Childhood Lupus with Microangiopathic Antiphospholipid Syndrome and Pulmonary Hemorrhage

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Background: Concurrent thrombotic and hemorrhagic manifestations are uncommon in patients with Antiphospholipid Syndrome. **Case characteristics:** A 10-year-old girl with fever, edema, rash and joint pains, who later developed deep venous thrombosis (DVT), stroke, thrombotic microangiopathic hemolytic anemia and pulmonary hemorrhage. Investigations confirmed Antiphospholipid syndrome associated with systemic lupus erythematosus. **Outcome:** She went into complete remission with intravenous immunoglobulins, plasmapheresis, immunosuppression and anticoagulation. **Message:** Thrombotic microangiopathic hemolytic anemia and anti-phospholipid syndrome can be the presenting manifestations of systemic lupus erythematosus..

Keywords: *Anti-phospholipid syndrome, Systemic lupus erythematosus, Thrombosis.*

Antiphospholipid syndrome (APS) is an acquired thrombophilic disorder characterized by presence of antibodies against a variety of phospholipids (PL) and PL-binding proteins, and uncommonly presents as Thrombotic microangiopathic hemolytic anemia (TMHA) [1,2]. Less than 1% patients of APS develop multiple organ thromboses and failure, defined as Catastrophic APS (CAPS) which has a mortality rate of nearly 50% despite treatment. Here we report a case of Systemic Lupus Erythematosus (SLE) with APS and TMHA in a child, who subsequently developed CAPS with multiorgan involvement and pulmonary hemorrhage, successfully treated with plasma exchange and intravenous immunoglobulin, (IVIg) along with immunosuppressive drugs and anticoagulants.

CASE REPORT

A 10-year-old girl presented with three weeks history of low grade fever, edema, rash over both lower limbs and polyarthralgia. She had pallor, anasarca, left sided subconjunctival hemorrhage, oral ulcers, livedo reticularis and purpura over lower limbs, bilateral pleural effusion, and ascites. Her initial investigations are summarized in ***Table* I**. Urine examination showed proteinuria (3+) with active urinary sediments. In view of multiorgan involvement, we suspected underlying connective tissue disorder. Serum Complement levels were low (C3 and C4 18.7 and 5.8 IU, respectively). Anti-nuclear antibodies (1:80) and anti double stranded DNA (>200 IU/mL) antibodies were positive. She was diagnosed as childhood lupus syndrome. Renal biopsy was not done as parents refused consent. She was given induction therapy with steroids and parenteral cyclophosphamide.

Next day, she developed deep vein thrombosis (DVT) of right lower limb, confirmed by Doppler Anti-cardiolipin antibodies (ACA) IgG and IgM titers were >300 GPL units/mL and 137 MPL units/mL, respectively with high Lupus anticoagulant activity (LA) (1:80 titer). Diagnosis of APS secondary to SLE was made. She was started on heparin, followed by oral warfarin. Rheumatoid factor and cryoglobulin levels were negative. She had right sided focal seizure involving face and upper limb. Magnetic resonance imaging (MRI) of brain showed multiple acute infarcts in bilateral frontal, parietal and occipital regions. She also had progressively worsening anemia with reticulocytosis, thrombocytopenia, azotemia, and elevated lactate dehydrogenase level (***Table* I**). Peripheral blood smear showed fair number of fragmented red blood cells, suggestive of associated TMHA. Direct and Indirect Coomb's tests were negative. Coagulation profile and D-dimer levels were normal.

Subsequently she developed sudden onset breathlessness, cough, hemoptysis and respiratory failure requiring mechanical ventilation. Chest radiograph showed bilateral, diffuse alveolar opacities suggestive of pulmonary hemorrhage. Echocardiography was normal. She received six sessions of plasmapheresis along with IVIg. She progressively improved, both clinically and biochemically. Chest radiograph normalized after three

days. After two weeks, her neurological status was normal, renal functions stabilized, and thrombocytopenia and microangiopathic hemolytic anemia resolved. Repeat tests after 12 weeks showed high titers of both ACA and LA. She was later switched to low dose prednisolone and Mycophenolate mofetil maintenance therapy, and was continued on oral anticoagulants.

DISCUSSION

Our patient of SLE had concurrent thrombotic and hemorrhagic manifestations, and was successfully treated with Immunosuppressive drugs, plasmapheresis and IVIg. About 30% to 40% of SLE patients have anti-phosphalipid antibodies, but only about 10% have APS, and less than 1% of APS patients progress to CAPS. Mmanifestations of APS can range from asymptomatic to life threatening multiorgan failure. DVT of lower extremities was observed in 29% to 55% of cases of APS in various studies, and more than half of the patients with symptomatic DVT had asymptomatic pulmonary embolism. Espinosa, *et al.* [3] in their study of 47 episodes of TMHA with APS (in 46 patients), reported CAPS in 23%. Nesher, *et al.* [4] reviewed 28 patients with SLE and TMHA; tests for LA or ACA were positive in 5 out of 8 patients. Prevalence of diffuse alveolar hemorrhage (DAH) in European patient cohort study of 1000 patients with APS was <1% [2]. Asherson, *et al.* [5] reported 6% patients of CAPS with DAH. Elazary, *et al.* [6] reported pulmonary hemorrhage in 13 out of 63 patients of APS, and observed that these patients were more likely to have mitral valve disease, skin disease, central nervous system (CNS) involvement, and higher titer of anti-phospholipid antibodies than other APS patients. Our patient had pulmonary hemorrhage during first attack itself and also had CNS and skin involvement.

TABLE I LABORATORY INVESTIGATIONS IN CASE PRESENTED

Parameter	*Day-1 of admission*	*Day-6 of admission*
Hemoglobin (g/dL)	6.9	4.7
Total leukocyte count (× 103 / mm3)	3.0	4.0
Platelet count (× 103 /mm3)	72	30
Corrected reticulocyte count (%)	2.0	5.0
Blood urea nitrogen (mg/dL)	24	84
Serum creatinine (mg/dL)	0.96	2.6
Sodium (mmol/l)	136	133
Potassium (mmol/l)	3.5	4.6
Corrected calcium (mg/dL)	8.6	8.1
Phosphorus (mg/dL)	4.5	5.8
Total bilirubin (mg/dL)	0.3	3.0
SGPT (IU/L)	18	22
Uric acid (mg/dL)	5.4	6.5
Lactate dehydrogenase (IU/L)	450	1900

Differential diagnosis of TMHA includes hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, malignant hypertension and disseminated intravascular coagulation [3]. Systemic endothelial cell damage leading to widespread microvascular thrombosis appears to be a central phenomenon in the pathogenesis of all TMHA syndromes. Treatment of CAPS associated TMHA includes anticoagulation therapy, steroids, plasma-pharesis and IVIg [8]. Most patients receive a combination of these therapies [3]. Rituximab has been tried in few refractory cases [9].

We conclude that TMHA is a rare complication in patients with APS, and can be the first clinical manifestation of this syndrome. Early diagnosis and aggressive institution of treatment is the key to successful outcome.

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