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A case of a pregnant patient with antiphospholipid antibody syndrome, deep vein thrombosis, and heparin-induced thrombocytopenia who suffered an intrauterine fetal death

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Summary

Antiphospholipid antibody syndrome (APS) is an autoimmune disease caused by the persistence of antiphospholipid antibodies. Moreover, there is a significantly increased risk of pregnancy complications in women with APS. The treatment is antithrombotic therapy. However, heparin-induced thrombocytopenia (HIT) is known as a severe complication of heparin utilization. HIT is an autoimmune disease caused by anti-heparin antibodies. Nevertheless, patients with APS frequently receive heparin as treatment for thrombotic events. The authors report a case of a Japanese woman with Sjögren's syndrome (SjS) and deep vein thrombosis who became pregnant following assisted reproduction technology. However, she suffered an intrauterine fetal death associated with HIT.

Key words: Antiphospholipid antibody syndrome; Sjögren's syndrome; Heparin-induced thrombocytopenia; Intrauterine fetal death.

Introduction

Antiphospholipid antibody syndrome (APS) is a blood clotting-related disease. Pregnant women with APS have a significantly increased risk of recurrent miscarriage. Combined antithrombotic therapies, such as the use of aspirin and heparin, are used as treatments for patients with clotting defects such as APS; however, one of the serious side effects of heparin treatment includes thrombocytopenia (heparin-induced thrombocytopenia: HIT). This is a clinicopathological syndrome and the diagnosis requires a compatible clinical picture plus the detection of IgG antibodies directed against a complex of platelet factor 4 (PF4) and heparin. HIT is classified into types 1 and 2. Type 1 is not associated with heparin-dependent antibodies [1-3]. By contrast, type 2 is a complication of heparin therapy caused by heparin-bound platelet-activating antibodies that recognize PF4 [4]. In this report, the authors describe a patient who become pregnant following assisted reproduction technology with type 1 HIT caused by heparin therapy, who suffered an intrauterine fetal death (IUFD).

Case Report

The patient was a 36-year-old Japanese woman with Sjögren's syndrome (SjS). She was diagnosed with this in 2000 because she was positive for anti-SjS-related antigen A (SSA) and negative for SSB/Ro (SSA/Ro +, SSB/Ro –), but her medical condition had been stable. In 2010, she came to the present hospital because of infertility. All tests for fertility, including those for her husband's semen quality, were normal. Ovulation induction was carried out using clomiphene citrate. Her first and second pregnancies resulted in a missed abortion at nine weeks' gestation and a chemical pregnancy at the age of 32. *In vitro* fertilization (IVF) was performed when she was 34-years-old. The authors retrieved 21 oocytes and five of them were fertilized. All the embryos were cryopreserved to avoid the risk of ovarian hyperstimulation syndrome associated with fresh embryo transfer. She presented to the present hospital because of left leg pain and swelling at two weeks after the IVF attempt. She was diagnosed as having a deep vein thrombosis (DVT). Therapies with heparin (10,000 IU/day with sustained intravenous administration for seven days) and warfarin (three mg/day for six months) were started and a clot filter was installed in the inferior vena cava. Her condition then became stable.

She had a successful third pregnancy after frozen–thawed embryo transfer (ET) All five embryos were thawed and cultured for four days. Only one of them grew to the blastocyst stage and this was transferred to the patient. Drug therapy had been changed from warfarin to aspirin (100 mg/day) one month before the ET. She had been taking aspirin (100 mg daily) as therapy for the DVT. This anticoagulant treatment was changed from aspirin to heparin (5,000 IU twice daily by self-administered hypodermic injection) at nine weeks of gestation. The pregnancy progressed normally and did not reveal any fetal heart dysfunction or growth restriction at 13 weeks of gestation. However, IUFD was diagnosed at 17 weeks of gestation. The fetal and both parents' karyotypes were normal, and histological analysis of the placenta could not detect any abnormal findings. However, lupus anticoagulant, anticardiolipin, and anti-anti-antibodies a-β-d in the blood were detected twice. Therefore, she was diagnosed as having APS. A second round of IVF was carried out. After changing from aspirin to heparin

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before performing transvaginal ovarian follicle aspiration, the platelet count decreased significantly to 6.0×10^4/ml (53.5% decrease from the baseline count). Laboratory tests for HIT were performed immediately using the 4Ts pretest clinical scoring system for HIT [5]. The 4Ts score was 3 points, indicating a low risk, and anti-heparin antibodies could not be detected in the blood. IVF was carried out and the platelet count recovered quickly after cessation of heparin therapy.

Discussion

In this case, the cause of IUFD was unknown. However, the combination of APS and SjS likely contributed. SSA/Ro antibodies are considered to be responsible for neonatal lupus erythematosus, which can cause poor pregnancy outcomes. Luo *et al*. showed that APS might be the main factor to increase the risk of fetal loss in pregnant women who are SS-A/Ro positive [6]. There are only a few clinical reports of type I HIT, but tumors, pulmonary embolisms, diabetes, APS, and thromboclasis are reported as possible causes [7].

In conclusion, there are few reports on the management or helpful diagnostic criteria for treating patients with mixed collagen diseases such as SjS with serious complications. Nevertheless, further experience is required to establish the standard of care for these patients.

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