CASE REPORT

Pregnancy with mitochondrial disease complicated by threatened preterm labor and preeclampsia

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Mitochondrial disease exhibits various symptoms and is rarely seen in young women. We report the case of a patient with mitochondrial disease complicated with maternal inherited diabetes-deafness (MIDD) who suffered a severe clinical course. A 33-year-old primipara woman had a history of diabetes, diagnosed when she was 18 years old, and was treated with insulin injection. At 24 years old, genetic testing was performed and a point mutation of mitochondrial DNA in m3243 was identified. She was admitted to our hospital at 23 weeks of gestation because of threatened preterm labor and was treated with magnesium sulfate infusion. General malaise developed shortly after and the tocolytic agent was changed to ritodrine hydrochloride. She developed preeclampsia at 33 weeks of gestation and an emergency cesarean section was performed. After the cesarean section, UAE was performed due to uterine hemorrhage after birth and, because of infection, a hysterectomy was performed. An increased risk of preeclampsia, preterm birth and magnesium toxicity has been reported in pregnancies complicated with mitochondrial disease. Obstetricians need to recognize this disease as a perinatal risk factor.

Introduction

Mitochondrial diseases are disorders associated with the dysfunction of the mitochondria, which cause a variety of systemic disorders. We experienced a case of a pregnancy complicated with mitochondrial disease. The pregnancy was complicated with threatened premature labor, preeclampsia, and magnesium intolerance. However, her diabetes mellitus had been stable during the course of pregnancy despite administration of β2-stimulant, which revealed a point mutation of mitochondrial DNA (mtDNA) in m3243. Her hearing disability was apparent—she used a hearing aid—and she was diagnosed with maternal-inherited diabetes with deafness (MIDD). Because of recurrent miscarriage, she had visited an infertility clinic. Her hemoglobin A1c level was 5.6% before pregnancy. However, slight decease in the activity of coagulation factor XII was observed and low-dose aspirin was prescribed. She had conceived naturally but, because of her pre-pregnancy medical history, she was referred to our institution at 9 weeks of gestation.

At the initial visit, the patient’s anthropometrics and vital signs were as follows: height, 150 cm; body weight (BW), 42.3 kg; body mass index (BMI), 18.8 kg/m²; blood pressure (BP), 117/60 mmHg; and pulse rate, 86/min. Her family history was significant. Her father had diabetes mellitus and hypertension that were controlled by oral medication, and her mother’s sister was hearing impaired—she used a hearing aid—and was diagnosed with maternal-inherited diabetes with deafness (MIDD). Her mother had hypertension that was controlled by oral medication.

Case

The patient was a 33-year-old, gravida 3, primiparous, pregnant woman. She had a history of 3 spontaneous abortions. The patient had type 1 diabetes mellitus, diagnosed at 18 years of age, and had been receiving insulin injections since that time. At 24 years old, she underwent genetic testing at another facility, which revealed a point mutation of mitochondrial DNA (mtDNA) in m3243. Her hearing disability was apparent—she used a hearing aid—and she was diagnosed with maternal-inherited diabetes with deafness (MIDD). Because of recurrent miscarriage, she had visited an infertility clinic. Her hemoglobin A1c level was 5.6% before pregnancy. However, slight decease in the activity of coagulation factor XII was observed and low-dose aspirin was prescribed. She had conceived naturally but, because of her pre-pregnancy medical history, she was referred to our institution at 9 weeks of gestation.

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impaired. Figure 1 presents the family tree of this patient. At 23 weeks and 4 days of gestation, during a routine examination, cervical shortening (cervical length, 20 mm) was detected. She also had irregular uterine contraction, but with a closed cervix. She was admitted to our hospital with a diagnosis of threatened premature delivery. She received 50 U of insulin subcutaneously upon admission, and her blood glucose levels were well controlled. Because she was known to have diabetes, we selected magnesium sulfate as the tocolytic agent. However, soon after the magnesium sulfate infusion (1 g/h) was started, she complained of severe generalized fatigue and muscle weakness. Even though her serum Mg$^{2+}$ level was 6.6 mg/dl, which was within the therapeutic range, we changed the tocolytic agent to ritodrine hydrochloride with a starting dose of 50 μg/min. The ritodrine hydrochloride dose was gradually increased to control her uterine contractions. During that course, no subjective adverse symptoms were observed. At 31 weeks and 5 days of gestation, a routine laboratory blood test revealed an elevation in serum creatinine phosphokinase (CK) of 479 IU/l (normal

![Figure 1. Family tree of this patient. Her aunt has hearing disability.](image1)

![Figure 2. Dose of insulin and ritodrine hydrochloride. Changes in the daily total insulin dose and i.v. ritodrine dose/day according to gestational age.](image2)
Pregnancy with mitochondrial disease


range: 6–142 IU/l). Rhabdomyolysis was suspected. Thus, we decreased the dose of ritodrine hydrochloride, and serum CK values decreased to 161 IU/l. However, with the decrease of the tocolytic agent dose, uterine contractions became frequent, and betamethasone (12 mg/day for 2 days) was injected for the preparation of possible preterm delivery at 32 weeks 2 days of gestation. Following the medication, her blood glucose levels elevated and the insulin dose was transiently increased to 70 U/day (Figure 2). Two days later, generalized edema appeared and her body weight increased by 1.1 kg/week. At 32 weeks and 6 days of gestation, her BP was 110/60 mmHg and pathological proteinuria (331 mg/day) was observed. At 33 weeks of gestation, oliguria (145 ml/day) and an elevated serum liver enzyme level (AST, 91 IU/l; normal range, 11–30 IU/l; ALT, 186 IU/l; normal range 4–30 IU/l; LDH, 550 U/l; normal range 110–220 U/l). In addition, a decreased serum anti-thrombin III activity (64%) with a normal platelet count (22 × 10⁴/μl) was observed. Hence, we decided to perform a cesarean section, with an indication of breech presentation. The surgery was uneventful. Bleeding was measured at 670 g. Placental weight was 444 g and no significant finding was observed by Hematoxylin-Eosin (HE) staining. The female neonate weighed 1,694 g (appropriate for date) with APGAR scores of 7 and 9 at 1 and 5 minutes, respectively, and was admitted to our neonatal intensive care unit (NICU). Two hours after the cesarean section, severe postpartum hemorrhage from the uterine cavity was observed. Emergency enhanced CT showed active bleeding into the uterine cavity. Blood products transfused were 6 units each of red blood cells and fresh frozen plasma. An emergency bilateral uterine artery embolization (UAE) was performed by gelatin sponge and hemostasis was achieved. Three hours after the UAE, her BP elevated to 160/90 mmHg; she complained of dyspnea and low SaO₂ (80%) was observed. Her chest radiogram revealed increased cardiothoracic ratio (CTR) and pulmonary edema. A diagnosis of severe preeclampsia was made. Thus, she was intubated for mechanical ventilation for one day in the intensive care unit (ICU). After extubation, oral nifedipine was administered. Her BP gradually normalized and her proteinuria disappeared by postoperative day 10. At that time, she complained of fever with shaking chills, and her blood test showed elevated levels of CRP and WBC. Antibiotics (aztreonam and clindamycin via i.v.) were started and an enhanced CT revealed enlarged uterus with gas in the myometrium (Figure 3A). We performed dilatation and curettage on postpartum day 16 to evacuate the uterine content and a small amount of foul smelling blood clots were removed. Bacteroides fragilis was identified from her venous blood culture. On the 19th day after delivery, we decided to perform a hysterectomy to control the uterine infection. A total abdominal hysterectomy was performed and 324 g of uterus was resected with 550 g blood loss during the operation. The uterus was edematous with thick myometrium and foul odor. Pathological examination revealed diffuse necrosis and ischemic change in the myometrium (Figure 3B). After the operation, she recovered from the severe infection and was discharged 13 days after the hysterectomy. The neonate was stable but, because of prematurity, she was not discharged until 36 days old.

Discussion

The incidence of mitochondrial disease is reported as one in every 4,000 to 7,500 persons. The mitochondria

Figure 3. Enhanced CT image and resected uterus. (A) Enhanced CT horizontal plane. The arrow indicates the gas in the myometrium of uterus. (B) A macroscopic view of the resected uterus. Anterior wall was incised. Thickening and dark coloration of the endometrium was observed.
Malignant syndrome (MIDD) is characterized by symptoms such as weakness, headache, myopathy, external ophthalmoplegia (CPEO), maternal inherited diabetes-deafness syndrome (MIDD), and others. Our patient had already been diagnosed as having MIDD from the mutation of m3243 in the mtDNA.

Pregnancy with mitochondrial disease may have many complications. There are reports of complications with threatened preterm labor, fetal growth restriction and preeclampsia. However, it has not been clarified that symptoms such as myopathy temporarily worsen during pregnancy.

It has been reported that the m3243 mutation in mtDNA has been detected in about 1% of patients with diabetes mellitus. Suzuki et al. reported complications in 113 cases of diabetes patients with mutation of the m3243 gene. They found sensory hearing loss in 92%, cardiomyopathy in 30.4%, encephalomyopathy in 16.1%, and conduction disorder of the heart in 26.1%. Eighty-six percent of them were administered insulin injections.

Women with diabetes mellitus associated with mitochondrial disease have been reported to be at high risk for preeclampsia and threatened premature labor. de Laat et al. conducted a retrospective investigation of the pregnancy courses of 60 cases of mothers with m3243 mutation in the mtDNA. Their mean gestational age at delivery was 38 weeks and 4 days (1 SD: 3 weeks). A significant increase in the preterm delivery rate was found to be 25.3% (odds ratio 4.2; 95% CI: 2.6–6.8, \( P < 0.0001 \)). In addition, the incidence of preeclampsia was 12% with a median onset at 32.5 weeks of gestation, and 36% of those were delivered by cesarean section. Say et al. reported in a review that 2 out of 10 cases showed toxic symptoms from magnesium sulfate administration. The mechanism was speculated to be magnesium ions that compete with calcium ions in the mitochondria, which impairs the phosphorylation.

In this case, we experienced a variety of complications in the management of pregnancy with mitochondrial disease. In the management of a pregnant patient with mitochondrial disease, we recommend careful observation and flexibility in the selection of treatments.

**Conflict of interest**

The authors declare that there are no conflicts of interest.

**References**