Recurrent intestinal perforations as a presentation of antiphospholipid syndrome

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Antiphospholipid syndrome (APS) is a rare but important cause of thrombosis. It is suspected in patients who present with recurrent thrombosis or thrombosis in an unusual site. Gastrointestinal involvement is rare in this syndrome. Moreover, intestinal perforation in APS is very rare.

We report a 19-year-old female patient who developed recurrent spontaneous intestinal perforations in which repeated laparotomies were undertaken and different diagnoses were entertained. The patient had received different treatments but without improvement. Antiphospholipid syndrome (APS) was suspected and diagnosed, and subsequently anticoagulant therapy was started. To our knowledge, this is a first report describing recurrent small intestinal perforation in a patient with APS.

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Case

A 19-year-old single female patient was referred to the emergency room of King Abdulaziz University Hospital, in Jeddah, Saudi Arabia, complaining of generalized abdominal pain and vomiting of 2 days duration. The pain had started in the right lower quadrant, gradually increased in severity and became generalized. It was continuous, severe, aggravated by any movement, and associated with vomiting of whatever she ingested and a low-grade fever. There was no change in bowel habits and no history of previous similar pain. She gave a history of previous laparotomy in another hospital because of a ruptured ovarian cyst 4 years before presentation. There was no other significant medical history, she was not on any medication, and there was no significant familial disease apart from diabetes mellitus and hypertension in her mother. There was no family history of thrombosis or recurrent miscarriage.

On examination, the patient was mildly dehydrated. Her temperature was 38 C, pulse rate 120/minute, and blood pressure 110/85 mm Hg. Her abdomen was tender all over with rigidity and sluggish bowel sounds. Examinations of other systems were unremarkable. The total leukocyte count was $17.3\times10^3/\mu L$, neutrophils were 88.5%, and Hb 9.7 g/dL. Other tests, including the platelet count, PT, PTT, urea, creatinine, electrolyte and liver function tests, stool and urine analyses, were within normal range. The chest x-ray was normal. An abdominal x-ray showed a dilated small intestine. A diagnosis of peritonitis, possibly secondary to perforated appendicitis, was made and the patient was operated on.

The abdomen was opened through a previous lower midline incision, revealing a turbid fluid, mildly inflamed appendix, and a small perforation in the terminal ileum, while other abdominal organs were normal. Appendectomy was done with closure of the perforation. Postoperatively the patient improved and was discharged on the 5th postoperative day.

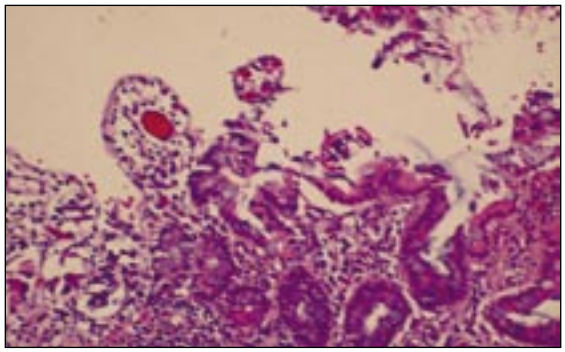

Figure 1. Histopathology of the resected part of ileum showed infarction, thrombotic microangiopathy, thrombosis in some blood vessels and acute inflammatory cells.

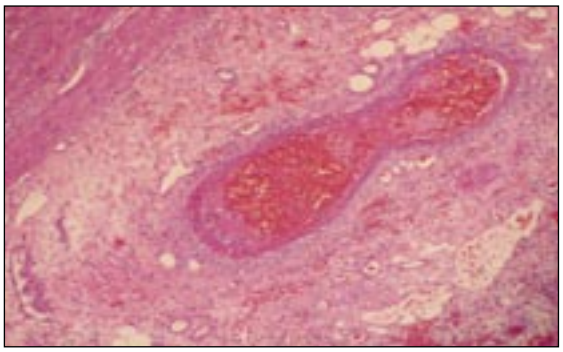

Figure 2. Higher magnification of Figure 1, showing thombosis of some blood vessels.

Two days later, the patient presented to another hospital with the same complaint of abdominal pain. The patient was febrile and tachycardic. The abdomen was tender all over with rigidity and sluggish bowel sounds. The patient was operated upon, and the laparotomy showed multiple perforations in the terminal ileum. A segment of ileum that contained the perforations was resected and an end-to-end anastomosis was done (details of the histopathology were not available). The patient was referred once again to our hospital.

During this admission, the patient had 15 laparotomies to close multiple small bowl perforations. Each time the patient developed abdominal pain with tachycardia and the abdomen was tender and rigid with absent bowel sounds. There were about 3 to 7 days between each laparotomy. The perforations developed over different sites and sometimes over the previous one.

During the first laparotomy, biopsies were taken from the perforations in which the histopathology showed mucosal ulceration and transmural inflammation with a serosal reaction suggestive of Crohns disease. The patient was started on steroids, but there was no response and the patient developed multiple small bowl perforations during treatment. Serology for *Salmonella typhi*, *S. paratyphi*, *Brucella*, hepatitis B and C and HIV were negative. After the 7th laprotomy, tuberculosis was suspected and biopsy samples were taken from the perforations and sent for TB culture. The patient was started on empirical anti-TB therapy, but there was no response and the patient developed multiple perforations during the treatment. The TB culture was negative and, therefore, the anti-TB therapy was discontinued.

During the 13th laprotomy, a segment of ileum was resected because it contained multiple perforations. The histopathology of the resected specimen showed infarction, thrombotic microangiopathy, thrombosis in some blood vessels and acute inflammatory cells, but there were no well-defined granuloma or a malignancy. The picture was highly suggestive of ischaemic bowel disease (Figures 1 and 2). Hypercoagulability syndrome was suspected, a blood sample was taken for hematological study and heparin was started. Protein C, protein S and antithrombin III were within normal ranges. Activated protein C was resistant and antinuclear antibodies were negative. Anticardiolipin was positive, IgG was 70 phospholipid (GPL) units/mL (negative <12.0 GPL units/mL), and IgM was 7 MPL units/mL (negative <6.0 MPL units/mL) measured by ELISA. Lupus anticoagulant was moderately positive. Both anticardiolipin antibodies and lupus anticoagulant were repeated six weeks later and remained positive. Measurement was carried on a BCS coagulation analyser (Dade Behring USA).

During the treatment with anticoagulant, the patient developed small bowl perforations twice, which were closed. An INR of 2.5-3.5 was achieved and the patient was discharged in good condition on warfarin with the INR maintained between 3 and 4. During the follow up for 3 years following the diagnosis and management, there was no problem apart from admission once for bleeding tendency secondary to warfarin overdose.

Discussion

Anti-phospholipid syndrome (APS) is an acquired thrombophilic state characterized by recurrent arterial and venous thrombosis, recurrent pregnancy loss, and the presence of circulating anti-phospholipid antibodies.[1]

The clinical features of APS are due to the pres-

ence of anti-phospholipid antibodies (APL), which are directed against phospholipid-binding proteins (2-glycoprotein I) and not against the phospholipid antigens per se. There are two types of APL, anticardiolipin antibodies (aCL) and lupus anticoagulants (LA).[1,2] Anticardiolipin antibodies (aCL) are positive in more than 80% to 90% of patients with APS (9). These antibodies are measured using commercially available enzyme-linked immunosorbent assay (ELISA) kits.[1,3] The lupus anticoagulants (LA) test is a measure of the ability of APL autoantibodies to prolong phospholipid-dependent clotting reactions.[1,3]

Anti-phospholipid antibodies are associated with a wide variety of clinical presentations, which include thrombosis, recurrent pregnancy loss, and involvement of other organs such as the skin, cardiovascular, hematological and central nervous system. Venous thrombosis, especially deep venous thrombosis of the legs, is the most common manifestation. It can also occur in unusual sites such as the inferior vena cava, and the axillary, ocular, renal and hepatic veins. Arterial thromboses are less common than venous thromboses and most frequently manifest with features consistent with ischaemia or infarction. Arterial thrombosis may affect the intracranial, retinal, coronary, mesenteric or peripheral arteries. The ratio of venous-to-arterial thrombosis in APS is 2:1, and in both cases thrombosis tends to be recurrent.[4]

Gastrointestinal tract (GIT) involvement in APS is rare, and is usually present as mesenteric venous thrombosis. Other manifestations reported include Budd-Chiari syndrome, hepatic and splenic infarction, pancreatitis, omental and intestinal infarction, and esophageal variceal bleeding due to portal vein thrombosis.[10] Arterial thrombosis and thrombosis in the small blood vessels of the GIT are less common than venous thrombosis and usually lead to gangrene and perforations; other causes of intestinal perforation such as infections, inflammatory bowel disease and vasculitis have to be excluded.[4,5,6] A review of the literature showed 11 cases of gastrointestinal ischaemia in patients with APS,[10] 1 case of large bowel perforation,[11] 1 case of esophageal perforation,[12] and 1 case of intestinal stenosis.[13]

The diagnosis of APS depends on the presence of at least one of the two clinical criteria (vascular thrombosis or complications of pregnancy) and at least one of two laboratory criteria. Clinical criteria include arterial, venous and/or small vessel thrombosis as well as recurrent (three or more) miscarriages, one fetal death or prematurity due to severe pre-eclampsia or placental insufficiency. Laboratory criteria only consider aCL at medium-high titers or LA, any of them positive twice at least 6 weeks apart.[1,7]

The acute thrombotic events in APS are treated with anticoagulation.[7-8] The duration and intensity of therapy need to be tailored to individual patients. Arterial thrombosis carries a much higher risk of morbidity and mortality due to cerebral ischaemia and may necessitate more intensive and prolonged anticoagulant therapy.[2,8,9] Long-term anticoagulation is usually recommended due to the risk of recurrence, which may be as high as 69% to 91% in untreated APS patients.[1,8]

Plasmapheresis has been recommended in patients with catastrophic APS to reduce the amount of circulating immune complexes, but early, adequate anticoagulation remains the primary treatment.[2,7] Immunotherapy with corticosteroids or immunoglobulins to modulate the immune response has been tried in selected cases, but were not of benefit in controlled trials.[2,6]

In conclusion, APS is an important cause of recurrent thrombosis or thrombosis in an unusual site. It can cause thrombosis in small blood vessels of the GIT, which can lead to ischaemia and perforation. Lack f awareness of the condition may result in unnecessary investigations and inappropriate treatment with an increased morbidity risk. We suggest that recurrent small intestinal perforations might be part of the clinical spectrum of APS.

References

1. Manjiri KC, Nelson-Piercy N. Acquired thrombophilias and pregnancy, Best Practice & Research Clinical Obstetrics & Gynaecology. 2003:491-507

2. Durrani OM, Gordon C, Murray PI. Primary Antiphospholipid Antibody Syndrome (APS): Current Concepts, *Survey of Ophthalmology*. 2002;47(3):215-38

3. Hughes GR. Thrombosis, abortion, cerebral disease, and the lupus anticoagulant. *Br Med J (Clin Res Ed)*. 1983;287:1088-1089.

4. Hughes G, Harris NN, Gharavi AE. The Anticardiolipin syndrome. *J Rheumatol*. 1986;13(3):486-9.

5. Pierangeli SS, Gharavi AE, Harris EN. Testing for antiphospholipid antibodies: problems and solutions. *Clinical Obstetrics and Gynecology*. 2001;44:48-57.

6. Bick RL. The Antiphospholipid-thrombosis syndromes. Fact, fiction, confusion, and controversy. *Am J Clin Pathol*. 1993;100:477-480.

7. Greaves M, Cohen H, MacHin SJ, Mackie I. Guidelines on the investigation and management of the antiphospholipid syndrome. *Br J Haematol*. 2000;109(4):704-15.

8. Espinoza LR. Antiphospholipid antibody syndrome: treatment. *Lupus*. 1996;5:456-457.

9. Asherson RA. The catastrophic antiphospholipid syndrome, 1998. A review of the clinical features, possible pathogenesis and treatment. *Lupus*. Suppl 1998;7:S55-S62.

10. Choi BG, Jeon HS, Lee SO, Yoo WH, Lee ST, Ahn DS. Primary Antiphospholipid syndrome presenting with abdominal angina and splenic infarction, *Rheumatol Int*. 2002;22(3):119-21.

11. Locher C, Raynaud J, Chamsedine D, Labayle D, Fischer D. Large bowel perforation disclosing primary antiphospholipid syndrome, *Gastroenterol Clin Biol*. 2000;24(10):970-1.

12. Cappell MS; Esophageal necrosis and perforation associated with the anticardiolipin antibody syndrome; *Am J Gastroenterol*. 1994;89(8):1241-5.

13. Tincani A, Bozzetti F, Tardanico R, Cerri G, Lazzari F, Balestrieri G. Antiphospholipid antibodies and intestinal pathology; *J Rheumatol*. 1993; 20(12):2169-70.