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Seronegative Antiphospholipid Syndrome.

Deepika M*, K Saraswathi, and R Geethalakshmi.

Department of Obstetrics and Gynecology, Sree Balaji Medical College & Hospital, Chennai, Tamil Nadu, India.

ABSTRACT

Antiphospholipid syndrome or antiphospholipid antibody syndrome (APS or APLS) is an autoimmune condition in which there is an hypercoagulable state caused by antiphospholipid antibodies. APS provokes thrombosis in both arteries and veins , pregnancy-related complications such as miscarriage, stillbirth, preterm delivery, preeclampsia & IUGR. The diagnosis of APS requires one clinical event, i.e. thrombosis or pregnancy complication, and one positive laboratory test for antibodies . There is a research on the most promising other antibodies of this heterogeneous aPL family, which includes antibodies to a zwitterionic phospholipid, namely Phosphatidylethanolamine, Phospholipid-binding plasma proteins, Phospholipid-protein complexes and Anionic phospholipids . Here is such a case with APLA NEGATIVE presenting with recurrent pregnancy loss.

Keywords: Antiphospholipid antibody, Pregnancy loss

Corresponding author

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INTRODUCTION

APS is classified as primary & secondary, depending on its association with other autoimmune disorders. Primary APS is diagnosed in patients demonstrating the clinical and laboratory criteria for the disease without any other autoimmune diseases. Secondary APS is diagnosed in patients with other autoimmune disorders, such as systemic lupus erythematosus (SLE).

Women with the clinical features of APS should be tested for all 3 antiphospholipid antibodies for the diagnosis of APS: lupus anticoagulant (LAC), anticardiolipin (aCL) antibody, and anti-beta-2glycoprotein I antibody. These antibodies predispose to clotting in vivo, predominantly by interfering with the antithrombotic role of Phospholipds. The antiphospholipid (aPL) autoantibodies binds on negatively charged PLs or moieties formed by the interaction of negatively charged PLs with other lipids, PLs, or proteins thereby provoking the clotting mechanism.

Sero negative antiphospholipid syndrome (SNAPS) was first introduced in 2003 by Hughes and Khamashta [3] to describe patients with clinical features highly suggestive of APS but with persistently negative Lupus Anticoagulant, antiCardioLipid and anti-β2 glycoprotein I (anti-β2GPI) antibodies.

CASE REPORT

27 years Mrs.R, presented to us, with a history of recurrent pregnancy losses with an obstetric code of P2L0A1, for further management. She had regular menstrual cycles since menarche till last abortion after which it was irregular, once in 45 days to 60 days. She was married since 5 years, NCM conceived spontaneously after 1 year of marriage, she was a booked and immunized case outside, and antenatal period was uneventful till around 8 month of gestation, with no history suggestive of gestational diabetes mellitus, hypertensive disorders of pregnancy, thyroid disorder. After which, an unexplained IUD happened, and it was expelled vaginally by induction. Dead born, didn't show any external congenital anomalies and weights around 1–1.5 kg. HPE of placenta showed Placental infarcts. One year after this pregnancy, she again conceived spontaneously, she was not on aspirin. This pregnancy also continued till around 8 month of gestation without any history suggestive of risk factors, after which she had unexplained IUD and it was also expelled a dead born fetus of about 1- 1.5 kg with no obvious congenital anomalies by vaginally. Placental examination was not done and there is no history suggestive of abruption placenta. She again conceived spontaneously after one year of the last pregnancy loss. She was aborted spontaneously at 60 days of amenorrhea, no histopathological evidence of the products of conception was not done. D&C done for the same. After the last pregnancy loss for the last one year her menstrual cycles was irregular with 3-4 days flow in 45-60 days cycle.

We investigate her for the pregnancy losses, she was not diabetic, hypothyroid, and normotensive, her sonographic picture doesn't reveal any abnormality in reproductive organs. Her cycles was regularized with oral contraceptive pills for 3 cycles. Her antiphospholipid profile for anticardiolipin antibodies, lupus anticoagulant and anti β2 glycoprotein were negative with an interval of 12 weeks duration in inter-pregnancy period. After discontinuation of pills, she was started on aspirin 75 mg OD even before conception and also with peri-conceptional folic acid. In the next cycle itself, she conceived spontaneously. In addition to aspirin 75 mg OD and folic acid, she was started on LMWH 40 mg OD after the appearance of fetal cardiac activity by sonography. Her first trimester triple screening test was normal, she was immunized, target scan was normal, all her interval growth scan was normal, there was no occurrence of preeclampsia, IUGR or GDM in this pregnancy too. She was monitored with coagulation profiles monthly, which was normal Prophylactic dose of steroids was given at 32 weeks. Tab. Aspirin was continued till 36 weeks and LMWH was continued till 2 days prior to surgery. In view of BOH, patient was taken up for elective LSCS at 37 weeks and delivered alive female baby of B.wt. 2.6 kg. Postoperative periods are uneventful.

DISCUSSION

Incidence

Women have been reported to account for approximately 80% of patients with APS .Among them 24% of thrombotic events have been found to occur during pregnancy or in the postpartum period. A 2015 retrospective analysis by the European Registry on Obstetric Antiphospholipid Syndrome (EUROAPS) found

very good maternal-fetal outcomes in women whose obstetric APS [OAPS] was treated.[2] The HLA-DR3 phenotypes seem to predispose to the formation of aCL antibodies and antinuclear antibodies (ANAs).

The effects mediated by the antiphospholipid antibodies are,

- They react with endothelial structures there by disturbing the balance of prostaglandin E2/thromboxane production.
- Interaction with platelet Phospholipids, leading to increased platelet aggregation.
- Dysregulation of complement activation.
- The aPLs interacts with the phosphatidylserine exposed during trophoblast syncytium formation, which increases the possibility of direct effect of these autoantibodies on placental structures.

In patients with primary APS, the presence of the 3 aCL isotypes plus LAC has been associated with a higher number of recurrent spontaneous abortions, compared with other possible combinations of aCL isotypes. (Human aCL antibodies cause placental necrosis).

The aCL antibodies bind to b2GPI, is a platelet adhesin glycoprotein and cardiolipin. Exposure of endothelial cells to anti-b2GPI antibodies leads to the inhibition of endothelial cell activation, which is indicated by decreased expression of the adhesion molecules E-selectin, intercellular adhesion molecule, and vascular cell adhesion molecule and of monocyte adhesion.

SERONEGATIVE ANTIPHOSPHOLIPID SYNDROME (SNAPS)

Patients with clinical manifestations highly suggestive of APS but persistently negative for conventional antiPhospholipids are classified as having seronegative APS. Ongoing research has revealed the existence of non-criteria antibodies proposed to be relevant to APS and that can be potentially included in the disease's classification criteria. We present a literature review on the most promising antibodies of this heterogeneous aPL family, which includes antibodies to a zwitterionic phospholipid, namely phosphatidylethanolamine, phospholipid-binding plasma proteins, phospholipid-protein complexes and anionic phospholipids other than cardiolipin.

DIAGNOSIS OF SERO NEGATIVE APS:

There is considerable evidence that IgA antiphospholipid antibody tests may be a useful diagnostic tool in APS [11].

Antibodies to domain I (DI) of β2GPI have attracted particular interest as they are strongly associated with thrombosis.[12]

CO-EXISTING AUTO IMMUNE DISORDES

Landry-Guillain-Barré-Strohl syndrome

Landry-Guillain-Barré-Strohl syndrome (LGBSS) of acute inflammatory demyelinating poly radiculoneuropathy, which is rare in pregnancy, can occur in patients with APS and lupus.

Patients usually present with progressive bilateral and symmetrical muscle weakness accompanied by mild sensory symptoms, including paresthesia, numbness, and tingling. The disease can progress to involve the respiratory muscles, resulting in respiratory failure. Two thirds of the patients have a history of viral-like infections 1-3 weeks prior to the onset of symptoms.

PERINATAL OUTCOME

The aPL antibodies are found in 10-15% of women at high risk for fetal growth restriction. Neonatal morbidity and mortality is been influenced by indicated preterm delivery for maternal severe preeclampsia or fetal growth restriction.

Neonatal lupus dermatitis, a variety of systemic and hematologic abnormalities, and isolated congenital heart block have been associated with APS and SLE.

DIAGNOSIS

CLINICAL CRITERIA

- One or more clinical episodes of arterial, venous, or small-vessel thrombosis, occurring within any tissue or organ
- One or more unexplained deaths of morphologically normal fetuses at or after first trimester.
- One or more premature births of morphologically normal fetuses at or before 34 weeks' gestation because of eclampsia or severe preeclampsia or features consistent with placental insufficiency.[6]
- Three or more consecutive, unexplained spontaneous abortions before 10 weeks' gestation, in which the maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal abnormalities are excluded.

LABORATORY CRITERIA

Criteria for laboratory testing, which are consistent with current clinical management guidelines from the American Congress of Obstetricians and Gynecologists, include the following[9,10] :

- Anticardiolipin antibodies – Anticardiolipin IgG or IgM antibodies present at moderate or high levels (ie, >40 GPL or MPL or >99th percentile) in the blood on 2 or more occasions at least 12 weeks apart
- Lupus anticoagulant - LAC detected in the blood on 2 or more occasions at least 12 weeks apart, according to the guidelines of the International Society on Thrombosis and Hemostasis[5,8]
- Anti-beta$_2$ -glycoprotein I antibodies IgG or IgM – Present in titers above the 99th percentile for normal as defined by the laboratory performing the test, on 2 or more occasions at least 12 weeks apart

The diagnosis of APS requires that the patient have at least 1 clinical criteria and 1 laboratory criteria

Antiphospholipid (aPL) antibodies are detected by conventional and specific enzyme-linked immunoassays and reported in semi quantitative terms such as negative, low positive, medium positive, or high positive.[1,4]

- LAC is detected by phospholipid (PL)-dependent clotting assays,
- The activated partial thromboplastin time (aPTT) is prolonged for aCL or anti-beta$_2$ -glycoprotein I antibodies.

TREATMENT

OBSTETRIC CARE

Patients should be counseled in all cases regarding symptoms of thrombosis and and should be educated regarding the symptoms, and examined frequently for, the signs or symptoms of thrombosis or thromboembolism, preeclampsia, or decreased fetal movement.

USG is recommended every monthly to check for the fetal well being and it can also predict the occurrence of preeclampsia in the early stages.

- Anticoagulation therapy with LOW MOLECULAR WEIGHT HEPARIN is indicated from the first trimester itself .[3,7]
- Along with that low dose of aspirin (75 mg once daily) is substituted prophylatically.
- Recently INTRAVENOUS IMMUNOGLOBULIN THERAPY is indicated.

In this patient we have started on the low dose aspirin therapy preconceptionally along with the folic acid supplementation and vitamin D supplementation.

COUNSELING

The patient should be counseled about maternal and obstetric problems, including symptoms of thromboembolism, fetal loss, severe preeclampsia, fetal growth restriction, and preterm delivery, decreased fetal movements. Consultation with specialists should be considered.

CONCLUSION

The ANTIPHOSPHOLIPID ANTIBODY should be evaluated in patients with recurrent pregnancy loss or recurrent miscarriages. If the APLA is positive the treatment should be started before the conception and to be continued till term. If the APLA is negative for all three tests and is not occurring with any other autoimmune disorders SERO negative APS should be considered and the patient should be started on Aspirin and LMWH peri-conceptionally for better fetal outcome.

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