Case Report

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Potential Inherited Causes of Recurrent Prosthetic Mitral Valve Thrombosis in a Pregnant Patient Suffering from Recurrent Miscarriage

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An effective anticoagulation is critical in pregnant patients with prosthetic heart valves. Inherited disorders may interfere with the coagulation cascade and may be associated with obstetrical complications as well as with prosthetic valve-derived complications. The patient in the present case had a history of recurrent prosthetic heart valve thrombosis (PHVT) despite an effective anticoagulation. She underwent a thrombolysis with low-dose prolonged infusion of tissue-type plasminogen activator for the management of her recurrrent prosthetic valve thrombosis. The genetic testing showed homozygous mutations of methylenetetrahydrofolate reductase (MTHFR) A 1298 C and heterozygous mutations of ß-fibrinogen 455 G-A. Inherited disorders such as MTHFR A 1298 C and fibrinogen 455G/A polymorphisms may be involved in the pathogenesis of recurrent PHVT and/or pregnancy loss. **(Korean Circ J 2014;44(4):268-270)**

KEY WORDS: Pregnancy; Heart valves; Thrombophilia; Abortion, spontaneous; Thrombosis.

Introduction

Pregnancy is associated with an increased risk of thrombosis among women with mechanical prosthetic heart valves. An anticoagulation management is important for both, mother and fetus.[1)] An increased thrombogenicity in pregnancy may be associated with several factors such as inherited coagulation defects, which may result in recurrent pregnancy loss and other thromboembolic complications.[2)] Herein, we present a pregnant patient who had a history of recurrent pregnancy loss and developed recurrent prosthetic heart valve thrombosis (PHVT) despite optimal anticoagulation.

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Case

A 23-year-old pregnant woman (10 weeks of gestation) with mechanical mitral prosthetic valve (operated 5 years ago) was due to an exertional dyspnea admitted to our hospital. She did not notify her medical doctor about her pregnancy and had continued to intake 7.5 mg of warfarin on her own. The international normalized ratio (INR) was 2.4 on admission and the blood pressure was 130/80 mm Hg. The patient had a previous history of pregnancy loss at the 16th week. Transthoracic echocardiography on admission revealed increased Doppler gradients (maximum/mean gradient: 17/10 mm Hg) and decreased mitral valve area (MVA) of 1.5 cm^2 indicating a prosthetic valve obstruction. Transesophageal echocardiography delineated a thrombus area of 1.5 cm^2 on the mitral prosthesis (Fig. 1A). Thrombolytic therapy (TT) with low dose (25 mg) and slow infusion (6 hours) of tissue-plasminogen activator (tPA) was administered as described recently.[3)] After TT, the MVA increased to 2.8 cm^2 and the transmitral gradient decreased (maximum/mean gradient: 11/5 mm Hg) with a complete lysis of the thrombus (Fig. 1B). An elective curettage was performed to avoid a potential embryopathy due to the relatively high dose warfarin consumption. Two years later, the patient suffered from two pregnancy losses at the 18th and 20th week respectively. Anticardiolipin immunoglobulin (Ig) G

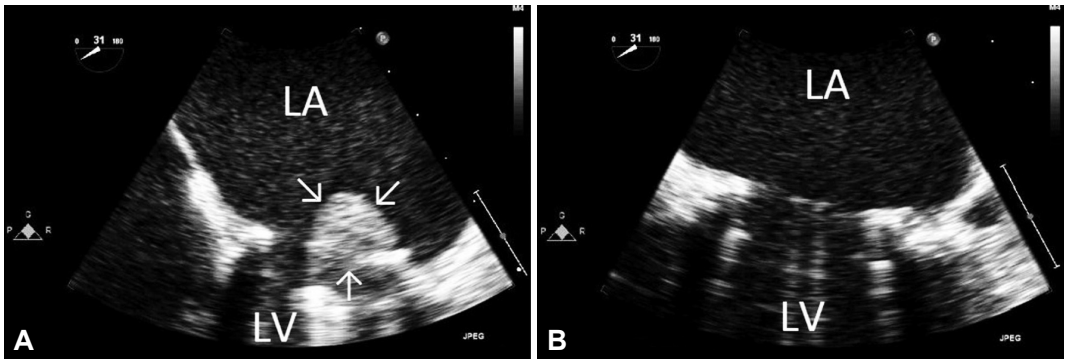

Fig. 1. Transesophageal echocardiography demonstrates the prosthetic valve thrombosis (arrows) (A). The thrombus is successfully lyzed by low dose slow infusion of tissue-plasminogen activator (B). LA: left atrium, LV: left ventricle.

and IgM, lupus anticoagulant and toxoplasma antibodies were studied and showed all negative results. Factor VIII and fibrinogen levels were within normal limits. Genetic testing was performed using CVD Strip Assay Kit (ViennaLab Diagnostic GmbH) and no mutations were observed in the Factor V Leiden, factor V H1299R, prothrombin G20210A, factor XIII V34L, methylenetetrahydrofolate reductase (MTHFR) C677T, plasminogen activator-inhibitor 1 4G-5G, GPIIIa L33P, ACE, ApoB R3500Q and ApoE. However, homozygous mutations of MTHFR A 1298C, and heterozygous mutations of ß-fibrinogen 455 G-A were detected. One year ago, the patient became pregnant again and suffered another episode of obstructive PHVT in the 33rd week of her gestation despite strict anticoagulation (low molecular weight heparin with effective antifactor Xa levels in the first trimester and INR between 2.5 and 4 in the second and third trimester). The PHVT was again succesfully thrombolyzed (totally 50 mg of tPA). She delivered by cesarean section an alive and healthy newborn at the end of the 37th week of gestation.

Discussion

Methylenetetrahydrofolate reductase A 1298C homozygous and ß-fibrinogen 455 G-A heterozygous mutations were detected in a pregnant patient with a history of recurrent pregnancy loss and a recurrent prosthetic valve thrombosis despite optimal anticoagulation. The pathogenesis of PHVT is multifactorial and pregnancy is one of the risk factors that may enhance thrombosis.[4)5)] There is a 4-fold to 10-fold increased thrombotic risk throughout gestation and postpartum period.[6)] On the other hand, some women affected by thrombophilia show an increasing hypercoaguable state during their pregnancy and may suffer obstetrical complications such as recurrent pregnancy loss.[2)] Approximately 20% of the thromboembolic events in pregnancy are arterial and the other 80% are venous.[7)]

The relationship between genetic mutations and PHVT and/or miscarriage in pregnancy is unknown. MTHFR is a key enzyme in the folate-dependent remethylation of homocysteine. A reduction in MTHFR level or an activity by specific gene mutations induces hyperhomocysteinemia, characterized by mild to moderate increased plasma homocysteine levels, that has been shown to be a risk factor for arterial or vascular thrombotic events, including myocardial infarction, stroke, deep vein thrombosis and recurrent spontaneous abortus.[8)9)] To our knowledge, MTHFR A 1298 C mutation related with recurrent PHVT was not reported previously.

Beta-fibrinogen 455 G/A polymorphism is a gene mutation that may lead to alterations in the activity of fibrinogen which plays an active role in the coagulation cascade.[10)] In several publications, it has been shown to be associated with an increased erythrocyte aggregation and to predispose the development of stasis in coronary arteries and the left atrium.[10)11)] This gene mutation may also contribute to a thrombus formation on surfaces such as prosthetic valves that is already prone to stasis. However this potential relationship has not been reported also. In the presented case was the mutation heterozygous for the fibrinogen 455G/A allele and it remains unclear whether this may be especially related to recurrent PHVT and/or miscarriages in the presence of additional homozygous MTHFR A 1298 C mutation. Since surgical treatment carries a high mortality risk not only for the mother but also for the fetus during a pregnancy with PHVT, TT may be a reasonable option and seems effective and safe with low doses and slow infusion rates.[3-5)]

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