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Author(s)	Suzuki, Yutaro; Yamamura, Mie; Kikuchi, Keisuke; Hattori, Rifumi; Umazume, Takeshi; Minakami, Hisanori
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Title: Echocardiography findings in a case with Ballantyne syndrome

Short running title: Echocardiography in Ballantyne syndrome

Yutaro Suzuki¹, Mie Yamamura¹, Keisuke Kikuchi², Rifumi Hattori¹, Takeshi Umazume³, Hisanori Minakami³

1 Department of Obstetrics and Gynecology, Obihiro-Kosei General Hospital, Obihiro, Hokkaido, Japan

2 Department of Pathology, Obihiro-Kosei General Hospital, Obihiro, Hokkaido, Japan

3 Department of Obstetrics, Hokkaido University Graduate School of Medicine, Sapporo, Japan

Corresponding author: Hisanori Minakami

Department of Obstetrics, Hokkaido University Graduate School of Medicine, Kita-ku N14 W6, Sapporo 060-8638, Japan

Email: minasho@med.hokudai.ac.jp

Abstract

Marked fluid retention occurs in Ballantyne syndrome, but few reports are available on changes in cardiac morphology in this syndrome. A woman with generalized edema, dyspnea, fetal hydrops (skin edema and ascites), thickened placenta, and elevated plasma BNP level (344 pg/mL) was admitted to our hospital at gestational week (GW) 20-3/7. Blood pressure remained within the normal range. However, acute increases in left atrial volume index, pulmonary artery systolic pressure, and hyperdynamic left ventricular function (as evidenced by increased left ventricular ejection fraction to 74% with cardiac index of 5.1 L/min/m²) occurred preceding fetal death at GW 21-4/7 in the presence of increased inferior vena cava diameter (23 mm) and relatively low systemic vascular resistance of 752 dyn·s/cm⁵. These findings suggested life-threatening heart failure and required cesarean delivery at GW 21-5/7 resulting in complete recovery. The placenta suggested cytomegalovirus infection.

Key words: heart failure, renin-angiotensin-aldosterone system (RAAS), soluble fms-like tyrosine kinase-1 (sFlt-1), triple edema syndrome

Introduction

Ballantyne syndrome, also called mirror syndrome, is characterized by triple edema, including fetal and placental hydrops and maternal edema.^{1,2} Other clinical signs include hypertension (in 57% – 78% of patients), proteinuria (20% – 56%), pulmonary edema (21%), and intrauterine fetal death (IUFD) (56%), as described in a previous review by Braun *et al.*¹ Triple edema occurs regardless of the etiology underlying fetal hydrops, including rhesus isoimmunization, twin–twin transfusion syndrome, viral infection and fetal malformations, and fetal or placental tumors.¹

As excessive water retention is a cardinal sign of Ballantyne syndrome and as pulmonary edema with dyspnea can be considered as a sign associated with heart failure, aberrant water metabolism may be involved in the pathogenesis leading to altered cardiac morphology as well as function. Anemia and hemodilution are seen frequently in Ballantyne syndrome,¹ which may imply an increase in the circulating plasma volume that would result in cardiac overload. To our knowledge, however, there has been only one report regarding cardiac morphology and function determined on echocardiography in patients with Ballantyne syndrome.³

The endocrine environment is markedly altered after pregnancy; the renin-angiotensin-aldosterone system (RAAS) is activated and plays a critical role in the increased circulating blood volume in pregnancy⁴ and soluble fms-like tyrosine kinase-1 (sFlt-1) derived mainly from the placenta may be a key factor responsible for increased vascular permeability⁵ leading to edema in pregnancy. Recently, we encountered a case of Ballantyne syndrome in which determinations of cardiac status on echocardiography and blood variables pertinent to RAAS as well as sFlt-1 were performed simultaneously. The patient gave informed consent for this presentation.

Case

A 33-year-old nulliparous Japanese woman presented with generalized edema, dyspnea, oliguria, and malaise, and was admitted to Obihiro-Kosei General Hospital at gestational week (GW) 20-3/7. Her pregnancy was unremarkable and her weight was 53.6 kg at the antenatal care visit on GW 18-0/7 (Table 1). Fetal hydrops (skin edema and ascites) and thickened placenta (4.8 cm), decreased blood oxygenation (SpO₂ 93%), bilateral pleural effusion on chest X-ray, spot urine protein:creatinine ratio (mg/mg) of 0.45, and increased body weight (59.6 kg) were noted on admission (Table 1). Ultrasound examination suggested fetal anemia, as evidenced by increased fetal middle cerebral peak systolic velocity to 51 cm/s (corresponding to 1.9 multiples of the median) with no structural anomalies, but blood test suggested that hydrops fetalis was unlikely to be due to Rh alloimmunization or congenital infections (including parvovirus B19, syphilis, toxoplasmosis, and cytomegalovirus) in this case (see footnote for Table 1). Use of a diuretic (furosemide) initiated at GW 21-3/7 was effective in prevention of fluid retention (monitored by maternal weight), but ineffective for creatinine clearance (monitored by serum creatinine) (Fig. 1B). Blood pressure was consistently normal and proteinuria was transient (Table 1). However, acute increases in left atrial volume index (LAVI, 53.1 mL/m²), pulmonary artery systolic pressure (PASP, 50.1 mmHg), left ventricle mass index (LVMI, 81.9 g/m²), and left ventricular ejection fraction (LVEF, 74%) occurred at GW 21-3/7 (Fig. 1A) in the presence of sustained increased inferior vena cava diameter (IVCD) of 23 mm. IUFD occurred on the next day at GW 21-4/7. Dyspnea suggestive of heart failure and immature uterine cervix necessitated cesarean section at GW21-5/7. The patient gave birth to a stillborn female infant weighing 678 g. The placenta was swollen and histological examination confirmed placental hydrops and suggested cytomegalovirus infection (Fig. 1C). The patient required 5-day mechanical ventilation with tracheal intubation postpartum and left hospital without sequelae on postpartum day (PPD) 15. She lost 9.1 kg of weight in 7 days postpartum (see footnote for Table 1).

Markedly elevated B-type natriuretic peptide (BNP) to 344 pg/mL already at GW 20-3/7 (Table 1) together with echocardiography findings (Fig. 1A) suggested heart failure. Blood hCG and sFlt-1 levels were markedly increased to > 1000000 IU/L and 43900 pg/mL, respectively at GW 21-3/7, but RAAS components, including plasma renin activity (PRA) and plasma aldosterone concentration (PAC), were within the respective normal ranges (see footnote for Table 1).

Discussion

To our knowledge, there has been only one other case in which detailed echocardiography was performed in Ballantyne syndrome.³ In the present case, increased BNP in response to cardiac overload (as evidenced by increased LAVI and IVCD), hyperdynamic left ventricular function (as evidenced by increased LVEF and cardiac output), and pulmonary congestion (as evidenced by acute increase in PASP) (Fig. 1, left) occurred in the presence of rather lower systemic vascular resistance compared to the data reported previously by Simmons *et al.*⁹ All of these findings were consistent with those in the previous case with Ballantyne syndrome³ suggesting that

heart failure is common in this syndrome. Acute change in these echocardiography findings in a short time (within a week) may have been associated with an acute increase in circulating plasma volume. This would explain why hemodilution is seen in approximately 50% of cases with Ballantyne syndrome.¹ It was speculated that changes in some parameters on echocardiography may have been more marked immediately after childbirth if tested (as shown in dotted lines in Fig. 1A) because the blood that perfused the placenta and pregnant uterus and excess water retained in the interstitial space may have returned to the general circulation.

Dyspnea and triple edema (maternal edema, hydrops fetalis, and placental hydrops) may have been due to excessive fluid retention in the lung, maternal interstitial space, fetus, and placenta causing greater changes in perinatal maternal weight; increased weight gain (6.0 kg in 17 days) preceding episodes that required in-hospital care and large weight loss (9.1 kg) in the first week postpartum in this patient as well as in our previous case (weight gain of 5.3 kg in the last 1 week of pregnancy and weight loss of 11.7 kg in the first week postpartum).³ Gestational weight gain may vary according to ethnicity. However, among 128,838 Japanese women with singleton pregnancies,¹⁰ the mean (SD) weekly weight gain was 0.26 (0.12) kg and total gestational weight gain was approximately 9.6 (4.4) kg. Median (2.5th – 97.5th) weight gain in the last 2 weeks of pregnancy was 0.76 (–1.66 – 4.01) kg and median (2.5th – 97.5th) weight loss in the first week postpartum was 4.70 (0.40 – 9.20) kg for otherwise healthy Japanese women with singleton pregnancies.⁸ Thus, it was evident that a greater degree of water retention in the interstitial space occurred via plasma leakage from the circulation, possibly due to increased vascular permeability in the present case as well as our previous case with Ballantyne syndrome.

The sFlt-1 is derived mainly from the placenta and causes vascular endothelial dysfunction.⁵ Elevated sFlt-1 level is seen exclusively in Ballantyne syndrome when tested regardless of the etiology leading to fetal hydrops^{3,11–14} and may be a causative factor of vascular hyperpermeability. This explains increased interstitial fluid, i.e., edema, but not increased plasma volume in Ballantyne syndrome. The activated RAAS with increased PAC level is considered to be responsible for the increased plasma volume in pregnancy⁴ and PAC was indeed markedly elevated in our previous case with Ballantyne syndrome,³ but not in the present case. PAC can be released by hCG directly via stimulation of the luteinizing hormone receptor expressed in the adrenal gland.¹⁵ Elevated hCG level is seen in Ballantyne syndrome,² as was seen in the present case. However, it is unknown whether the elevated hCG level plays a role in the clinical manifestations of Ballantyne syndrome via stimulation of PAC release.

The findings in this case emphasized cardiac overload due to increased circulating plasma volume occurring in Ballantyne syndrome. The elevated sFlt-1 level may be responsible for triple edema, but the role of elevated hCG level and causative factors for increased circulating plasma volume are not yet known.

Conflict of Interest

None declared.

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Figure Legend

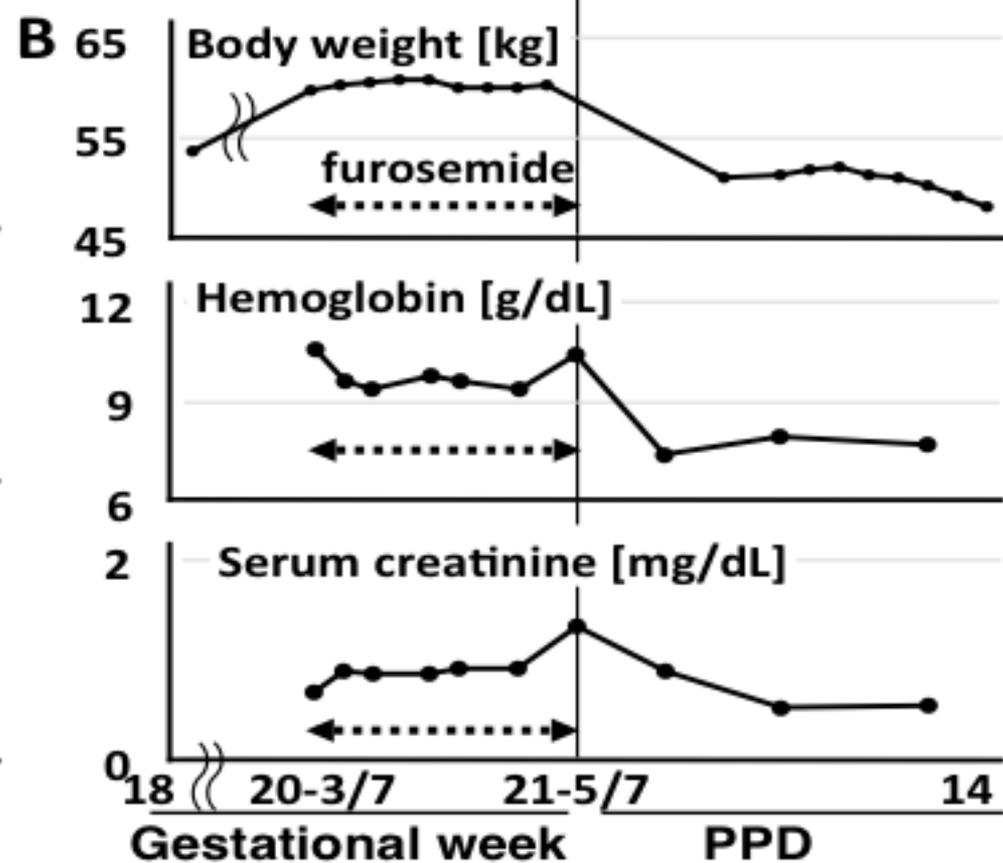
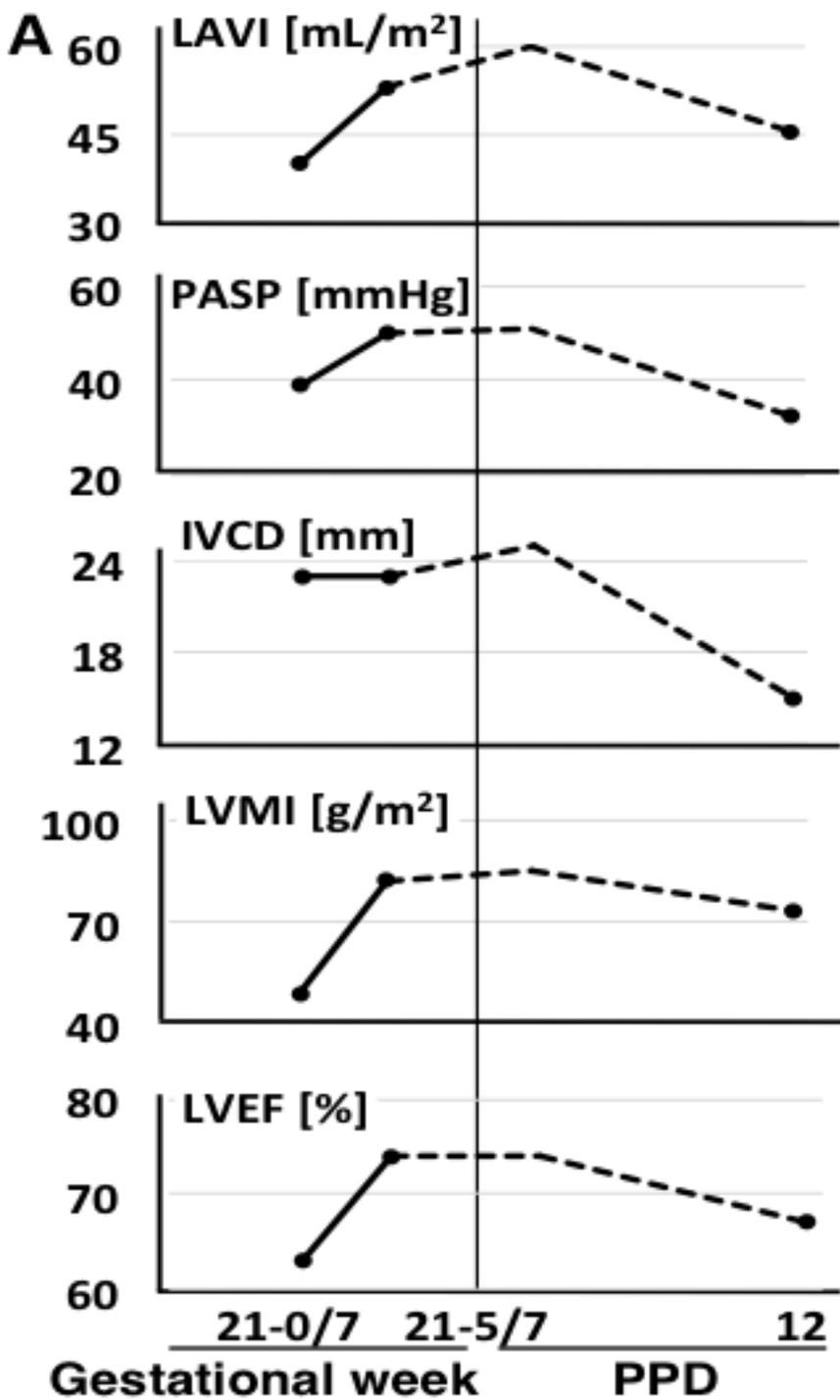
Figure 1. Findings in a woman with Ballantyne syndrome

A: Perinatal changes in echocardiographic measurements. Echocardiography was performed at GW 21-0/7, GW 21-3/7, and on postpartum day (PPD) 12. The dotted lines were based on our speculations. The vertical line indicates the day of delivery (GW 21-5/7). Cardiac index and systemic vascular resistance were 5.1 L/min/m² and 752 dyn·s/cm⁵, respectively at GW 21-3/7. Institutional reference values (mean [SD]) for pregnant women in the second trimester are as follows: 23.1 (7.1) mL/m² for left atrial volume index (LAVI), 62.0 (10.4) g/m² for left ventricle mass index (LVMI), 64.2 (4.6)% for left ventricular ejection fraction (LVEF), and 13.2 (3.3) mm inferior vena cava diameter (IVCD). The reference interval for pulmonary artery systolic pressure (PASP) is unknown.

B: Perinatal changes in maternal weight and blood hemoglobin and creatinine levels. Intravenous furosemide was initiated at GW 21-3/7 and continued until delivery; 40 mg/day for one day followed by 80 mg/day for three days and 200 mg/day for 6 days.

C: Microscopic findings in the placenta.

Left (stained with Hematoxylin Eosin), a white arrow indicating an inclusion body; Right, cytomegalovirus-immunohistochemistry. These suggested that the placenta was infected with cytomegalovirus.



C

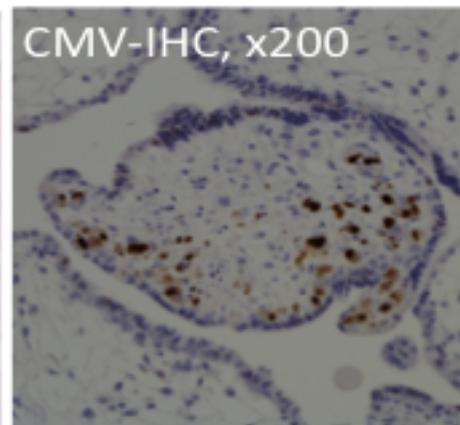
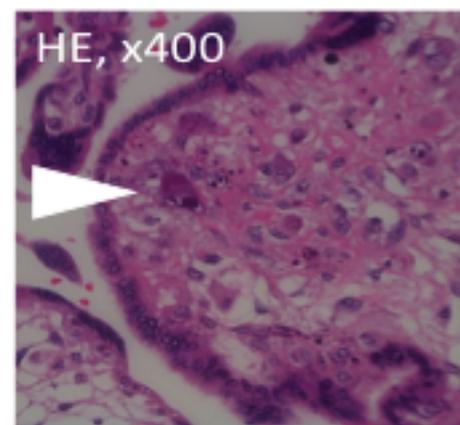


Table 1. Pertinent data in a patient with cytomegalovirus-induced Ballantyne syndrome

Gestational week (GW)	12-3/7	18-0/7	20-3/7	21-0/7	21-3/7*	PPD3	PPD12
<i>Physical findings</i>							
Maternal weight (kg)	52.0	53.6	59.6	60.7	60.0		50.0
Blood pressure (mmHg)			113/54	115/58	124/70	89/40	102/53
Urinary PCR (mg/mg)			0.45		0.10	0.11	0.11
<i>Blood data</i>							
Hemoglobin (g/dL)	12.3		10.6	9.8	9.4	7.4	7.7
Platelet ($\times 10^9/L$)	103		81	63	58	75	117
Antithrombin activity (%)			75	57			69
AST/ALT (IU/L)			21/8	21/7	26/8	22/9	19/13
Creatinine (mg/dL)			0.66	0.87	0.92	0.88	0.53
BNP (pg/mL)			344		453		157
High-sensitivity troponin I (pg/mL)					<2.0	<2.0	
PRA (ng/mL/hour)					6.8		3.8
PAC (pg/mL)					678		118
s-Flt-1 (pg/mL)					43900		
hCG (IU/L)					>1000000		

*, one and two days before intrauterine fetal death (at GW 21-4/7) and caesarean section (at GW 21-5/7), respectively; AST/ALT, aspartate aminotransferase/alanine aminotransferase; BNP, B-type natriuretic peptide; hCG, human chorionic gonadotropin; PAC, plasma aldosterone concentration; PCR, protein:creatinine ratio; PPD, postpartum day; PRA, plasma renin activity; sFlt-1, soluble fms-like tyrosine kinase-1. Reference values for blood variables were as follows: mean sFlt-1 concentration is approximately 1000 pg/mL for healthy women in the second trimester;⁶ and median (range) values are 15088 (1542–73485) IU/L for serum hCG in women at GW 21,⁷ 7.2 (1–20) ng/mL/h, and 397 (94–1750) pg/mL for PRA and PAC, respectively in healthy women in the second trimester.⁸ IgG and/or IgM antibodies against microorganisms, including *Toxoplasma gondii* (IgG, < 7.5 IU/mL; IgM, < 0.8 [signals/cut-off]), *Cytomegalovirus* (IgG, 27.6 [EIA index]; IgM, 0.22 [antibody index]), and *Parvovirus B19* (IgM, 0.16 [antibody index]) determined at GW 20-3/7 did not suggest recent infections by these microorganisms. Body weight was 60.2 kg on the day of delivery and 51.1 kg and 48.0 kg on PPD 7 and 14, respectively