE maintenance has been successful for 2 patients in whom immunosuppressant therapy had failed, leading to stable aPL titers and no clinical symptoms. All 3 patients had severe skin necrosis at presentation where the first 2 patients had triple positive aPL and the third patient was only LAC positive. Therefore treatment with combination therapy of TPE, LMWH and glucocorticoids appears to be quite effective for single as well triple positive APS patients with skin necrosis.

Long-term effects of TPE maintenance are unknown.

CRediT authorship contribution statement

All authors were involved in the treatment of the three patients. **FNC** and **AJGJ** wrote the manuscript and all authors approved the manuscript. All patients gave consent for using their information in the manuscript.

Declaration of Competing Interest

None declared.

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