—Case Reports—

Intravenous Unfractionated Heparin vs. Therapeutic Plasma Exchange in Patients with Autoimmune Disease with Acute Thrombotic Events: Sampling in a Case of Catastrophic Antiphospholipid Syndrome

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A variety of autoimmune disorders are associated with an increased risk of thrombosis. Previous studies have suggested combined therapy of heparin and therapeutic plasma exchange (TPE) with fresh frozen plasma (FFP) as the replacement fluid is beneficial in some cases of acute flare-up of autoimmune diseases complicated by thrombotic events. Nevertheless, it remains unknown whether clinicians do more harm than good by exposing patients to a "thrombotic storm" through simultaneous administration of heparin and the clotting factors in the FFP during TPE. A variety of data are currently available on therapeutic interventions for autoimmune diseases complicated with acute thrombosis; however, there is limited evidence on the exact efficacy of each individual approach and combinations of these measures. Herein, we report a case of catastrophic antiphospholipid syndrome (CAPS) to highlight the difficulty of therapeutic decision-making when complicated interactions occur between heparin and TPE. To our knowledge, this is the first case report of a patient diagnosed with CAPS successfully treated with a novel therapeutic strategy of escalating the heparin dosage when performing TPE by monitoring the partial prothrombin time to reduce the risk of the progression of thrombosis.
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Introduction

At present, intravenous (IV) heparin remains a common therapeutic strategy for patients who have suffered thrombotic events. The major anticoagulant effects of heparin are largely mediated through its interaction with antithrombin III (AT-III), which further catalyzes inactivation of the coagulation enzymes thrombin (factor IIa), factor Xa, factor IXa, and factor XIIa[1]. By inactivating thrombin, heparin not only prevents the formation of fibrin but also inhibits thrombin-induced activation of factor V and factor VIII[2], which ultimately contribute to antithrombotic effects.

Therapeutic plasma exchange (TPE) is commonly used in many autoimmune diseases that exhibit acute relapses. TPE can remove circulating auto-antibodies and other immune reactants from plasma. After extracting large quantities of plasma, the cellular blood components are returned to the patient with a replacement fluid, usually fresh frozen plasma (FFP), to prevent hypovolemia[3]. Consequently, TPE helps to alleviate the acute symptoms of autoimmune diseases and can prevent life-threatening conditions via eliminating harmful substances from the blood.

Previous studies have shown a variety of autoimmune disorders are associated with an increased risk of thrombosis[4,5]. Administration of heparin IV is one of the most efficacious initial managements for autoimmune diseases complicated by thrombosis[1]. Moreover, TPE often plays a crucial role in the treatment of immune disorders during an acute flare-up. One notable advantage of TPE is that it may alleviate or prevent acute and severe complications by physically eliminating damaging antibodies from the

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plasma[3]. However, high levels of coagulation factors are theoretically associated with increased risk of thrombosis[6]. Therefore, TPE would have the disadvantage of heightening the likelihood of thrombosis as FFP contains numerous clotting factors[7]. Thus, physicians face an agonizing dilemma when choosing the most suitable treatment approach for autoimmune diseases complicated by thrombosis.

Herein, we describe a case of catastrophic antiphospholipid syndrome (CAPS) to highlight the difficulty of therapeutic decision-making related to the interaction between heparin and TPE and patient outcomes.

Case Report

A 30-year-old male with systemic lupus erythematosus (SLE) under medical control for 12 years who was also diagnosed two years ago with antiphospholipid syndrome (APS) secondary to SLE presented to the emergency department with progressive shortness of breath after exercise in the previous three months. Assessment of the patient's medical history revealed APS had been diagnosed in the context of high anti-cardiolipin IgM titers in two tests performed at least 12 weeks apart; it also revealed a transient ischemic attack (TIA) which had manifested with a sudden onset of blurred vision and left upper limb weakness that lasted for 30 minutes and resolved spontaneously. No evidence of acute infarction was detected on contrast-enhanced brain magnetic resonance imaging (MRI). Since then, the patient's APS had remained stable under treatment with aspirin, methylprednisolone, and cyclosporin.

Upon admission, physical examinations revealed jugular venous engorgement and an accentuated pulmonic closure sound. Cardiac catheterization was performed as heart failure was suspected on echocardiogram and chest X-ray studies. A diagnosis of pulmonary hypertension was confirmed by right heart catheterization, which revealed a pulmonary artery pressure of 83/55 mmHg and a mean pressure of 64 mmHg. He was treated with IV treprostinil (20 mg/20 mL daily), oral sildenafil (60 mg daily), and oral bosentan (125 mg daily) subsequently. However, the patient's treatment was further complicated by development of acute kidney injury with a peak serum creatinine of 1.8 mg/dL (baseline level 1.0 mg/dL) and proteinuria of 8.3 g/day on day 6 of hospitalization. Serologic work-up (**Fig. 1**) also indicated new-onset thrombocytopenia with a platelet count of 59,000/mm^3, prolonged prothrombin time (PT) of 24.5 s, prolonged partial prothrombin time (aPTT) of 56.2 s, D-dimer peak of over 3,500 ng/mL, and elevated lactate dehydrogenase (LDH) of 2,203 U/L. Rheumatologic laboratory analyses revealed positive antinuclear antibodies (ANA; 1:160; speckled pattern), positive anti-cardiolipin IgM (42 MPL-U/mL), equivocal anti-double-stranded DNA antibody (108.291 U/mL), negative anti-Smith antibody (9.625 U/mL), low C3 (22.1 mg/dL) and low C4 (3.91 mg/dL). Moreover, a sudden change in consciousness occurred that night. Brain CT was arranged and showed neither profound intracranial hemorrhage nor vessel infarction (**Fig. 2**). A diagnosis of CAPS with thrombotic microangiopathy (TMA) was established based upon the development of multiorgan failure in less than a week after hospitalization, small vessel occlusion suspected in the kidney with presentation of acute renal injury, and positive anti-cardiolipin antibody. A blood smear revealed reserved ADAMTS 13 activity and no schistocytes, which did not support hemolytic uremic syndrome (HUS) or thrombotic thrombocytopenia (TTP). Given the degree of immunosuppression with burden of a rapid thrombosis and lack of other lupus-flare manifestations such as progressive arthritis or skin rashes over time, CAPS secondary to SLE was assessed to be more likely than solitary SLE exacerbation. The patient was transferred to an intensive care unit and received the standard treatment for CAPS (**Fig. 1**).

As the patient's clinical findings had worsened, a temporary hemodialysis catheter was inserted. TPE was performed using the Prismaflex Version 8.2 (Baxter) system with a Plasmaflo OP-08W membrane (Asahi Kasei). Five daily sessions of TPE were immediately initiated, each lasting for 90 min, and the prescribed plasma exchange volume was 2,500 mL. Pulse therapy with IV methylprednisolone (1 g daily, followed by a tapered dosage of 60 mg daily) and anticoagulant with continuous heparin infusion (25,000 U daily) were also prescribed. However, the patient's clinical condition subsequently worsened further and he developed severe abdominal pain without internal bleeding; however, ascites were noticed on abdominal CT, along with ecchymosis over the extremities noted on day 7 of hospitalization. Fluctuating coagulation indicators including aPTT, platelet counts, and D-dimer were also recorded (**Fig. 1**). Given suspected progressive formation of a thrombus after the first session of TPE, the dosage of the heparin pump was increased to 200 U/h over the baseline value during the second session of plasma exchange, and we set an ideal target range of aPTT of 45-60 s according to our institution's protocol. After this adjustment, the thrombotic occlusion

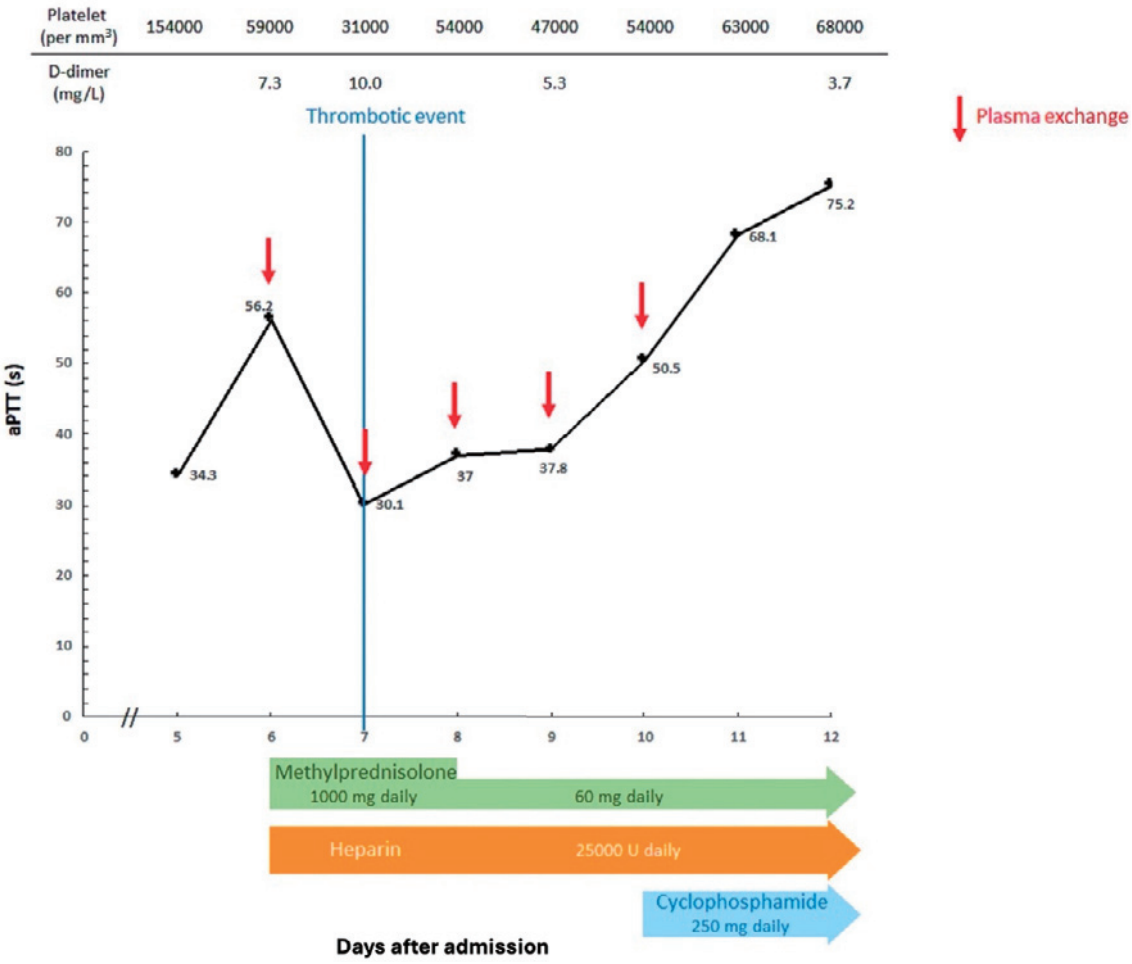

Fig. 1 Clinical and Laboratory Data on the Patient

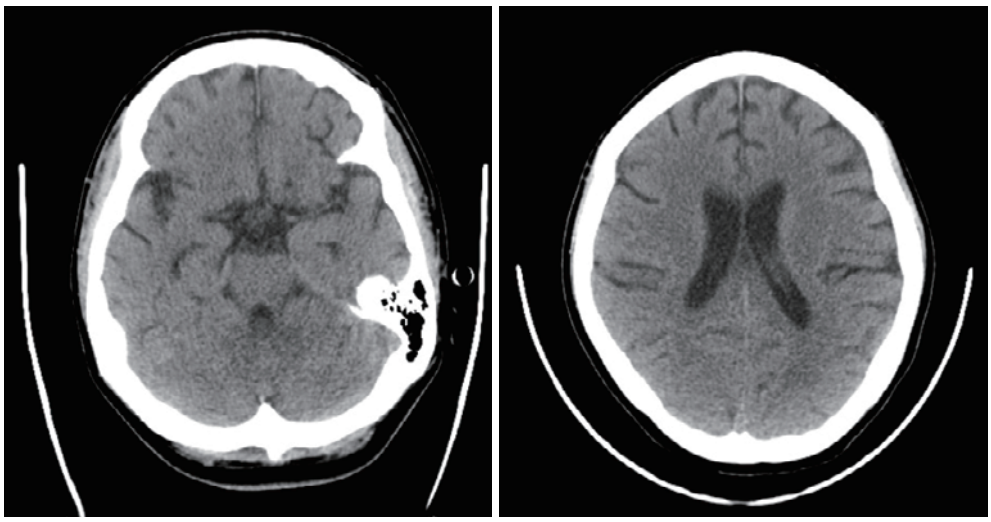

Fig. 2 Computed tomography (CT) of the brain showed neither profound intracranial hemorrhage nor vessel infarction

stabilized and the laboratory profile showed a rise in the aPTT value. Likewise, the dosage of the heparin pump was kept at the escalated value (200 U/h over baseline) in consecutive sessions of TPE. Concomitant treatment with IV cyclophosphamide (250 mg daily) was given from day 10 onwards. With this multimodal therapy, the patient's general condition improved and aPTT gradually reached the target range. After a 2-month period of man-

agement with heparin and prednisolone (10 mg daily), the patient became hemodynamically stable and was discharged with a favorable prognosis.

Discussion

TPE appears to be an effective approach for removing damaging plasma components that cause morbidity in a variety of renal, hematological, neurological, and rheumatic diseases. The American Society of Apheresis (ASFA) has published guidelines for the use of TPE for numerous distinct conditions associated with thrombotic microangiopathy (TMA), including CAPS, thrombotic thrombocytopenia purpura (TTP), and heparin-induced thrombocytopenia (HIT)[8]. TPE is often necessary in these urgent clinical scenarios to rapidly inhibit thromboembolism.

In the TPE protocol, the plasma volume is usually prescribed as 1 to 1.5 times the patient's estimated plasma volume (EPV). The EPV can be calculated using EPV = (0.065 × weight [kilograms]) × (1 − hematocrit); this simple formula is more widely used than other established formulas[9,10]. These measurements are accurate and are straightforward to perform for most routine cases. However, certain situations may lead to inaccurate estimation of EPV. For example, whether thromboemboli have formed or not during progression of each disease should be one of the parameters considered. However, at present, definitive guidelines regarding volume of plasma in such unique cases have not yet been established.

In our case, the diagnostic criteria for CAPS were met, including multi-organ failure in less than a week, microangiopathic thromboses in the kidney, and the presence of positive anti-cardiolipin antibody[7]. CAPS is typified by arterial, venous, or small vessel thrombosis leading to multiorgan failure with diverse clinical manifestations. The kidney is the most frequently affected organ, mainly presenting as renal insufficiency, proteinuria or hematuria. Pulmonary complications may also occur, featuring pulmonary embolism or acute respiratory distress syndrome. Besides, CNS involvement with encephalopathy or stroke, cardiac problems mainly manifesting as heart failure, and skin complications such as livedo reticularis may be detected in patients with CAPS[11]. Our patient exhibited a large portion of the aforementioned symptoms, indicating a potential thrombus formation. A microthrombus may have been present in our case, but we were unable to confirm this in the clinical imaging study. It is possible that renal biopsy and pulmonary angiography might verify thrombus formation in the kidney and/or pulmonary artery.

The moment CAPS was suspected, we administered concomitant pulse therapy, anticoagulant therapy, and TPE as suggested by most published studies. FFP was infused as the replacement fluid during TPE, and the volume was calculated using the EPV formula mentioned above[9]. However, the patient developed multiple progressive TMA despite triple therapy. We first confirmed the degree of anticoagulation by interpreting the aPTT, and then increased the dose of heparin to 200 U/h above baseline value during TPE to prevent new thrombotic events triggered by the clotting factors in FFP. After this modification, gradual improvements in the patient's clinical condition and laboratory parameters were observed. In view of this patient's favorable response to the management described above, we applied same protocol in consecutive sessions of TPE to prevent further thromboembolism.

When combined heparin and TPE therapy is required in an acute flare-up of TMA-associated diseases, such as the case of CAPS presented herein, it is still unclear whether clinicians do more harm than good by exposing the patient to a "thrombotic storm" through simultaneous infusion of heparin and the clotting factors in FFP[12]. Thus, the question remains: in order to harmonize medical therapies, should we taper down the patient's plasma volume or should we increase the heparin dosage during TPE?

To address this issue, we reviewed the available data on this complex scenario. Due to the rarity of CAPS and the absence of randomized controlled studies, no evidence-based management protocols exist. In 1998, a triple therapy of steroids plus anticoagulant plus TPE and/or intravenous immunoglobin (IVIG) was proposed[13]. However, the exact efficacy of each individual approach, combinations of these measures, and additional curative strategies remain uncertain. Asherson et al.[14] conducted a large study on the treatment of CAPS and found that only anticoagulants significantly reduced the risk of death, whereas another comprehensive review concluded that triple therapy most significantly reduced the mortality rate[15]. Yet another study showed that anticoagulants had the most beneficial effect on prognosis[16]. The combination of rituximab with conventional immunosuppressive treatment has also been reported to work synergistically to achieve therapeutic efficacy in cases of CAPS through the depletion of CD20+ precursors of B cells, decreased antiphospholipid titers, and modulation of the inflammatory response[17]. Compart-

mental pharmacokinetic modelling has quantified the impact of rituximab on exposure to TPE in CAPS patients, demonstrating that rituximab could play a role in the treatment of refractory CAPS, regardless of its potential side effects seen in other settings[18].

According to our previous experience, we generally recommend increasing the dosage of heparin during TPE to avoid the formation of thrombi. Moreover, monitoring the patient's aPTT level after each session of TPE and keeping aPTT within a safe range could help to prevent the progression of TMA.

In the context of CAPS, the use of plasma may restore the balance of natural anticoagulants and help to prevent a thrombotic storm. However, very few studies have evaluated the true clinical impact of TPE on therapeutic anticoagulation. Kaplan et al.[19] emphasized that as heparin is removed from the plasma during TPE, adjustment of the dosage of heparin may be necessary to maintain therapeutic drug levels. In contrast, Hodulik et al.[20] demonstrated that TPE is associated with an increase in aPTT in patients receiving therapeutic anticoagulation. However, these coagulation changes do not appear to significantly increase the risks of thrombosis or bleeding. Thus, both of these studies highlight the difficulty of characterizing the combined hemostatic impact of TPE and heparin, especially as prospective reports are limited and the small numbers of case reports or studies with modest sample sizes have reported heterogenous results.

To date, there are no definitive guidelines for treating TMA-associated diseases during an acute flare-up. Escalating the heparin dosage during TPE might strike a balance between coagulation and anticoagulation, as favorable results after such adjustment were observed in the case reported herein. Based on the limited studies available and our own experience as physicians, either tapering down the FFP volume during TPE or adopting double-filtration plasmapheresis (DFPP) using albumin solution could help to beneficially avoid a thrombotic storm. Moreover, a combination of these treatment alternatives may also feasibly minimize the undesirable side effects associated with exposure to both plasma and anticoagulants. Overall, additional prospective studies and randomized controlled trials are required to define the efficacy of each of these curative strategies.

Monitoring the therapeutic dosage of IV heparin in treating APS is recommended and can be achieved through an aPTT or anti-Xa assay[21]. Given that aPTT levels may interfere with lupus anticoagulant-induced effects[21], additional testing using an anti-Xa assay in our case may provide a more accurate way to monitor the effects of heparin.

The interaction between IV heparin and TPE has not been well-explored due to the limited evidence available. It remains a challenge for physicians to decide the optimal management when treating patients with autoimmune diseases complicated by acute thrombotic events. Our case suggests that escalating the heparin dosage during TPE by monitoring a relevant indicator may be a reasonable option to prevent the formation of new thrombi during disease progression. Further detailed investigations are urgently needed to solve this dilemma.

Conflict of Interest: None.

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