A 34-year-old pregnant woman was diagnosed with mixed connective tissue disease (MCTD), complicated with postpartum pulmonary hypertension (PH). She was taking 10 mg oral prednisolone during pregnancy. At 29 weeks’ gestation, systolic blood pressure increased and proteinuria developed, and she was admitted for preeclampsia. However, at 32 and 3/7 weeks’ gestation, her blood pressure elevated to 195/117 mmHg, and her platelet count decreased to 96 × 10³/μl. Thus, she was diagnosed as severe preeclampsia, and an emergency cesarean section was performed. At postpartum 1 day, she complained of dyspnea and palpitation. Pericardial effusion and right ventricle enlargement were detected on cardiac ultrasound. Her tricuspid regurgitation peak gradient was elevated (40 mmHg), indicating the presence of PH. Accordingly, prednisolone 30 mg/day was administered, and her dyspnea improved. Her blood pressure decreased and her proteinuria disappeared on day 10 postpartum. She was discharged on day 14 with oral prednisolone. Evaluation of cardiac and pulmonary functions before pregnancy in MCTD-complicated patients and careful observation for PH during and after pregnancy is recommended.

Introduction

The clinical characteristics of the patients with mixed connective tissue disease (MCTD) has overlapping features with those of systemic lupus erythematosus (SLE), scleroderma, and polymyositis.1) MCTD is diagnosed by a high titer of anti-U1 ribonucleoprotein (RNP) antibodies. A population survey conducted in Norway reported an incidence of 2.1 per million adults per year and a prevalence of 38 per million adults;2) and, in Japan, the prevalence of MCTD was reported as approximately 54.1 per million adults in 1997.3)

Pulmonary hypertension (PH) is the leading cause of death in MCTD patients. The frequency of PH in MCTD is reported to be 3.94% in Japan,3) whereas a multicenter study conducted in Norway identified PH in 3.4% of all MCTD patients.4)

Few reports have documented the impact of MCTD-PH on pregnancy. One previous case report described a pregnant woman with MCTD-PH who developed renal crisis after caesarean delivery,5) and in a cohort of 14 consecutive pregnant women with PH, only one case of MCTD-PH was identified.6) In the abovementioned previous study, the patient’s condition worsened during pregnancy, requiring therapeutic abortion.6)

Herein, we present a rare case of pregnancy complicated with MCTD.

Case report

The case was of a 34-year-old woman (gravida 3, para 3) diagnosed with MCTD at age 29 after previous delivery, following initial symptoms of Raynaud’s phenomenon. At that time, cardiac ultrasound (CU) revealed no abnormal findings, and she was treated with beraprost sodium, methotrexate, prednisolone, azathioprine, and sulfasalazine (Figure 1). She was followed at our internal medicine department until her current pregnancy. The MCTD was well controlled by the medications, as indicated by the decrease in anti-U1 RNP antibody titer from 1:256 to 1:64 (Table 1).

Her first visit to our Obstetric department was in gestational week 5. Her blood pressure was 100/80 mmHg, and the spot urine dipstick for proteinuria was

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negative. Due to the pregnancy, she had been taking only 7 mg oral prednisolone. She had bilateral arthritis of the hand joints. In week 23 of gestation, her anti-U1 RNP antibody titer had increased back to 1:256 (Table 1). In addition, her C-reactive protein (CRP) level was elevated. Accordingly, the dose of oral prednisolone was increased to 10 mg/day. Her pregnancy course was uneventful until 27 weeks of gestation when an ultrasound examination of her fetus showed growth restriction (< 10%tile). In week 29 of gestation, the anti-U1 RNP antibody titer and CRP level remained stable (Table 1).

At 29 weeks of gestation, her systolic blood pressure increased to over 140 mmHg and proteinuria (2+: dipstick test) was observed, and she was admitted to our center with a diagnosis of preeclampsia. After admission, she was administered oral methyldopa (1,000 mg/day), and her blood pressure was controlled within the normal range. However, at 32 and 1/7 weeks of gestation, her blood pressure was elevated to the range over 160/110 mmHg. As determined by 24-h ambulatory blood pressure monitoring (Figure 2), her mean daytime and night time blood pressures were 134/90 mmHg (maximum 182/112 mmHg) and 177/109 mmHg (maximum 195/117 mmHg), respectively. Thus, an additional dose of 250 mg methyldopa was prescribed at bedtime (total dose, 1,250 mg/day). However, the severe hypertension was not improved and her platelet count decreased to 96 × 10^3/μl. Because of worsening hypertension and thrombocytopenia, an emergency cesarean section was performed at 32 weeks and 4 days of gestation. She delivered a 1,470 g (less than 10%tile of the Japanese standard for neonatal weight; data form the Japan Society of Pediatrics 2010) female infant with an Apgar score of 8/9 at 1 and 5 minutes. The infant was admitted to the Neonatal Intensive Care Unit but did not require ventilation support, and the neonatal course was uneventful.

On postpartum day one, the patient complained of dyspnea and palpitation. Her room-air SpO2 decreased to 90% and oxygen (2 l/min) via a nasal cannula was administered. Her arterial blood gas showed an increased alveolar-arterial blood gas gradient of 64.3 mmHg, and

**Table 1. Changes of serum anti-U1 RNP antibody and CRP values before and during the current pregnancy**

<table>
<thead>
<tr>
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<th>Before pregnancy</th>
<th>During remission</th>
<th>Current pregnancy</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>MCTD onset</td>
<td>(age, 29 y)</td>
<td>(age, 30 y)</td>
</tr>
<tr>
<td>Anti-U1 RNP antibody</td>
<td>256</td>
<td>64</td>
<td>256</td>
</tr>
<tr>
<td>CRP (mg/dl)</td>
<td>0.17</td>
<td>0.35</td>
<td>1.73</td>
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<td></td>
<td>(normal range, 0–0.2)</td>
<td></td>
<td>1.9</td>
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<td>0.96</td>
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The values for non-pregnant normal ranges of CRP is shown. MCTD, mixed connective tissue disease; RNP, ribonucleoprotein; CRP, C-reactive protein; PPD, postpartum day.

**Figure 1. Pre-pregnancy clinical features and treatments of the patient.**
Beraprost, beraprost sodium (dose/day); PSL, prednisolone (dose/day); MTX, methotrexate (dose/day); AZP, azathioprine; SSZ, sulfasalazine.
oxygen diffusion impairment was suspected. Chest x-ray showed a slightly increased cardiothoracic ratio (54%), with normal translucency in the both lung fields. The Electrocardiography and Spirometry data were in the normal ranges. The CU examination then performed revealed pericardial effusion with enlargement of the right ventricle. Her tricuspid regurgitation peak gradient (TRPG) was elevated to 40 mmHg, and ejection fraction was in the normal range (61%). There was no left ventricular hypertrophy and a tentative diagnosis of PH was made. The enhanced chest CT showed pericardial effusion, however, there was no sign of pulmonary embolism. Subsequently, the dose of prednisolone was increased to 30 mg/day, resulting in improvement of her dyspnea and TRPG was lowered to 25 mmHg, as determined using ultrasonography. On day 10 postpartum, her anti-U1 RNP antibody titer had returned to normal (1:64), and the proteinuria had disappeared (Table 1), and, on day 11 postpartum, her blood pressure had normalized (130/90 mmHg). The patient was discharged from the hospital.

Discussion

In Japan, MCTD is reportedly complicated by PH in approximately 4% of cases. It was found, in a previous report that determined clinical and immunologic outcomes for a cohort of 47 patients with MCTD, that most of the patients who died from their disease had PH. In autopsies performed, the lungs uniformly showed intimal proliferation and medial hypertrophy of the pulmonary arteries. In our case, the diagnosis of MCTD was made in a few years before the present pregnancy, and the disease was well controlled by oral medications.

MCTD has the overlapping clinical features of other connective tissue diseases, such as SLE, and a high positivity for several autoantibodies (SSA, SSA/Ro, U1-A RNP, etc.) has been reported by Yamamoto et al. A correlation between SLE nephritic exacerbations and serum levels of anti-U1 RNP has also been reported. And a report by Hoet et al. showed a correlation between changes in anti-U1 RNA antibody levels and MCTD activity. The anti-U1 RNA antibodies were detected only in anti-RNP sera and such antibodies primarily present in SLE and SLE overlap patients.

A review of 15 pregnancies from 14 women with severe PH was reported by Bonnin et al. In their case study, there were 4 cases of idiopathic PH, 6 cases of congenital heart disease, 1 case of fenfluramine-associated PH, 1 case of human immunodeficiency virus–associated PH, 2 cases of chronic thromboembolic PH, and only 1 case of MCTD-PH. They reported a total of 5 maternal deaths out of 14 patients (a mortality rate of 36%). There were two fetal deaths, one of which occurred in the patient.
with MCTD-PH. In that case, therapeutic abortion was performed at 21 weeks’ gestation due to worsening PH in the pregnancy. Her symptoms were improved after the abortion and remained stable thereafter.

Cesarean delivery under regional anesthesia with invasive monitoring was deemed a safe mode of delivery, although there is no evidence of its benefit for women with this condition. Nonetheless, for patients with PH, pregnancy should be discouraged, and therapeutic abortion is generally recommended, particularly when deterioration occurs in the early stages of pregnancy. Thus, we recommend that the patient with MCTD may benefit from an evaluation for the presence of PH before or during pregnancy.

Conclusions

The majority of MCTD-complicated pregnancies are relatively safe before, during, and after delivery. However, if PH is present along with MCTD, the disease may be life-threatening. Herein, we presented a case of pregnancy complicated with MCTD and PH in the postpartum period. There have been a limited number of reports dealing with the risk of PH on pregnancy but, based on this case, we recommend evaluating the cardiac and pulmonary functions before planning pregnancy for MCTD-complicated patients and careful observation is required for the presence of PH during the pregnancy and postpartum period in these patients.

Patient consent

Written informed consent was obtained from the patient for all treatment procedures and for publication of this case study.

Conflict of interest

None.

References