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A probable case of catastrophic antiphospholipid syndrome: Should high-dose steroids be given in the setting of polymicrobial sepsis?

Shanna Ariane Tucker[1], Justin Choi[1] and Dhruv Khullar[1,2]

Abstract

In this clinical vignette, we present a case of a 59-year-old woman with catastrophic antiphospholipid syndrome likely triggered by polymicrobial sepsis. The diagnostic criteria and clinical manifestations of catastrophic antiphospholipid syndrome are reviewed. We also compare diagnostic criteria and clinical manifestations with other clinical entities in the differential diagnosis, including thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome, disseminated intravascular coagulation, sepsis, and inflammatory bowel disease. Catastrophic antiphospholipid syndrome is a rare, but lethal condition, and treatment recommendations are based on expert consensus and analyses of the international Catastrophic Antiphospholipid Syndrome Registry. Current management guidelines recommend triple therapy, with anticoagulation, glucocorticoids, and plasma exchange or intravenous immunoglobulins. This case brings this rare clinical entity to the attention of clinicians and emphasizes the need for more research to understand the best management. It also raises the question of whether high-dose steroids should be continued for treatment of catastrophic antiphospholipid syndrome in the setting of a severe sepsis.

Keywords

Catastrophic antiphospholipid syndrome, antiphospholipid syndrome, antiphospholipid antibodies, polymicrobial sepsis, gastrointestinal bleeding, inflammatory bowel disease

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Introduction

Catastrophic antiphospholipid syndrome (CAPS) is a life-threatening variant form of the more well-known antiphospholipid syndrome (APS), occurring in ~1% of patients with APS. CAPS is characterized by a rapid onset of progressive thrombosis of the microvasculature, resulting in multi-organ failure. The condition has a mortality rate of 37%–50%,[1,2] and early diagnosis and treatment are crucial for survival.

The diagnosis of CAPS can be challenging, as it often mimics other illnesses and can progress rapidly. Criteria for definitive diagnosis include involvement of three or more organs or organ systems within 1 week, laboratory confirmation of antiphospholipid antibody (aPL), and histopathologic evidence of small-vessel occlusions. aPL includes IgG and IgM immunoassays to cardiolipin and beta2-glycoprotein and functional assay for lupus anticoagulant. If a tissue sample cannot be obtained, a diagnosis of "probable CAPS" can be made clinically.[1]

A trigger can be identified in about 65% of CAPS cases—the most common being infection, surgery, malignancy, and withdrawal of therapeutic anticoagulation.[1–3] The standard treatment includes anticoagulation and steroids, but it is not clear how to best manage patients with both CAPS and a severe infection.

Here, we present a case of probable CAPS triggered by severe sepsis in the setting of a steroid taper.

Case presentation

A 59-year-old woman with a recent diagnosis of ulcerative colitis (UC) presented with 3 days of bloody diarrhea and abdominal pain associated with anorexia and weight loss. She

[1]Department of Medicine, Weill Cornell Medicine/New York-Presbyterian Hospital, New York, NY, USA
[2]Department of Healthcare Policy & Research, Weill Cornell Medicine, New York, NY, USA

Corresponding Author:
Shanna Ariane Tucker, Department of Medicine, Weill Cornell Medicine/New York-Presbyterian Hospital, 505 East 70th Street, Floor 4, Weill Cornell Internal Medicine Associates, New York, NY 10021-4872, USA.
Email: sat9137@nyp.org

was initially afebrile and hemodynamically stable. Her examination was notable for cachexia and a diffusely tender abdomen without peritoneal signs. Laboratory studies were notable for the following: white blood cell count 15.9×10^3 cells/μL, hemoglobin 11.2 g/dL, creatinine 0.6 mg/dL, platelet count 128×10^3 cells/μL, international normalized ratio (INR) 1.3, prothrombin time (PT) 16.6 s, partial thromboplastin time (PTT) 42.8 s, lactate was 2.11 mmol/L, erythrocyte sedimentation rate (ESR) 20 mm/h, C-reactive protein (CRP) 6.37 mg/dL, and ferritin 93 ng/mL. Her acute symptoms were thought to be due to an UC flare and she was started on intravenous (IV) methylprednisolone and oral mesalamine.

Initial cross-sectional imaging showed new main portal vein thrombosis (PVT) extending into the right and left portal vein branches causing liver hypoperfusion and moderate-to-severe pancolitis. Full anticoagulation with unfractionated heparin was started, given stable hemoglobin and mild hematochezia initially. However, the patient subsequently experienced large-volume hematochezia resulting in hypotension and was transferred to the intensive care unit. At that time, laboratory studies demonstrated increased leukocytosis to 51×10^3 cells/μL, reduction in hemoglobin to 9 g/dL (from 11.2), supratherapeutic PTT above 150, and elevated lactate of 7.4 mmol/L. Repeat computed tomography (CT) imaging found new ischemic enterocolitis. Heparin was held and the patient received a red blood cell transfusion.

The patient then underwent successful transjugular intrahepatic portosystemic shunt (TIPS) placement. Her abdominal pain improved, and leukocytosis and lactic acidosis resolved. Hemoglobin level and vital signs remained stable. Given clinical stability, heparin was restarted several days later because of concern that bowel ischemia and gastrointestinal bleeding were secondary to mesenteric ischemia from both reflex arterial constriction and mesenteric venous outflow obstruction in the setting of an occlusive PVT.

A hypercoagulable workup revealed positive lupus anticoagulant. Anti-beta 2-glycoprotein, anti-cardiolipin, fluorescein-labeled proaerolysin (FLAER) test for paroxysmal nocturnal hemoglobinuria (PNH), and *JAK2* mutation were all negative. She reported a history of miscarriage, raising the possibility for APS. She was up-to-date on all age-appropriate cancer screening.

The patient's hematochezia eventually subsided with corticosteroids, mesalamine, and heparin. Given her improvement, she was transitioned from IV methylprednisolone to prednisone. However, she then developed acutely worsening abdominal pain and hematochezia, prompting transition back to methylprednisolone and an increased dose of mesalamine. She continued to become more lethargic and developed acute thrombocytopenia from 152 to 50×10^3 cells/μL over 24 h (confirmed by scan). Heparin-induced thrombocytopenia (HIT) was confirmed with a strongly positive HIT Ab at 2.8 and a positive serotonin release assay. Anticoagulation was switched to argatroban. While on argatroban, the patient experienced an episode of large-volume hematochezia and became obtunded. CT head imaging was negative for an intracranial hemorrhage. An infectious workup revealed polymicrobial bacteremia with *Escherichia coli, Klebsiella pneumoniae*, and *Proteus sp* and *Candida tropicalis* fungemia. She was started on appropriate antibiotics and antifungal therapy, and steroid dosing was tapered given polymicrobial bacteremia and invasive candidiasis.

Serial CT venogram imaging demonstrated expanding sagittal venous sinus thrombus and new cerebral venous thromboses despite therapeutic anticoagulation therapy. The patient was transitioned to bivalirudin but continued to deteriorate, developing disseminated intravascular coagulation (DIC) and septic shock. She was transitioned to comfort care after a detailed family discussion and passed away shortly thereafter.

Discussion

In this case report, we present the case of a 59-year-old woman with inflammatory bowel disease (IBD) who presented with bloody diarrhea and abdominal pain. Her initial imaging was notable for an extensive PVT causing liver hypoperfusion and intestinal ischemia. She was treated with stress dose steroids and anticoagulation, and her course was complicated by polymicrobial bacteremia and invasive candidiasis prompting tapering of steroids. Her condition then rapidly deteriorated, with expanding cerebral venous thromboses, despite therapeutic anticoagulation, as well as DIC and septic shock.

The differential diagnosis includes probable CAPS, thrombotic thrombocytopenic purpura (TTP)–hemolytic-uremic syndrome (HUS) (TTP-HUS), DIC, sepsis, and severe IBD flare. While our patient does not meet all diagnostic criteria for CAPS, her positive aPL and history of miscarriage are more suggestive of CAPS than other diagnoses (Table 1). Without tissue histopathological evidence, a definitive diagnosis of CAPS is not possible. Nonetheless, the patient meets criteria for probable CAPS, given involvement of at least three organs—including liver (PVT), brain (venous thromboses), and ovary (right ovarian vein thrombosis)—and aPL positivity. As shown in Table 1, aPL positivity narrows the differential to CAPS, sepsis, and IBD flare. Sepsis is unlikely to explain her entire clinical course, given multiple thromboses on initial presentation. IBD remains a possibility, though the patient's thrombotic burden was out of proportion to the severity of hematochezia, which overall had improved since admission. There were no schistocytes seen on peripheral blood smear by scan to suggest TTP-HUS. The clinical features that argue against CAPS are the clinical time course and lack of renal involvement. Her symptoms developed over weeks, while CAPS classically develops rapidly (within 1 week). Renal involvement from microvascular disease is a common clinical feature (71%–74%) of CAPS, but was not present in this patient.[1–3] Finally, it should be noted that a false-positive aPL is possible in the setting of heparin. However, the patient's overall constellation of symptoms makes CAPS the most likely diagnosis.

While the pathogenesis of CAPS is not completely understood, multiple mechanisms have been proposed. The disease process is thought to be driven by a proinflammatory state due to cytokine storm.[1,2] aPL antibodies increase patients' baseline

Table 1. Comparison chart.

	Our patient	CAPS	Sepsis	TTP-HUS	DIC	IBD
aPL	+	+++	+/−	−	−	+/−
Fever	−	+/−	+	+/−	+/−	+
Leukocytosis	+	+/−	+	+/−	+/−	+
Clinical Course	2.5 weeks	1 week	Days	Days	Days	Days–weeks
Fibrinogen	Normal/low	Normal	Normal/low	Normal	Low	Normal
Hemolytic anemia	+	+/−	+/−	++	+/−	−
Schistocytes	−	+/−	+/−	++	+/−	−
Thrombocytopenia	+	+/−	+/−	++	+	−

This chart compares the clinical features of patient presented in case and other similar disease processes: presence of antiphospholipid antibody (aPL), catastrophic antiphospholipid syndrome (CAPS), thrombotic thrombocytopenic purpura–hemolytic-uremic syndrome (TTP-HUS), disseminated intravascular coagulation (DIC), and inflammatory bowel disease (IBD).

genetic tendency toward thrombosis, but a "second hit" likely initiates thrombus formation and thrombotic storm. Infection is thought to be the most common "second hit."[1–3] IBD is not known to be a trigger for CAPS, but there has been at least one case report previously described in the literature.[4]

First-line treatment of CAPS includes anticoagulation (usually with heparin) and high-dose corticosteroids. Intravenous immunoglobulins (IVIGs) and/or plasma exchange are recommended in life-threatening situations.[1,5] Heparin is the ideal anticoagulant for CAPS because it also inhibits complement activation and seems to inhibit aPL from binding to cell surface targets.[6,7] However, because this patient developed HIT, she was transitioned to argatroban and later bivalirudin, neither of which are known to have these additional effects. Similarly, corticosteroids are standard treatment to reduce cytokine release and dampen the cytokine storm that underlies the pathogenesis of CAPS.[1,2,5] In this case, however, steroids were tapered given polymicrobial bacteremia.

Conclusion

We discussed a challenging case of probable CAPS in which HIT and polymicrobial bacteremia made it difficult to continue standard therapy for CAPS. Currently, there are no guidelines for steroid therapy in patients with CAPS and severe infections. The European Forum on Antiphospholipid Antibodies maintains a CAPS Registry to provide the timely information on the characteristics of this life-threatening disease, but there remain many unanswered questions about optimal treatment, particularly for patients with severe concomitant infections. Our case demonstrates the need for further research to help guide treatment for such patients.

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ORCID iD

Shanna Ariane Tucker https://orcid.org/0000-0001-5419-075X

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