CASE REPORT

Recombinant tissue plasminogen activator for massive pulmonary thromboembolism

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SUMMARY

Pulmonary thromboembolism (PTE) can result in significant adverse maternal and fetal outcomes. Monteplase—a recombinant tissue plasminogen activator—is considered effective for the treatment of PTE; however, only a few reports have described cases wherein surgical procedures were performed following treatment with monteplase. Here, we present a patient diagnosed with a massive PTE at 28 weeks of gestation leading to maternal cardiac arrest and intrauterine fetal death. The patient was treated with percutaneous cardiopulmonary support and monteplase. Thrombolysis was achieved 30 min after its administration. The patient went into spontaneous labour and delivered a stillborn vaginally. Using gauze tamponade and uterotonic agents, haemostasis was achieved after 4 h, and bleeding completely ceased after 7 h. Thus, we suggest that a thrombolytic agent can be administered in critical cases, even if delivery is expected shortly.

BACKGROUND

Pulmonary thromboembolism (PTE)—a serious complication of deep venous thromboembolism (VTE) and septic thrombophlebitis—typically has a poor prognosis, with a high death rate in severe cases. In pregnancy, the incidence of VTE is 5–12/10 000 cases, which is 7–10 times the incidence in non-pregnant women.¹ As a result, PTE is a leading cause of maternal mortality among pregnant women²; in Japan, it ranks first as the cause of death in this population. For massive PTE, thrombolytic therapy is the gold standard treatment.^{3–5} Monteplase, a third-generation thrombolytic agent, has a longer half-life, higher clot sensitivity and a more rapid onset of action compared with conventional thrombolytic agents such as alteplase.⁶ Furthermore, monteplase is the only recombinant tissue plasminogen activator for PTE approved by the public medical insurance system in Japan.

There have been few case reports describing surgical procedures following the administration of monteplase for PTE. We present a woman who developed PTE at 28 weeks of gestation, resulting in maternal shock and cardiac arrest as well as intrauterine fetal demise (IUF). She was successfully treated with percutaneous cardiopulmonary support (PCPS) and monteplase and shortly thereafter, went into spontaneous labour.

CASE PRESENTATION

A healthy 40-year-old gravida 2, para 1 woman at gestational age 28 weeks+4 days was found unconscious at 10:30 at home. Two days prior, she had

suddenly lost consciousness, but spontaneously recovered after a few minutes. The following day, she again experienced transient loss of consciousness at home. Her obstetrician diagnosed the patient with iron deficiency anaemia and she returned home. On this presentation, she was found to be tachycardic, and the other vital signs were stable. Echocardiography indicated right heart overload. Acute PTE was suspected, and she was emergently transported to our tertiary obstetric centre at 15:45.

This pregnancy had been otherwise uncomplicated. Her first pregnancy was uneventful and resulted in a vaginal delivery at 40 weeks of gestation. Her medical history included multiple uterine fibroids. The family history indicated no remarkable findings.

On arrival, she was alert and conscious (Glasgow Coma Scale 15 (E4 V5 M6)). Blood pressure and heart rate were 110/81 mm Hg and 158 bpm, respectively. The systolic blood pressure was 98% on 5 l/min of oxygen via a face mask. Ultrasonography revealed a fetal heart rate of 140 bpm and no findings suggesting placental abruption. Contrast-enhanced CT was immediately performed and confirmed massive PTE in the bilateral main pulmonary arteries (figure 1) and thrombosis in the left popliteal artery. At 16:35, prior to the initiation of anticoagulation therapy, a non-stress test showed fetal bradycardia (60–90 bpm) and the patient suddenly became hypotensive.

TREATMENT

The patient was administered a bolus of 5 000 units of heparin and maintained on a continuous intravenous infusion of heparin at 13.9 units/min (20 000 units/day). At 17:10, IUF was confirmed. At 17:15, she underwent endotracheal intubation and was transferred to the intensive care unit. At 17:40, the heart showed pulseless electrical activity owing to acute myocardial infarction and cardiac massage was initiated. At 17:55, PCPS catheters were inserted in the right femoral artery and vein, and PCPS circulation was initiated.

Echocardiography revealed that the left ventricle could not dilate because of compression by the wall of the right ventricle, which was extremely dilated as a result of right heart overload. A cardiovascular surgeon was consulted, who advised that complete and safe surgical removal of the clots would be difficult since the extensive thrombosis also appeared to involve the peripheral vessels. At 23:15, the patient received an intravenous injection of

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Figure 1 Contrast-enhanced CT images on admission (A–C); after thrombolytic therapy (D); and of an embolus collected during the removal of the percutaneous cardiopulmonary support catheters (E). A massive pulmonary thromboembolism was observed in the bilateral main pulmonary arteries, which disappeared after 19 days.

1 6000 00 units of monteplase (21 000 units/kg). Heparin administration was discontinued and manual compression of the PCPS catheter insertion area was initiated. Thirty minutes after

monteplase administration, echocardiography showed improvement in the right heart overload and left ventricular diastolic dysfunction.

Figure 2 Time-course chart showing time-series data on vital signs, treatment methods, bleeding volume and amounts of blood products transfused. FFP, fresh frozen plasma; HR, heart rate; PCPS, percutaneous cardiopulmonary support; RCC, red cell concentrate; SBP, systolic blood pressure; SpO₂, saturation of peripheral oxygen.

OUTCOME AND FOLLOW-UP

On the next day (28 weeks+5 days of gestation), the patient went into spontaneous labour at approximately 00:00 and a decision to proceed with vaginal delivery with blood product transfusion was made. At 01:24, she delivered a stillborn female child weighing 1150 g. Although there were no lacerations in the birth canal, the patient experienced 2238 ml of bleeding from the placental bed. The uterine cavity and vagina were packed with gauze, and a continuous intravenous drip infusion of a uterotonic agent was administered. As bleeding from the PCPS catheter insertion area gradually decreased, manual compression was discontinued at 02:25. At 09:00, anticoagulation therapy with 20 000 units/day of heparin was restarted.

After 3 days, the patient was weaned from both the PCPS and respirator. Part of the emboli was collected at the time of PCPS catheter removal (figure 1). The total bleeding volume was 8 671 ml. A total of 44 units of red cell concentrates, 48 units of fresh-frozen plasma and 30 units of platelet concentrates were transfused. Changes in vital signs, the bleeding volume and the transfusion amounts of blood products are shown in (figure 2). She was discharged to home in a stable condition without sequelae 29 days after admission.

DISCUSSION

A recent review on maternal death⁷ states that if there is a high clinical suspicion of PTE, a loading dose of heparin may be warranted pending the results of a definitive test. In this case, we cannot exclude the possibility that the patient's PTE would not have significantly progressed if we had requested the previous obstetrician to administer heparin or we had initiated heparin immediately after her arrival.

In patients with severe PTE, immediate recovery of the right ventricular function has been reported to decrease the associated death rate.⁸⁻⁹ Since immediate surgical removal of clots was considered to be difficult, we chose to pursue thrombolytic therapy with alteplase. Compared with conventional thrombolytic agents, alteplase has a longer half-life, higher clot sensitivity and a more rapid onset of action. However, alteplase has been associated with several issues such as adequate haemostasis when delivery occurs while alteplase activity is present or at the PCPS catheter insertion area. The incidence of bleeding after the administration of alteplase following surgical procedures was reported to be 20–25%.⁶⁻¹⁰⁻¹¹ However, there have been no reports on the bleeding risk in patients who underwent surgical procedures or labour and delivery after alteplase administration. Studies have shown that the elimination half-life of alteplase was 23.66 min in the α phase (half-life for transfer of the intravenously injected drug to tissue) and 7.82 h in the β phase (half-life for drug excretion); furthermore, using the fibrin plate method, the half-life of alteplase activity was found to be 29.43 min and this activity disappeared 4 h after administration.¹² Since these were in vitro studies, we could not be certain of obtaining the same results in vivo, but considered that alteplase activity disappears or decreases 4 h after administration and thrombus formation can be expected when bleeding occurs owing to delivery or surgical procedures. We therefore decided that if delivery occurred within 4 h after alteplase administration, we would promote postpartum uterine contractions, stop bleeding from the placental bed using gauze tamponade and apply compression in the wound area. In the present case, thrombolysis was almost achieved 30 min after alteplase administration and the right ventricular overload resolved. Delivery occurred 2 h after alteplase administration,

but, fortunately, there were no birth canal lacerations and bleeding from the placental bed was controlled using gauze tamponade, which eventually ceased. Owing to blood transfusions, the patient remained haemodynamically stable. Bleeding from the PCPS catheter insertion area decreased 4 h after alteplase administration. Seven hours after alteplase administration, bleeding had completely stopped. Our report demonstrates that alteplase is a potent, quick-acting thrombolytic agent and its activity decreases 4 h after administration and completely disappears after 7 h. Therefore, alteplase can be used when considering the time of administration, the time of delivery or surgery in pregnant women in whom delivery is expected and/or surgical procedures planned after its administration. Animal experiments have confirmed the absence of placental transfer or teratogenicity¹³⁻¹⁴; however, the safety of alteplase in humans has not yet been established. Additional cases are necessary to establish a safe administration method.

Learning points

- ▶ Pulmonary thromboembolism (PTE) is more common in pregnancy.
- ▶ PTE can result in significant adverse maternal and fetal outcomes, including maternal cardiac or respiratory arrest and intrauterine fetal demise.
- ▶ Thrombolytic therapy is the gold standard treatment for PTE.
- ▶ Alteplase is a potent, quick-acting thrombolytic agent, and its activity decreases 4 h after administration and completely disappears after 7 h.
- ▶ Alteplase administration requires careful planning of the time of delivery and/or surgical procedures.

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Competing interests None.

Patient consent Obtained.

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