CASE REPORT

Antiphospholipid Syndrome Complicating Pneumococcal Meningitis

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Background: Antiphospholipid syndrome is a multisystem auto-immune disorder characterized by arterial or venous thrombosis in children. **Case characteristics:** 11-year-old child with pneumococcal meningitis also had cerebral sinus vein thrombosis and pulmonary artery segmental thrombosis. **Observation:** Pro-thrombotic evaluation showed positive lupus anticoagulant at baseline and after 12 weeks. Investigations for lupus were negative at admission and after one year of follow-up. **Message**: Antiphospholipid syndrome is a possibility even in thrombosis occurring in the setting of meningitis.

Keywords: *Antiphospholipid antibodies (APLA), Cerebral thrombosis, Infection*.

Antiphospholipid syndrome (APS) is a multisystem auto-immune disorder characterized by arterial or venous thrombosis in children [1]. APS is commonly associated with an underlying systemic lupus erythematosus (SLE) [1]. Many bacterial and viral infections also can trigger anti-phospholipid antibodies [2]. We report a young girl with pneumococcal meningitis complicated by APS without underlying SLE.

CASE REPORT

An 11-year-old developmentally normal girl child referred to our hospital for complaints of fever for 10 days, headache and vomiting for 7 days and altered sensorium for 2 days. At admission, her Glasgow Coma Scale (GCS) was 11/15, she had photophobia, mild neck stiffness and early papilledema on fundus examination. Hence, diagnosis of meningitis with raised intracranial tension was considered at admission. Cerebrospinal fluid study was suggestive of pyogenic meningitis; latex agglutination test for pneumococcus was positive. Contrast enhanced computed tomography (CT) of brain showed filling defects in bilateral transverse sinuses and part of superior sagittal sinus with possible cerebral sinus venous thrombosis; magnetic resonance imaging (MRI) of brain confirmed the same. She was managed with ceftriaxone, low-molecular weight heparin, and anti-cerebral edema measures, including 3% saline infusion. She improved gradually but on day 5 of admission developed second spike of fever, tachypnea with intercostal retractions. Chest *X*-ray showed left lower zone consolidation with pleural effusion. In the view of purulent pleural aspirate, intra venous cloxacillin was added to cover for staphylococcus infection and intercostal drainage tube was inserted. Child developed multiple abscesses at intravenous cannulas sites requiring incision and drainage. Blood culture, pleural fluid culture, urine culture and pus culture were sterile. In the view of persistent high grade fever even after adequate duration of initial antibiotics, possibilities of resistant pneumococcal infection was considered; antibiotic was changed to meropenam and vancomycin. Child improved gradually and received antibiotics totally for 21 days in the view of empyema.

Child required two blood transfusion (Packed Red Blood Cells 10 mL/kg) for anemia during the hospital stay. As Direct Coomb test (DCT) was positive, the fall in hemoglobin was considered secondary to hemolysis and only saline-washed red blood cells used for transfusion. In the view of prolonged Activated partial thromboplastin time (aPTT), child was evaluated for APS. Lupus anticoagulant was positive by Dilute Russell's Viper Venom (DRVV) and anticardiolipin (Acl), anti-β2 glycoprotein-I antibodies were not detectable. Though the initial platelet count was low normal at admission (160×10^3 /L), the subsequent counts were within the normal range throughout the hospital stay and during follow-up. Other investigations for inherited thrombophilia could not be tested due to financial constraints. While screening for other sites of thrombosis, ultrasound Doppler of lower extremities did not reveal any thrombosis. CT angiogram of chest showed right descending pulmonary artery segment partial thrombosis. Switch over to warfarin was done by overlap manner. Aspirin was added along with warfarin and child was

discharged home without any neurological morbidity. Lupus anticoagulant after 12 weeks was positive and warfarin dose was titrated with the target of 2-3 international normalized ratios (INR). Repeat MR venogram after one year of anticoagulation therapy showed partial recanalization of superior sagittal sinus and right transverse sinus. Investigations for lupus (ANA and dsDNA) were negative at admission and even after one year of follow-up. Child was receiving oral anti-coagulation and doing well on regular follow-up.

TABLE I PATIENT INVESTIGATIONS

Investigation	*Patient Value*
Prothrombin time (PT)	13.4 sec (12 - 18 sec)
International normalized ratio (INR)	1.24 (1 - 1.5)
Activated partial thromboplastin time (aPTT)	45.1 sec (29.0 - 35.0 sec)
Antinuclear antibody (ANA)	Negative
D-dimer test	Positive
ds DNA	Negative
Direct coombs test (DCT)	1+
Sickling test	Negative
Hb electrophoresis	Normal
Mycoplasma IgM antibodies	Negative
HIV serology	Negative
Urea	36 mg/dL
Creatinine	0.7 mg/dL
Aspartate aminotransferase (AST)	76 IU/L
Alanine aminotransferase (ALT)	54 IU/L
Alkaline phosphatase (ALP)	148 IU/L
Gamma –glutamyl transferase (GGT)	28 IU/L
Serum total protein (STP)	6.6 gm/dL
Albumin	3.8 gm/dL
Total bilirubin	0.8 mg/dL

DISCUSSION

Antiphospholipid syndrome (APS) is the most common autoimmune thrombotic condition in children, with a mean age of diagnosis of 10 years [1]. The diagnosis of APS is based on one clinical event thrombosis or recurrent miscarriages, and the presence of lupus anticoagulant (LA), anticardiolipin (Acl) antibody, anti-β2 glycoprotein-I antibody in the plasma on two or more occasions at least 12 weeks apart [3]. Systemic autoimmune diseases, especially SLE, can be associated with APS. Many infections also have been found to be associated with antiphospholipid antibodies (aPL). Parvovirus B19, cytomegalovirus, varicella-zoster virus, HIV, streptococcal and staphylococcal infections, gram-negative bacteria and *Mycoplasma pneumoniae* are the most common infections associated with APS [2]. The proposed mechanisms are molecular mimicry and various infectious agents acting as super-antigens [4].

APS can involve any part of vasculature and the presence of lupus anticoagulant is strongly associated with thrombotic manifestations as compared to other antibodies [5]. The most common thrombotic event in children is deep vein thrombosis in the lower extremities followed by cerebral ischemic stroke and cerebral sinus vein thrombosis (CSVT) [1]. Though cerebrovascular disease is present in 32% of the children at the time of diagnosis of APS, mixed arterial and venous thrombosis as seen in our case is observed only in 2% of children [1]. CSVT is associated with a mortality of 3%-12% and neurological sequelae of 62% in survivors [6].

A recurrence rate of 29% has been described in pediatric APS and 21% of children developed SLE or lupus like syndrome during follow up [7]. Multiple transfusion requirements in our child can be attributed to mild Autoimmune hemolytic anemia (AIHA) in view of positive direct comb test (DCT 1+). The proposed mechanism for AIHA is triggering of a misdirected humoral response against one or more red blood cell surface antigens by pneumococcal infection [8]. As renal parameters, platelet counts and peripheral smear were normal throughout the admission, we did not consider HUS or thrombotic thrombocytopenic purpura (TTP) as the differential diagnosis in our case. All hemolytic features were resolved after the recovery from infection and child did not require any further transfusion support or immunosuppressive therapy during follow up.

Combined presentation of primary APS with AIHA is rare and only one case reported earlier [9]. Though meningitis *per se* can cause CSVT, the presence of right pulmonary artery thrombosis and positive lupus anti-coagulant even after 12 weeks confirmed the diagnosis of APS in our child. Pediatricians need to be aware that possibility of APS induced by pyogenic infection remains a distinct possibility in children having thrombotic events in such a setting.

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