Severe Abdominal Pain as a Presenting Symptom of Probable Catastrophic Antiphospholipid Syndrome

abstract

Catastrophic antiphospholipid syndrome (APS) in pediatric medicine is rare. We report 3 adolescents who presented with acute onset of severe abdominal pain as the first manifestation of probable catastrophic APS. The 3 patients, 2 male patients and 1 female patient were 14 to 18 years old. One had been diagnosed with systemic lupus erythematosus in the past, but the other 2 had no previous relevant medical history. All presented with excruciating abdominal pain without additional symptoms. Physical examination was noncontributory. Laboratory results were remarkable for high inflammatory markers. Abdominal ultrasonography was normal, and abdominal computed tomography scan showed nonspecific findings of liver infiltration. Only computed tomography angiography revealed evidence of extensive multiorgan thrombosis. All patients had elevated titers of antiphospholipid antibodies. The patients were treated with full heparinization, high-dose steroids, and intravenous immunoglobulin with a resolution of symptoms. One patient was resistant to the treatment and was treated with rituximab. In conclusion, severe acute abdominal pain can be the first manifestation of a thromboembolic event owing to catastrophic APS even in previously healthy adolescents. Diagnosis requires a high index of suspicion with prompt evaluation and treatment to prevent severe morbidity and mortality. *Pediatrics* 2012;130:e230–e235

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**KEY WORDS**  
abdominal pain, catastrophic antiphospholipid syndrome, adolescents

**ABBREVIATIONS**  
aPL—antiphospholipid antibodies  
APS—antiphospholipid syndrome  
aPTT—activated partial thromboplastin time  
CRP—C-reactive protein  
CT—computed tomography  
ESR—erythrocyte sedimentation rate  
IV—intravenous  
IVIG—intravenous immunoglobulin  
LMWH—low molecular weight heparin  
SLE—systemic lupus erythematosus

All authors have made a substantial contribution to the published manuscript and gave final approval of the version to be published. All authors are responsible for the reported case series.

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Antiphospholipid syndrome (APS) is a multisystem autoimmune disease characterized by persistent positivity of antiphospholipid antibodies (aPL) in the presence of vascular thrombotic events.1 Catastrophic APS is an exaggerated form of APS resulting in multiorgan failure and a high mortality rate.2–4 The low prevalence of pediatric catastrophic APS makes this syndrome hard to diagnose, as it requires a high index of suspicion. We report herein, 3 adolescents presenting with excruciating abdominal pain as the first manifestation of probable catastrophic APS.

CASE 1
A 14-year-old girl presented with abdominal pain over the preceding 2 weeks, accompanied initially by fever, vomiting, and diarrhea. Past medical history was noncontributory. Examination revealed tenderness over the right flank. Laboratory tests showed elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) with prolonged activated partial thromboplastin time (aPTT)-seconds (Table 1). She was treated with broad-spectrum antibiotics for suspected pyelonephritis. Abdominal and pelvic ultrasonographies were normal. Computed tomography (CT) showed an infiltrative process of the liver (Table 1). Suspecting malignancy, a liver biopsy was performed that showed congested blood vessels with thickened arterial walls. Plasma infusion before performing liver biopsy did not correct aPTT, raising suspicion of the presence of aPL. Titer levels of aPL are shown in Table 1. D-Dimers were 5402 ng/mL (normal < 500 ng/mL). Abdominal and chest CT angiography results are described in Table 1. Owing to severe abdominal pain and elevated titers of aPL, even though there was no clear evidence of thrombosis, she was started on low-molecular weight heparin (LMWH) and intravenous (IV) corticosteroid pulses. On day 16 of hospitalization, she began experiencing severe chest and epigastric pain, with elevated troponin. Echocardiography showed left ventricular dysfunction and pulmonary hypertension. Repeated chest CT angiography was compatible with pulmonary microthrombi (Table 1). She was switched to full heparinization treatment, IV corticosteroid pulses, and a 5-day course of plasmapheresis with intravenous immunoglobulin (IVIG) (Table 1), in addition to treatment with sildenafil and bosenfani for pulmonary hypertension. Despite treatment, her condition worsened with findings compatible with inferior wall myocardial infarction, increasing pulmonary pressure, and elevated levels of amylase and lipase. Because of progressive clinical deterioration, she was given rituximab (Table 1). During the next few days, a gradual improvement was noted in all parameters and she was given 3 additional doses of rituximab once a week with a gradual decrease in steroids until cessation. She was discharged on warfarin. Echocardiography a year later demonstrated mild left ventricular enlargement with good contractility and no evidence of pulmonary hypertension.

CASE 2
A 14-year-old boy presented with severe abdominal pain over the preceding 2 weeks accompanied by low-grade fever, vomiting, and diarrhea. Past medical history was noncontributory. Physical exam was positive for hepatosplenomegaly. On admission, a slight increase in liver function tests was noted, with decreased albumin. ESR and CRP were elevated (Table 1). aPTT-sec was prolonged. Urinalysis showed proteinuria of 511 mg per day. Results of abdominal sonography and abdominal CT are described in Table 1. Bone marrow biopsy was normal. He was started on broad-spectrum antibiotics. During hospitalization, abdominal pain increased, requiring multiple analgesic agents with no relief. Repeated abdominal CT was noncontributory (Table 1). In preparation for a liver biopsy, he was given plasma without normalization of the aPTT. Liver biopsy showed extensive foci of necrosis. Although required criteria for the diagnosis of systemic lupus erythematosus (SLE) were not met, treatment with steroids was initiated, and abdominal pain subsided. A few days later, a right, painful neck mass was observed. Duplex studies showed right internal jugular and subclavian vein thrombosis. aPL titers were found to be elevated (Table 1). Treatment was started with full heparinization and IV corticosteroid pulses (Table 1). After clinical improvement, he was switched to oral warfarin. On follow-up a year later, he feels well with no symptoms.

CASE 3
An 18-year-old male individual was hospitalized owing to severe abdominal and back pain. He had been diagnosed with SLE at the age of 13. Disease manifestations included arthritis, malar rash, Coombs-positive hemolytic anemia, and APS with past thrombotic events of right leg deep vein thrombosis, sinus vein thrombosis, and left cerebrovascular attack. He had been continuously treated with aspirin, LMWH, prednisone, and plaquenil. He had undergone a splenectomy owing to hemolytic anemia, 2 months before admission. Since the operation, he had been complaining of abdominal and back pain, increasing dramatically before admission. His physical exam was noncontributory. ESR and CRP were elevated. Abdominal ultrasonography results are described in Table 1. Magnetic resonance imaging of the thoracolumbar spine was normal. During hospitalization, back and abdominal pain persisted, requiring multiple analgesic agents, with no relief. Abdominal CT angiography revealed extensive thrombosis (Table 1). Treatment with full heparinization, IV corticosteroid
<table>
<thead>
<tr>
<th></th>
<th>Case I</th>
<th>Case II</th>
<th>Case III</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Previous diagnosis</strong></td>
<td>None</td>
<td>None</td>
<td>SLE, APS</td>
</tr>
<tr>
<td><strong>Precipitating event</strong></td>
<td>Infection</td>
<td>Infection</td>
<td>Operation, splenectomy</td>
</tr>
<tr>
<td><strong>Presenting symptoms</strong></td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Abdominal pain, back pain, and vomiting</td>
</tr>
<tr>
<td><strong>Inflammatory markers at presentation</strong></td>
<td>ESR 140 mm/h</td>
<td>ESR 115 mm/h</td>
<td>ESR 115 mm/h</td>
</tr>
<tr>
<td><strong>Serology for autoimmune disease</strong></td>
<td>CRP 14.6 mg/dL (N &lt; 0.5 mg/dL)</td>
<td>CRP 14 mg/dL (N &lt; 0.5 mg/dL)</td>
<td>CRP 16.5 mg/dL (N &lt; 0.5 mg/dL)</td>
</tr>
<tr>
<td></td>
<td>ANA titer &gt;1:160</td>
<td>ANA titer 1:80</td>
<td>ANA titer &gt;1:160</td>
</tr>
<tr>
<td><strong>Laboratory confirmation of antiphospholipid antibodies</strong></td>
<td>Anti dsDNA-normal</td>
<td>Anti dsDNA 24% (N = 0% to 20%)</td>
<td>Anti dsDNA 24% (N = 0% to 20%)</td>
</tr>
<tr>
<td></td>
<td>Anticardiolipin IgG 24</td>
<td>Anticardiolipin IgG B9 (N = 0–18 GPL-U/mL)</td>
<td>Anticardiolipin IgM 30 (N = 0–10 GPL-U/mL)</td>
</tr>
<tr>
<td></td>
<td>Anti B2 glycoprotein IgM 31</td>
<td>Anti B2 glycoprotein IgG 37</td>
<td>Anti B2 glycoprotein IgM 26 (N = 0–20 U/mL)</td>
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<tr>
<td></td>
<td>(N = 0–18 U/mL)</td>
<td>(N = 0–18 U/mL)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>LAC ratio 2.59 (N &lt; 1.2)</td>
<td>LAC ratio 3.75 (N &lt; 1.21)</td>
<td>LAC ratio 3.75 (N &lt; 1.21)</td>
</tr>
<tr>
<td></td>
<td>LAC-RVVT 2.88 (N &lt; 1.2)</td>
<td>LAC-RVVT 3.29 (N &lt; 1.31)</td>
<td>LAC-RVVT 3.29 (N &lt; 1–3.1)</td>
</tr>
<tr>
<td><strong>Initial sonographic findings</strong></td>
<td>Normal</td>
<td>Mildly enlarged liver</td>
<td>Unhomogeneous liver parenchyma with areas of hyperechogenicity</td>
</tr>
<tr>
<td><strong>Findings on CT</strong></td>
<td>Abdominal CT, Mildly enlarged liver with generally unhomogeneous parenchyma and hypodense areas in both lobes. Compatible with an infiltrative process: infectious, inflammatory or neoplastic.</td>
<td>Abdominal CT (1st): Hepatosplenomegaly with irregular pattern of the liver parenchyma. Mild ascites and abdominal lymphadenopathy.</td>
<td>Abdominal CT (2nd): Hepatosplenomegaly with unhomogeneous liver parenchyma and hypodense areas in the liver with moderate amount of ascites.</td>
</tr>
<tr>
<td><strong>Findings on CT angiography</strong></td>
<td>CT angiography of the abdomen (1st): Partially interrupted venous outflow, with incomplete filling of the hepatic veins.</td>
<td>Thrombus was identified by Doppler: Right internal jugular and right subclavian vein thrombosis</td>
<td>CT angiography of the abdomen: Portal and superior mesenteric vein thrombosis. The liver was enlarged with unhomogeneous parenchyma. The hepatic veins were not visualized clearly. The head of the pancreas was involved with hypodense parenchyma and unclear borders. There was marked infiltration of the mesenteric fat around the head of the pancreas, the aortic root, and the mesenteric root. Sigmoid bowel wall thickening and distention were noted. Mild amount of ascites.</td>
</tr>
<tr>
<td></td>
<td>CT angiography of the chest (1st): normal</td>
<td>CT angiography not done.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CT angiography of the chest (2nd): Diffuse ground-glass appearance of both lungs with normal filling of the pulmonary arteries, compatible with microthrombi. Also a superior vena cava thrombus.</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Progression of symptoms</strong></td>
<td>While on treatment with LMWH and pulse steroids</td>
<td>While on treatment with high-dose steroids</td>
<td>While on treatment with high-dose steroids and LMWH switched to warfarin</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Full heparinization</td>
<td>Full heparinization</td>
<td>Full heparinization</td>
</tr>
<tr>
<td></td>
<td>Pulse steroids (1g/d for 3 d with gradual tapering down)</td>
<td>Pulse steroids (1g/d for 3 d with gradual tapering down)</td>
<td>Pulse steroids (1g/d for 3 d with gradual tapering down)</td>
</tr>
<tr>
<td></td>
<td>IVIG (2g/kg)</td>
<td>IVIG (2g/kg)</td>
<td>IVIG (2g/kg)</td>
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<td>Plasmapherisis</td>
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<td></td>
<td>Rituximab (375 mg/m² once a wk for 4 wks)</td>
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</tbody>
</table>

*ANA, antinuclear antibody; anti dsDNA, anti double stranded DNA; LAC, lupus anticoagulant; LAC-RVVT, lupus anticoagulant Russell’s viper-venom time; N, normal value.

*a: All patients were tested for antibody titers of anticardiolipin IgG, IgA, IgM, antiB2glycoprotein IgG, IgA, IgM, and LAC. The table notes only those antibodies with elevated titers.

*b Confirmed on 2 different occasions at least 6 wk apart.
pulses, and IVIG was started (Table 1). With treatment, his pain subsided and he was discharged. On follow-up, a year later, he feels well with no symptoms.

**DISCUSSION**

In recent years, APS has been increasingly recognized in the pediatric population as either a primary syndrome, or associated with an underlying autoimmune disease. The term catastrophic APS is used to define an accelerated form of APS with multiple organ involvement, histopathological evidence of multiple small-vessel occlusion and laboratory confirmation of the presence of aPL antibodies. The diagnostic criteria for catastrophic APS are outlined in Table 2. Because of the difficulties in confirming definite catastrophic APS, the term “probable catastrophic APS” was used for patients who did not meet all 4 required criteria for diagnosis (Table 2).

We present herein, 3 adolescents with excruciating abdominal pain as the first manifestation of probable catastrophic APS (Table 3). Summary of the clinical, laboratory, and imaging data of these patients can be found in Table 1. In all patients, aPL positivity was confirmed at least twice, 6 weeks apart. Abdominal pain as an initial presentation of catastrophic APS has already been described in an analysis of patients from the Catastrophic Antiphospholipid Syndrome registry. However, this is the first case series describing the initial clinical, physical, and laboratory presentation, and raising the general pediatrician awareness for the possibility of catastrophic APS in children with severe abdominal pain. In the Catastrophic Antiphospholipid Syndrome registry, 46% of patients with catastrophic APS had no previous history of either primary APS or SLE. In our series as well, 2 of the patients had no previous history of thrombosis or autoimmune disease, making the diagnosis more difficult.

Precipitating factors are usually present in patients presenting with catastrophic APS. Infection, immobilization, and surgery were found to be the major precipitating factors contributing to the development of APS in the Pediatric-APS registry. In our patients, 2 had suffered from an intercurrent infection and the third had undergone a splenectomy.

The clinical manifestations of catastrophic APS depend mainly on 2 factors: the organs affected by the thrombotic event and the manifestations of the systemic inflammatory response syndrome. Our patients experienced severe abdominal pain as a manifestation of intra-abdominal thrombosis. Intra-abdominal involvement in catastrophic APS is common. In our patients, the pain was probably because of hepatic infarction. Thrombotic microangiopathy seems to be the major pathogenetic mechanism in catastrophic APS and one of the major features that differentiates catastrophic APS from classic APS. In classic APS, thrombotic complications are mostly large-medium vessel thrombosis. The histopathologic hallmark of catastrophic APS is the presence of micro thrombi and diffuse small-vessel ischemia, predominantly affecting the parenchymal organs. Small-vessel thrombosis may be difficult to diagnose by imaging studies; only indirect findings of a diffuse infiltrative process may suggest at thrombotic process. In 2 of our patients, only repeated CT angiography revealed evidence of major vessel thrombosis. Confirmation of small-vessel occlusion by histopathology is required for diagnosing catastrophic APS. One patient had clear histologic evidence of liver necrosis. The other’s liver biopsy showed vascular congestion, implying presence of micro thrombi.

Elevated inflammatory markers, seen in all 3 of our patients, indicated a systemic inflammatory response. A multisystem inflammatory response syndrome with excessive cytokine release and activation serves as 1 of the mechanisms of the disease.

Management of catastrophic APS includes treatment of the precipitating factors, stopping the thrombotic process and removing aPL and suppressing the excessive cytokine release. Two of our patients developed ongoing thrombosis while treated with LMWH or warfarin, indicating that IV heparin administration is mandatory. Treatment of the inflammatory response must be prompt and aggressive. Using

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**TABLE 2 Preliminary Criteria for the Classification of Catastrophic APS**

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>Evidence of involvement of 3 or more organs, systems, and/or tissues</td>
</tr>
<tr>
<td>2</td>
<td>Development of manifestations simultaneously or in less than a week</td>
</tr>
<tr>
<td>3</td>
<td>Confirmation by histopathology of small vessel occlusion in at least 1 organ or tissue</td>
</tr>
<tr>
<td>4</td>
<td>Laboratory confirmation of the presence of antiphospholipid antibodies (lupus anticoagulant and/or anticardiolipin antibodies)</td>
</tr>
</tbody>
</table>

**Definite catastrophic APS**

- All 4 criteria

**Probable catastrophic APS**

- All 4 criteria, except for 2 organs, systems, and/or tissues involvement

**Possible catastrophic APS**

- All 4 criteria, except for the absence of laboratory confirmation at least 6 weeks apart owing 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

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* 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 mm Hg), and/or proteinuria (>500 mg/24 h).

* For histopathological confirmation, significant evidence of thrombosis must be present, although vasculitis may coexist occasionally.

* If the patient had not previously been diagnosed as having an APS, the laboratory confirmation requires that presence of antiphospholipid antibodies must be detected on 2 or more occasions at least 6 weeks apart (not necessarily at the time of the event), according to the proposed preliminary criteria for the classification of definite APS.

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*Reference citations will be included in the final version of this document.*
REFERENCES


Corticosteroids alone has a poor prognosis.9 Corticosteroids should be considered in all patients with catastrophic APS in combination with IVIG and/or plasmapheresis.4,9 This type of treatment is responsible for the significant reduction in the mortality rate.9 The use of rituximab, an anti-CD20 monoclonal antibody, has recently been shown to be effective in treating patients with catastrophic APS resistant to standard treatment.13–15 The use of rituximab in our patient caused a dramatic change in the course of the disease, halting the inflammatory process.

CONCLUSIONS

Early diagnosis and aggressive therapy are essential for the successful treatment of catastrophic APS. Excruciating abdominal pain, out of proportion to findings on physical examination or basic imaging studies with highly elevated inflammatory markers, should raise the suspicion of catastrophic APS, even in previously healthy adolescents and lead to prompt investigation and treatment.

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The authors thank Mrs Phyllis Kornspan for her editorial services.

TABLE 3 Patients’ Criteria for the Diagnosis of Probable Catastrophic APS

<table>
<thead>
<tr>
<th>Criteria 1&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Criteria 2&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Criteria 3&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Criteria 4&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Positive Criteria&lt;sup&gt;c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organs Involved</td>
<td>Time until Development</td>
<td>Histopathology of Small Vessel Occlusion</td>
<td>Laboratory Confirmation of Antiphospholipid Antibodies&lt;sup&gt;b&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Case I</td>
<td>Liver, Cardiac, Pulmonary, Pancreas, Superior Vena Cava thrombus</td>
<td>16 d</td>
<td>Mild sinusoidal enlargement, with congested blood vessels and thickened arterial wall.</td>
<td>Positive antibodies: Anti-cardiolipin IgG, LAC ratio, LAC-RVVT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Criterion 2 is not met, as time until development is more than 1 wk</td>
<td></td>
</tr>
<tr>
<td>Case II</td>
<td>Liver, Renal (proteinuria), Right subclavian vein thrombosis, Right internal jugular vein thrombosis</td>
<td>3 wk</td>
<td>Extensive foci of necrosis, fibrin deposition and fibrosis</td>
<td>Positive antibodies: Anti-cardiolipin IgG, LAC ratio, LAC-RVVT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Criterion 2 is not met, as time until development is more than 1 wk</td>
<td></td>
</tr>
<tr>
<td>Case III</td>
<td>Liver, Intestine, Pancreas (hypodensic pancreas on imaging), Portal vein thrombosis, Superior mesenteric vein thrombosis</td>
<td>1 wk</td>
<td>Not preformed</td>
<td>Positive antibodies: Anti-cardiolipin IgM, Anti-β2-glycoprotein IgM, LAC ratio, LAC-RVVT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Criterion 3 is not met, as there is no histopathological evidence of small vessel occlusion</td>
<td></td>
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</table>

LAC, lupus anticoagulant; LAC-RVVT, lupus anticoagulant Russell’s viper-venom time.

<sup>a</sup> Please see criteria for the diagnosis of definite catastrophic APS and probable catastrophic APS in Table 2.

<sup>b</sup> Confirmed on 2 different occasions at least 6 wk apart.

<sup>c</sup> Because only 3 criteria are met in each case, the diagnosis is of probable catastrophic APS.


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