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Antiphospholipid Antibody Syndrome and Protein S Deficiency: Dual Problem in Pregnancy

Umme Ruman[1], Khondker Iqbal Karim[2]

Abstract

Patient with Antiphospholipid syndrome has a poor fetal outcome. Though it has some special diagnostic criteria and therapeutic options, best treatment options are yet to specify. Inherited thrombophilias are also associated with adverse pregnancy outcomes, although the evidence is less compelling. Protein S is a vitamin K-dependent anticoagulant which plays a vital role in the regulation of coagulation. Deficiency of Protein S leads to thromboembolism and fetal loss. We present here clinical course and treatment of a woman with history with two abortion. After diagnosis of both antiphospholipid antibody and Protein S deficiency, she was treated with low dose aspirin and hydroxychloroquin. With treatment she conceived again and delivered a healthy male baby at 36 weeks. Here we are focusing on pathogenesis and treatment aspect of the disease.

Keywords: Antiphospholipid syndrome, Protein S deficiency, Recurrent miscarriage.

Introduction

Antiphospholipid antibody syndrome is an autoimmune disease. Obstetric complication is its hallmark. Main pathology is formation of antibody against cell membrane phospholipid. It insights formation of blood clots in blood vessels. Therefore, it is a hypercoagulable state. Besides causing cardiovascular events, it is also responsible for pregnancy related complications. This may be primary or secondary. Presence of antiphospholipid antibody (aPL) alone, in the absence of typical clinical complications, does not indicate a diagnosis of APS; long-term asymptomatic aPL-positive patients exist. APS with healthy persons are termed as primary APS. When diagnosed in patients with underlying autoimmune disease (usually Systemic Lupus Erythematosus, or SLE), APS is termed secondary APS; Obstetrics manifestations of APS includes recurrent foetal loss, IUGR, pre-eclampsia, postpartum maternal thrombosis. Many other systemic manifestations are also there.

Protein S deficiency is a rare inherited thrombophilia with autosomal dominant inheritance. It functions as a cofactor to facilitate the action of activated protein C on factors Va and VIIIa. Protein S deficiency is associated with increased risk of thrombosis. Mild protein S deficiency may occur in pregnancy and treatment needs consideration regarding bleeding complication. Here, we describe a case of pregnancy with both antiphospholipid antibody syndrome and Protein S deficiency with successful feto-maternal outcome.

Case Report

A 27 years old lady had two first trimester pregnancy losses (at 5 weeks and 7 weeks) without any treatment. After that she was diagnosed as a case of antiphospholipid antibody syndrome and protein-S deficiency. She had no history of any arterial venous thrombotic event.

Her lupus anticoagulant (LA) was positive. It was confirmed by DRVV (Dilute Russell Viper Venom) screen time, plasma was 47.8 seconds (normal ranged: 31.36-40.44). DRVV screen ratio was also high. Initial APTT was 62 seconds (normal range: 21.5- 32.6). INR was 3.07 which was also higher than normal therapeutic range. Serum anti phospholipid antibody (IgG) was 6.24 and Cardiolipin antibody (Ig G) 11.34 which were below cut off value. Antinuclear antibody was positive. Serum protein S was 34 % (normal range: 55-123). Plasma antithrombin activity and protein C activity was normal.

The patient was treated with low dose aspirin (75mg/day) and hydroxychloroquine (200 mg twice daily). Two months after starting medications, she conceived. Low molecular weight heparin (LMWH) was started but she developed per vaginal bleeding during 13 weeks. So, it was discontinued. After subsidence of par vaginal bleeding, LMWH was started again and she again started to bleed par vaginally. Her platelet count was 169 $x10^9$ and APTT was 52 seconds. So, we decided to withheld LMWH. Low dose aspirin and hydroxylchloroquine was continued. Her pregnancy course

1. Classified Specialist, Obstetrics and Gynaecology, CMH Bogura
2. Classified Specialist, Anaesthesiology, CMH Bogura

Corresponding Author: Lieutenant Colonel Dr. Umme Ruman, Obstetrics and Gynaecology, CMH Bogura. E-mail: rumman09umme@yahoo.com

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was uneventful. Ultrasonography of anomaly scan was normal. At 34 weeks she was given injection dexamethasone 12.5 mg in two divided doses for fetal lung maturation. Her delivery was planned on 36 completed weeks.

Low dose aspirin was stopped five days prior to surgery. She delivered a healthy male baby of 2.8 kg through caesarean section. Liquor was adequate.

She was treated with Low molecular weight heparin 40 IU /day for 7 days postoperatively started 24 hours after surgery. Hydroxychloroquine was continued. Low dose aspirin was started again. She was scheduled for follow up to Rheumatologist 1.5 month puerperium.

Discussion

APLA associated with vasocclusive events without any underlying disease process is termed the primary antiphospholipid antibody syndrome1. The clinical criteria on which diagnosis is based include evidence of thrombosis like peripheral gangrene secondary to venous arterial or small vessel thrombosis. Repeated fetal loss before 10 weeks or unexplained after 10 weeks. Investigative criteria include presence of anticardiolipin antibodies (IgG or IgM isotype in medium to high titers), Lupus anticoagulant, anticardiolipin antibody, β2-glycoprotein, prolonged aPTT (activated partial thromboplastin time), and Dilute Russell's viper venom time, kaolin clotting time, Dilute PT on 2 or more occasions 6 weeks apart 2. Obstetric complications include, unexplained fetal death or still birth, recurrent pregnancy loss- three or more spontaneous abortion with no more than one live birth, unexplained second or third trimester fetal death, severe pre-eclampsia at less than 34 weeks gestation, unexplained severe IUGR, chorea gravidarum3.

How APLA causes thrombotic events, is not fully understood. Beta 2-glycoprotein I interact with endothelial cells and activates coagulation pathways coupled with inhibition of antithrombin III, activated protein C, inhibition of fibrinolysis and interference with tissue factor and thrombin promote thrombosis[4]. Most commonly detected classes of antiphospholipid antibodies are anti beta 2 glycoprotein 1, lupus anticoagulant and anticardiolipin antibodies. Deep vein thrombosis of the legs is the most common manifestation occurring in 30 to 55 percent of patients[5]. Other mentionable manifestations include thrombocytopenia and haemolytic anaemia. Pregnancy in APLA syndrome patients presents with increased risk for fetal loss. Multiple infarctions of the placenta due to micro thrombi is a frequent finding in APLA patients, if placental infarction is extensive, it may cause severe growth retardation of the fetus leading to repeated pregnancy losses [6]. Pre-eclampsia is also commonly seen in such patients. APLA can precipitate thromboembolic events at any time of the pregnancy or during the immediate postpartum period as pregnancy is a hypercoagulable state [7]. Low-molecular-weight heparin is the anticoagulant of choice in the treatment of pregnant women with the APLA syndrome [8].

Protein S deficiency is a rare inherited thrombophilia, autosomal dominant often associated with fetal losses in pregnancy. It is seen in approximately 1 in 500 to 1 in 3,000 people. Homozygous Protein S deficiency in neonates manifests as a catastrophic and fatal thrombotic complication termed Purpura Fulminans (PF)[9].

Pregnant women with Protein S deficiency are typically heterozygous. If partner of patient has this defect too, neonates should screen to identify homozygosity. Women with genetic or acquired thrombophilia are at very high risk of antenatal and postpartum venous thromboembolism and should receive thromboprophylaxis during pregnancy and puerperium[10,11].

Subcutaneous unfractionated or low molecular weight heparins (LMWH) are the anticoagulants of choice. Heparin does not cross the placenta, and thus there is no risk of teratogenesis or fetal hemorrhage. LMWH is the drug of choice because of reduced risk of osteopenia and thrombocytopenia and good safety record for mother and fetus, and convenient once-daily dosing for prophylaxis.

Recurrent fetal loss is a well-established complication of the APLA syndrome. Inherited thrombophilias are also linked to adverse pregnancy outcomes, although the evidence is less captivating. Women with APLA and inherited thrombophilias has a twofold higher risk of first and second trimester loss and a fivefold higher risk of late third trimester loss than women without thrombophilia[12]. Consensus guidelines recommend screening women with unexplained recurrent pregnancy loss for APLA[13,14]. Testing for inherited thrombophilia is controversial. It is not routinely recommended unless the results will affect management.

Conclusion

Simultaneous presence of APLA and protein-S deficiency is rare and very challenging during pregnancy for both physicians and patients. Multidisciplinary approach should be considered involving senior obstetricians, rheumatologist, neonatologists, trained nurse for a successful outcome.

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