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Case Report

A case of thrombolytic therapy with recombinant tissue plasminogen activator for mechanical valve thrombosis at 9 weeks of pregnancy in a Japanese woman

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ABSTRACT

A 29-year-old woman was admitted to our hospital due to diagnosis of pregnancy at 5 weeks and a day. She underwent valve replacement with mechanical heart valve (MHV: SJM valve) for congenital mitral valve regurgitation, when 11 years old. Warfarin 4 mg was used for anticoagulation. After admission, warfarin was replaced by unfractionated heparin (UFH). She developed exertional dyspnea at 8 weeks of pregnancy. Echocardiogram and fluoroscopy showed an immobile leaflet in the closed position. She was diagnosed with mechanical valve thrombosis. Cardiac surgery or thrombolytic therapy (TT) were treatment options. TT is not established, but is reported to be safer than cardiac surgery. Recently, low-dose, slow infusion of recombinant tissue plasminogen activator (rt-PA) therapy showed acceptable results. About 2.5 h after an intravenous injection of rt-PA, diastolic rumble improved to the normal range of leaflet. Thereafter, warfarin was restarted and there was no recurrence of symptoms and no abortion. She was readmitted for the scheduled Caesarean section (CS) at 32 weeks of pregnancy, and warfarin was replaced with UFH. At 34 weeks of pregnancy, a baby was delivered by CS. She suffered hemostasis after surgery under the anticoagulation. Postoperative day 31, both mother and a child were healthy and left the hospital.

<**Learning objective:** The coagulation status is activated and the fibrinolytic activity is reduced during pregnancy. Prosthetic valve thrombosis during pregnancy is known as a life-threatening event for mother and fetus. The treatment strategy for this complication is not well established. Low-dose, slow infusion of recombinant tissue plasminogen activator (rt-PA) therapy showed acceptable results. This case report shows that rt-PA therapy for the prosthetic valve thrombosis in a Japanese pregnancy woman could be an alternative treatment strategy to surgery.>

Introduction

There has been an increase in the number of female patients having a congenital heart disease who have given birth like healthy females [1]. However, maternal mortality and abortion rate were higher for patients with mechanical heart valve (MHV) than for those with no prosthetic heart valve [2].

The present report describes a case of prosthetic valve thrombosis in a Japanese patient at 9 weeks of pregnancy that was successfully treated with low-dose, slow infusion of recombinant tissue plasminogen activator (rt-PA) therapy [3] without hemorrhagic events. To date, there have been no reports of rt-PA therapy in a Japanese pregnant woman with MHV. In this case, a baby was successfully delivered by Caesarean section (CS) at 34 weeks of pregnancy. We describe the details of the CS and postoperative process.

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Case reports

A 29-year-old woman was admitted to our hospital due to diagnosis of pregnancy at 5 weeks and a day. She had undergone valve replacement with MHV for congenital mitral valve regurgitation, when 11 years old. Warfarin 4 mg was used for anticoagulation. After admission, warfarin was replaced with unfractionated heparin, due to concerns about the teratogenicity of warfarin. She developed exertional dyspnea, at 8 weeks and 4 days of pregnancy. On physical examination, the patient was afebrile with a regular pulse of 101 beats/min and a blood pressure of 102/57 mmHg. The O_2 saturation was 98% on room-air. Cardiorespiratory examination revealed diastolic rumble, and no edema. The chest radiograph showed pulmonary congestion (Fig. 1A). Electrocardiogram showed sinus tachycardia (Fig. 1B). Echocardiogram and fluoroscopy showed an immobile leaflet in the closed position (Fig. 1C–F) (Supplementary Data 1). Laboratory testing showed an activated partial thromboplastin time (APTT) 80 s D-dimer 1.0 μg/ml, fluorescent antinuclear antibody negative, and heparin-induced thrombocytopenia antibody negative.

Cardiac surgery or thrombolytic therapy (TT) were discussed between cardiologist, obstetricians, the patient, and the patient's family. Cardiac surgery in pregnancy is associated with high maternal and fetal mortality. Previously, low-dose, slow infusion of rt-PA therapy showed acceptable results [3]. The patient and patient's family choose TT. Therefore, we decided to perform TT after the approval of the Ethics Committee. Fig. 2 shows TT progress.

Loss of diastolic rumble was noted 2.5 h after the TT induction. Echocardiogram showed a leaflet was fixed (Fig. 1G,H) (Supplementary Data 2). Informed consent was obtained for the administration of warfarin during the 2nd and 3rd trimesters, despite the teratogenic potential and hemorrhagic risk. The patient was discharged from hospital without side effects from TT and warfarin. The patient did not have thrombotic events or abortion.

At 32 weeks of pregnancy, the patient was re-admitted to our hospital for delivery of the baby by CS at 34 weeks of pregnancy. Warfarin was replaced with unfractionated heparin a week before CS. Fig. 3 outlines the perinatal period. At 5 h post operation, heparin 15×10^3 IU/day infusion with a target APTT of 100 s was restarted, and then antithrombin III (AT-III) kept at >80%. At the time of total amount heparin 32×10^3 IU/day, target APTT was not attained, abdominal wall hematoma was increased. Thus, the heparin infusion was suspended after about three hours, and a target APTT of 60 s was reestablished. In addition, transcatheter arterial embolization was performed to the bleeding of the

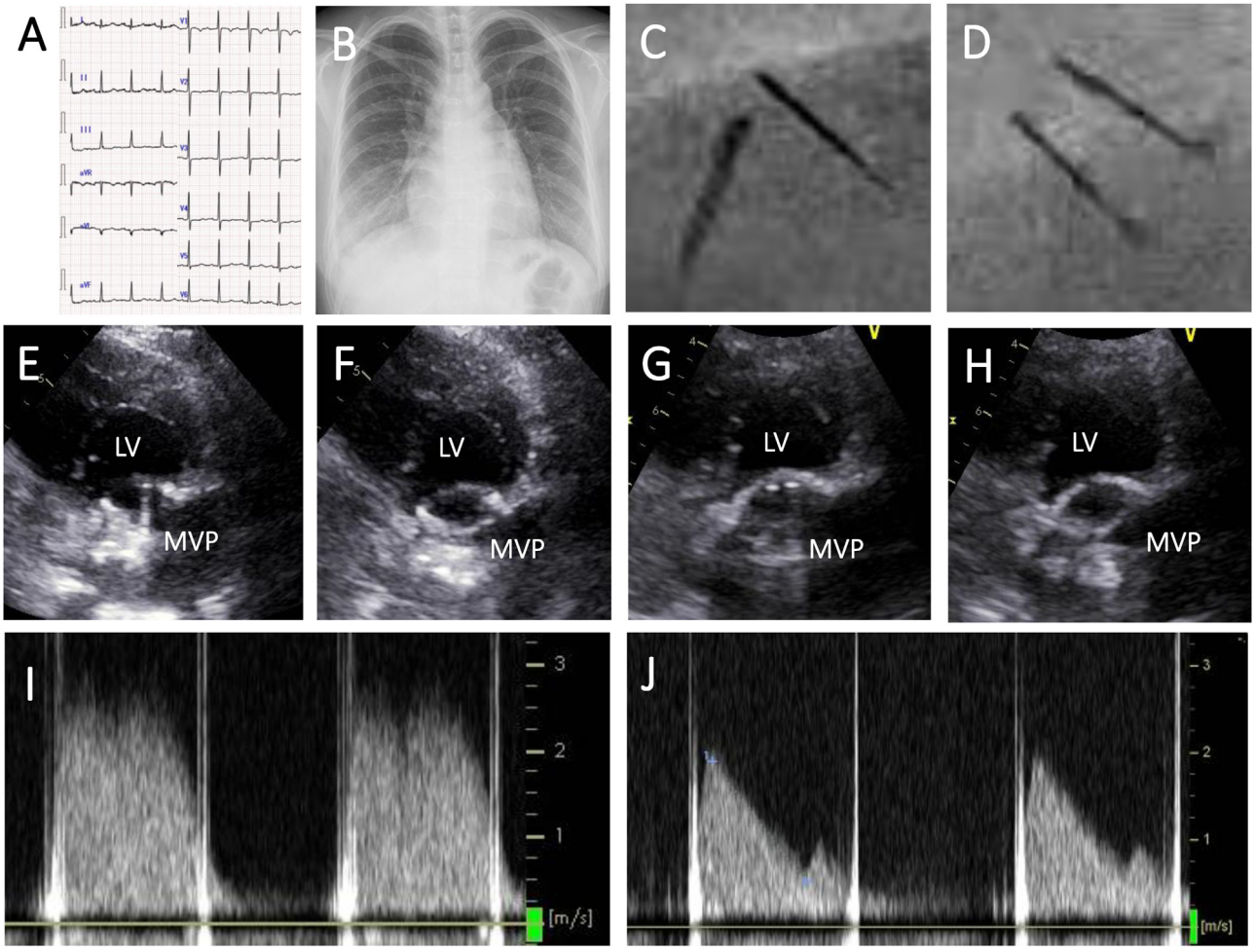

Fig. 1. Electrocardiogram showing sinus tachycardia (A). Radiograph showing cardiomegaly and pulmonary congestion (B). Fluoroscopy right anterior oblique view 30°, caudal 20° view showing mechanical heart valve (MHV) diastolic phase before thrombolytic therapy (TT) (C) and after TT (D). Transthoracic echocardiographic parasternal long-axis view showing MHV, before TT diastolic phase (E) and systolic phase (F). After TT diastolic phase (G) and systolic phase (H). Before TT, continuous wave Doppler showed a maximum trans-MHV pressure gradient 31 mmHg and a mean gradient of 22 mmHg (I). After TT, the maximum trans-MHV pressure gradient decreased from 31 mmHg to 15 mmHg and the mean gradient decreased from 22 mmHg to 6 mmHg (J).
LV, left ventricle; MVP, mitral valve prosthesis.

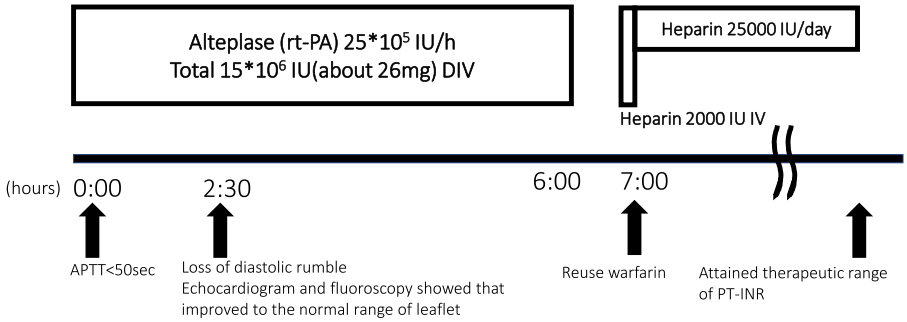

Fig. 2. Thrombolytic therapy of low-dose, slow infusion recombinant tissue plasminogen activator (rt-PA). The activated partial thromboplastin time (APTT) was <50 s, and alteplase (rt-PA) was administered at 25×10^5 IU/h IV drip. After 2.5 h, there was confirmed loss of diastolic rumble, and an improvment to the normal range of leaflet by echocardiogram and fluoroscopy. Six-hours infusion of 15×10^6 IU (about 26 mg) rt-PA was used. Heparin 37 IU/kg bolus and 19 IU/kg per hour infusion with a target APTT of 2.0 times the mean of the reference range was started one hour after the rt-PA infusion. At the same time, warfarin was reused. The patient was discharged from hospital after attaining therapeutic range of prothrombin time-international normalized ratio (PT-INR).

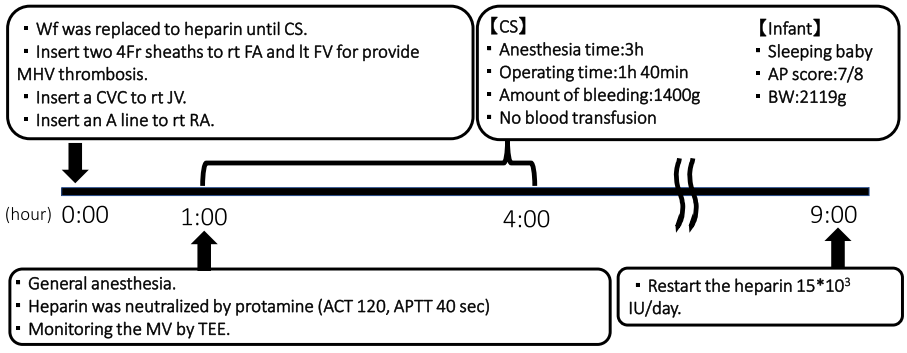

Fig. 3. Perinatal period progress. Insert two 4 Fr sheaths to rt FA and lt FV, and percutaneous cardiopulmonary support (PCPS) was stand-by. The patient underwent Caesarean section (CS) under general anesthesia, so the infant was a sleeping baby. The infant had no congenital deformity. At 5 h post operation, the heparin 15×10^3 IU/day was restarted.
Wf, Warfarin; rt, right; lt, left; FV, femoral vein; FA, femoral artery; JV, jugular vein; CVC, central vein catheter; RA, radial artery; AP, Apgar; ACT, activated clotting time; APTT, activated partial thromboplastin time; BW, body weight; MV, mitral valve; TEE, transesophageal echocardiography.

branched omental artery. On postoperative day 26, for bleeding to come down warfarin was restarted. On postoperative day 34, the patient and her infant were discharged from hospital without sequelas.

Discussion

Important changes during pregnancy include increased coagulability and decreased fibrinolytic capacity [4]. In a woman with an MHV, the need to maintain adequate anticoagulation to prevent MHV thrombosis has to be balanced against the risks of teratogenicity and bleeding [2]. The maternal mortality rate for a woman with an MHV was 30- to 200-fold increased compared with the normal pregnant population. The chance of a pregnancy free of serious adverse events was <60% for MHV, and half of pregnant women with MHV developed complications. The placental passage of rt-PA is minimal and not sufficient to cause unwanted fibrinolytic effects in the fetus [3]. Low-dose, slow infusion of rt-PA was reported to be an effective therapy, and a sufficient result was provided for this case. Japanese guidelines recommended vaginal delivery to pregnant women with MHV [5]. However, this case corresponded to poorly control anticoagulation therapy so that we recommended CS for patient. Warfarin use in pregnancy is associated with an augmented rate of abortion and the risk of warfarin-induced embryopathy [6]. A previous study suggested dose-dependent teratogenicity of warfarin. Less than 5 mg of warfarin showed lower risk of teratogenicity than above 5 mg [5]. In this case, the dose of warfarin was 4 ± 0.5 mg, and there were no deformities of the baby. There was a dilemma between anticoagulation to prevent thrombus reformation and postoperative bleeding after CS. An MHV patient with arterial thrombosis within a month had a non-cardiac surgery, post-operative heparin increased bleeding risk by 3%, but reduced arterial thrombosis risk by only 0.65%. However, it is reported that 20% of artery thromboembolisms were fatal, so even though infrequent, it cannot be ignored [7,8]. In this case, postoperative anticoagulant therapy with heparin was restarted at an early stage, but the patient had presented with bleeding. At first, we attempted to control APTT by increase or decrease of heparin dose. However, APTT was fluctuating violently. Thus, we kept the AT-III >80%, it could be fine to control APTT.

Conclusion

Successful treatment was achieved using rt-PA for prosthetic valve thrombosis in a patient at 9 weeks of pregnancy without hemorrhagic events. Low-dose, slow infusion of rt-PA therapy for prosthetic valve thrombosis in a pregnant woman could be an alternative treatment strategy to surgery.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jccase.2018.08.006.

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