IJMS
Vol 37, No 1, March 2012

Case Report

Thrombolytic Therapy for Cerebral Vein Thrombosis in Antiphospholipid Syndrome Secondary to Systemic Lupus Erythematosus

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Abstract

A 20-year-old woman was admitted to a Gynecology Hospital in her 6th month of pregnancy for high blood pressure and tonic-clonic seizure. Primary diagnosis was eclampsia, and for that reason she underwent cesarean section. She also had headache on frontal and parietal areas without nausea or vomiting. There was not a focal neurological sign. Rheumatology consultation was requested. Systemic lupus erythematosus and secondary antiphospholipid (APS) was confirmed. The patient had headache that continued several days after cesarean section, therefore, brain magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) were performed, and cerebral vein thrombosis was documented. Distal segment of right lateral sinus and sigmoid sinus were not appeared in brain MRV. Abnormal hypersignal intensity of right lateral sinus/coronal T2 was detected. Thrombolytic therapy with 20 mg tissue plasminogen activator on right sigmoid and transverse sinus was performed by an interventional neurologist. After this procedure, the patient's headache healed and she was discharged in a good condition.

Iran J Med Sci 2012; 37(1): 58-61.

Keywords • Systemic lupus erythematosus • antiphospholipid syndrome • venous thrombosis • tissue plasminogen activator

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Received: 18 July 2011
Revised: 6 August 2011
Accepted: 11 September 2011

Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease. The disease has two forms including a primary and a secondary. The primary form is an isolated diagnosis, and the secondary form is associated with lupus or other diseases like rheumatoid arthritis.

The correct diagnosis of the disease requires one clinical criterion such as thrombosis or abortion, and a positive moderate to high serum titer for anticardiolipin or Antiβ2glycoprotein. About 60 to 80% of patients with APS are women. Moreover, 10% of first-stroke victims, especially those who are young, and up to 21% of women with three or more consecutive fetal losses have APS.[1]

APS is a multisystem disease, and affects all organ systems. The most common manifestations are venous or arterial thrombosis and recurrent pregnancy losses. Venous thrombosis usually presents as a deep vein thrombosis. Other sites for venous thrombosis are hepatic (Budd-Chiari syndrome), brain and upper extremities veins. Arterial thrombosis is similar to other causes of thrombosis, except for the recurrent feature and unusual locations.[2]

Pregnancy morbidities in APS are abortion or fetal death, delayed intrauterine growth, Hemolysis ,elevated liver enzymes and low platelet count's (HELLP's) syndrome, oligohydramnios, pre-eclampsia, and uteroplacental failure. APS has many neurologic manifestations such as transient ischemic attack, stroke, chorea, multiple infarctions, dementia, transverse myelitis, seizures, migraine, multiple infarction, dementia, transverse myelitis, seizures, migraine, and cerebral pseudotumor.

Other clinical findings in APS syndrome are livedo reticularis, skin ulcers, superficial thrombophlebitis, gangrene vegetation of cardiac valves, non-bacterial thrombotic endocarditis (Libman-Sacks), renal artery or vein thrombosis, systemic and pulmonary hypertension.[3] Immunoglobulin G (IgG) or IgM anticardiolipin, Anti-β2glycoprotein I or lupus anticoagulant are found in patients with APS. Serum Antinuclear antibody (ANA) and anti-ds DNA are positive in 45% of patients with APS. Mild to moderate thrombocytopenia (more than 50000/mm^3) is common.[4]

Case Description

A 20-year-old woman admitted in a Gynecology Hospital in her 6th month of pregnancy because of high blood pressure. She was in her first pregnancy. Her vital signs were:

Blood pressure (BP)=180/110 mmHg, pulse rate (PR)=96 beats/min, respiratory rate (RR)=20/min, and body temperature (BT)=37°C.

One hour after admission, she suffered a tonic-clonic seizure. Abdominal sonography showed intrauterine growth retardation (IUGR), and brain CT-scan was normal. The primary diagnosis was eclampsia, but her uric acid level was 4.2 mg/dl. Urine analysis was normal, except for mild proteinuria. Edema was not seen in the patient.

Cesarean section (CS) was performed in the Gynecology Ward. Fetus morphology was normal, but died after one day. Further evaluation of the patient revealed arthritis on metacarpophalangeal (MCP) joints and erosion on soft palate. The heart, lung and abdomen were normal on physical examination, but she had epigastric pain. She also had headache on frontal and parietal areas without nausea or vomiting.

Ophthalmoscopic examination of her retina revealed minor papillary edema without bleeding .There was no focal neurological signs. Rheumatology consultation recommended the evaluation of lupus and APS.

Results of laboratory data were as follow:

White blood cells (WBC)=4000 count/mm^3, Hemoglobin (Hb)=11.5 mg/dl, Platelets=112000 count/mm^3, mean corpuscular volume (MCV)=80 fL, blood urea nitrogen (BUN)=24 mg/dl, creatinine (Cr=1) mg/dl, urine analysis; protein: ++, blood: +, and cast: negative, urine protein/24 hrs: 350 mg, ANA: 10 (up to 1), anti-dsDNA: 12 (up to 1.2), complement 3 (C3), C4, CH50: lower than normal, anticardiolipin (IgG): 89 (up to 15), lupus anticoagulant: positive, antiβ2glycoprotein was negative.

The erythrocyte sedimentation rate (ESR) and c- reactive protein (CRP) tests were done and the values were 35 mm/h and 2+respectively.

The patient had headache that continued several days after CS. It was very severe and resistant to routine medications, so magnetic resonance imaging (MRI) and magnetic resonance venography (MRV) were planned.

Imaging Findings

White and gray matter, cerebral ventricles and brain stem were normal.

Distal segment of right lateral sinus and sigmoid sinus were not appeared in brain MRV (figure 1).

Abnormal hypersignal intensity of right lateral sinus/coronal T2 was detected. White and gray matter signal, cerebral ventricles and brain stem were normal (figure 2).

The patient was diagnosed as SLE with secondary APS.

Because of refractoriness of the headache to routine medications, thrombolytic therapy with 20 mg tissue plasminogen activator (t-PA) on right sigmoid sinus and transverse sinus was performed by an interventional neurologist seven weeks after she was first hospitalized.

After this procedure the patient's headache improved, and she was discharged from the Hospital in a good condition. She was then prescribed 7.5 mg prednisolone, 400 mg hydroxychloroquine, 80 mg aspirin, and 5mg warfarin. Anti coagulation therapy with warfarin was prescribed after thrombolytic therapy and has continued ever since. Her international normalized ratio (INR) has been maintained between 2.5-3. She has been visited by a rheumatologist every month, and has not any problem of the nervous system.

Duration of anticoagulation therapy is controversial and in some papers lifelong anticoagulation therapy is recommended.

Discussion

Lupus-induced APS is a major risk factor for thrombosis and abortion during pregnancy. Co-morbid illnesses like pregnancy-induced hypertension (PIH) are also common.[5]

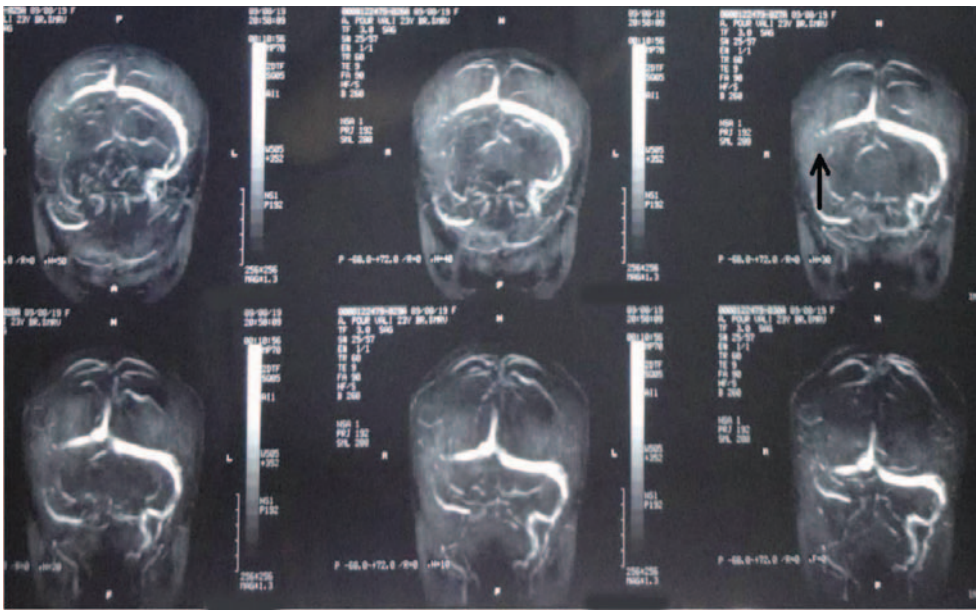

Figure 1: Brain MRV: Distal segment of right lateral sinus and sigmoid sinus are not appearent.

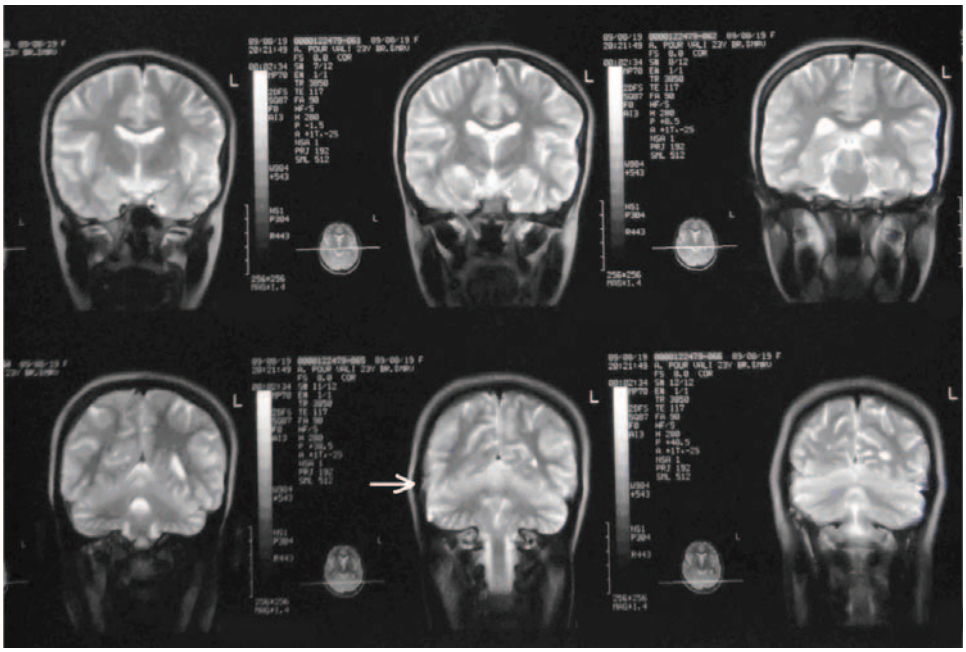

Figure 2: Brain MRI: Abnormal hypersignal intensity of right lateral sinus/coronal T2.

Venous thrombosis is more common than arterial thrombosis in the APS.[6] The most common site of thrombosis is calf veins, but renal and hepatic veins, and retinal and cerebral sinuses may be involved. The most common site of arterial thrombosis is the cerebral vessels, but in coronary, renal and mesenteric arteries have also been noted.

Brey et al. evaluated the presence of lupus anticoagulants (LAs) and anticardiolipin in 160 cases and 340 controls. After adjustment for potential confounders, the relative odds of stroke for women with an anticardiolipin of any isotype or a lupus anticoagulants was 1.87 (95% CI: 1.2 to 2.8).[7]

Cerebral vein thrombosis (CVT) is more common in women than in men (Female to male ratio: 3 to 1.[8] This is related to pregnancy, puerperium and use of oral contraceptive pills (OCP).[9] The main risk factors for CVT include prethrombotic conditions such as protein C and S deficiency, factor V Leiden, prothrombin and methylene tetrahydrofolate reductase mutation, oral contraceptive pills, pregnancy, malignancy, infection, and head injury.

Three major signs and symptoms of CVT are isolated intracranial hypertension (characterized by headache, vomiting and papillary

edema), focal syndromes such as seizure and focal neurological deficits, and encephalopathy characterized by stupor and coma.[10]

Headache is the most common symptom of CVT. It is more common in females than in males. Headache onset is gradual and usually localized. The site of headache is not closely related to the localization of the involved sinuses.[11] Sometimes headache is accompanied by aura-like migraine headache. The cornerstone of APS treatment is anticoagulation with heparin or warfarin. Currently, new generations of anticoagulants like pradaxa and xarelto are available as well. Alternative agents, especially in catastrophic conditions are prostacyclins, glucocorticoids, rituximab, and thrombolytic drugs like streptokinase or tissue plasminogen activator inhibitor.[12]

Tissue plasminogen activator inhibitor is a thrombolytic agent that was approved by FDA for the treatment of ischemic stroke. It binds to fibrin in thrombotic clot, and then converts plasminogen to plasmin.

There are not randomized clinical trials comparing systemic and local thrombolytic therapies.[13]

Death (15%), and intracranial and extracranial hemorrhage are the major side effects of treatment with tissue plasminogen activator inhibitor. There are data showing that for CVT treatment local thrombolytic agents are more effective than systemic heparin anticoagulation. There are few case reports about tissue plasminogen activator inhibitor injection in the treatment of APS.[14]

Given the APS pathogenesis and presence of impaired fibrinolysin system in this disease, we will probably see some changes in treatment strategy of this syndrome in the future.[15]

Conclusion

The present case was lupus-induced secondary APS that was diagnosed first time in pregnancy. The main problem of the case was CVT. Due to early diagnosis and intervention with tissue plasminogen activator inhibitor her general condition improved and she has no major problems.

Conflict of Interest: None declared

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