Transient Antiphospholipid Syndrome in an Infant With Segmental Small Bowel Infarction

By B. Haluk Güvenç, Nazan Sarper, Ayşê Tuzlaçî, and Necati Günaltay
Kocaeli, Turkey

The clinical picture of venous or arterial thrombosis in the presence of circulating antiphospholipid antibodies is referred to as the antiphospholipid syndrome. A 5-month-old baby girl who was quite healthy so far was referred to our clinic with irritability, vomiting, and abdominal distension for 30 hours. Surgical exploration exposed a gangrenous ileal segment about 15 cm long. The postoperative period was unremarkable. Histopathologic material from the bowel resection showed massive necrosis of the mucosa in accordance with venous obstruction.

Improved clinical recognition of the antiphospholipid syndrome (APLS) since its first description in 1983 shows the increased need for clinical definition of the syndrome, the measurement of different types of antiphospholipid antibodies (APLA), and better understanding of the pathophysiology and treatment.

A variety of conditions including systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren’s syndrome, progressive systemic sclerosis, idiopathic thrombocytopenic purpura, malignancies, infections (especially viral), or drug-induced conditions can present in association with lupus anticoagulants (LAC) or APLA. Presentation of thromboembolic phenomena associated with a high titer of LAC or APLA without an underlying autoimmune or infectious disorder is referred to as the primary APLS. Although the incidence remains undetermined, von Scheven et al state that primary APLS appears to be more common than was realized initially and should be included in the differential diagnosis of unexplained thrombosis in children.

Anticardiolipin antibodies (aCL) have been described in diverse clinical situations, linked to the risk of thrombosis in different vascular locations. They have been rarely associated with intestinal thrombosis in adult patients. To our knowledge, our case is the first report of a segmental intestinal infarction with transient APLS in the pediatric population.

Case Report

A 5-month-old baby girl was admitted to the emergency room with irritability and bilious vomiting for 30 hours. The physical examination showed abdominal distension, signs of peritoneal irritation with diffuse abdominal pain, and muscular defense. Plain abdominal x-ray showed distal small bowel obstruction with multiple air-fluid levels. Emergency exploratory laparotomy exposed presence of hemorrhagic peritoneal fluid with necrosis of an ileal segment about 15 cm long located less than 3 cm proximal to ileocecal valve (Fig 1). There was no associated anomaly. Resection of the small bowel segment was done with an end-to-end ileo-ileal anastomosis. The postoperative period was unremarkable. Histopathologic material from the bowel resection showed massive necrosis of the mucosa in accordance with venous obstruction.

The region was devastated severely by the Marmara (Turkey, 1999) earthquake soon after the patient’s discharge. Thus, investigation to identify the risk factors for the mesenteric thrombosis could only be made after the 45th postoperative day. Laboratory investigations found anticardiolipin antibodies (isotype Ig G) and decreased protein C level. Protein S and antithrombin III were within normal levels (Table 1). She had no previous medical problems, was quite healthy, and had no family history of connective tissue disorders. There were no clinical signs and symptoms suggestive of SLE. The diagnosis of antiphospholipid syndrome with ileal segmentary venous thrombosis was made.

The patient was once again lost to follow-up for about 6 months, and no anticoagulant therapy could be administered. She was quite healthy on her readmission at 8 months postoperatively. ACL and protein C were found within normal limits, and there was no use for anticoagulant medication. There has been no evidence of a recurrent thrombotic event during the 24-month follow-up period.

From the Departments of Pediatric Surgery and Pediatrics, Kocaeli University School of Medicine, Kocaeli, Turkey.
Address reprint requests to Prof. Dr. B. Haluk Guvec, Kocaeli University, Tip Fakultesi Hastanesi, Cocuk Cerrahisi ABD, Derince, Izmit TR-41900, Turkey.
© 2004 Elsevier Inc. All rights reserved.

INDEX WORDS: Primary antiphospholipid syndrome, small bowel, infarction.
DISCUSSION

Mackay et al\textsuperscript{16} reported a circulating endogenous anticoagulant, which interfered with activation of prothrombin in the presence of phospholipid in 1982. In this report, a 13-year-old boy suffered from deep venous thrombosis. This was said to differ from the previously reported cases because there was no evidence of drug exposure, SLE, other medical diagnoses, and autoimmune phenomena. Hughes\textsuperscript{1} a year later referred to this clinical picture as APLS.

The 4 major manifestations of the syndrome are arterial or venous thrombotic events, recurrent spontaneous abortions, and thrombocytopenia.\textsuperscript{17} Any of the first 3 major manifestations in the presence of a valid and reliable test for APLA are sufficient to diagnose the syndrome.

APLA stands for a group of antibodies, mostly directed to various phospholipids of anionic origin (cardiolipin, phosphatidylcholine, phosphatidylserine, phosphatidyl acid, and phosphatidyl ethanolamine). APLA can be detected in serum with one of the following assays: testing of lupus anticoagulant (LAC) presence, testing the false-positivity of VDRL (standard test for syphilis), and determination of anticardiolipin antibodies (aCL) concentration by ELISA. The ELISA test detects

\begin{table}[h]
\centering
\caption{Laboratory Investigation of Patient With Ileal Venous Thrombosis}
\begin{tabular}{|l|c|c|c|}
\hline
 & Thrombotic Episode & Second Postoperative Month & Eighth Postoperative Month \\
\hline
Hemoglobin (g/dL) & 10.1 & 10.2 & 12.6 \\
Leucocyte count (mm\textsuperscript{3}) & 15 300 & 14 100 & 8300 \\
Platelet count (mm\textsuperscript{3}) & 267 000 & 352 000 & 230 000 \\
Prothrombin time (second) & 12 (12.2 normal) & 12.4 (12.8 normal) & 12.8 (12.6 normal) \\
Activated partial thromboplastin time (second) & 24.1 (26 normal) & 30.5 (28 normal) & 32.9 (28 normal) \\
Fibrin degradation products (mg/mL) & Normal & <5 & <5 \\
Fibrinogen (mg/dL) & 471.6 & & \\
Protein C (mg/dL) & 47 & & 83 \\
Protein S (mg/L) & 13.8 & & \\
Antithrombin III & & & \\
(A normal 80–120) & 108 & & \\
aCL (IgG) GPL U/mL & & & \\
(Normal < 14) & 46 & 11.2 & \\
aCL (IgM) MPL U/mL & & & \\
(Normal < 10) & 5 & 9.7 & \\
LAC & Negative & & \\
DsDNA & Negative & & \\
SsDNA & Negative & & \\
Complement 3 g/L (Normal 0.8–2.0) & 0.93 & & \\
Complement 4 g/L (Normal 0.1–0.4) & 0.3 & & \\
Direct Coombs & Negative & & \\
F V Leiden mutation & & & \\
(Normal 1691 G/G) & 1691 G/G & & \\
Prothrombin mutation & & & \\
(Normal 20210 G/G) & 20210 G/G & & \\
Hemoglobin A1 & 95.1 & & \\
Hemoglobin F & 1.8 & & \\
Hemoglobin A2 & 3.1 & & \\
Hemoglobin S & 0 & & \\
\hline
\end{tabular}
\end{table}

Abbreviations: aCL, anticardiolipin antibodies; LAC, lupus anticoagulant; DsDNA, double-stranded DNA; SsDNA, single-stranded DNA.

NOTE. Transaminases, BUN, and creatinin values were within normal limits.
the IgG and IgM isotypes. aCL test results are interpreted as follows: negative, less than 10 GPL/MPL units; low positive, 10 to 20 GPL/MPL units; moderate positive, 20 to 100 GPL, 20 to 60 MPL units; high positive, greater than 100 GPL, greater than 60 MPL units. In current reports, investigation of both antibodies is recommended because patients may have one antibody system and yet not the other. In 90% of the cases, both aCL and LAC tests are positive, but in the report by Falcini et al, 2 cases of primary APLS had only LAC with aCL studies being always negative.

A proliferative vasculopathy is assumed to be the cause of the vascular occlusion in APLS rather than thrombosis or vasculitis. Petri wishes to rename the lupus anticoagulant as a procoagulant, assuming that antiphospholipid antibody may prove to be misnomer.

Although the aPTT is generally prolonged, a hypercoagulable state exists, resulting in thrombotic tendencies rather than a bleeding diathesis. The most frequent target tissues for APLA are endothelial cells, thrombocytes, monocytes, natural anticoagulant system, and placenta. Thrombocytopenia may be attributable to antibodies against phospholipids in platelet membranes. Proposed mechanisms for thrombosis resulting from antiphospholipid antibodies include the inhibition of prostacyclin release from vascular endothelium, leading to an increase in platelet aggregation. Inhibition of the activity of anti-coagulants such as protein C, antithrombin III, or thrombomodulin result in increased platelet aggregation and thrombosis. A similar result is observed by binding beta2 glycoprotein I (a plasma cofactor associated with antiphospholipid antibodies) to platelet membrane or to the prothrombinase complex.

APLA may intervene at various sites of the coagulation process at which phospholipids participate, such as platelet wall phospholipids (platelet factor III) that interact with factor X and factor V in the presence of calcium causing prolonged prothrombin and partial thromboplastin times, thus, behaving in vitro as anticoagulants. But the in vivo interaction of APLA at other sites of the coagulation cascade, such as phospholipids that associate with endothelial cell cofactor thrombomodulin, may be more prominent.

Laboratory tests of our case found a normal platelet count, normal partial thromboplastin time, and decreased protein C level. Even though detailed laboratory investigations could only be performed during the late period of the thromboembolic event, aCL antibodies analyzed by ELISA were moderately positive for IgG isotype after 45 days. Direct coombs test, LAC, ANA, ds DNA, and ss DNA were negative. She had no family history of a thrombotic event or connective tissue disorder. During an acute thrombotic event, patients generally have thrombocytopenia. In a study of 100 patients with APLS, only 52% had thrombocytopenia. Although the aPTT is generally prolonged, minimally prolonged or normal aPTT can be found in some cases as in our case. A number of studies report that raised IgG APLA levels are more closely associated with thrombosis, fetal loss, and thrombocytopenia than are raised IgM.

Ruiz-Anguelles et al report protein C deficiency associating primary APLS and suggest protein C deficiency to be caused by interaction of APLA with phospholipids associated with thrombomodulin. Baca et al report 10 consecutive cases of primary APLS, some of which have transient protein C and high aCL levels during their clinical progress. They screened their patients every 3 to 6 months. One of their cases fulfilled the criteria for SLE 3 years after the onset of symptoms. Von Sheven et al point out a greater remission rate for primary than for secondary APLS. Becton and Stine mention a rare association of transient lupus anticoagulants with hemorrhage and not thrombosis. Recently, Szer has reported a case of transient positive (aCL) and protein C deficiency as another clinical presentation of APLS. She points to the incidence of bleeding diathesis occurring in children with transiently acquired, presumably postviral, LAC and low factor II levels.

Our patient did not have a second crisis, is symptom free, and the APL antibodies are within normal levels 8 months after the operation. Protein C system is physiologically immature in children less than 4 years of age. Protein C deficiency was transient in our patient probably because of physiologic maturation. The clinical presentation was acute abdomen and did not suggest a specific infection or disseminated intravascular coagulopathy. We also ruled out other causes of thrombosis such as sickle cell anemia, AT III deficiency, Factor V Leiden, and prothrombin 20210 mutation. Although there was no history or confirmation of a recent infection, transient APLA in the current case may still be caused by a possible (viral) infection.

APLS presenting with intestinal infarction is relatively rare in the reported literature and is limited to adult cases. There appear to be 9 reports of a poor outcome. The clinical picture is protracted with intestinal angina in those cases of vasculitis, whereas acute infarction is present in cases of thrombosis. Some are related to SLE, whereas others are reported as primary APLS. Our case is the only pediatric case in the reported literature of APLS causing segmental intestinal infarction.

Optimal treatment and prevention of the syndrome still is unclear. Long-term, probably lifelong anticoagulation therapy is indicated in patients with a history of thrombotic episode. Although low dose of aspirin is suggested to reduce the risk of recurrent thrombosis, antiagregant therapy alone is not enough to prevent thrombotic attacks. Anticoagulant therapy with warfarin
is recommended with and without aspirin. Steroids, plasmapheresis and immunosuppressors are also used during acute attacks. Accumulated data do not justify therapeutic intervention on the basis of the presence of a lupus anticoagulant alone. There is also an increased risk of hemorrhage during play and sport in children receiving long-term anticoagulant treatment. We could not administer any antiagregant or anticoagulant medication because the patient was lost to follow-up in the period of positive APLA. It is important to have a heightened sense of awareness of bowel complications in patients with primary and secondary APLS because the true incidence may be underestimated.

ACKNOWLEDGMENT

The authors thank Prof. Dr Nejat Akar, MD, who contributed the study with molecular genetic investigation.

REFERENCES

19. Lie JT: Vasculopathy in the antiphospholipid syndrome; thrombosis or vasculitis, or both? J Rheumatol 16:713-715, 1989