Pregnancy-triggered antiphospholipid syndrome in a patient with multiple late miscarriages

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ABSTRACT: Antiphospholipid syndrome (APS) is a multisystemic disorder of coagulation-causing thrombosis in the arterial and venous system as well as pregnancy-related complications such as miscarriage, stillbirth, preterm delivery and pre-eclampsia. The disease is characterized by the autoimmune production of antibodies against phospholipid, a substance found in the cell membrane. We here report the case of a patient with four second trimester miscarriages, who apart from a heterozygous plasminogen activator-inhibitor-1 mutation, had no risk factors explaining her condition. In the subsequent pregnancy she was therefore put on low-molecular-weight heparin, aspirin and granulocyte colony-stimulating factor. Antiphospholipid antibodies (APL), which had been negative before gestation, increased and remained high throughout pregnancy, thus suggesting a pregnancy-induced or -aggravated APS. The patient was kept on the above-mentioned medication and delivered a healthy male baby by Caesarean section after an otherwise uneventful pregnancy. Thus, in order to diagnose and treat pregnancy-triggered APS in patients with unexplained recurrent miscarriage, screening for APL should also be performed at several time points after conception.

Key words: recurrent miscarriage / antiphospholipid antibodies / antiphospholipid syndrome / Beta2-Glycoprotein I / G-CSF

Introduction

Antiphospholipid syndrome (APS) is an autoimmune, multisystemic disorder and is diagnosed by the presence of lupus anticoagulant and anti-ardiolipin antibodies in association with venous and/or arterial thrombosis or pregnancy complications (Wilson et al., 1999). Several studies have demonstrated that the presence of antiphospholipid antibodies (APL) in pregnant women correlates positively with recurrent pregnancy loss (Cohen and Regan, 1995). So far, thrombotic events at the feto-maternal interface have been attributed to cause impaired implantation and shallow placentation in patients with APS. In turn, anticoagulant treatment during early pregnancy has been shown to significantly improve the live birth rate in women with APS (Rai et al., 1997).

In this case report, we describe a woman with four consecutive second trimester miscarriages, who was successfully treated by a novel therapeutic scheme consisting of heparin, aspirin and granulocyte colony-stimulating factor (G-CSF).

Case report

We here report the case of a 32-year-old five gravida one para, 173 cm, 70 kg woman, who presented at our institution after four second trimester miscarriages, one at 14, two at 16 and one at 22 weeks of gestation. Low-molecular-weight heparin was administered in one prior pregnancy until the 16th week of gestation and shortly after cessation of heparin administration, she spontaneously aborted. Histological analysis of the placenta revealed multiple infarctions. The fetus, however, did not show any abnormalities. The patient had no history of thromboembolism or blood clotting disorders. A laporoscopy combined with hysterectomy performed prior to conception revealed no tubal obstructions or uterine abnormalities. Ultrasound examination of uterus and ovaries revealed no abnormalities. Chromosome analysis showed a 46XX phenotype. No Factor V Leiden, prothrombin or Methylene tetrahydrofolate reductase (MTHFR) mutation could be detected. The patient was positive for heterozygous mutation of plasminogen activator-inhibitor-1 (PAI-1). The 36-year-old husband also presented no chromosomes abnormalities (46XY) and had a heterozygous mutation in the gene coding for PAI-1 (4G/5G).

His past medical history did not reveal any relevant disease. After conceiving naturally, the patient was extensively treated with low-molecular-weight heparin at three daily doses of 40 mg Enoxaparin-Natrium, 50 mg aspirin once daily, and twice weekly G-CSF (Lenograstim rHuG-CSF 13.4 million IU) and folic acid 400 μg per os.

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Laboratory tests for D-Dimeres, prothrombin-fragments, APL, anti-Xa-units and IgG, IgA and IgM directed against Beta-2-Glycoprotein I (β2-GPI) were repeated several times throughout pregnancy. Detection of cardiolipin IgM antibodies revealed normal levels (<12 IE/ml) at 5 weeks, but a surprising increase at 13 weeks of gestation (15 IE/ml). Cardiolipin IgM antibodies were then 14 IE/ml at 26 + 2 weeks of gestation, 38 IE/ml at 33 + 1 weeks and 16 IE/ml at 33 + 6 weeks. β2-GPI is an antigen associated with APL (Giannakopoulos et al., 2009). β2-GPI specific IgM antibodies (normal levels < 20 IE/ml) were slightly increased at 5 weeks (55 IE/ml) of gestation and increased more than 3-fold in the 10th week of gestation (179 IE/ml). The β2-GPI specific IgG antibodies remained increased throughout gestation (19th week: 130 IE/ml, 21st week: 100.5 IE/ml, 26th week: 107 IE/ml, 28th week: 98.2 IE/ml, 30th week: 85 IE/ml, 32nd week: 134 IE/ml, 33rd week: 109 IE/ml, 34th week: 114.4–155.1 IE/ml). However, the patient’s IgG anti-β2GPI and IgG anti-β2GPI levels remained within the normal range, and lupus anticoagulant tests produced normal results.

The course of the pregnancy was uneventful, with only minimal bleeding in the second trimester after a smear was taken, because an infection was suspected. Blood pressure was frequently measured and urine was tested for proteinuria but our patient did not present with mild pre-eclampsia-like syndrome. At 38 weeks of gestation, a healthy male baby was delivered by secondary Caesarean section due to insufficient progress during first stage of labour. Birthweight was 3080 g APGAR 9/10/10, umbilical artery (UA) pH 7.39. Postnatally, progress was uneventful with continuation of heparin treatment until 4 weeks post-partum.

Discussion

The reported case illustrates the relevance of screening for APL antibodies before and during pregnancy in cases of unexplained recurrent miscarriage, as it may become apparent throughout pregnancy. APL is defined as the persistent presence of APL in patients with recurrent venous or arterial thromboembolism or pregnancy morbidity (Giannakopoulos et al., 2009; Lim, 2009). However, antibodies relevant to the gestational outcome may not be persistent. In our patient, APL were low before she conceived, but increased during gestation leading to a rise of cardiolipin and β2-GPI antibody levels. Accordingly, Donohoe et al. (2002) observed fluctuations in APL levels in patients with APL. Topping et al. described patients that were APS negative before pregnancy and showed positive APS titres in the first trimester. As opposed to our patient, none of the patients Topping described had a persistent elevation of APS parameters throughout pregnancy. The patients who did miscarry in the study by these investigators were the ones who were diagnosed with APS before pregnancy and who showed persistent APS titres (Topping et al., 1999). Pregnancy may trigger an underlying APS, which may well be causative for the previous miscarriages of our patient. Accordingly, in a prior pregnancy, miscarriage only took place after cessation of heparin administration at 16 weeks of gestation and histological examination of the placenta revealed multiple infarctions.

Low-molecular-weight heparin and aspirin are the treatment for APL in cases of recurrent miscarriage (Lim, 2009). Our case illustrates that the administration of heparin and aspirin should not be stopped after the first trimester because APL might increase in the course of gestation. This continuation of treatment might also be beneficial for late pregnancy complications, such as pre-eclampsia and preterm labour that are also associated with APS and APL (Abrahams, 2009).

Before our patient conceived for the sixth time, the putative cause of her miscarriages was not known. On the basis of the study by Scarpellini and Sbracia (2009), who demonstrated a benefit of G-CSF treatment in women with unexplained recurrent miscarriages, we decided to administer G-CSF.

It was recently suggested that elevated IgA anti-β2GPI antibody titres may identify additional patients who have clinical features of APS but who do not meet current diagnostic criteria (Aguilar-Valenzuela et al., 2009). However, our patient showed normal levels of IgA anti-2GPI. Still, IGA anti-β2GPI should also be determined in patients with recurrent miscarriages, if other causes have been excluded.

In summary, we describe a case of recurrent miscarriages with pregnancy-triggered, or at least pregnancy-aggravated, APS. Thus, in patients with unexplained recurrent miscarriage screening for APS might be advisable not only before but also throughout pregnancy. Furthermore, this group of patients could benefit from heparin and aspirin treatment during the complete pregnancy, including childbirth.

References