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Catastrophic antiphospholipid syndrome refractory to high-dose intravenous immunoglobulin responsive to therapeutic plasma exchange

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ABSTRACT

Catastrophic antiphospholipid syndrome (CAPS) involves sudden multiorgan dysfunction from thrombosis due to antibodies that cause platelet activation and endothelial dysfunction. Treatment variably combines anticoagulation, corticosteroid use, therapeutic plasma exchange (TPE), and high-dose intravenous immunoglobulin (IVIG). A 42-year-old male with antiphospholipid syndrome (APS) presented with severe thrombocytopenia, encephalopathy, cardiac ischemia, and acral purpuric cutaneous lesions. CAPS was identified and he received heparin infusion, methylprednisolone, and IVIG. On day 7 he developed new purpuric lesions on his right foot despite detectable arterial pulses representing new microthrombosis refractory to IVIG. He was treated with TPE which resolved the right foot ischemia and eventually his CAPS. To our knowledge, this is the first patient with CAPS reported that failed initial treatment with IVIG and subsequently had excellent response to TPE. Our observations also support recent literature indicating that onset of thrombocytopenia in APS is a warning of progression to CAPS requiring treatment escalation.

KEYWORDS

Catastrophic antiphospholipid syndrome, high-dose intravenous immunoglobulin, microvascular, thrombosis, therapeutic plasma exchange, thrombocytopenia, thrombosis

History

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Introduction

Catastrophic antiphospholipid syndrome (CAPS) is the sudden development of multiorgan dysfunction from microcirculatory thrombosis associated with antiphospholipid antibodies [1]. Diagnostic criteria include: 1) evidence of at least three organ systems involved, 2) development of manifestations occurring within 1 week, 3) small-vessel thrombotic occlusion on histopathology, and 4) presence of antiphospholipid antibodies, ideally with subsequent demonstration of serial positivity [2]. Common precipitants are infection (47%), malignancy (18%), surgery (17%), and subtherapeutic (or discontinuation of) anticoagulation (11%) [1]. Despite treatment that variably combines anticoagulation, corticosteroids, therapeutic plasma exchange (TPE), cyclophosphamide, and high-dose intravenous immunoglobulin (IVIG), estimated mortality is 44% [3]. Due to insufficient available evidence, the RARE-Bestpractices group guideline could not distinguish between therapeutic efficacy of IVIG versus TPE [4].

We describe a CAPS patient who failed initial treatment with IVIG and subsequently had excellent response to TPE. Our observations question the therapeutic equivalency of IVIG versus TPE. Our case further highlights that severe thrombocytopenia in APS is a hallmark warning of progression to CAPS requiring treatment escalation.

Case

A 42-year-old male presented to a community hospital with 4 days of abdominal/back pain, emesis, and diarrhea. He had known antiphospholipid syndrome (APS) diagnosed in 2015 after presenting with leg ischemia requiring left common iliac artery stent placement. He was anticoagulated with warfarin until INR monitoring noncompliance prompted switch to therapeutic-dose dalteparin in 2018. He stopped dalteparin 3 weeks earlier due to change in employment and loss of medication coverage.

He presented tachycardic and hypotensive, with lower-limb ischemia, and required intubation for progressively decreased level of consciousness. After urgent transfer to a vascular surgery center, computerized tomography angiography revealed chronic thrombosis in his left iliac artery stent, with flow reconstitution secondary to collaterals. Fever (39.5°C) was documented, and meropenem and norepinephrine were given for possible septic shock; however, infection was never identified (negative blood, urine, and endotracheal tube cultures). Heparin anticoagulation precluded lumbar puncture.

He developed progressive foot mottling with diminished peripheral pulses. Due to APS and limb ischemia, he received methylprednisolone 1000 mg IV, and heparin infusion targeting therapeutic anti-Xa levels (range, 0.35–0.70 U/mL) (Figure 1A).

His platelet count fell over 24 hours from admission value of 90×10^9/L (previous baseline, 120) to 56×10^9/L. The combination of progressive thrombocytopenia and clinically evident multisite microvascular thrombosis prompted a working diagnosis of

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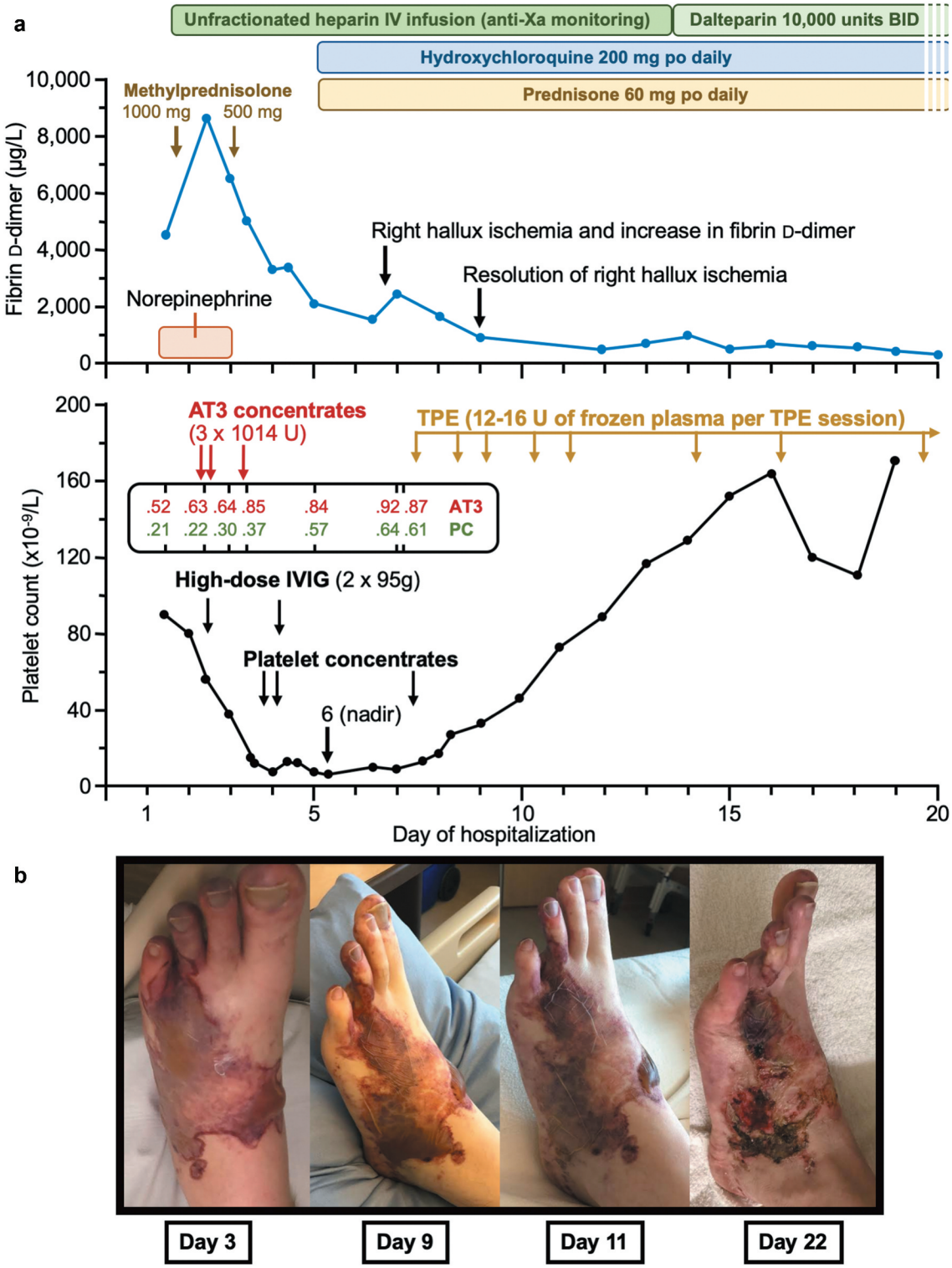

Figure 1. Clinical and laboratory summary of patient with CAPS.

(a) Clinical and laboratory course. The x-axis is presented as days of hospitalization. The top panel summarizes medical treatment (heparin, hydroxychloroquine, corticosteroids), serial fibrin D-dimer levels, and onset and resolution of right hallux ischemia. TPE was performed on hospital days 7, 8, 9, 10, 11, 14, 16, 20, 22, and 23. The bottom panel summarizes blood product administration (antithrombin III concentrates, high-dose immunoglobulin, platelet concentrates, and frozen plasma), serial platelet counts, and timing of therapeutic plasma exchange. (b) Serial photographs of left foot (hospital days 3, 9, 11, and 22). AT3, antithrombin III (concentrates); BID, twice-daily; IVIG, intravenous immunoglobulin; PC, protein C (activity); po, per os; TPE, therapeutic plasma exchange; U, units.

catastrophic APS (CAPS), supported by presumed microthrombotic involvement of mesentery (abdominal pain), kidneys (acute kidney injury), central nervous system (encephalopathy), heart (troponin elevation), and skin (acral purpuric lesions despite arterial pulses, Figure 1B). Skin biopsy was not taken (concern regarding wound healing). Patient agitation precluded brain MRI. Heparin infusion continued and—as TPE is not available at our vascular surgery center—he received IVIG 95 g (1 g/kg for body weight = 123 kg/height = 185 cm; ideal BW = 79.5 kg; dosing weight = 96.9 kg) and antithrombin III (ATIII) concentrates

(given for disseminated intravascular coagulation [DIC], presumed microvascular thrombosis, and reduced ATIII activity levels [0.52 U/mL]). On day 3, he received methylprednisolone 500 mg IV, was extubated, and norepinephrine discontinued. Skin mottling of his right foot resolved but the left foot lesions remained. Meropenem was switched to levofloxacin despite no conclusive infection.

On day 4, he received his second dose of IVIG. On day 5, he started prednisone and hydroxychloroquine; his platelet count reached 6×10^9/L (nadir). On day 7, he developed new purplish discoloration of his right hallux indicating likely new thrombosis refractory to IVIG (or, potentially, a prothrombotic adverse effect of IVIG [5]). In response to the new thrombosis and refractory thrombocytopenia, TPE was initiated with serial fibrin D-dimer levels used as surrogate for thrombotic burden/hemostasis activation. With TPE his right foot ischemia completely resolved, with platelet count recovery. On day 23, he was discharged with prednisone 60 mg daily, hydroxychloroquine 200 mg daily, dalteparin 10,000 units subcutaneous twice-daily (coverage resumed), with outpatient TPE on days 27, 30, 34, and 37, without further thrombosis.

Table I lists pertinent laboratory values during his hospitalization; notable values included: triple-positive APS, severe reduction in protein C activity (potentially contributing to microthrombosis), and laboratory markers indicating a diagnosis of overt DIC [6]. Hemolysis testing returned negative.

Discussion

This case of CAPS calls into question the therapeutic equivalency of high-dose IVIG versus TPE. Progression in thrombocytopenia and thrombosis occurred despite therapeutic-dose heparin, corticosteroids, and high-dose IVIG (a prothrombotic role of platelet transfusions cannot be excluded). With TPE, using frozen plasma as replacement, the microthrombotic lesions resolved, D-dimer progressively decreased, and the platelet count recovered, indicating an excellent response.

Our conclusions are limited as this is a single case and the role of any particular treatment in altering the patient's clinical course cannot be precisely ascertained. For example, IVIG likely contributed to the patient's initial improvement in clinical status and certain laboratory markers (e.g. rising protein C activity, falling D-dimer levels). Nevertheless, dramatic clinical improvement was associated with initiation of TPE, particularly platelet count recovery and prompt resolution of right hallux ischemia that had developed despite IVIG. Although a definitive diagnosis of CAPS requires biopsy-proven microvascular thrombosis, in our patient, the presence of multi-site thrombosis, particularly in both lower limbs despite arterial pulses, is strong evidence for microthrombosis [7]. Nevertheless, criteria were only met for "probable CAPS" [2].

The RARE-Bestpractices Guidelines recommends first-line therapy of corticosteroids, anticoagulation, and either IVIG or

Table I. Pertinent laboratory values.

Laboratory parameter	Value	Reference range
Markers of disseminated intravascular coagulation[a]		
Platelet count, nadir	6 x 10^9/L	150–400 x10^9/L
International normalized ratio, peak	2.1 (9 s increase in prothrombin time)	0.8–1.2
Fibrin D-dimer, peak	8620	<500 µg/L FEU/L
Fibrinogen, nadir (day 6)	1.9	1.6–4.2 g/L
Antithrombin activity, nadir	0.52	0.77–1.25 U/mL
Protein C activity, nadir	0.21	0.70–1.80 U/mL
Free protein S activity, nadir	0.64	0.78–1.61 U/mL
Testing for antiphospholipid and autoimmune antibodies		
Nonspecific inhibitor	Present (2 assays)[b]	Absent
Anti-cardiolipin IgG	50.5[b]	<15 GPL unit/mL
Anti-cardiolipin IgM	6.0	<12.5 GPL unit/mL
Anti-β2-glycoprotein IgG	35[b]	<20 SGU/mL
Antinuclear antibodies	Negative	Negative
cANCA and pANCA	Negative	Negative
C3 complement	0.85	0.79–1.52 g/L
C4 complement	0.18	0.16–0.38 g/L
Testing for heparin-induced thrombocytopenia (HIT) antibodies		
Serotonin-release assay	Negative	Negative
Anti-PF4/polyvinylsulfonate antibodies (polyspecific)	0.43 (weakly positive)	<0.40 optical density U/mL
Biochemistry testing		
Creatinine, peak	150	64–111 µmol/L
Creatine kinase, peak	17,016	<200 U/mL
Troponin I, peak	569	<30 ng/L
Lactate, peak	3.7	0.5–2.2 mmol/L
Hemolytic screen	Negative	Negative

Laboratory studies shown are from the January 2019 admission for CAPS.

[a]The patient met International Society on Thrombosis and Hemostasis (ISTH) criteria for overt decompensated DIC, as follows: platelet count <50 (2 points); prothrombin time >6 s prolonged (2 points); elevated fibrin D-dimer (2 points); and normal fibrinogen (0 points), for total of 6 points (5 or more points is consistent with overt decompensated DIC) [5].

[b]Triple-positive APS diagnosed on the basis of positive nonspecific inhibitor and positive testing for anti-cardiolipin and anti-β2 glycoprotein I IgG antibodies. Previous levels of anti-cardiolipin IgG antibodies (53.8 U/mL, Mar 2016; 69.6 U/mL, Oct 2016) were similar to those measured at the time of CAPS.

c-ANCA, cytoplasmic-antineutrophil cytoplasmic antibody; FEU, fibrinogen equivalent units; GPL, IgG phospholipid unit; *p*-ANCA, perinuclear-ANCA; PF4, platelet factor 4; SGU, standard IgG beta-2 glycoprotein unit; U, units

TPE [4]. This combination appears to significantly lower mortality (OR 0.51, 95%CI, 0.27–0.95; n = 357) compared to other therapies based on a meta-analysis of 4 studies [8–12]. The guidelines were unable to compare IVIG versus TPE due to insufficient available evidence and therefore endorsed either modality for first-line therapy [4]. Expert opinion was provided stating TPE should be used for coinciding hemolytic anemia and IVIG for concurrent immune thrombocytopenia [4]. Otherwise, there is little guidance regarding the use of IVIG versus TPE.

This case illustrates that certain patients may respond better to TPE over IVIG. Perhaps poorly understood prognostic factors could identify patients more suited to TPE instead of IVIG. Alternatively, perhaps TPE is superior to IVIG but not enough data have accumulated to prove this statistically. In the interim, it appears reasonable for CAPS patients to receive TPE with or without IVIG [13] before second-line agents such as rituximab. IVIG may remain a preferred emergent treatment for patients who cannot immediately access TPE, pending transfer to a center with such capacity, or in resource-restricted environments, where TPE is simply not available.

Thrombocytopenia during the catastrophic phase of APS has been recently evaluated in high-risk, triple-positive patients using a cross-sectional study [11]. Of 119 APS patients, 6 developed CAPS [11]. All 6 patients had unremarkable baseline platelet counts; however, a few days prior to CAPS each patient developed thrombocytopenia with a mean platelet count of 60×10^9/L at CAPS diagnosis [11]. Thus, new-onset thrombocytopenia may be a warning sign of CAPS development in previously well APS patients [11]. Our patient also followed this pattern with progressive severe thrombocytopenia (platelet nadir, 6) accompanying multiple sites of thrombosis. A registry study [14] also reported a high frequency of thrombocytopenia (67%) among patients with CAPS.

Conclusion

This case highlights that IVIG and TPE may not be therapeutically equivalent modalities for some patients with CAPS and that further research is required to better understand the role of each modality as first-line treatment of CAPS. Additionally, this case reinforces previous observations that new-onset thrombocytopenia in an APS patient is a potential warning sign of progression to CAPS.

Author Contributions

T.E.J. wrote the first draft of the paper. T.E.W. revised the manuscript following peer-review. All authors contributed to patient care. All authors edited the manuscript and approved the final version.

Informed Consent

Informed written consent was obtained directly from the patient for publication and distribution of case-specific details and images.

T.E.W. has received lecture honoraria from Alexion and Instrumentation Laboratory, and royalties from Informa (Taylor & Francis); has provided consulting services to Bayer, CSL Behring, Ergomed, and Octapharma; has received research funding from Instrumentation Laboratory; and has provided expert witness testimony relating to thrombocytopenic and coagulopathic disorders. In the last 24 months, M.A.C. has received honoraria for sitting on Data Safety Monitoring Boards from Bayer, honoraria for advisory boards, preparation of educational material, or presentations from Servier Canada, Asahi Kasei, Hemostasis Reference Laboratory, Pfizer, CSL Behring, and Diagnostica Stago. Additionally, he discloses having participated in various medicolegal activities relating to thrombosis, anticoagulant drugs, or other aspects of hematological practice. Dr Crowther holds the Leo Pharma Chair in Thromboembolism research; the funding for this is held in perpetuity at McMaster University and the interest is used to support Dr Crowther's research activities. The other authors report no conflicts of interest.

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References

1. Carmi O, Berla M, Shoenfeld Y, Levy Y. Diagnosis and management of catastrophic antiphospholipid syndrome. Exp Rev Hematol. 2017;10(4):365–374. doi:10.1080/17474086.2017.1300522.
2. Asherson RA, Cervera R, de Groot PG, Erkan D, Boffa MC, Piette JC, Khamashta MA, Shoenfeld Y; Catastrophic Antiphospholipid Syndrome Registry Project Group. Catastrophic antiphospholipid syndrome: international consensus statement on classification criteria and treatment guidelines. Lupus. 2003;12(7):530–534. doi:10.1191/0961203303lu394oa
3. Bucciarelli S, Espinosa G, Cervera R, Erkan D, Gómez-Puerta JA, Ramos-Casals M, Font J, Asherson RA; European Forum on Antiphospholipid Antibodies. Mortality in the catastrophic antiphospholipid syndrome: causes of death and prognostic factors in a series of 250 patients. Arthritis Rheum. 2006;54(8):2568–2576. doi:10.1002/art.22018
4. Legault K, Schunemann H, Hillis C, Yeung C, Aki EA, Carrier M, Cervera R, Crowther M, Dentali F, Erkan D, et al. McMaster RARE-Bestpractices clinical practice guideline on diagnosis and management of the catastrophic antiphospholipid syndrome. J Thromb Haemost. 2018;16(8):1656–1664. doi:10.1111/jth.14192
5. Marie I, Maurey G, Hervé F, Hellot MF, Levesque H. Intravenous immunoglobulin-associated arterial and venous thrombosis; report of a series and review of the literature. Br J Dermatol. 2006;155(4):714–721. doi:10.1111/j.1365-2133.2006.07390.x.
6. Taylor FB, Toh CH, Hoots WK, Wada H, Levi M. Towards definition, clinical and laboratory criteria, and a scoring system for disseminated intravascular coagulation. Thromb Haemost. 2001;86(5):1327–1330. doi:10.1055/s-0037-1616068
7. Warkentin TE. Ischemic limb gangrene with pulses. N Engl J Med. 2015;373(7):642–655. doi:10.1056/NEJMra1316259.
8. Cervera R, Bucciarelli S, MA P, JA G-P, Plaza J, Pons-Estel G, Shoenfeld Y, Ingelmo M, Espinos G; Catastrophic Antiphospholipid Syndrome (CAPS) Registry Project Group (European Forum on Antiphospholipid Antibodies). Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of a series of 280 patients from the CAPS Registry. J Autoimmun. 2009;32(3–4):240–245. doi:10.1016/j.jaut.2009.02.008
9. Berman H, Rodríguez-Pintó I, Cervera R, Gregory S, de Meis E, Rodrigues CE, Aikawa NE, de Carvalho JF, Springer J, Niedzwiecki M, et al. Pediatric catastrophic antiphospholipid syndrome: descriptive analysis of 45 patients from the CAPS registry. Autoimmun Rev. 2014;13(2):157–162. doi:10.1016/j.autrev.2013.10.004
10. Hanouna G, Morel N, Le Thi Huong D, Josselin L, Vauthier-Brouzes D, Saadoun D, Kettaneh A, Levesque K, Le Guern V, Goffinet F, et al. Catastrophic antiphospholipid syndrome and pregnancy: an experience of 13 cases. Rheumatol (United Kingdom). 2013;52(9):1635–1641. doi:10.1093/rheumatology/ket167
11. Pontara E, Banzato A, Bison E, Cattini MG, Baroni G, Denas G, Calligaro A, Marson P, Tison T, Ruffatti A, et al. Thrombocytopenia in high-risk patients with antiphospholipid syndrome. J Thromb Haemost. 2018;16(3):529–532. doi:10.1111/jth.13947.
12. Shiber S, Molad Y. Catastrophic antiphospholipid syndrome: a case series. Isr Med Assoc J. 2013;15(9):549–552. doi:10.3329/bjmed.v23i2.14992.
13. Ruffatti A, De Silvestro G, Marson P, Tonello M, Calligaro A, Favaro M, Del Ross T, Hoxha A, Mattia E, Pengo V. Catastrophic antiphospholipid syndrome: lessons from 14 cases successfully treated in a single center. A narrative report. J Autoimmun. 2018;93;124–130. doi:10.1016/j.jaut.2018.07.001
14. Rodríguez-Pintó I, Moitinho M, Santacreu I, Shoenfeld Y, Erkan D, Espinosa G, Cervera R. the CAPS Registry Project Group (European Forum on Antiphospholipid Antibodies). Catastrophic antiphospholipid syndrome (CAPS): descriptive analysis of 500 patients from the International CAPS Registry. Autoimmun Rev. 2016;15(12):1120–1124. doi:10.1016/j.autrev.2016.09.010.