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CASE REPORT

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Use of Agratroban in Catastrophic Antiphospholipid Antibody Syndrome

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ABSTRACT

Catastrophic antiphospholipid antibody syndrome (CAPS), as first described by Asherson is an accelerated variant of antiphospholipid antibody syndrome (APS) resulting in multiorgan failure primarily due to unabated multiple small vessel thrombotic occlusions in various organs. Although less than 1% of patients with APS develop this complication, early recognition and treatment is crucial in preventing the reported mortality rate of 50%. Despite available consensus treatment guidelines that include a combination of anticoagulant therapy, corticosteroids, intravenous immunoglobulin, and plasma exchange for all patients with this potentially fatal condition, the mortality rate remains extremely high. This case report provides insights on the potential use of agratroban as a more efficient anticoagulant treatment to address the primary thrombotic pathogenesis of CAPS. This case report illustrates that plasma exchange may not be critical in the treatment of all cases of CAPS and should be used in a more tailored fashion. We also propose that direct thrombin inhibitors be the anticoagulants of choice for CAPS to overcome both the tremendous thrombotic potential of CAPS and to circumvent circulating cytokines that inhibit the effectiveness of unfractionated heparins.

INTRODUCTION

Catastrophic antiphospholipid antibody syndrome (CAPS), as first described by Asherson[1], is an accelerated variant of antiphospholipid antibody syndrome (APS) resulting in multiorgan failure primarily due to unabated multiple small vessel thrombotic occlusions in various organs. Although less than 1% of patients with APS develop this complication[2], early recognition and treatment is crucial in preventing both the reported mortality rate of 50%[3] and much of the functional morbidities such as amputations, cognitive dysfunction, dementia, hemiparesis, quadriplegias, chronic kidney disease, and cardiomyopathies.[4]

The heterogeneity of disease expression has led to the development of consensus criteria for the definition and classification of patients with CAPS. The Tenth International Congress on APS established preliminary criteria for the classification of CAPS[5] that have since been validated.[6] These criteria include: 1) Evidence of involvement of three or more organs, systems, and/or tissues, 2) Development of manifestations simultaneously or within one week, 3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue, and 4) Confirmation of the presence of antiphospholipid antibodies. Presenting with all four criteria establishes "definite" criteria for CAPS. Lack of histopathologic evidence is defined as probable CAPS. From the analysis of the initial 176 patients included in the CAPS international registry headed by Cervera, 89 (51%) of the previously compiled patients with CAPS were classified as "definite" and 70 (40%) as "probable". The most recent registry update shows that most registry patients lacked biopsy confirmation of microthrombosis.[7]

The consensus statement also delineates treatment guidelines that include a combination of anticoagulant therapy, corticosteroids, intravenous immunoglobulin, and plasma exchange for all patients with this potentially fatal condition.[6] Yet, and despite all therapies advised, the mortality rate remains extremely high.[7] The treatment guidelines indicate the use of anticoagulants in the form of intravenous unfractionated heparin (UFH) as the mainstay of treatment in patients with CAPS. This is based on a CAPS registry retrospective analysis confirming the lower rate of mortality in anticoagulated patients compared with those not receiving anticoagulants (36.9% vs. 77.8%, respectively; $P<0.0001$).[8] The residual 36.9% mortality rate despite standard anticoagulant therapy with UFH may emphasize the point that CAPS is an illustration of a "thrombotic storm", as postulated by Kitchens, with the activation of coagulation products, simultaneous depression of fibrinolysis, and consumption of natural anticoagulant proteins perpetuating a vicious cycle.[9] This case report raises the question whether more patients can be spared the mortality and morbidity of CAPS by the use of more modern and potent forms of anticoagulant therapy such as direct thrombin inhibitors.

CASE REPORT

A 49 year old female with a prior history of an unprovoked deep venous thrombosis (DVT) of the right lower extremity was found to have antiphospholipid antibody syndrome on the basis of inhibitor on mixing studies and a positive anticardiolipid antibody titer. She had been adequately anticoagulated for 5 years without further thrombotic complications.

On September 2, 2010, she presented to the Emergency Department with dependent edema, diffuse abdominal pain, and severe atypical headaches that started one week prior to admission to the hospital. Her INR upon admission was 1.7 while on treatment with 7.5 mg of warfarin daily. Her documented INR one week prior was 4.1 on the same dose of warfarin. On admission, warfarin was discontinued and she was placed on enoxaparin 1 mg/kg subcutaneously twice a day. She presented with new onset thrombocytopenia with a platelet count of 79. Her platelet count one

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week prior was 123. On mixing studies, her prothrombin time (PT) did correct but the partial thromboplastin time (PTT) did not fully correct. The quantitative D-Dimer was markedly high at 4390. Amylase, lipase, ANA, and complement levels were normal. She underwent CT imaging and liver spleen scanning, which showed enlargement of the liver and spleen. A venous Doppler of the abdominal vasculature indicated turbulent hepatic artery flow and high velocity at 207 cm/sec. The SGOT and alkaline phosphatase doubled within several days after admission. Her platelet count decreased to a low of 54K on her eighth hospital day.

Despite the use of full anticoagulation therapy with enoxaparin, the patient continued having severe abdominal pain requiring intravenous morphine for adequate pain control. On the nineth hospital day, she was treated with agratroban at 2 mcg/kg/min, resulting in immediate resolution of her pain. On the following day, she was then given IVIG at .08 grams/kg daily for three days and rituximab at 375 mg/m2 and repeated in 2 weeks. She also received Solumedrol at 1.5 grams intravenously over 3 days and was started on oral prednisone. Given the inhibitor effect causing a false elevation of the PTT, the D-Dimer and the patient's abdominal pain were used as disease process indices and a fixed-dose agratroban regimen was used. She did require an adjustment to her agratroban dose to 3 mcg/kg per min as she experienced minor abdominal pain accompanied by a mild increase in her D-Dimer. Within 4 days her D-Dimer dropped to 750 ng/ml and her platelet count normalized. She received a total of 6 days of agratroban therapy and was transitioned to fondaparinux 10 mg subcutaneously daily and aspirin 81 mg daily.

Discussion

This case illustrates the clinical tempo and complexities of the pathologic microangiopathic thrombotic disease process associated with CAPS, which, in turn, demands a high index of suspicion, early detection, and aggressive therapy in order to avert its high morbidity and mortality. Our patient lacked histologic proof for small vessel thrombotic involvement; however, it is felt that the likelihood for CAPS was very high given her history of venous thrombosis in the past in conjunction with a persistent positive antiphospholipid serology and multi-organ involvement developing over a short period of time. Our patient had clinical signs and radiographic evidence of microangiopathic thrombus generation in at least the CNS, liver, and spleen. In deed, clinical evidence of multiple organ (three or more) involvement developing over a short period of time is the cornerstone of CAPS.[7] This is due to diffuse small vessel ischemia and thromboses predominantly affecting the parenchymal organs. CAPS has been shown to be associated with endothelial cell activation as a result of antigen–antibody reactions on the surface of endothelial cells or monocytes. The activation of endothelial cells and the accompanying upregulation of adhesion molecules and tissue factor are likely to be pivotal for development of CAPS. The clinical manifestations of CAPS depend on (A) the organs that are affected by the thrombotic events and the extent of the thrombosis, as well as (B) manifestations of the systemic inflammatory response syndrome (SIRS), which are presumed to be due to excessive release of cytokines from affected and necrotic tissues.[10]

In spite of the initial anticoagulation with the use of enoxaparin, which would afford a more consistent anticoagulant effect in the setting of high circulating cytokines, the patient continued to have severe and worrisome symptoms. This prompted the use of direct thrombin inhibition with agratroban to abrogate the intense thrombotic potential of our patient's disease process. Subsequently, it was very impressive to see how rapidly the patient's symptoms responded to the anticoagulant effect of agratroban.

The international CAPS registry has established consensus guidelines on the treatment of CAPS. However, the consensus guidelines still advocate the use of unfractionated heparin as the anticoagulant of choice. The use of agratroban addresses most of these pathophysiological issues and therefore represents a more rational anticoagulant therapeutic approach to CAPS. Agratroban is a small molecule direct thrombin inhibitor discovered in Japan in 1970.[11] Attributes that make agratroban ideal for the treatment of CAPS include: 1) rapid onset of anti-thrombin action, 2) rapid reversibility of its anticoagulant effect, 3) potent inhibition of free and clot bound thrombin, 4) absence of antibody formation, and 5) smaller size that helps to penetrate thrombi in the microvasculature. It attenuates ischemia/reperfusion injury not only by inhibiting coagulation, but also by inhibiting inflammatory reactions mediated by leucocytes and platelets.[12,13] Fixed-dose agratroban regimens have been used successfully in patients with heparin-induced thrombocytopenia and elevated PTTs due to antiphospholipid antibody syndrome.[14]

The other important aspect of this case report is the lack of plasma exchange in the management of CAPS. Even though the CAP registry regards the use of both plasma exchange and IVIG as second-line treatment therapies, neither are level I evidence based, but are considered reasonable therapies in CAPS.[15] Based on a recent retrospective survival analysis from the CAPS registry analyzing the case reports of 250 patients included in the CAPS, the CAPS registry now advocates the use of a combination treatment with anticoagulant therapy using either UFH or enoxaparin with corticosteroids plus plasma exchange as first-line therapy in patients with CAPS.[16] This contrasts sharply to the treatment approach use in our case report. Based on the fact that the CAPS registry analysis is retrospective and based on subgroup analysis, it can be argued that mortality differences seen in the 149 patients diagnosed before 2001 and 78 patients diagnosed between 2001 and February 2005 were not due to the use of the three modalities it now advocates. These differences in mortality may be due to increased clinical familiarity and sensitivity to the diagnosis of CAPS as well as a younger mean age and time to CAPS diagnosis of both groups analyzed. With regards to the role of plasma exchange, it has seen shown that this is the treatment of choice in patients with features of microangiopathic hemolytic anemia in which small vessel occlusive disease is present.[17]

The use of rituximab is also worth mentioning. Rituximab, a chimeric antiCD20 monoclonal antibody, may help eliminate autoreactive B cells and thus limit the rapid inflammatory process involved in CAPS. It has been used successfully especially in refractory cases of CAPS.[18-20] It remains to be demonstrated if rituximab is more efficient in reducing the offending antiphosphoslipid antibodies than physical removal by plasma exchange.

This case provides insights on the potential use of agratroban as a more efficient anticoagulant treatment to address the primary thrombotic pathogenesis of CAPS. Additionally, this case also illustrates that plasma exchange may not be critical in the treatment of all cases of CAPS and should be used in a more tailored fashion. We

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propose direct thrombin inhibitors as the anticoagulants of choice for CAPS for overcoming both the tremendous thrombotic potential of CAPS and to circumvent circulating cytokines that inhibit the effectiveness of unfractionated heparins. Our findings advocate for randomized trials through the international CAPS Registry, comparing UFH to newer anticoagulant agents such as agratroban.

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