CASE REPORT

Catastrophic antiphospholipid syndrome: A multisystem disease necessitating a multidisciplinary approach

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ABSTRACT

Catastrophic Antiphospholipid Syndrome (CAPS) is a rare and potentially fatal condition characterized by extensive vascular thrombosis leading to multiple organ failure in the presence of positive Antiphospholipid Antibodies (aPL). We report the case of a 16-year-old girl with a history of positive aPL who presented with severe abdominal pain one week after a double J-stent placement. Initial lab results showed mild anemia and slightly prolonged coagulation studies. On the second day, the patient had worsening anemia, thrombocytopenia, and elevated inflammatory markers, namely a high ferritin level. A hypodense liver lesion suggestive of infarction was revealed, and histology confirmed the presence of thrombosis. Later, a necrotic skin lesion formed, and increasing proteinuria on a urine dipstick was detected. As a result, a preliminary diagnosis of CAPS was made. Prompt anticoagulation, corticosteroids, therapeutic plasma exchange, and Rituximab were used in the treatment. The patient recovered and was sent home on an indefinite anticoagulation regimen.

Key Words: *Catastrophic antiphospholipid syndrome; Liver infarction; Skin necrosis;, Kidney involvement; Proteinuria*

CASE PRESENTATION

A 16-year-old girl presented to our hospital with severe abdominal pain. The pain was acute and not associated with oral intake, ch-change in bowel habits, or other symptoms. Her past medical history is only significant for congenital bilateral glaucoma, which was diagnosed in childhood and complicated by residual decreased visual acuity despite medical and surgical treatment. Past surgical history includes unilateral double J insertion one week before presentation due to right kidney hydronephrosis by obstructive urolithiasis. The patient was prescribed Non-Steroidal Anti-Inflammatory (NSAID) drugs for pain management. Otherwise, her current home medications included acetazolamide 250 mg twice daily and eye drops. Upon presentation, vital signs were within the normal limits: BP 110/60 mmHg, HR: 83 bpm, T: 36.3 0oC , oxygen saturation: 99%. Physical examination revealed diffuse abdominal pain primarily localized in the right upper quadrant and epigastric regions. There was no evidence of guarding, rebound tenderness, or other peritoneal signs. Initial blood tests showed a WBC count of 9920/ mm3 (4000/ mm3-10,000/mm3), Hemoglobin 10.2 g/dl (12 g/dl-18 g/dl), MCV 72.8 fL (79 fL-93 fL), Platelets 155 k/mm3 (150 k/mm3 3-400 k/mm3), Serum Cr 0.51mg/dL (0.6 mg/dL-1.2 mg/dL), BUN 5 mg/dL (8 mg/dL-25 mg/dL). Serum electrolytes were normal except for a mildly decreased serum bicarbonate concentration of 20 mmol/L (24 mmol/L-30 mmol/L). LDH was also slightly elevated at 288 IU/L (110 IU/L-265 IU/L). Liver enzymes were normal; however, coagulation studies showed a slightly prolonged PT and PTT at 18 and 41 seconds, respectively with INR of 1.4. Urinalysis showed: SG 1.004 (1.015-1.025), pH 7.5, trace proteins, positive blood, and numerous RBCs. Given the severe upper abdominal pain, history of NSAID use, and microcytic anemia, suspicion was geared towards a potential peptic ulcer disease. As such, an upper endoscopy was scheduled for the following morning. However, a few hours before the procedure, the patient developed severe epigastric and right upper quadrant discomfort associated with hemodynamic instability. She developed a fever of 38 0°C, hypotension with a blood pressure of 80/50 mmHg, and tachycardia of 120 bpm. Upon abdominal examination, involuntary guarding was evident. Blood tests showed a drop in hemoglobin to 8.79 g/dl, thrombocytopenia at 71 k/mm3, and leukocytosis of 12600mm3.

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Workup for the anemia was taken and revealed an iron level of 10 mcg/dL (60 mcg/dL-170 mcg/dL), TIBC of 253 mcg/dL (240 mcg/dl–450 mcg/dL), ferritin of 2548 ng/ml (4.6 ng/ml-204 ng/ml), haptoglobin of 380mg/dL (40 mg/dL-240 mg/dL). Additional tests revealed fibrinogen 1200 mg/dL (200 mg/dL-400 mg/dL), D-dimer 2605 ng/ml (<500 ng/ml), C3 167 mg/dL (88 mg/dL-201 mg/dL), C4 9.16 mg/dL (15 mg/dL-45 mg/dL). Examination of the blood film revealed the presence of a few schistocytes (0-1/hpf) together with giant platelets. An infectious process was suspected, so pan-cultures were taken, and an urgent abdomen CT with IV contrast was conducted. (Figure 1)

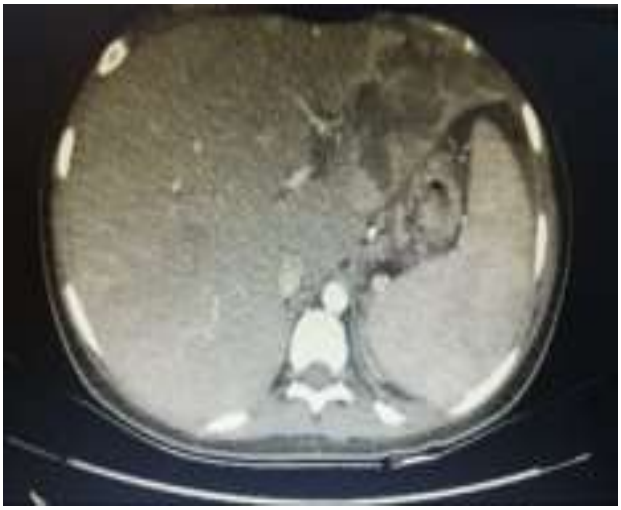

Figure 1) *Left Hypodense Liver Lesion*

Imaging revealed a large, irregular, hypodense lesion in the left hepatic lobe, diffuse periportal thickening, and a moderately enlarged liver with regular borders. No significant other findings were reported. The kidneys were normal in size with bilateral non-obstructing kidney stones, and the right double J was in place without symptoms of pelvicalyceal dilatation. Hepatic artery Doppler ultrasonography was done to rule out thrombotic events and the results returned negative. Given the clinical and hemodynamic deterioration, the patient was started on broad-spectrum antibiotics, and an urgent laparotomy was performed for exploration. Excision of the suspicious liver lesion was performed, and the tissue was sent to pathology. Histopathological examination of the hepatic lesion revealed significant fibrosis in the portal tracts, significant bridging fibrosis, and multiple inflammatory cells (lymphocytes, eosinophils, and few PMNs). There was evidence of congested blood vessels with thickened arterial walls and rare thrombosis. The sinusoids were dilated, and the lobules showed severe central necrosis, leukocytic infiltration, and congestion. This overall pattern was compatible with vascular and thrombotic disorders. The clinical picture went with hepatic infarction in the setting of a vascular disorder. Autoimmune workup was requested promptly and was positive for anticardiolipin, anti-lupus anticoagulant, and anti-beta-2 glycoprotein antibodies in high titers. Upon further questioning, the family disclosed that tests taken years earlier had, on many occasions, shown evidence of high titers of Antiphospholipid Antibodies (aPL). However, due to the lack of evidence of a thrombotic event, it was considered that the patient did not have Antiphospholipid Syndrome (APS); hence prophylactic anticoagulation was not initiated. Once it was determined that the patient had a hepatic infarction likely caused by APS the patient was transferred to the Intensive Care Unit (ICU) for observation and started on therapeutic anticoagulation with Enoxaparin 60 mg subcutaneously every 12 hours. A painful purpuric lesion on the patient's left ear appeared four days later. (Figure 2).

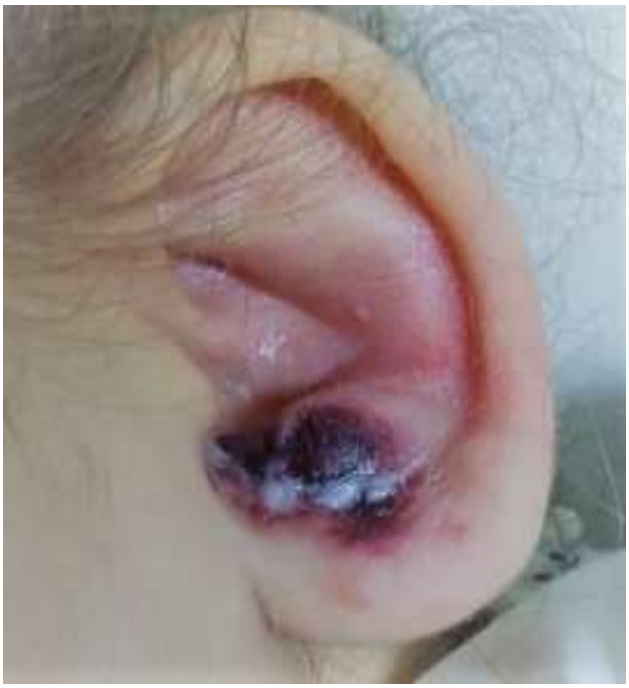

Figure 2) *Necrotic Skin Lesion*

A urinalysis at that time revealed the presence of many RBCs and proteinuria of 1+ on a dipstick in a diluted specimen with a specific gravity of 1.009 and a pH of 7. It was impossible to determine the Urine Proteins to Creatinine Ratio (UPCR), which is used to gauge the degree of proteinuria. Her kidney function remained normal. A tentative diagnosis of catastrophic antiphospholipid syndrome was made. It was agreed to start therapy immediately because of the disease's high mortality rate. Therapeutic plasma exchange was initiated immediately after a non-cuffed dialysis catheter was inserted. Methylprednisolone was administered for three consecutive days at a dose of 1 g intravenously daily, followed by oral therapy containing the daily equivalent of 1 mg/kg of prednisone. Rituximab was added after five consecutive plasma exchange sessions every other day. The abdominal pain subsided, the skin lesion started to mend, and the blood tests returned to normal, namely the Platelet count, with a decline in all inflammatory markers. After bridging with Enoxaparin, the patient was successfully sent home on warfarin. Two weeks after being discharged, she was scheduled for another dose of Rituximab.

DISCUSSION

Antiphospholipid Syndrome (APS) is a rare autoimmune disorder characterized by a hypercoagulable state and usually presents with either venous or arterial thrombosis. It can be either primary or secondary [1]. In its severe form, Catastrophic Antiphospholipid Syndrome (CAPS) leads to multiorgan thrombosis and failure. Diffuse thrombotic micro-vasculopathy, which manifests within a brief period, distinguishes CAPS from APS. The latter often affects medium to large vessels. When first described, the syndrome had a fatality rate of 50%, which is why the term "catastrophic" was attributed to the disease [2, 3].

Another distinguishing feature of CAPS is the presence of Systemic Inflammatory Response Syndrome (SIRS), which is not present in more typical APS [4]. There are limited data concerning the incidence of APS. However, it is suggested that the global incidence is around 5 persons per 100,000 persons per year. One percent of them are diagnosed with CAPS which gives it an incidence of about 5 persons per 10,000,000 persons per year globally [1, 2]. In the CAPS registry, seven out of ten cases of CAPS were women. The mean age of incidence was 37 years, with subjects ranging between 11 to 60 years [5]. Among patients with CAPS, Primary APS affected 60%, SLE affected 30%, lupus-like disease affected 4%, and other autoimmune diseases affected 6%. Moreover, 46% of patients with no prior history of thrombosis experienced de novo CAPS [6]. There is a lack of knowledge on the pathophysiology of APS and, consequently, CAPS. Due to the rarity of the syndrome and the low index of suspicion, where the illness might be mistaken for other prothrombotic conditions such as acute sepsis, studies and blood samples from patients affected by CAPS have been scarce. Nevertheless, the pathophysiology is believed to be complex and to include both the innate and adaptive immune systems. The theory behind CAPS is that autoantibody activation of platelets, monocytes, and endothelial cells leads to micro-thrombosis. The thrombotic storm theory, which suggests that thrombosis begets more thrombosis, has been connected to the fast and life-threatening course of CAPS. Moreover, despite a primary, inherited vulnerability to clot formation in patients with APS known as the "first hit," the elevated thrombophilic risk is insufficient to initiate clot formation. A thrombus can only form with a "second hit" from an inflammatory or environmental factor [2, 3, 7, 8].

More than half of patients diagnosed with CAPS had triggers or precipitating factors. Infections were found to be the most common, occurring at a rate of 49%, with surgical treatments coming in as the second most common at 17%. Other causes include, in decreasing order of prevalence: systemic lupus erythematosus, medications, withdrawal of anticoagulants, low PT international normalized ratio, and pregnancy complications [2]. CAPS has various clinical characteristics depending on the organ systems impacted by the thromboses. Thrombotic events were most prevalent in intra-abdominal organs. In other words, the most established symptom on presentation was abdominal pain [2, 5]. Clinical manifestations are also the result of the emergence of dramatic Systemic Inflammatory Response Syndrome (SIRS). Both processes (thromboses and SIRS) are life-threatening. The excessive release of cytokines is thought to be the cause, presumably from the necrotic and affected tissues [9]. The most often damaged organs are the kidneys, which primarily exhibit renal insufficiency and proteinuria [10]. Only 18% of individuals have kidney involvement at presentation, but up to 80% will develop kidney disease. Mild proteinuria in a patient with several additional APS-related organ involvements is attributable to APS nephropathy until proven otherwise. Hence a renal biopsy can be postponed if the mild proteinuria is stable and kidney function is normal [11]. Other commonly involved organs include the lungs (59%), which manifest as ARDS and/or pulmonary emboli, the central nervous system (56%), which manifests as infarcts, encephalopathy, or seizures, and the heart (50%), which manifests as nonbacterial Libman–Sacks endocarditis, the skin (45%) which manifests as skin necrosis, purpura, or livedo reticularis, and even the intestines, spleen, pancreas, adrenal glands, and bone marrow may also be targeted. Because of the liver's dual blood supply, infarctions are uncommon. However, in the context of APS, hepatic infarctions have been described [2, 8, 11-13]. The following criteria were developed to guide a diagnosis of CAPS: first, involvement of three or more organs; second, development of symptoms in less than a week; third, histological proof of intravascular thrombosis; and fourth, positive antiphospholipid antibodies on two occasions at least 12 weeks apart. Confirmation of a definitive diagnosis of CAPS would have to involve all four criteria. A diagnosis of probable CAPS is entertained in the following cases: if all requirements are present, however, if antiphospholipid antibodies could not be obtained 12 weeks apart due to the death of the patient; if all criteria are present with only two organs involved; if the first, third, and fourth criteria are present with a third event occurring between a week and a month despite administration of anticoagulation; or if the first, second, and fourth criteria are present [5]. Measurement of Antiphospholipid Antibodies (aPL) is required to verify a diagnosis of APS and/or CAPS, which includes measurements of Antibodies to Cardiolipin (ACL) and Beta2-Glycoprotein (anti-b2-GPI) I, as well as a functional assay for the Lupus Anticoagulant (LA) phenomenon [14]. Although up to 5% of the population may be positive for Antiphospholipid Antibodies (aPL), only a tiny percentage of the population is diagnosed with APS, so not every "positive" aPL test is clinically meaningful [11,15]. If CAPS is present, it may manifest as microangiopathic anemia, thrombocytopenia, and a few schistocytes on a blood smear. Schistocytes, if present, are frequently scarce in CAPS, in contrast to the abundant numbers reported in TTP patients. It should be noted that thrombocytopenia was the most common finding among the CAPS registry patient [2].

CAPS, like other inflammatory illnesses, can induce increases in acute phase reactants like ESR, CRP, factor VIII, and fibrinogen. In one study, higher ferritin levels (816 g/L-847 g/L) were found in 71% of CAPS patients, emphasizing the role of inflammation in CAPS pathogenesis. Furthermore, ferritin levels in these patients were considerably greater than those with the typical APS. Indeed, a novel notion known as "hyperferritinemic syndrome" has emerged, characterized by elevated levels of proinflammatory cytokines [8]. Furthermore, hypocomplementemia was seen in 47% of patients with primary APS, low CH50 levels in 46% of patients, low C3 values in 33%, and low C4 values in 24%. Deposits of C1q, C4, C3, and C5b-9 were recently shown to co-localize with b2-GPI and IgG in the afflicted artery wall of a patient with primary APS. This depicts the sequential interaction of all classical and alternative route components. The complement and coagulation pathways are intertwined. Growing evidence suggests that the complement system may be activated in aPL patients and operates as a cofactor in the etiology of aPL-associated clinical outcomes [16, 17]. Small-vessel involvement is one of the hallmarks of this disease, and histopathologic proof of considerable thrombosis in at least one organ or tissue is one of the prerequisites for the diagnosis of definite CAPS. As a result, the most straightforward technique is to perform a biopsy of the most accessible organ involved, such as the skin or kidney. To diagnose APS nephropathy, at least one of the following lesions must be found during a kidney biopsy: acute TMA lesion, arterial and arteriolar recanalizing thrombi, interlobular fibrous intimal hyperplasia, fibrous arterial occlusion, or focal cortical atrophy [3, 12]. CAPS treatment focuses on treating the thrombotic event with anticoagulants and inhibiting the cytokine cascade. In addition to addressing the precipitating events, the most used treatment for CAPS is 'triple therapy,' which includes anticoagulation, corticosteroids Therapeutic Plasma Exchange (TPE), and/or Intravenous Immunoglobulins (IVIG).

Other immuno -modulatory drugs, notably Rituximab and Eculizumab

are being investigated as potential treatments for resistant and/or relapsing CAPS [3-11]. There is no evidence that one form of anticoagulation is superior to another; nonetheless, unfractionated heparin is often favored in this severely ill population due to its ease of reversibility. Furthermore, it appears that heparin's anti-inflammatory action is pivotal in CAPS. Vitamin K antagonist initiated after heparin is the chosen anticoagulant, with a target INR level of 2.5-3.0, and it should be continued indefinitely. Direct oral anticoagulants should be avoided because there is insufficient evidence of their effectiveness and safety in CAPS patients [4, 12, 13]. Corticosteroids suppress nuclear factor- B, which is a crucial mediator in SIRS and APS-mediated thrombosis [11]. Early addition of IVIG or TPE is recommended in patients with life-threatening organ failure to block pathological autoantibodies and/or increase their clearance. Current CAPS guidelines favor TPE treatment, particularly in patients with microangiopathic features, and emphasize that those who received TPE as first-line therapy had a low mortality rate. A direct comparison of patients who received TPE and IVIG versus those who received triple therapy TPE without IVIG revealed no statistically significant difference [11, 18]. In patients with severe, refractory, or recurrent CAPS, Rituximab may be used as an adjunct therapy. Rituximab may help control some criteria, such as thrombocytopenia or skin ulcers. Patients in the CAPS registry who received Rituximab had a higher chance of recovery than those in Bucciarelli's cohort, indicating that Rituximab may improve patients' outcomes. Because the disease is rare and only a few patients have been treated with Rituximab, there is no consensus on the best dosing regimen—the most used were either four weekly doses of 375 mg/m2 or two infusions of 500 mg-1000 mg at 7 days or 14 days apart [6, 11, 12].

Complement inhibition may play a role in APS since aPL can activate the complement system, promoting endothelial cells, neutrophils, monocytes, and tissue factor expression. According to case reports, Eculizumab (anti-C5 monoclonal antibody) can improve prognosis in individuals with catastrophic APS, particularly those with post-renal transplantation TMA. Furthermore, cyclophosphamide should be included in the treatment regimen when CAPS occurs in the context of SLE [11, 12, 16]. Even with effective treatment, CAPS death rates remain high. Early studies indicated a 50% mortality rate, but more recent evidence reveals that mortality has decreased to 33%. When coupled with systemic lupus erythematosus features, the fatality rises to around 47%. Infections, stroke, heart failure, and multiorgan failure are the leading causes of death. However, most patients who survive CAPS will remain symptom-free once anticoagulation is started. Some might experience recurring episodes of CAPS, usually at a median of 12.5 months following the previous occurrence [2, 7]. In our patient, aPL positivity has been present for years, according to her parents but had not resulted in any thrombotic event and was not treated but merely observed over time. The first presentation of her APS was a CAPS presentation.

The recent surgical procedure was thought to be the trigger. The presenting complaint was abdominal pain, later discovered to be caused by a liver infarction. This was followed by skin necrosis four days later. Although we were not confident that the kidneys were involved, her increasing proteinuria on dipstick could have been due to APS nephropathy, keeping in mind that false positive proteinuria results could be due to the presence of hematuria (due to nephrolithiasis) and an alkaline pH. Unfortunately, UPCR was unavailable. We suspected CAPS because of the involvement of the liver, skin, and possibly the kidneys (proteinuria). The patient met all four criteria for a definite diagnosis of CAPS. She also had elevated inflammatory markers, which suggested SIRS with the increased cytokine release and activation. Furthermore, C4 levels were low, indicating a probable involvement from the classical complement pathway. A liver biopsy was critical in confirming the accurate histological diagnosis, allowing for effective therapy, and enhancing the overall prognosis. In our case, Low molecular-Weight Heparin (LMWH) was utilized as anticoagulation due to practical considerations such as the convenience of administration, assuring a higher level of comfort, and requiring less monitoring. The patient was then successfully transitioned onto warfarin. Because of the severity of the first symptoms, Rituximab was employed as a first-line treatment in conjunction with triple therapy.

CONCLUSION

CAPS is an uncommon, life-threatening illness with a wide range of clinical symptoms, making diagnosis difficult. A high index of suspicion is critical to facilitate early detection and care. CAPS management is frightening and challenging because individuals can worsen rapidly. Anticoagulation, corticosteroids, intravenous immunoglobulin, and/or therapeutic plasma exchange are the suggested empirical treatments. As a result, catastrophic APS management necessitates a multidisciplinary team approach, including but not limited to rheumatology, hematology, intensive care, infectious disease, and nephrology specialists.

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