Catastrophic Antiphospholipid Syndrome after Infection

Chiung-Lin Chen, Hsuan-Ming Lin, Chiz-Tzung Chang, and Chiu-Ching Huang

College of Medicine, China Medical University
Kidney Institute, China Medical University Hospital,
Taichung, Taiwan, Republic of China

Abstract

BACKGROUND: Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis, pregnancy morbidity, thrombocytopenia and the appearance of serum antiphospholipid antibody. Catastrophic APS (CAPS) is a variant of APS, which is usually life-threatening with rapid progressive multiple organ failure. Infection is the most common trigger factor. 

CASE REPORT: A 33-year-old woman had acute hepatic dysfunction, pulmonary edema and general edema after an episode of urinary tract infection. APS was favored according to her clinical presentation and laboratory examination. Pulse steroid was administered. Severe thrombocytopenia, hemolytic anemia, acute renal failure, and cerebral vascular thrombosis developed despite high-dose steroid therapy. We prescribed daily plasma exchange and anticoagulation therapy for her catastrophic APS. Thrombocytopenia, anemia, renal dysfunction, and liver dysfunction recovered gradually after titers of antiphospholipid antibody improved.

CONCLUSION: For unusual thrombocytopenia and multiple organ dysfunction after an infection episode, CAPS should be considered and plasma exchange can be applied if there is no contraindication.

KEY WORDS: Catastrophic antiphospholipid syndrome, infection, multiple organ failure, thrombocytopenia, plasma exchange

Introduction

Antiphospholipid syndrome (APS) is a systemic autoimmune disorder characterized by a combination of arterial and/or venous thrombosis, pregnancy morbidity, a mild-to-moderate thrombocytopenia, and raised titers of antiphospholipid antibodies (aPL), namely the lupus anticoagulant (LA) and/or anticardiolipin antibodies (aCL). Catastrophic APS (CAPS, also known as “Asherson’s syndrome”) is an unusual (< 1%) but usually life-threatening variant of APS, characterized by rapid appearance of multiple thromboses (mainly small-vessel thrombosis) that lead to multiple organ failure. Catastrophic events may be triggered, in > 50% of patients, by a recognized factor, mainly infections, trauma or surgery, anticoagulation withdrawal, malignancies and lupus flares. CAPS frequently appears during pregnancy (1). We report a case of CAPS presented with severe thrombocytopenia, multiple organ failure and brain infarction after an infection episode.

Case Report

A 33-year-old woman without specific medical history got acute onset of fever, dysuria, and left flank pain 4 days after mountain-climbing. Both of her children, who had kept a rabbit as a pet for 1 month, got the hand-foot-mouth disease one week prior to her illness. She was treated as acute pyelonephritis at a local hospital. Within 2 weeks after admission, she developed acute pulmonary edema and pleural effusion with a body weight gain of 7 kg. Acute heart failure with ejection fraction 52% was diagnosed by echocardiogram. She was transferred to our hospital. Her
blood pressure was 150/80 mmHg, and physical examination revealed a low-grade fever, respiratory distress, and a general edema. On auscultation, her breathing sound was decreased in bilateral lower lung field. Laboratory studies showed the following: white blood cell (WBC): 17,330/µL, hemoglobin (Hb): 7.6 g/dL, platelet counts: 89,000/µL, prothrombin time (PT): 17.7 seconds, activated partial thromboplastin time (APTT): 45.4 seconds, high-sensitive C-reactive protein: 26.32 mg/dL, total bilirubin: 1.73 mg/dL, aspartate transaminase (AST): 65 IU/L. The gamma-glutamyl transpeptidase (γ-GT) level was normal. The blood urea nitrogen (BUN) was 60 mg/dL, but the plasma creatinine was 1.02 mg/dL. There was no electrolyte abnormality. Her serum albumin was 3.0 mg/dL. Urinalysis revealed 4+ protein and a positive test for urine red blood cells. Her ANA and anti-dsDNA antibodies were negative and the titers of C3 & C4 were normal. Anti-cardiolipin antibody (ACA) was positive (IgG: 41.382 GPL-U/mL, IgM: 20.575 MPL-U/mL). Blood smear showed fragmented RBCs. Blood tests for lepospirosis and brucellosis were all negative. Plerual effusion studies showed a transudate nature fluid. With the presence of anemia, thrombocytopenia, serositis, proteinuria, acute liver injury, and positive ACA, she received steroid pulse therapy (methylprednisolone 500 mg/day) for 5 consecutive days under the impression of APS.

Severe thrombocytopenia (platelet < 10,000/µL) with petechia over lower extremities developed after pulse therapy. Acute renal failure with serum BUN 128 mg/dL, creatinine 6.48 mg/dL and albumin 2.1 mg/dL were also noted. The 24-hour urine total protein was 5,321 mg. An episode of acute onset of left hemiplegia without affecting her consciousness developed in the meantime and the brain magnetic resonance (MRI) showed acute infarction in the right fronto-parietal lobe (territory of right distal middle cerebral artery) (Fig. 1). Catastrophic variant of APS was diagnosed. She received temporal hemodialysis thrice weekly for renal support and daily plasma exchange with anticoagulation therapy for her catastrophic APS since the 20th day of the hospital course. Her renal function gradually recovered after one week’s hemodialysis. Her thrombocytopenia became normal after 3 weeks’ plasma exchange when the levels of ACA gradually diminished and turned to negative after undergoing the above therapies. She had no discomfort during the therapies. She was discharged without any neurologic sequelae. The patient’s hospital course is illustrated in Fig. 2.

**Discussion**

In 1992, Asherson described an unusual variant of APS termed the catastrophic antiphospholipid syndrome (also known as Asherson’s syndrome), the hallmark of which is rapid multiple organ failure caused by widespread small-vessel thrombi (2). Table 1 (3) lists the diagnostic criteria for APS, and Table 2 (4) shows the criteria for CAPS. Our patient presented with acute brain infarction and medium titer of anti-
Catastrophic Antiphospholipid Syndrome

Cardiolipin antibody, which met the APS criteria listed in Table 1. Her clinical course met criteria 1, 2 and 4 of CAPS. We did not perform histopathology examination due to her bleeding tendency secondary to her severe thrombocytopenia and coagulopathy. Probable catastrophic APS is favored.

The differential diagnosis of this patient includes system lupus erythema (SLE) and thrombotic thrombocytopenic purpura (TTP)-hemolytic uremic syndrome (HUS). SLE shares some presentations with CAPS; however, this patient did not meet all criteria of SLE (5). TTP-HUS characterized by thrombocytopenia and widespread micro-macrovessel thrombosis are also similar to the clinical course of CAPS, but the presence of cardiolipin antibody with prolonged activated partial thromboplastin time (APTT) in this patient made TTP-HUS less likely.

The classical APS is characterized by the presence of antiphospholipid antibodies which bind target phospholipid molecules, mainly through β2-glycoprotein I (β2GPI). A meta-analysis study for the pathogenesis of CAPS in more than 300 patients showed that there were increasingly apparent triggering factors presented in half of the patients. These factors including trauma (including surgical, both major and minor), anticoagulation withdrawal, a variety of carcinomas and, most importantly and commonly, infections, which were identified in 24% of these patients. Besides the infection itself, the antibiotics are also one of the hit mechanisms of the autoimmune manifestation. The molecular mimicry between the pathogen and the β2GPI may be the pathogenic cause of APS (6). This patient’s illness began after an infection episode (urinary tract infection) and she had recent infectious disease contact history (her children’s viral infection). Infection may be the pathogenic factor of CAPS in our patient. Both animal studies and clinical reports have shown that CAPS can be triggered by viral or bacterial infection (6). Acute pyelonephritis (APN) was diagnosed according to the symptoms of dysuria, flank pain and fever. The symptoms disappeared after treatment at local hospital. We did not know whether there existed a possible viral

---

**Table 1. Summary of the updated Sapporo classification criteria for antiphospholipid syndrome (APS)**

<table>
<thead>
<tr>
<th>Clinical criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular thrombosis: &gt; 1 arterial, venous, or small vessel thrombosis</td>
</tr>
<tr>
<td>Pregnancy morbidity: &gt; 1 fetal death (at or beyond the 10th week of gestation); &gt; 1 premature birth before the 34th gestation because of eclampsia, severe preeclampsia, or placental insufficiency; or &gt; 3 consecutive (pre) embryonic losses (before the 10th week of gestation)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Laboratory criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lupus anticoagulant positivity on &gt; 2 occasions at least 12 weeks apart</td>
</tr>
<tr>
<td>Anticardiolipin antibody (IgG and/or IgM) in medium or high titer (i.e., N40, or above the 99th percentile), on two or more occasions at least 12 weeks apart</td>
</tr>
<tr>
<td>Anti-β2-glycoprotein-I antibody (IgG and/or IgM) in medium or high titer (i.e., above the 99th percentile) on two or more occasions at least 12 weeks apart</td>
</tr>
</tbody>
</table>

Definite APS is present if at least one of the clinical criteria and one of the laboratory criteria are met.

**Table 2. Diagnostic criteria of catastrophic APS**

1. Evidence of involvement of three or more organs, systems and/or tissues
2. Development of manifestations simultaneously or in less than a week
3. Confirmation by histopathology of small vessel occlusion in at least one organ or tissue
4. Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)

(1) Definite catastrophic APS
   - All 4 criteria
(2) Probable catastrophic APS
   - All 4 criteria, except for involvement of only two organs, systems and/or tissues
   - All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart due to the early death of a patient never previously tested for aPL prior to the catastrophic APS event
     - Criteria 1, 2 and 4
     - Criteria 1, 3 and 4 and the development of a third event in more than a week but less than a month, despite anticoagulation
infection transmitted from her children or other specific microorganism infection. Although all the culture results and viral markers were negative, her prolonged low-grade fever, leukocytosis and high C-reactive protein level made infection a highly possible pathogenic factor of CAPS.

The kidney is the organ most commonly affected by CAPS, usually resulting in acute renal failure, severe hypertension, and laboratory evidence of glomerular damage (proteinuria and hematuria) (4). In this case, fluid overload was one of the initial presentations, and acute kidney injury progressed later. Renal replacement therapy was applied until the renal function improved with body fluid balance. We did not perform renal biopsy due to her severe thrombocytopenia.

Treatment of APS remains centered on anticoagulation; however, it has also included the use of corticosteroids and other immunosuppressive therapies (4). Provenzano and Acharya hypothesized that CAPS was precipitated rapidly by a lack of adequate anticoagulation in a few days (7). There was one case report about a young woman with CAPS, who had clinical finding of acute renal failure and cerebral infarction similar to this case. The patient was successfully treated with corticosteroid and immunosuppressive agents (8). Thrombotic thrombocytopenic purpura (TTP)-hemolytic uremic syndrome (HUS) may be induced by APS, and it can be treated well by PE and corticosteroids (9). This patient underwent PE following the appearance of TTP-HUS and brain infarction. We did not apply anticoagulant at first due to initial thrombocytopenia and the bleeding tendency, and oral warfarin was prescribed after platelet count improved and brain infarction developed. The patient’s condition improved gradually after decline of pathogenic ACA antibodies.

In conclusion, APS should be considered when thrombocytopenia and multiple organ dysfunction (especially kidney) developed after infection. CAPS should be treated with the combination of anticoagulant and steroid as early as possible if no contraindication is present. In patient’s refractory to steroid therapy, plasma exchange should be considered.

References