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**Vivekanandan Senthamil Pari, Lakshmi M, Sampath Kumar,
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ABSTRACT

Introduction: Antiphospholipid syndrome is characterized by recurrent thrombosis and/or pregnancy loss with the presence of circulating antiphospholipid antibodies. Its clinical manifestations range from asymptomatic to catastrophic antiphospholipid syndrome. This condition is a rare presentation of antiphospholipid syndrome and has a very high mortality rate.

Case Report: Herein, we present a 20-year-old female patient are presented with peripheral cyanosis, computed tomography angiogram of abdomen and lower limb vessels showed arterial occlusion, and renal infarcts. She also developed seizures during hospital stay. With suspicion of vasculitis she was started on methyl prednisolone with other appropriate medications after sending blood for relevant investigations. She responded to medications, meanwhile her antiphospholipid antibody was positive with skin biopsy taken from affected limb showing microthrombi in dermal capillaries with inflammatory exudates. These features are in favor of a diagnosis of a catastrophic antiphospholipid syndrome, which will be discussed in this case report.

Conclusion: Catastrophic antiphospholipid syndrome is a rare entity occurring in 0.8–1% of patients with antiphospholipid antibody syndrome and it has a very poor prognosis. But early, aggressive treatment improves the recovery rate and requires a high degree of suspicion.

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CASE REPORT

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Keywords: Recurrent thrombosis, Catastrophic antiphospholipid syndrome, Antiphospholipid antibodies

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INTRODUCTION

Antiphospholipid syndrome (APS) is characterized by recurrent thrombosis and/or pregnancy loss with the presence of circulating antiphospholipid antibodies. A severe, rapidly progressive form characterized by involvement of at least three different organ systems within one week duration with histopathological evidence of small and large vessel occlusion is termed catastrophic antiphospholipid syndrome. It occurs in 0.8–1% of cases

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of APS as seen in various case series and has a mortality of about 50%. It presents with features suggestive of DIC (Disseminated intravascular coagulation) or TTP/HUS (thrombotic thrombocytopenic purpura/hemolytic uremic syndrome) and needs to be treated aggressively in view of the rapid progression and high mortality.

CASE REPORT

We present a case of a 20-year-old unmarried female presented to the emergency room with bluish discoloration of toes and fingers which started four days prior and was progressive, first involving the left and then the right leg toes and then fingers. It was associated with numbness and pricking type of pain. She also had breathlessness for three days which was insidious in onset, progressing from NYHA (New York Heart Association) class II to IV in three days. She also gave history of fever for four days which was low grade with no associated chills or rigors. She also had history of recurrent oral ulcers and rashes on the face on exposure to sunlight for the last six months. Her menstrual cycles were normal. She had no comorbid illnesses and no significant past medical history. On examination she was well oriented, febrile, pale, had peripheral cyanosis and bilateral pitting pedal edema. Her blood pressure was 200/110 mmHg, respiratory rate was 28 breaths/min. Chest examination revealed S3 gallop and there were crepitations heard in bilateral lung fields. Abdomen and nervous system were unremarkable. Arterial pulses distal to the femoral artery were absent in both lower limbs (Figure 1).

Baseline blood investigations revealed anemia, raised total counts, normal platelet counts, PTT (partial thromboplastin time) about twice the normal with normal prothrombin time and a serum creatinine of 1.3 mg/dL with urea of 41 mg/dL. Urinalysis revealed 2+ proteinuria and no sediments. Peripheral smear showed no evidence of hemolysis. Arterial blood gas analysis showed hypoxia and metabolic acidosis with partial respiratory compensation. Chest X-ray showed bilateral pulmonary congestion. Electrocardiography had T-wave inversion in leads V1-V4 and left ventricular hypertrophy. Echocardiography was essentially normal with an ejection fraction of 60%. However, the levels of cardiac enzymes CK-MB and troponin T were slightly elevated and BNP was high (5000 ng/L). Cultures which were sent came out to be negative later. Vasculitis with acute pulmonary edema was suspected and patient was started on nitroglycerine infusion, diuretics and antihypertensives and connective tissue work up sent. Meanwhile the computed tomography (CT) angiography of lower limbs and renal vessels showed complete occlusion of anterior tibial and peroneal artery a few centimeters above the ankle with complete occlusion of dorsalis pedis bilaterally; both kidneys showed multiple wedge shaped parenchymal defects and the mid, distal segments, branches of renal arteries were small in calibre.

By the second day of admission, the patient developed severe respiratory distress and had to be ventilated, started on imipenam, low molecular weight heparin and i.v. methyl prednisolone therapy (1g/day for 5 days followed by oral prednisolone) was initiated pending the connective tissue work up reports in view of the critical condition of the patient and strong suspicion of vasculitis. On the fourth day of hospital stay the patient had one episode of generalized tonic clonic seizures, the CT scan of brain done for the same which was unremarkable and patient was switched from imipenam to piperacillin-tazobactam along with levetriacetam for the seizures. Skin biopsy was taken at the line of demarcation on the gangrenous digits to look for evidence of vasculitis/microthrombi. The connective tissue work up revealed ANA (Antinuclear antibodies), ds-DNA (double stranded DNA) and APLA (antiphospholipid antibody) positivity and ANCA (antinuclear cytoplasmic antibodies) were negative. Skin biopsy showed microthrombi in the dermal capillaries with surrounding inflammatory infiltrates (Figures 2–4).

Patient was gradually improving and was extubated, later switched to oral prednisolone and mycophenolate mofetil as per nephrologist's opinion. The patient's blood pressure was stable with oral antihypertensives and she was initiated on oral anticoagulant therapy. Amputation of the gangrenous digits/limbs was planned later. Her recovery was uneventful and was discharged on oral

Figure 1: Photograph showing peripheral cyanosis.

Figure 2: Micrograph of skin with dermal capillaries showing multiple microthrombi (H&E stain, x100).

Figure 3: High power showing microthrombi within dermal vessels surrounded by inflammatory infiltrates (H&E stain, x200).

Figure 4: Special stain highlighting the microthrombi within the vessels (Masson trichrome stain, x200).

medications with advice to follow-up. On follow-up after 12 weeks repeat APLS was sent and it was positive. In this case, this is the first presentation of the patient and she came with features of limb ischemia secondary

to microthrombosis, proteinuria with renal vascular changes and accelerated hypertension and she also had central nervous system involvement in the form of seizures. The above three features occurring within one week, with APLA positivity done twice more than six weeks apart, all point towards a diagnosis of catastrophic antiphospholipid syndrome (CAPS).

DISCUSSION

In this case, the initial differential diagnoses thought of were vasculitis, antiphospholipid syndrome with thromboses, sepsis with DIC, thrombotic thrombocytopenic purpura/hemolytic uremic syndrome.

In view of probable clinical diagnosis of vasculitis and CT angiography was suggestive of arterial occlusion she was started on steroids but later c-ANCA and p-ANCA reports turned out to be negative and skin biopsy was not suggestive of any specific vasculitis.

Another differential diagnosis considered was sepsis with disseminated intravascular coagulation since patient had thrombocytopenia leukocytosis. Hence she was initiated on broad spectrum antibiotics, but there was no evidence of bleeding or consumptive coagulopathy and microbiological cultures were negative.

We had also thought of thrombotic thrombocytopenic purpura/hemolytic uremic syndrome but there was no history of antecedent or current diarrhea, no evidence of hemolysis such as schistocytes on peripheral smear, hyperbilirubinemia or elevated LDH and no evidence of coagulopathy either.

So, putting all the positive findings together, we have acute ischemia of all four limbs, renal ischemia, acute pulmonary edema with normal left ventricular systolic function, central nervous system involvement in the form of seizures, deranged PTT and thrombocytopenia with normal PT and no evidence of bleeding or hemolysis with negative cultures and immunopathological evidence of systemic lupus erythematosus with antiphospholipid antibody positivity (ANA and ds-DNA, APLA positive and skin biopsy showing microthrombi with no evidence of vasculitis), all event occurring within a span of one week and thus fitting into the diagnosis of catastrophic antiphospholipid syndrome.

A small subset of patients with APS can go on to rapidly progressing widespread thrombotic disease with multiorgan failure, which is called “catastrophic APS” or Asherson syndrome and has a high mortality even with treatment. Hence the problem needs to be identified early and treated aggressively.

The current criteria for classification purposes and to facilitate early recognition of catastrophic APS as suggested by Asherson et al. are given in Table 1 [1].

Catastrophic APS occurs in 0.8–1% of the patients with APLA syndrome according to various studies [2, 3]. The basic pathology of the disease process remains the same as in antiphospholipid syndrome but at an accelerated

Table 1: Preliminary criteria for the classification of catastrophic antiphospholipid syndrome [4]

<p>(1) Evidence of involvement of three or more organs, systems and/or tissues^a</p> <p>(2) Development of manifestations simultaneously or in less than a week</p> <p>(3) Confirmation by histopathology of small vessel occlusion in at least one organ or tissue^b</p> <p>(4) Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)^c</p> <p>Definite catastrophic APS</p> <ul style="list-style-type: none"> • All four criteria <p>Probable catastrophic APS</p> <ul style="list-style-type: none"> • All four criteria, except for only two organs, systems and/or tissues involvement • All four criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never tested for aPL before the catastrophic APS • 1, 2 and 4 • 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation 	<p>a. Usually, clinical evidence of vessel occlusions, confirmed by imaging techniques when appropriate. Renal involvement is defined by a 50% rise in serum creatinine, severe systemic hypertension (>180/100 mmHg) and/or proteinuria (> 500 mg/24 h).</p> <p>b. For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.</p> <p>c. If the patient had not been previously diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on two or more occasions at least six weeks apart (not necessarily at the time of the event) according to the proposed preliminary criteria for the classification of definite APS.</p>
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Abbreviations: APS – Anti-Phospholipid Syndrome

rate. The process of thrombosis and inflammation starts off with activation or apoptosis of platelets, endothelial cells, or trophoblasts. This causes negatively charged phosphatidylserine in the affected tissues to migrate from the inner to the outer cell membrane. Circulating β_2 -glycoprotein I (β_2 GPI) binds to phosphatidylserine on these cells, and then APL binds to a β_2 GPI dimer. This leads to a series of events like activation of the complement cascade extracellularly, initiation of an intracellular signaling cascade, probably through the C5a and β_2 GPI surface receptors and also recruits and activates inflammatory effector cells such as neutrophils, monocytes, and platelets, leading to the release of pro-inflammatory products (e.g., tumor necrosis

factor [TNF]- α , oxidants, proteases) triggering off a prothrombotic state [4]. In a meta-analysis, it was found that in about one-fourth of the patients, precipitating factors contribute to the development of catastrophic APS (infections, drugs, minor surgical procedures, anticoagulation withdrawal, etc.) and none was found in the remaining 75–80% cases [3].

The prognosis for patients with CAPS is poor with 25–50% mortality unless treated aggressively. Various modalities of treatment have been tried (no randomized trials). The combination of anticoagulation, glucocorticoids, immunosuppressants and plasma exchange with or without intravenous immune globulin (IVIG) has been associated with recovery rates ranging from 50–8% [2, 3, 5]. As per the analysis of case reports of 250 patients included in the International CAPS Registry up to February 2005 by Bucciarelli et al., systemic lupus erythematosus was identified as prognostic of a higher mortality rate. A higher recovery rate was associated with combined treatment with anticoagulants plus corticosteroids plus plasma exchange (77.8%), whereas, concomitant treatment with cyclophosphamide did not demonstrate additional benefit [5]. In patients resistant to standard therapies, case reports indicate that use of monoclonal antibodies may be beneficial. In a case report by Shapira et al. of a patient with recurrent CAPS, despite maximal anticoagulation, immunosuppression, and plasma exchange, benefit was shown with eculizumab, a monoclonal antibody against the C5 component of complement [6]. In another case, rituximab, the B cell-depleting anti-CD20 monoclonal antibody, was successfully employed [7].

In another study, majority of patients with catastrophic APS who survived their initial illness remained free of further thromboembolic events when treated long-term with oral anticoagulants [8]. Approximately, 20–26% had recurrent APS-related events, but none had another episode of multiorgan failure. Among the recurrent thromboembolic events, 40% occurred in a perioperative period [8]. In another meta-analysis it was found that relapses occurred in about 3.2% of APLA positive patients and it was also suggested that there could be an association between MHA (microangiopathic hemolytic anemia) and relapse of catastrophic APS [9, 10].

CONCLUSION

Catastrophic antiphospholipid syndrome is a rare entity occurring in patients with antiphospholipid antibody syndrome and it has a very poor prognosis. But early, aggressive treatment which usually consists of a combination therapy of anticoagulation, corticosteroids, IVIG and plasma exchange, improves the recovery rate. Hence this diagnosis has to be kept in mind in a scenario of acute limb ischemia and patient started on treatment at the earliest.

Author Contributions

Vivekanandan Senthamil Pari – Substantial contributions to conception and design, Acquisition of data, Analysis and interpretation of data, Drafting the article, Revising it critically for important intellectual content, Final approval of the version to be published

Lakshmi M – Acquisition of data, Drafting the article, Final approval of the version to be published

Sampath Kumar – Acquisition of data, Drafting the article, Final approval of the version to be published

Sathyamurthy P – Acquisition of data, Drafting the article, Final approval of the version to be published

Sudhakar MK – Acquisition of data, Drafting the article, Final approval of the version to be published

Sandhya Sundaram – Acquisition of data, Drafting the article, Final approval of the version to be published

Guarantor

The corresponding author is the guarantor of submission.

Conflict of Interest

Authors declare no conflict of interest.

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