Jejunal Ischemia in a 15 year old Female with Primary Antiphospholipid Antibody Syndrome: A Case Report and Review of Literature

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ABSTRACT

Antiphospholipid antibody syndrome (APS) is increasingly being recognized in pediatrics as a cause of vascular thrombosis. Thrombotic events are diverse and could affect any organ system. Intestinal involvement however, is rarely reported for both the pediatric and adult population. This paper describes the first locally reported case of primary APS with jejunal ischemia in the pediatric age group. It aims to highlight the pertinent clinical features as seen in this patient. A review of literature is also provided on the current issues on clinical significance of antiphospholipid antibodies and on optimal anticoagulation treatment to prevent recurrence of thrombosis.

Key Words: antiphospholipid antibodies, antiphospholipid antibody syndrome, thrombosis, jejunal ischemia, pediatric, heparin

Introduction

Antiphospholipid antibody syndrome (APS) is a multisystem autoimmune disorder characterized by arterial and venous thrombosis, recurrent fetal loss, and persistent circulating antiphospholipid antibodies (aPL).[1] The syndrome may occur as "primary", with no apparent cause, or "secondary", when it is associated with an underlying systemic disease, most common of which is systemic lupus erythematosus(SLE).[1,2,3]

While APS in adults has been well described, only a few studies of children with APS have been reported. During the last 5 years, APS is increasingly recognized as a cause of vascular thrombosis in the pediatric population.[4] In a recently published international registry consisting of 121 children with APS, the most common thrombotic site was in the lower extremities (40%), which is comparable with that reported from adult studies (32%). The brain was the second most common site (32%), which is higher than that reported for adults (16-21%) [5]. APS presenting with intestinal involvement however, is relatively rare in both pediatric and adults (0.8% and 1.5%, respectively), with a poor outcome in an important proportion of cases.[5,6] The true incidence of intestinal ischemia and infarction associated with APS may be underestimated because of a lack of general awareness that bowel complications may occur in patients with APS .

The following is the first locally reported case of primary APS with intestinal involvement in the pediatric age group. The case report aims to highlight important clinical features of APS in this organ system and review the present issues concerning clinical significance of elevated antiphospholipid antibodies in the pediatric age group.

Case Report

A 15 year old female presented in the pediatrics department with intermittent epigastric pains which was burning in character for 5 days. This was not associated with fever, bowel or urinary disturbances. Her mother brought her to a private clinic where a urinalysis revealed "infection". She was given Cotrimoxazole and antacids and was asked to follow up after 5 days. The epigastric pains however, worsened in severity and became associated with several episodes of vomiting and decrease in appetite. She was brought to another private clinic where an initial diagnosis of gallstones versus pancreatitis was made. Abdominal xray and ultrasound of the abdomen were done in the same clinic but showed normal results. She was transferred to the author's service on the same day for further management.

Her past medical history revealed that at five years of age, she was hospitalized for pneumonia but developed severe frontal headaches and vomiting 3 days after discharge. CT scan of the head during her readmission revealed an epidural hematoma on the right straight sinus, on the left occipital region, posterior interhemispheric and posterior superior sagittal sinus. No vascular malformation was seen nor a hematologic disorder identified to account for the bleed. She was managed as 'stroke in the young" and was discharged with slurred speech and inability to ambulate but these residuals resolved after a month without speech and physical therapies. Family history was negative for coagulation disorders but acute pancreatitis was present in two family members. Her father allegedly died because of it while a paternal aunt survived an episode. Prior to this hospitalization, she was an average senior high school student in a private school in Manila. She denied smoking, intake of alcoholic beverages and use of prohibited drugs. She had regular monthly periods lasting for 4-5 days. Her last normal menstrual period was a month prior to this

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admission. She denied any sexual experience.

On admission, she was weak looking but ambulatory. Her BMI- for- age was normal between 75th to 85th percentile. Physical examination revealed only direct epigastric tenderness. An initial diagnosis of acid peptic disease rule out acute pancreatitis was made. Acid control using Omeprazole was started. She was placed on nothing by mouth and intravenous fluid was kept at maintenance rate. Laboratory investigations revealed slight leucocytosis: white blood count, 12.1 x 10^9 /L; hemoglobin, 137 g/L; platelet count, 280 x 10^9/L; prolonged prothrombin time, 50.42%, INR , 1.61, normal partial thromboplastin time , 27.3 ; normal ESR, 9 mm/hr; amylase and lipase were normal, 51 U/L and 142 U/L, respectively; SGPT was slightly elevated at 74 (normal, 30-65 IU/L); kidney and other liver function tests were normal.

In the first 36 hours, she had worsening of abdominal pain associated with vomiting of coffee ground material and episodes of hypotension. Fluid resuscitation at 10 ml/kg boluses and empiric broad spectrum antibiotics were initiated. Pediatric surgery was called for opinion and further evaluation. Subsequent laboratory investigations were as follows: CT scan of the abdomen revealed a slightly inflamed pancreas with generalized ascites; < 5 ml of peritoneal fluid obtained from paracentesis was clear yellow and normal for amylase and negative for gram stain. Chest xray was normal. Repeat complete blood count showed increased leucocytosis, white blood count 32.1 x 10^9/L, hemoglobin 147 g/L, adequate platelets. Blood and peritoneal fluid were sent for culture. She eventually developed peritoneal signs which indicated exploration. Operative findings showed a segment of gangrenous jejunum. About 2 liters of ascitic fluid was evacuated and 90 cm of infarcted jejunum was resected. The pancreas, spleen, liver, gallbladder were all normal. Histopathologic diagnosis showed that segments of the small intestine had hemorrhagic gangrene and varying degrees of ischemia. There was apparent fibrin thrombi in small vessels. The lamina propria was edematous with no acute inflammatory cells and sparse chronic inflammatory cells.

Post-operatively, work up for vasculitis was started but due to financial constraints, only complement and antinuclear antibody titers were done. Serum complement fraction was normal, 1240 mg/ L (normal, 938- 1493). Antinuclear antibody (ANA) and anti neutrophil cytoplasmic antibody were negative. She was discharged improved 6 days after operation.

Further work-up for vasculitis was done in the outpatient clinic. Coagulation studies which included activated partial thromboplastin time (aPTT), kaolin clotting time (KCT), dilute Russell's viper venom time (dRVVT) were all normal. Protein C, Protein S and Antithrombin III to rule out other disease conditions that could cause thrombosis were all within normal limits. Her **prothrombin** time (PT) was however persistently prolonged, INR range: 1.3- 1.64. Her anti-cardiolipin antibody (aCL) of the IgG isotype measured by a standardized ELISA was present in high titers, 64.88 U/ml. This determination was done 2 weeks after her discharge from the hospital. At this time her repeat white blood count was normal, 8.7 x 10^9/L and erythrocyte sedimentation rate was also normal, 9 mm/hr. A repeat aCL was requested 14 weeks after the onset of symptoms and showed persistence in low to moderate titers at 24 U/ml. Viral serology which included HBsAg, anti HCV and AntiHAV IgM were all non reactive. Blood and peritoneal fluid cultures turned out negative for growth.

This patient was diagnosed as having APS based on the findings of thrombosis in the small intestinal vessels, associated with elevated titers of circulating antiphospholipid antibody, in this case, the aCL, and by excluding other congenital or acquired thrombophilic conditions. In the early stages of her disease, no evidence of a systemic autoimmune syndrome was found. The disease was therefore labeled as primary.

The patient was treated with low molecular weight heparin for 2 weeks and then placed on warfarin prophylaxis for six months to maintain the international normalized ratio (INR) between 2.0- 3.0. Four months after discharge, her repeat aCL was normal, 12.64 U/ml. No further evidence of vascular thrombosis was seen in the 3-year follow up.

Discussion

APS is defined by the association of laboratory evidence of antibodies against phospholipids (aPL) and arterial or venous thrombosis. (Table 1) With the exception of pregnancy morbidity, the recently revised criteria for adults are currently also used for pediatric patients, but there is still no validation of these criteria in children.[1,7]

Table 1. Revised Criteria for the Classification of Antiphospholipid Syndrome (APS), 2004

Clinical Criteria	Laboratory Criteria
1.Vascular thrombosis: one or more clinical episodes of arterial or venous or small vessel thrombosis, in any tissue or organ. Thrombosis confirmed by imaging or Doppler studies or histopathology. For histopathologic confirmation, thrombosis should be present without significant inflammation in the vessel wall	1. Anticardiolipin antibody (aCL) of IgG and/or IgM isotype present in medium or high titer (above 40G phospholipids units or M phospholipids units or above the 99th percentile),on two or more occasions at least 12 weeks apart, measured by a standardized ELISA
2. Pregnancy morbidity (not applicable in the pediatric age group)	2. Lupus anticoagulant (LA) present in plasma on two or more occasions at least 12 weeks apart
	3. Anti-beta 2 glycoprotein 1 antibody of IgG or IgM isotype, present in serum or plasma, on two or more occasions, at least 12 weeks apart, measured by standard ELISA.

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

It is increasingly recognized in pediatrics as the most common acquired hypercoagulation state of autoimmune etiology.[8] Thrombotic events reported were very diverse and could include arteries and veins at any level of the vascular tree in various organ systems. The most common presentation in the pediatric age group was deep venous thrombosis in the lower extremities, followed by cerebrovascular disease in the form of a stroke. The data were comparable to those reported in the adult population.[5]

APS presenting with intestinal involvement is relatively rare in both the adult and pediatric age group. In the European phospholipid cohort which included a 5 month old patient, gastrointestinal manifestations were recorded in only 1.5% of 1000 identified APS cases.[6] In the recently published international registry of 121 identified pediatric APS, only one patient, representing 0.8% of cases with intestinal involvement in the form of mixed mesenteric artery and venous thrombosis, was registered.[5] The true incidence of intestinal ischemia and infarction may be underestimated because of lack of awareness that APS may present with intestinal involvement or that intestinal complications may occur in patients with APS.

The patient presented by the author is the first locally reported case of intestinal ischemia due to APS in the pediatric age group. Being much older than the similarly reported cases in the literature, she shared many clinical features with those reported in the adult population[6]. Abdominal pain was a major presenting complaint. Other clinical manifestations present were vomiting, gastrointestinal hemorrhage, and abdominal distention due to ascites. In this patient, the final common pathway, just like in majority of patients with APS presenting with intestinal ischemia, was bowel infarction. When infarction occurred, the patient developed peritoneal signs, hemodynamic instability and signs of sepsis. Her previous history of a stroke mirrors the relatively high percentage (30%) of previous thrombotic events in adult patients with APS who presented with intestinal complications in the literature.[6]

The presence of aPL is a very important serologic finding in APS.[1] The aPL are a heterogeneous group of antibodies. (Table 2) The most commonly detected groups are lupus anticoagulant (LA), anticardiolipin antibodies (aCL) and anti-B2-glycoprotein (aB2-GP1).

There is no definitive association between specific clinical manifestations and a particular group of aPL such that it is mandatory to test for these aPL because patients may be negative in one test but may be positive according to another. In general, aCL is more sensitive. The specificity of aCL for APS increases with titer and is higher for the IgG than for the IgM and IgA isotypes.[1,9] The high titers of aCL in this patient is comparable to the findings in the large cohort of pediatric patients where the presence of aCL was detected in 81% of the population studied.[1]

Table 2. Diagnostic Tests for APS

Coagulation assays detecting LA	aPTT, dRVVT, KCT, TTIT,* prothrombin time
Enzyme-linked immunosorbent assays for aCL	IgM, IgG, B2 GP1**

* aPTT, activated partial thromboplastin time; KCT, kaolin clotting time; dRVVT, dilute Russell's viper venom time; TTIT, tissue thromboplastin inhibition test

** a phospholipid binding protein

The significance of the elevated titers of aPL in the pediatric age group was discussed in many articles. Although there is a strong association between aPL and thrombotic complications, the mechanisms responsible for thrombosis in patients with APS have not been fully understood. Many hypotheses have been offered to explain how aPL antibody triggers or is associated with thrombosis. One of the leading hypothesis is that these antibodies have the ability to induce tissue factor in endothelial cells and monocytes, induce platelet aggregation and endothelial cell adhesion.[10] Studies in animals indicate that these antibodies 'mimic' viral and bacterial peptides to effect the above actions and that the necessary intermediate event is complement activation.[1,10,11]

Many patients with elevated aPL never experience thrombosis. Low titer aCL and aB2-GP1 antibodies have been reported in 11% and 7% of healthy children, respectively.[12] It is believed that a 'second hit' may be necessary for thrombosis to occur. A second hit could refer to predisposing factors that would increase the risk of thrombosis in aPL-positive patients. A study among adults found that 50% of patients with acute thrombosis had coincident risk factors for thrombosis.[13]

In the review of available literature, predisposing conditions for intestinal ischemia include the presence of prothrombotic risk factors such as hypertension, dyslipidemia, diabetes mellitus, atherosclerosis, smoking, and use of contraceptives.[14] These factors are not applicable or have little impact in the pediatric population and because of this, children and adolescents are seen as 'clean samples' to assess the clinical relevance of aPL. It can then be suggested that in the pediatric population, the finding of high titers of aCL in association with thrombosis have a higher sensitivity and specificity.

Precipitating factors identified for the development of intestinal ischemia were infections, neoplasms and trauma. Among these three, only acquired infection may be possible in this young patient as she presented with a history of urinary tract infection, although blood, urine and peritoneal fluid cultures were negative for any growth and viral serology titers were all non reactive. Indeed, there is an increased incidence of infection-induced antibodies in the pediatric age group compared to adults.[8] Antiphospholipid antibodies have been described in patients with a broad range of infections including hepatitis, malaria, acute varicella zoster, and human immunodeficiency virus 1. In these cases, antiphospholipid antibodies do not persist when the disease becomes inactive.

The main histologic finding showing mucosal infarction and ischemic changes with minute thrombi in small vessels

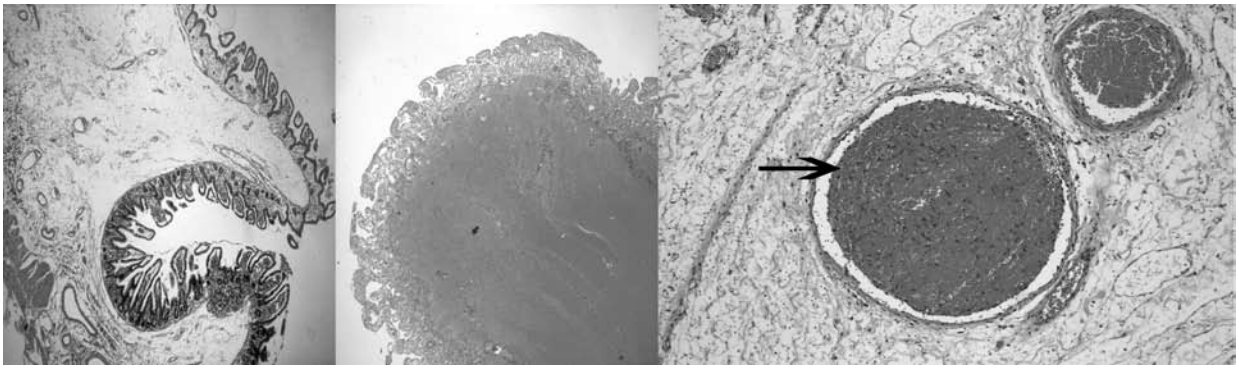

Figure 1. Sections from the small intestine show varying degrees of ischemia, with frank hemorrhagic infarction. There is apparent fibrin thrombi within small vessels and only few chronic inflammatory cells.

was comparable to those found among adults with intestinal involvement except that the presence of microthombosis was reported more frequently among patients with catastrophic APS.[6] (Figure 1)

In the treatment of patients with aPL-related thrombosis, there is still no consensus on the approach to prevent future thrombotic events. The duration and intensity of antithrombotic therapy are not yet clearly established. Some authors suggest that it should be continued until aPL are present, whereas others believe that life-long prophylaxis is needed.[15,16] Only a few data are available on the recurrence rate of thrombosis in pediatric patients with APS. There are several issues that need to be addressed in this age group. Warfarin dose is age and weight dependent and would require monitoring because of changing requirements.[17] Long term anticoagulation may expose them to a high risk of bleeding during sports or prolonged menstruation in the case of female adolescents. Many experts at present adapt a policy to perform moderate intensity anticoagulation therapy (target INR, 2.0- 3.0) in children who had an aPL-related thrombotic event, just like in this case as this has not been associated with recurrence of thrombosis or bleeding.[18,19,20,21,22]

The outcome of primary APS should be monitored in this patient because the relationship of primary APS and SLE is still unclear. In recent years, some cases of primary APS that evolved into SLE have been reported.[23] The percentage of progression to SLE among pediatric patients with primary APS observed in one study was 21.4%.[24] Another study reported that a significant proportion of children who present with primary APS may progress to SLE between 6 months to 14 months after its initial presentation.[25] The total follow up period for this case report is 3 years and to date, there was no progression to SLE or lupus-like syndrome documented.

Lastly, genetic factors are thought to play a role in the susceptibility of an individual to develop symptoms of APS. This patient had two close relatives diagnosed to have "pancreatitis". The possibility of a familial occurrence of APS is an attractive thought that warrants further investigation in the subsequent follow up of this patient. Just like many polygenic autoimmune diseases, associations with human leukocyte antigen have been reported.[26] Various studies suggest a familial occurrence of aCL antibodies and LA with or without clinical evidence of APS. This familial tendency can be genetically determined since APS, aCL and LA occur in families carrying haplotypes which contain HLA-DR4, -DR7, and –DRw53.[27] Genetic studies of beta 2-glycoprotein-1 (GP1) polymorphisms have been determined and valine/leucine polymorphisms could be a genetic risk for having anti-beta(2)-GP1 antibodies and APS. However, larger cohort studies would be needed to better understand these genes that might be involved in APS because antigen specificity of aPL and the pathophysiology of APS are highly heterogenous and multifactorial.[28]

This case report described the clinical manifestations and laboratory findings in an adolescent female with jejunal ischemia due to APS. It aims to increase the awareness of pediatricians and other clinicians of the need to screen for this syndrome in all cases of mesenteric thrombosis or colitis for which there is no alternative explanation. This is particularly important in the presence of recurrent manifestations. Systematic screening is also recommended for all APS patients complaining of abdominal pain. Early appropriate intervention may prevent the need for surgical exploration and may be instrumental in avoiding the disastrous consequences of bowel infarction.

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