Two Cases of Refractory Pediatric Antiphospholipid Syndrome[[1]](#footnote-1)

by

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Abbreviations:

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| APS | Antiphospholipid syndrome |
| CAPS | Catastrophic antiphospholipid syndrome |
| CRP | C reactive protein |
| IVC | Inferior vena cava |
| DOAC | Direct oral anticoagulant |
| LMWH | Low molecular weight heparin |
| IV | Intravenous |
| IVIG | Intravenous immunoglobulin |
| SLE | Systemic lupus erythematosus |
| UFH | Unfractionated heparin |

ABSTRACT

APS is an autoimmune disease in which patients are at increased risk of thrombosis and/or pregnancy complications. CAPS is a form of severe APS with multisystemic involvement and microvascular thrombi. Both entities are treated with anticoagulation and multimodal immunotherapy regimens. We present two APS cases in which patients did not meet criteria for CAPS, but needed CAPS-like treatment to stop the progression of thromboses. This case series stresses the importance of stringent follow-up in APS to ensure regression of thromboses. It also emphasizes the need of aggressive immunotherapy in refractory APS.

INTRODUCTION

The epidemiology of pediatric APS is not well defined. About half of APS are idiopathic, the remaining are secondary to rheumatologic diseases, infections or medications. One percent of APS present as catastrophic APS, which has a 50% mortality rate due to multisystemic involvement (1, 2). Evidence-based data for treatment of pediatric APS is scant.

RESULTS

Case 1

A 17-year-old boy with uncontrolled ulcerative colitis presented with superior sagittal sinus thrombosis. He was treated with methylprednisone for his colitis and IV UFH for his thrombosis. He was then transitioned to warfarin. Initial thrombophilia work-up (protein C, protein S, factor V Leiden, prothrombin G20210A and MTHFR mutations) was negative.

Two weeks later, he experienced worsening headaches and right arm paresthesia. He was slightly thrombocytopenic (99 x 109/L). Head imaging showed extension of the superior sagittal sinus thrombosis. Therefore warfarin was stopped and reversed with oral vitamin K. UFH perfusion was started. He underwent mechanical thrombectomy for persisting neurologic symptoms despite therapeutic anticoagulation.

Over the next weeks, new venous thromboses (jugular, inferior vena cava, subhepatic, renal and iliac) and massive bilateral pulmonary emboli occurred while under therapeutic IV UFH. APS was suspected. The antiphospholid profil showed a positive lupus anticoagulant antibody and negative anticardiolipin and anti-beta2 glycoprotein-1 antibodies.

Treatment was intensified with high-dose methylprednisolone, cyclophosphamide, rituximab, IVIG, and 7 days of apheresis.

APS secondary to ulcerative colitis was diagnosed. He was retransitioned to warfarin with no further thrombotic events within a 9-year follow-up.

Case 2

A 16-year-old boy presented with epigastric pain, dyspnea, and 3 month history of hematuria and lower extremity purpuric ulcerative lesions. Laboratory tests revealed thrombocytopenia (41 x 109/L), increased CRP (302 mg/L), high INR (1.31 sec) and prolonged aPTT (39.3 sec). Imaging studies showed proximal bilateral venous thrombosis of the legs and massive pulmonary emboli. APS was suspected. A retractable IVC filter was placed. An UFH perfusion was started initially at half-dose because of thrombocytopenia, then increased to full dose the next day. Anti-Xa levels were therapeutic after 5 days. The patient was eventually transitioned to LMWH.

High-dose methylprednisolone, rituximab and IVIG were administered. Lupus anticoagulant was confirmed; anticardiolipin and anti-beta2 glycoprotein-1 antibodies were negative.

On day 9 of admission, follow-up imaging showed proximal extension of the pulmonary artery thrombus. Treatment was intensified with a 5-day course of apheresis. Hydroxychloroquine was introduced. The IVC filter was withdrawn.

Idiopathic APS was diagnosed. The patient was discharged on therapeutic LMWH and hydroxychloroquine. He had a favourable outcome with no further complications within a 2-year follow-up.

Both patients had a negative immunologic and hematologic workup for secondary causes of APS.

DISCUSSION

APS is an autoimmune disease characterized by autoantibodies against phospholipid-binding proteins and arterial, venous or capillary thrombosis, or pregnancy morbidity (1). Most commonly involved antibodies are lupus anticoagulant, IgM or IgG anticardiolipin and IgM or IgG beta2 glycoprotein-1, but other antibodies can also be found (1). The diagnosis of APS is established based on the expert consensus clinical criteria last updated in 2006 (Table 1) (3). Other frequent clinical manifestations not included in the diagnostic criteria are thrombocytopenia, livedo reticularis, cardiac valvular disease, nephropathy and neurologic manifestations such as chorea (1). *Both patients met APS diagnostic criteria with multiple thromboses and 2 positive lupus anticoagulant antibodies 12 weeks apart*.

CAPS is a severe entity in which there are multisystemic microvascular thrombi with a high mortality rate of 50% (4, 5). The criteria for CAPS were established by expert consensus in 2003 (Table 1) (2). Biopsies are often difficult to obtain because of clinical instability, thrombocytopenia and crucial anticoagulation (2, 4, 5).

Underlying triggers including infection, pregnancy, lupus, malignancy, surgery or medication should be sought for and treated in APS and CAPS (2, 6).

Both patients had multisystemic disease with thrombocytopenia and extensive progressing thromboses, raising several differential diagnoses (Table 2). *These diagnoses were excluded in both patients. Patient 2 had an increased baseline thrombotic risk because of his known ulcerative colitis. However, when he developed new thromboses while under therapeutic anticoagulation a more extensive work-up was initiated.*

The extent of the rheumatologic work-up for APS/CAPS depends on the patient’s clinical presentation. *Rheumatologic diseases were excluded in patient 1. In patient 2, hematuria and skin ulcers were evocative of anti-glomerular basal membrane disease, ANCA associated vasculitis and systemic polyarteritis nodosa. These etiologies were excluded by negative autoantibodies, 18F-FDG PET/CT scan and skin and kidney biopsies* (7).

UFH or LMWH is typically first-line anticoagulation in patients with APS. Since aPTT may be high in APS, it is important to monitor heparin activity with anti-Xa levels. Patients can be transitioned to warfarin for long-term anticoagulation (8). DOACs are currently contraindicated as they were associated with an increased risk of thrombosis in one recent randomised trial (9). *Patient 1 failed to respond to therapeutic anticoagulation. He developed life-threatening thromboses, which prompted aggressive second line treatment. Patient 2 had life-threatening pulmonary emboli and was thrombocytopenic, a relative contraindication to therapeutic anticoagulation. Thus, he was treated aggressively with an IVC filter, reduced anticoagulation and immunosuppression as first-line therapy.*

*Patient 2 also received hydroxychloroquine.* Hydroxychloroquine can be used as adjunctive therapy in lupus related APS and in primary APS, although the latter practice is not evidence-based. Prospective trials studying the efficacy of hydroxychloroquine in adults with primary APS are being conducted (8). Hydroxychloroquine is commonly used as maintenance therapy in patients with SLE for its immunomodulatory effects (10,11). It is also known to inhibit platelet activation and to have an antithrombotic effect without additional bleeding risk (12).

High-dose glucocorticoids with rapid tapering in conjunction with UFH or LMWH are front line therapies in non life-threatening CAPS. In patients with life-threatening thrombosis or with cerebral or cardiac involvement, an intensified treatment that includes high-dose glucocorticoids, apheresis and IVIG is warranted (1, 2, 4, 8). If there is no improvement, rituximab and eculizumab can also be used (4). The addition of pulse cyclophosphamide is indicated in CAPS secondary to lupic nephritis or neurolupus (4).

There is accumulating evidence of complement activation in the pathogenesis of APS and CAPS (1, 6, 13). Recent studies suggest rare germline mutations of complement regulation genes, acting as a “first hit”, predispose some individual to APS and specifically to CAPS. Aggravating factors such as pregnancy, infections or inflammation then act as a “second hit” (12). Thus, eculizumab may be used in refractory APS and CAPS, and is specifically indicated if patients show signs of thrombotic microangiopathy (1, 2, 4, 6, 8, 13). *This was not the case in either patient; they did not need eculizumab*.

Global consensus in the literature is to treat CAPS aggressively with multimodal therapies. There is no validated evidence-based step-wise approach for treatments of these patients. Multimodal treatments need to be individualized.

In conclusion, we present two patients with severe APS who required CAPS-like treatment to stop the progression of thromboses. This brief report stresses the importance of both having a high index of suspicion of APS in cases of thrombosis progression despite effective anticoagulation, and the necessity for frequent follow-up imaging to ensure regression of thromboses. These cases also illustrate the potential need for multimodal aggressive treatment including anticoagulation, apheresis and immunosuppressive therapies in the management of severe pediatric APS.

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LEGEND LIST

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