Elevation of maternal serum sFlt-1 in pregnancy with mirror syndrome caused by fetal cardiac failure

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Abstract

Mirror syndrome (MS) is characterized by the combination of maternal generalized edema, fetal hydrops and placental hypertrophy. A shift of the serum placenta-derived angiogenic factor like sFlt-1 in MS is similar to that in pre-eclampsia (PE). We experienced a MS case caused by cardiac myopathy in the fetus with normal cardiac structure. A 27-year-old primiparous woman at 28 weeks of gestation had systemic edema without hypertension and proteinuria. Her symptoms rapidly disappeared after delivery. Compared with previously reported MS cases with maternal hypertension or proteinuria, the serum sFlt-1 level was lower in our case. Severity of maternal symptoms in MS might be paralleled with the serum sFlt-1 level. Additionally, serum hCG level in MS is much higher than that in PE. Maternal edema rather than hypertension and proteinuria can be more remarkable in MS compared with PE. It can be potentially explained by increased serum hCG level.

INTRODUCTION

Mirror syndrome (MS) is characterized by a combination of maternal systemic edema, fetal hydrops and placental hypertrophy. MS can be developed in a wide spectrum of pathologic conditions related to fetal hydrops. Maternal symptoms including systemic edema and pleural effusion are likely to appear later than the second trimester although it depends on the pathological conditions in the fetus [1]. In a recent retrospective study, fetal hydrops with MS tends to be developed earlier than those without MS [2]. Whereas MS shares many common features with pre-eclampsia (PE), low maternal hematocrit concentrations and mild anemia are pointed out as specific features in MS [1]. Pathogenic factors associated with MS remain unclear. In the present case, MS was developed in pregnancy complicated with fetal cardiac myopathy manifested at 28 weeks of gestation. Abnormal peripheral levels of placental biomarkers were confirmed concomitantly with the development of MS.

CASE

A 27-year-old woman, gravida 1, para 0, was conceived naturally and had prenatal care in a local clinic. At 26 weeks of gestation, mild fetal ascites appeared. She was recommended to have additional ultrasound examination two weeks later. At 28 + 1 weeks of gestation, she had dyspnea with weight gain of 9 kg during the preceding 2 weeks. She was transferred and was admitted in our hospital.

Her blood pressure was normal and proteinuria was not detected. She had mild dyspnea and pitting edema in the lower extremities. Moderate pleural effusion was found in chest
X-ray. The laboratory data on admission are summarized in Table 1. Anemia, low serum albumin level and elevated d-dimer value were confirmed. The serum human chorionic gonadotropin (hCG) level was 192 289 mIU/ml, extremely higher than the average in the third trimester of normal pregnancy (15 881mIU/ml).

Ultrasound examination revealed massive ascites, pericardial fluid and remarkable subcutaneous edema in the fetus (Fig. 1A–C). In addition, placental hypertrophy (Fig. 1D) and polyhydramnios were observed. Tricuspid regurgitation, hypokinetic biventricular movement and the thinning of the myocardium (Fig. 1C) were detected in the fetus, suggesting the cardiac dysfunction. MS was diagnosed on the day of admission (28 + 1 weeks) in our hospital based on the ultrasonographic findings of fetal hydrops and placental hypertrophy concomitantly with maternal edema.

There was a concern about worsening of maternal respiratory condition and deterioration of fetal well-being by expectant management. She had an emergency cesarean section on the same day of admission (28 + 1 weeks) and delivered a female infant (1538 g, Apgar scores; 4 at 1 min and 6 at 5 min). The placenta was edematous and weighed 460 g. In microscopic examination, stromal edema was observed in the majority of the villi (Fig. 2). The systemic edema and the pleural effusion in the mother was improved rapidly after the delivery. She was discharged on postpartum Day 6.

The neonate was managed in NICU soon after the birth. In agreement with the prenatal assessment, hypokinesia of bilateral ventricles with thinning of myometrium was confirmed. Serological tests for possible congenital viral infections including adenovirus, coxsackievirus, cytomegalovirus and rubella virus were all negative. There was no sign of anemia with the serum hemoglobin level of 13.3 g/dl. Hypokinesia of bilateral ventricles and thinning of myometrium with reduced ejection fraction was detected on the ultrasound exam in the neonate. Congenital abnormality other than the cardiac dysfunction was not found. Cardiorespiratory arrest requiring resuscitation occurred twice on postnatal Days 12 and 16. Her cardiac function was gradually improved with administration of cardiotonics and diuretics. The girl was discharged at 8 months after birth. The etiology of the heart failure remained unclear.

By enzyme-linked immunosorbent assay (Quantikine ELISA kits, R&D systems, Minneapolis, MN, USA), we measured the concentrations of soluble fms-like tyrosine kinase 1 (sFlt-1),

| Parvovirus | Negative (IgM and IgG) | Blood type | O (+) |
|------------|------------------------|------------|-------|
| Toxoplasma | Negative (IgM and IgG) | SpO2       | 94%   |
| Cytomegalovirus | Negative (IgM and IgG) | Total protein | 4.2 (g/dl) |
| Rubella   | Negative (IgM and IgG) | Albumin    | 2.3 (g/dl) |
| Leukocyte | 9.9 (10³/μl)           | ALT        | 18 (U/l) |
| Erythrocyte | 287 (10⁹/μl)          | Uremic acid | 5.9 (mg/dl) |
| Platelet  | 143 (10⁹/μl)           | BUN        | 7.1 (mg/dl) |
| Hemoglobin| 8.4 (g/dl)             | Cre        | 0.62 (mg/dl) |
| Hematocrit| 24.5 (%)               | CRP        | 0.03 (mg/dl) |
| MCV       | 85.4 (fl)              | PT-INR     | 0.86   |
| MCH       | 29.3 (pg)              | APTT       | 26.5 (s) |
| hCG       | 192 289 (mIU/ml)       | D-dimer    | 36.3 (μg/ml) |

Figure 1: Fetal ultrasound test on the admission day. Massive ascites (A), subcutaneous edema (B), pericardial fluid (C) and placental hypertrophy (D).
placental growth factor (PIGF) and soluble endoglin (sEng), well-known biomarkers for PE in the maternal serum samples on the day of cesarean section right before delivery and two days after the surgery (Fig. 3). High levels for sFlt-1 and sEng and low PIGF level was detected on the day of delivery (sFlt-1: 7580 pg/ml, PIGF: 81 pg/ml, sEng: 25.4 ng/ml). Their levels were reduced on postpartum day 2 (sFlt-1: 1410 pg/ml, PIGF: 22 pg/ml, sEng: 14 ng/ml). The sFlt-1/PIGF ratios were 94 on the day of delivery and 64 on postpartum Day 2.

**DISCUSSION**

To our knowledge, this is the first report of MS caused by cardiac myopathy in the fetus with normal cardiac structure. In a previous systematic review of MS cases [1], two cases of Ebstein anomaly but no cardiac myopathy were identified. Therefore, this case proposes that cardiac myopathy can be one of pathological fetal conditions developing MS [1, 2].

The present case demonstrated placental hypertrophy in prenatal ultrasonography and hydropic change of villous stroma in microscopic examination. These placental abnormalities in MS are a secondary phenomenon caused by deterioration of fetoplacental circulation [3, 4]. Additionally, we found remarkable increase in serum hCG level. Elevation of serum hCG is known as a feature of MS [5]. Considering that hydantidiform mole, another disease characterized by hydropic change of villi, also shows high hCG level in the peripheral blood, hCG might be related to placental damage caused by edematous tissue change.

Maternal symptoms rapidly disappear after delivery in MS as was observed in the present case. MS is similar to PE in which maternal symptoms including hypertension and renal dysfunction appears exclusively during gestation [1]. This analogy of clinical features between the two pregnancy complications might be associated with the fact that a shift of the serum placenta-derived angiogenic factor levels in MS is similar to that in PE [6]. Consistent with our findings, the elevation of sFlt-1/PIGF ratio and sEng level in MS limited to gestational period has been reported in a few previous studies [5, 7, 8]. More interestingly, normalization of the angiogenic factor levels after fetal transfusion was described in a case of MS caused by parvovirus B19 infection [5]. In contrast to the shared elevation of sFlt-1/PIGF ratio, the increase in serum hCG level as observed in MS is not common in PE.

Compared with previously reported MS cases with maternal hypertension or proteinuria [1, 2, 7], the serum sFlt-1 level was lower in our case. Maternal symptom before delivery was limited to pleural effusion and systemic edema without proteinuria and hypertension in our case. Taken together, severity of maternal symptoms in MS might paralleled with the serum sFlt-1 level.

It is known that sFlt-1 damages endothelial function and enhances vascular permeability by opposing the protective action
of VEGF [9]. Maternal systematic edema in MS could be partially explained by this mechanism. However, it remains unclear why maternal edema rather than hypertension and protein urea can be more remarkable in MS as observed in the present case, although the increase in sFlt-1 level is shared with PE. It is possible that increased serum hCG level in MS is involved in the worsening of maternal edema. In fact, administration of hCG is known to be a trigger of ovarian hyperstimulation syndrome which is a disease characterized by enhanced vascular permeability causing ascites.

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CONFLICT OF INTEREST STATEMENT
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ETHICAL APPROVAL
The design of this work has been approved by the University of Tokyo ethics committee.

CONSENT
Informed patient consent has been obtained.

GUARANTOR
T.N. accepts full responsibility for this work.

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