CASE REPORT

Changes in echocardiography and blood variables during and after development of Ballantyne syndrome

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SUMMARY

We report a pregnant woman who was monitored by echocardiography and determination of blood variables, including components of the renin–angiotensin–aldosterone system (RAAS), cardiac biomarkers and soluble fms-like tyrosine kinase-1 (sFlt-1), during and after the development of Ballantyne syndrome. Generalised maternal oedema with dyspnoea following fetal and placental hydrops necessitated a caesarean section at 33 weeks of gestation. Changes in blood variables and simultaneous echocardiography changes indicated acutely enhanced RAAS and hyperdynamic left ventricular function in response to excessive volume overload (as evidenced by brain-type natriuretic peptide level of 523 pg/mL) in the absence of increased systemic vascular resistance. Elevated sFlt-1 (15 600 pg/mL) and human chorionic gonadotrophin (404 000 IU/L) levels were also noted. The increased plasma aldosterone concentration (2070 pg/mL) may have been responsible for the increase in circulating plasma volume, and the increased sFlt-1 level was responsible for generalised maternal oedema. It remains unclear which factor(s) triggered RAAS activation.

BACKGROUND

Ballantyne syndrome, also called mirror syndrome or triple oedema, is a rare disorder affecting pregnant women with presentation of fetal and placental hydrops and maternal oedema.^{1–2} A review of 56 reported cases¹ has indicated that Ballantyne syndrome can occur in the presence of hydropic fetus regardless of its aetiology. The common maternal symptoms include weight gain/maternal oedema (89.3%), hypertension (60.7%), mild anaemia/haemodilution (46.4%) and albuminuria/proteinuria (42.9%).¹

Pregnant women are characterised by a greater increase in blood volume for gestational weight gain; average weight gain is a prepregnancy body weight of 20%,³ while the blood volume increases in pregnancy by 40%.⁴ The renin–angiotensin–aldosterone system (RAAS) is activated in pregnancy and the increased plasma aldosterone concentration (PAC) is considered to play a crucial role in the increase in circulating plasma volume.⁵ As excessive water retention may be a cardinal sign of Ballantyne syndrome; aberrant water metabolism may be involved in the pathogenesis. Anaemia and haemodilution associated with Ballantyne syndrome¹ imply increases in the circulating plasma volume, which may cause cardiac overload. However, to the best of our knowledge, there

have been no reports of the simultaneous determination of blood variables related to RAAS and echocardiography with blood cardiac biomarkers in patients with Ballantyne syndrome. We recently encountered a case of Ballantyne syndrome in which determination of blood variables pertinent to RAAS and echocardiography were performed simultaneously. The patient gave informed consent for this presentation.

CASE PRESENTATION

A 34-year-old nulliparous Japanese woman with gestational week (GW) 28–4/7 was referred to us for fetal hydrops; bilateral pleural effusion, ascites and generalised skin oedema were found in the fetus at that time. The results of blood tests and ultrasound examination suggested that hydrops was unlikely to be due to Rh alloimmunisation, anaemia, structural anomalies or congenital infections (including parvovirus B19, syphilis, toxoplasmosis, *Cytomegalovirus*, herpes simplex and herpes zoster) in this case. The placenta thickened to 6 cm at GW 29. Bilateral thoracoamniotic shunting was performed at GW 30–4/7, resulting in reductions in skin oedema and pleural effusion, and the disappearance of ascites within 1 week. However, generalised maternal oedema and dyspnoea with decreased SpO₂ to 96% under room air necessitated an emergency caesarean section at GW 33–5/7. A female infant weighing 1808 g was born with 1 min and 5 min Apgar scores of 8 and 7, respectively, and umbilical arterial blood pH of 7.35. The placenta was swollen (weight 1480 g) and histological examination confirmed placental hydrops. The patient developed neither hypertension nor significant proteinuria in pregnancy throughout pregnancy or the postpartum period.

INVESTIGATIONS

Serial determination of blood variables, including plasma renin activity (PRA), PAC, human chorionic gonadotrophin (hCG), soluble fms-like tyrosine kinase-1 (sFlt-1), brain-type natriuretic peptide (BNP), N-terminal fragment of precursor protein BNP (NT-proBNP) and high-sensitivity troponin I (hs-TnI), was performed (figure 1)^{6–9} with simultaneous echocardiography (figure 2). These tests have shown the following occurrences in the last week of pregnancy (from GW 32–6/7 to the day of delivery at GW 33–5/7) in this patient: markedly elevated hCG and sFlt-1 levels already at GW 32–6/7, acute superimposed enhancement of RAAS,

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Figure 1 Perinatal changes in blood variables in a woman with Ballantyne syndrome. Postpartum day. The vertical line indicates the day of delivery. Reference values for blood variables were as follows: the mean sFlt-1 concentrations were 1000–1500 and 4000–8000 pg/mL for healthy women in the third trimester and women with pre-eclampsia, respectively and median (range) values were 13 852 (518–74 719) IU/L for serum hCG, 6.5 (2–20) ng/mL/h for PRA, 667 (123–2010) pg/mL for PAC and 29 (5–108) pg/mL for NT-proBNP in healthy women in the third trimester. In the last week pregnancy, PRA (6.6–87 ng/mL/h) and PAC (920–2070 pg/mL) increased acutely accompanied with parallel increases in BNP (115–523 pg/mL), NT-proBNP (474–2960 pg/mL) and hs-TnI (5.3–35 pg/mL) levels and haemodilution. It was interesting to note that sFlt-1 and hCG levels were markedly elevated to 12 400 and 15 600 pg/mL, and 373 000 and 404 000 IU/L at GW 32–6/7 and 33–4/7, respectively. BNP, brain-type natriuretic peptide; GW, gestational week; hCG, human chorionic gonadotrophin; hs-TnI, highly sensitive troponin I; NT-proBNP, n-terminal fragment of precursor proteinBNP; PAC, plasma aldosterone concentration; PPD, postpartum day; PRA, panel reactive antibody; sFlt-1, soluble fms-like tyrosine kinase 1.

progressive haemodilution, acute increases in BNP, NT-proBNP and hs-TnI possibly in response to cardiac overload (evidenced by increase in left ventricular end-diastolic dimension, left atrial volume index, inferior vena cava diameter, hyperdynamic left ventricular function (evidenced by increased left ventricular ejection fraction and cardiac index and pulmonary congestion (evidenced by acute increase in pulmonary artery systolic pressure (figure 2). Antenatal systemic vascular resistance (SVR) was lower in this patient compared with that reported in healthy pregnant women.¹⁰

This patient exhibited an increased change in body weight peripartum; a weight gain of 5.3 kg in the last 1 week pregnancy and weight loss of 11.7 kg in the first week postpartum occurred in this patient, while the median (2.5th–97.5th) weight gain in the last 2 weeks of pregnancy was 0.76 (–1.66 to 4.01) kg and the corresponding weight loss in the first week postpartum was 4.70 (0.40–9.20) kg for otherwise healthy Japanese women.¹¹

TREATMENT

Oxygen inhalation at a rate of 3 L/min via a nasal cannula was given for 4 days (on the day of delivery and 3 days postpartum). Furosemide (15 mg) was given once intravenously on the day of delivery, but after the caesarean section. Continuous intravenous unfractionated heparin (417 U/h) was given for the first 3 days postpartum.

OUTCOME AND FOLLOW-UP

The patient left hospital on postpartum day 8 without complications. Her infant had chylothorax and developed respiratory distress syndrome requiring thoracic drainage and mechanical ventilation with tracheal intubation for 19 and 21 days, respectively. The infant left hospital weighing 2.9 kg at the age of 58 days in good condition.

DISCUSSION

To the best of our knowledge, this is the first case report in which PAC was measured in a patient with Ballantyne syndrome. Increased PRA level (30 ng/mL/h) has been documented previously in only one case with this syndrome,¹² consistent with our findings; PRA acutely increased from 6.6 to 87 ng/mL/h, concomitant with an increase in PAC from 920 to 2070 pg/mL in the last week of pregnancy in our case. The PAC level determined by our method ranged from ~30 to 120 pg/mL for non-pregnant adults, and the median (range) PAC value was 667 (123–2010) pg/mL for otherwise healthy pregnant women in the third trimester.⁶ We speculated that the increased PAC was responsible for excessively increased circulating plasma volume causing haemodilution in this patient. PAC can be released by hCG directly via stimulation of the luteinising hormone receptor expressed in the adrenal gland,¹³ but the increase in PRA occurred concomitant with the increase in PAC in this case.

Figure 2 Perinatal changes in echocardiographic measurements in a woman with Ballantyne syndrome. Postpartum day. Echocardiography was performed by a single trained operator (TU) at GW 32–6/7, 33–0/7, 33–4/7, day of delivery (GW 33–5/7) and postpartum days 1, 2, 7, 30 and 121. The vertical line indicates the day of delivery. GW, gestational week; IVCD, inferior vena cava diameter; LAVI, left atrial volume index; LVDd, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PPD, postpartum day; SVR, systemic vascular resistance.

Elevated levels of hCG and sFlt-1 were shown to be associated with Ballantyne syndrome:^{2 14 15} maternal serum hCG level is significantly higher for hydropic infants with Ballantyne syndrome than those without (453 000 vs 80 000 IU/L, respectively);² median (range) plasma sFlt-1 level is significantly higher for mothers with Ballantyne syndrome than those without (3974 (3083–10 780) vs 824 (260–4712) pg/mL, respectively);¹⁴ and plasma sFlt-1 levels were 11 650 pg/mL in a woman with cytomegalovirus-induced Ballantyne syndrome¹⁵ and 14 117 pg/mL in a woman with parvovirus B19-induced fetal and placental hydrops.¹⁶ In addition, in the presence of placentomegaly regardless of its aetiology, elevated levels of sFlt-1 were observed in one case with triploidy (karyotype 69, XXY) at GW 14 (2953 pg/mL) and in another case with hydatidiform moles at GW 18 (4865 pg/mL).¹⁷ The sFlt-1 may be derived mainly from the placenta,¹⁸ cause vascular endothelial dysfunction¹⁸ and was suggested to be elevated in women with abnormal placental perfusion.⁷ Although it is still unclear whether hydropic placenta or enlarged placenta is more likely to produce sFlt-1 and hCG, we speculated that the elevated sFlt-1 level in the presence of increased maternal circulation associated with higher PAC level caused maternal oedema via enhanced vascular permeability.

Women with Ballantyne syndrome often show clinical signs of pre-eclampsia, such as hypertension and proteinuria.¹ However, the present echocardiography results together with previous findings¹⁰ suggested differences in haemodynamics between the two conditions. Antenatal SVR was lower in this case compared with that reported in healthy pregnant women,¹⁰ while the SVR is higher for women with pre-eclampsia than for healthy

pregnant women.¹⁰ This difference may have reflected a difference in the circulating plasma volume, increased and decreased plasma volume, compared with those in healthy pregnant women in this case and pre-eclampsia,¹⁹ respectively.

This case suggested superimposed RAAS enhancement in the pathogenesis of Ballantyne syndrome. It remains unclear which factor(s) triggered RAAS enhancement in this case.

Learning points

- It is unclear whether excessive enhancement of the renin–angiotensin–aldosterone system (RAAS) is involved in the pathogenesis of Ballantyne syndrome.
- This case demonstrated acute enhancement of RAAS occurring concomitant with the development of Ballantyne syndrome.
- Elevated plasma aldosterone concentration may have been responsible for excessive water retention in this case of Ballantyne syndrome.
- It remains unclear which factor(s) triggered RAAS enhancement in this case.

Contributors TU, TY, MM, and HM participated in the medical treatments of the patient. TU, TY, and HM analysed the data and wrote the manuscript.

Competing interests None declared.

Patient consent Obtained.

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