CASE REPORT

Catastrophic Antiphospholipid Syndrome Presenting as Ischemic Pancreatitis in Systemic Lupus Erythematosus

Ajit Vyas[1], Huseyin Kadikoy[1], Waqar Haque[1], Abdul Abdellatif[1,2]

Departments of [1]Medicine and [2]Division of Nephrology, Baylor College of Medicine. Houston, TX, USA

ABSTRACT

Context Antiphospholipid syndrome is often associated with systemic lupus erythematosus. Both syndromes have different clinical manifestations based on organ involvement. Antiphospholipid syndrome commonly causes spontaneous abortions, cerebral vascular occlusion, and deep venous thrombosis. Catastrophic antiphospholipid syndrome occurs when three or more organ systems are affected by thromboses in less than a week. **Case report** We report a unique case of a young woman with a history of systemic lupus erythematosus and antiphospholipid syndrome who presented with recurrent ischemic pancreatitis. Pancreatitis was refractory to anticoagulation and low dose steroids. Secondary to recurrence of pancreatitis and other organ involvement, she was treated as a presumed case of catastrophic antiphospholipid syndrome. Aggressive treatment with plasmapheresis, corticosteroids, cyclophosphamide, and anticoagulation eventually led to her recovery. **Conclusion** Awareness of this rare, rapidly fatal medical condition prompts vital, early intervention to improve patients' survival. This case report aims to add to the limited therapeutic data available as well as suggest a possible approach to treating this rare syndrome with very high morbidity and mortality.

INTRODUCTION

Antiphospholipid syndrome and systemic lupus erythematosus are commonly associated. Systemic lupus erythematosus is characterized by skin manifestations such as malar rash, arthralgias, cardiac manifestations including pericarditis and endocarditis, neurologic manifestations, as well as hematological and immunological changes. Antiphospholipid syndrome is characterized by the presence of antiphospholipid antibodies with characteristic clinical manifestations. The antiphospholipid antibodies consist of lupus anticoagulant, anti-cardiolipin, and anti-beta$_2$-microglobulin antibodies [1, 2]. The clinical manifestations of antiphospholipid syndrome include venous thromboses, arterial thromboses, thrombotic microangiopathy, and recurrent fetal loss [3]. The thromboses in antiphospholipid syndrome can affect any vascular bed, so potentially any organ system in the body can be involved. Catastrophic antiphospholipid syndrome occurs when three or more organ systems are affected by thromboses in less than a week. Catastrophic antiphospholipid syndrome occurs in only 1% of antiphospholipid syndrome patients [4]. However, it is an important clinical entity to consider due to mortality rates up to 50%.

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Correspondence Abdul Abdellatif
Division of Nephrology, Department of Medicine, Baylor College of Medicine, One Baylor Plaza, BCM 620, Houston, TX 77030, USA
Phone: +1-713.798.8350; Fax: +1-713.798.3510
E-mail: abdula@bcm.edu

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CASE REPORT

A 20-year-old African American woman presented to the emergency center with abdominal pain, nausea, and vomiting. Her medical history is significant for systemic lupus erythematosus and antiphospholipid syndrome. Systemic lupus erythematosus was diagnosed four years prior to presentation on the basis of fever, malar rash, arthralgias, and alopecia. The patient also has hypertension and chronic kidney disease with a baseline creatinine of 3 mg/dL (reference range: 0.8-1.5 mg/dL) secondary to her underlying disease. Antiphospholipid syndrome was diagnosed one year prior to admission when she presented with a deep venous thrombosis. She has been placed on subcutaneous low-molecular weight heparin for anticoagulation for the past year, but she has not been fully compliant.

Two months prior to admission, the patient was hospitalized for acute pancreatitis. For a differential diagnosis of pancreatitis see Table 1. During her hospital course, she developed methicillin-resistant *Staphylococcus aureus* bacteremia, acute renal failure, and a right brachial deep venous thrombosis. Renal biopsy confirmed lupus nephritis with microangiopathic disease (Figure 1). She was discharged after re-initiation of anticoagulation with

Table 1. Differential diagnosis of common causes of pancreatitis.

Toxic	Methanol, ethanol, scorpion venom
Metabolic	Hypercalcemia, hyperlipidemia
Mechanical	Pancreatic cancer, gallstones, periampullay diverticulum, duodenal stricture
Infection	Hepatitis B, CMV, HIV, leptospira, salmonella, cryptosporidium
Drugs	Metronidazole, salicylates, estrogen, penatmidine
Congenital	Pancreas divisum
Trauma	Trauma to the abdomen, blunt damage to abdomen
Genetic	CFTR mutations
Vascular	Systemic lupus erythematosus vasculitis, atheroembolism, ischemia
Miscellaneous	Alpha-1-antitrypsin deficiency, pregnancy

subcutaneous low-molecular weight heparin and warfarin and being apparently asymptomatic.

Upon current presentation, her abdominal pain was localized to the epigastric and periumbilical regions without radiation. The pain was sharp, stabbing, and intermittent. She had vomited every other day for two weeks prior to admission, with her vomitus being non-bloody and consisting primarily of food contents. She also had diarrhea with three non-bloody, watery bowel movements the day prior to admission. Her blood pressure was elevated at 157/110 mmHg.

Her laboratory data revealed lipase was 231 U/L (reference range: 6-51 U/L); amylase was 159 U/L (reference range: 30-110 U/L); anti-nuclear antibody was positive; Anti DNA titer was 1:80 (negative if less than 1:40) and equal to, or higher than, 1/2,560 SSA/Ro (positive if higher than 1/8); IgG level was normal (670 mg/dL; reference range: 751-1,560 mg/dL); C3 was 79 mg/dL (reference range: 79-152 mg/dL); C4 was 22 mg/dL (reference range: 16-38 mg/dL). Duplex ultrasound of the abdomen showed no biliary dilatation, no calculi or wall thickening in the gallbladder, negative sonographic Murphy's sign, and no portal vein or splenic vein thrombosis. A non-contrast CT of the abdomen and pelvis after her admission was limited, but showed inflammatory changes around the pancreas with small amounts of peripancreatic fluid, thickening of the stomach wall, and free fluid in the pelvis, all consistent with pancreatitis (Figure 2). She was also found to have worsening kidney function with a creatinine of 5.3 mg/dL. APACHE II score was calculated to be 22, indicating 28.6% mortality. SLEDAI (systemic lupus erythematosus severity index) was calculated to be 29.

The patient was treated as presumed catastrophic antiphospholipid syndrome. Initial treatment included six sessions of plasmapheresis without intravenous immunoglobulin to avoid further kidney damage, and

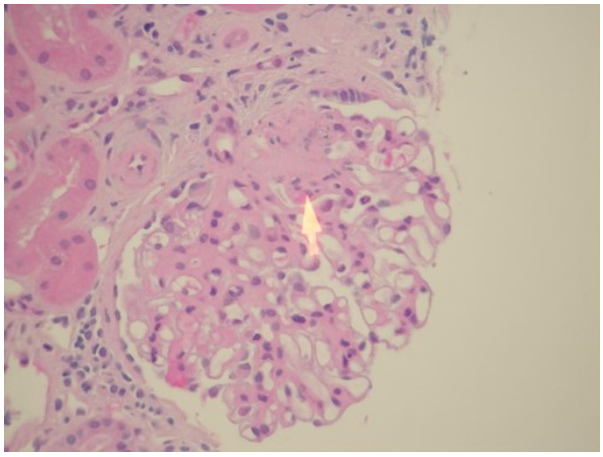

Figure 1. The biopsy specimen showing markedly thickened vessels, sclerotic glomeruli, and glomeruli with Class IV glomerulonephritis.

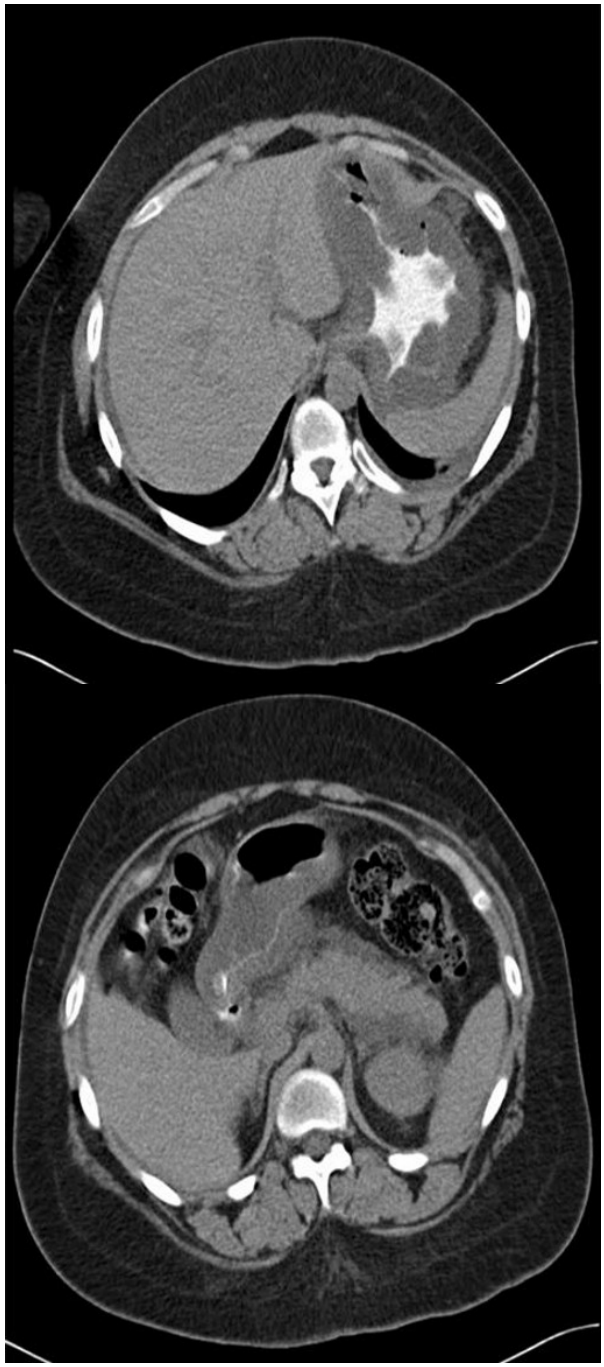

Figure 2. CT scan showing inflammatory changes around pancreas with small amounts of peripancreatic fluid, thickening of stomach all, and free fluid in the pelvis, all consistent with pancreatitis.

one dose of cyclophosphamide. After six sessions of plasmapheresis, the patient showed significant clinical improvement with resolution of her abdominal pain. Kidney function also improved with creatinine returning to baseline. Her blood pressure was difficult control, but eventually stabilized on a combination of a beta blocker, a calcium channel blocker, and a loop diuretic. The patient was discharged 4 weeks after initial presentation on prednisone 30 mg once per day, metoclopramide 5 mg every 6 hours, clonidine 1 patch per week, nifedipine 60 mg twice per day, and hydroxychloroquine 400 mg once per day. A repeat abdominal CT scan 5 week after the acute event showed complete resolution of pancreatitis (Figure 3).

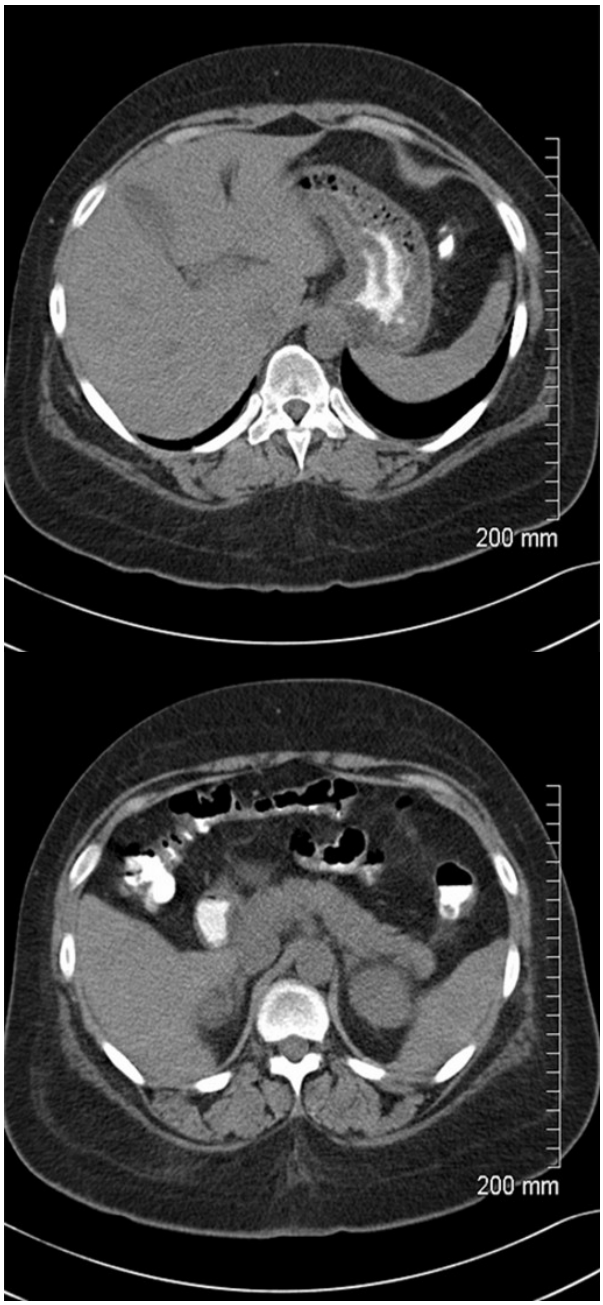

Figure 3. CT scan showing normal pancreas with no fluid accumulation in the pelvis, and normal stomach wall.

The patient remains free of recurrence of ischemic pancreatitis at 16 month follow-up.

DISCUSSION

Antiphospholipid antibodies have a high prevalence in the general population. Some estimates place their prevalence among asymptomatic, healthy subjects at 1 to 5%, and much more common in patients with systemic lupus erythematosus, with 30-40% prevalence [5]. Lupus anticoagulant antibodies are actually a heterogeneous set of antibodies that are identified by prolongation of coagulation cascade assays. Although they delay coagulation in the assay, lupus anticoagulant antibodies are often prothrombotic in vivo as well. Similarly, the anti-cardiolipin and anti-beta$_2$-microglobulin antibodies are defined by their ability to bind phospholipids or phospholipid-binding proteins on immunoassays [2, 6].

However, in certain individuals, these antibodies are active and cause clinical manifestations, primarily thromboses and fetal loss. The clinical manifestations against the background of these antibodies give rise to the antiphospholipid syndrome [7]. This condition is typically manageable using standard anticoagulation therapy. However, in a subset of individuals with antiphospholipid syndrome, the thromboses are widespread and affect several organ systems simultaneously, leading to a high rate of mortality. This entity has been termed catastrophic antiphospholipid syndrome [8]. In catastrophic antiphospholipid syndrome, the thromboses tend to be in the form of thrombotic microangiopathy, in contradistinction to the predominantly venous thromboses seen in antiphospholipid syndrome. Definitive catastrophic antiphospholipid syndrome occurs when three or more organ systems are affected by thromboses in less than a week in patients who have tested positive for antiphospholipid antibodies twice at least six weeks apart. There should also be confirmation by histopathology of small vessel occlusion in at least one organ or tissue. Patients who meet most but not all criteria are labeled as having probable catastrophic antiphospholipid syndrome [9].

Our patient displayed many features of catastrophic antiphospholipid syndrome, given that she also has systemic lupus erythematosus. In addition to her pancreatitis and worsening kidney function, she had worsening hypertension that required multiple anti-hypertensive medications to manage. Given her clinical picture and our high clinical suspicion, we decided to treat her as if she had catastrophic antiphospholipid syndrome. Due to the aggressive nature of the syndrome, the high mortality rate, and the lag time in obtaining full laboratory results, treatment should be instituted as soon as the syndrome is suspected.

There are several treatment options for catastrophic antiphospholipid syndrome, but no definitive regimen. As the number of patients with catastrophic antiphospholipid syndrome worldwide is small, there are no prospective, randomized, controlled trials on

therapeutic strategies [10]. First line therapies include anticoagulants and corticosteroids. Plasmapheresis and intravenous immunoglobulin are second line treatments. Given our patient's history and lack of clinical response to anticoagulation, plasmapheresis was attempted. Other treatments have been described in the literature, such as the use of rituximab, an anti-CD20 monoclonal antibody that acts against B-cells [11, 12]. However, the use of these alternate modalities has been limited to a few small case series.

In light of the association between antiphospholipid syndrome and systemic lupus erythematosus, it is interesting to consider how catastrophic antiphospholipid syndrome manifests itself in systemic lupus erythematosus patients. As Bayraktar *et al*. have shown, patients with catastrophic antiphospholipid syndrome in systemic lupus erythematosus are more likely to be female and younger, have cerebral and pancreatic involvement, receive corticosteroids and cyclophosphamide, demonstrate a lower prevalence of high IgG anti-cardiolipin, and have a higher risk for mortality after adjusting for age, sex, organ involvement, and treatment [13]. Patients with catastrophic antiphospholipid syndrome in systemic lupus erythematosus who were treated with a combination of plasmapheresis, corticosteroids, and anticoagulation had a survival rate of 65% [14]. Our patient fit these criteria fairly well, as she was female, young, had pancreatic involvement, and responded well to plasmapheresis.

CONCLUSION

This case reaffirms the heightened degree of clinical awareness required to treat patients who present with signs of organ failure and have a history of systemic lupus erythematosus and antiphospholipid syndrome. Fortunately for our patient, her clinical picture improved after six cycles of plasmapheresis, corticosteroids, and cyclophosphamide. The patient has not had recurrent pancreatitis for 18 months of follow-up. However, given her multiple comorbidities, it is important to retain a high degree of suspicion for ischemic complications and catastrophic antiphospholipid syndrome due to its high mortality rate.

Conflict of interest The authors have no potential conflicts of interest

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