



Title	Unusual clinical course of preeclampsia heralded by generalized edema
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3 **Unusual clinical course of preeclampsia heralded by generalized edema**

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11 Running foot: Unusual preeclampsia heralded by edema

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19

20 **Abstract**

21 **Background:** Preeclampsia monitored by the amount of proteinuria usually does not
22 show amelioration during pregnancy.

23 **Case:** A 37-year-old nulliparous woman was admitted to our hospital at gestational
24 week (GW) 24^{-1/7} due to rapid weight gain (6.2 kg/4 weeks) and oligohydramnios.
25 Hypertension (151/91 mmHg) appeared at GW 25^{-0/7} and proteinuria not detected at
26 GW 24^{-0/7}, became significant (0.55 g/day) at GW 25^{-2/7}. During the two successive
27 weeks after administration of betamethasone at 12 mg twice and transabdominal
28 amnioinfusion with 250 mL of Ringer's acetate solution at GW 25^{-3/7}, generalized
29 edema, proteinuria, and thrombocytopenia markedly improved: body weight, 78.0 –
30 69.0 kg; proteinuria (g/day), 7.1 – 1.3; and platelet count ($\times 10^9/L$), 111 – 230. However,
31 intrauterine infection accompanied by non-reassuring fetal status necessitated
32 emergency cesarean section at GW 28^{-3/7}.

33 **Conclusion:** Extraordinary body weight gain can herald the occurrence of
34 preeclampsia and this weight gain together with signs of preeclampsia can
35 ameliorate even during pregnancy, although its mechanism is unclear.

36

37 **Keywords:** gestational edema, preeclampsia, thrombocytopenia, vascular permeability

38

39 Introduction

40 Women with preeclampsia are likely to show excessive water retention [1]. Although
41 generalized edema can precede the development of preeclampsia [2], there is as yet no
42 technical term applicable to the condition of edema alone. Preeclampsia usually does
43 not show amelioration during pregnancy. **Here, we present a pregnant woman in**
44 **whom preeclampsia was heralded by generalized edema and clinical signs of**
45 **preeclampsia acutely ameliorated during pregnancy.**

46

47 Presentation of the case

48 This study was approved by the institutional review board of the Hokkaido University
49 Hospital and was undertaken following the provisions of the Declaration of Helsinki.

50 A 37-year-old nulliparous Japanese woman presented with marked edema (weight gain
51 of 6.2 kg/4 weeks) (Fig. 1) and oligohydramnios (amniotic fluid index [AFI] of 4.8 cm)
52 in the absence of hypertension, proteinuria, or placental edema and was admitted to our
53 hospital at gestational week (GW) 24^{-1/7}. Hypertension (151/91 mmHg) and proteinuria
54 (0.55 g/day) appeared at GW 25^{-0/7} and GW 25^{-2/7}, respectively. **Primary**
55 **aldosteronism**, autoimmune diseases, or thyroid diseases were considered unlikely by
56 endocrinologists and immunologists (Table 1). Administration of betamethasone for
57 fetal lung maturation (intramuscular 12 mg twice) and amnioinfusion with 250 mL of
58 Ringer's acetate solution for oligohydramnios (AFI of 0.4 cm) were performed at GW
59 25^{-3/7} (Fig. 1). An AFI of 11.5 cm at GW 25^{-4/7} gradually decreased to 3.8 cm at GW
60 27^{-6/7}. Treatment with oral nifedipine (20 mg/day) was initiated at GW 26^{-0/7}. The
61 maternal body weight began to decrease after showing a peak value at GW 25^{-5/7} and
62 platelet counts began to increase after showing a nadir value at GW 26^{-6/7}, while

63 hematocrit values were stable (Fig. 1). Proteinuria (g/day) also began to decrease after
64 showing a peak value of 7.1 at GW 26^{-6/7} to 1.3 at GW 27^{-3/7}, respectively, while blood
65 pressure remained high (140 – 170/75 – 95 mmHg).

66 Four days after the second amnioinfusion (250 mL of Ringer's acetate solution) at GW
67 27^{-6/7} for oligohydramnios (AFI of 3.8 cm), the patient exhibited fever of 38.6°C with
68 elevated C-reactive protein level (5.7 mg/dL) and WBC count (20200/ μ L), as well as
69 non-reassuring fetal status at GW 28^{-3/7}. A growth restricted (-1.45 SD) female infant
70 weighing 820 g was born by emergency cesarean section. Pathological examination of
71 the placenta revealed chorioamnionitis (stage III). The infant survived septicemia with
72 *Abiotrophia defectiva* and left our hospital on hospital day 85. Magnetic resonance
73 imaging (MRI) of the infant's brain performed on hospital day 82 was unremarkable.
74 The mother leaving our hospital on postpartum day 8 showed normal blood pressure
75 (127/69 mmHg) and non-significant proteinuria (negative on dip stick test) at 1 month
76 postpartum.

77

78 **Discussion**

79 This patient exhibited two unusual features of pregnancy. First, her preeclampsia was
80 heralded by extraordinary weight gain between GW 20 and 24. Second, her
81 preeclampsia monitored by changes in body weight (degree of edema), proteinuria, and
82 platelet counts showed amelioration during pregnancy.

83 We previously encountered a woman who exhibited rapid weight gain (6.0 kg in the last
84 7 days of pregnancy) with gradual declines in antithrombin activity and platelet count
85 until delivery [2]. In this previous case, the risk of pulmonary edema necessitated
86 cesarean section at GW 37 in the absence of hypertension and proteinuria, and

87 pulmonary edema actually developed postpartum followed by hypertension, but the
88 diagnosis of preeclampsia had to wait until 5 days after delivery at which time
89 proteinuria developed [2]. Thus, a type of preeclampsia with edema as its initial sign
90 indeed exists. The present case also showed a gradual decline in platelet count (Fig. 1)
91 and modestly reduced antithrombin activity (72% of normal activity level). Pregnant
92 women with reduced antithrombin activity and/or platelet counts are suggested to be
93 suffering from increased blood vessel permeability [3, 4]. The appearance of edema is
94 likely a consequence of endothelial leakage of plasma into the interstitial space.
95 Consequently, plasma volume is reduced by approximately 20% in women with
96 preeclampsia [5] and more in women with eclampsia [6]. The rapid and extraordinary
97 weight gain in our patient may be explained by the same mechanism as that in women
98 with preeclampsia.

99

100 Amounts of protein in the urine increase with advancing gestation irrespective of the
101 presence or absence of hypertension [7]. In the presence of increased blood vessel
102 permeability, adequate water intake results in edema formation with stable hematocrit
103 value, but insufficient water intake results in increased hematocrit value, and finally a
104 decrease in body weight designated as “dehydration.” Thus, in the presence of increased
105 blood vessel permeability, maternal body weight is unlikely to decrease in the absence
106 of changes in hematocrit value. However, the present case exhibited marked weight
107 reduction with stable hematocrit value and a decrease in proteinuria. As the period until
108 delivery after the diagnosis of preeclampsia is approximately 2 weeks [7], this patient
109 received steroid administration and amnioinfusion, resulting in an increase of AFI from
110 0.4 to 11.5 cm. It remains unclear whether these treatments contributed to the favorable

111 changes in various parameters seen in this patient.

112

113 **Disclosure**

114 All authors declare that they have no financial relationship with a biotechnology
115 manufacturer, a pharmaceutical company, or other commercial entity that has an interest
116 in the subject matter or materials discussed in the manuscript.

117

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139

140 **Figure Legend**

141 Figure 1: Changes in maternal body weight (○), platelet counts (●), and hematocrit

142 value (×)

143 PPD, postpartum day

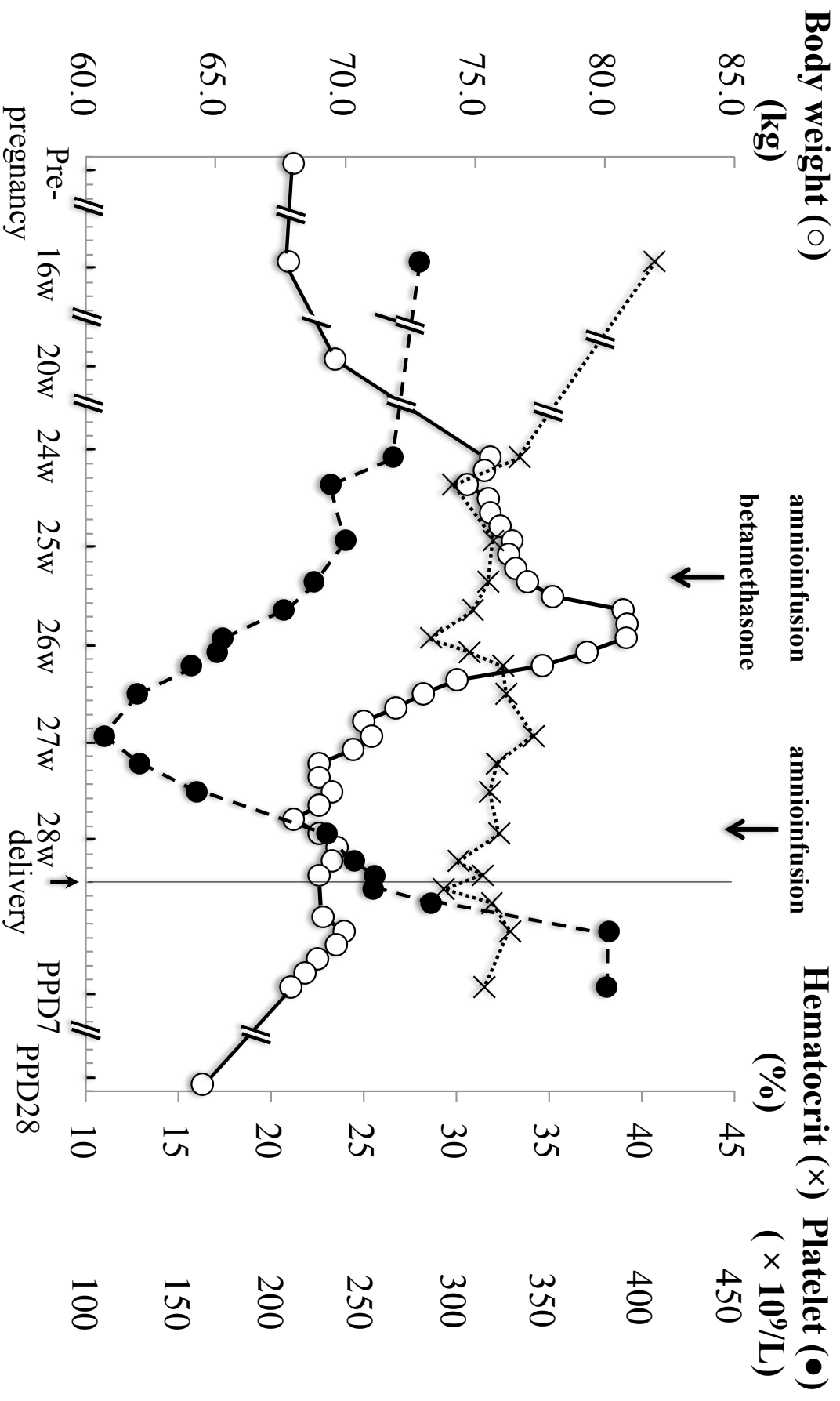


Table 1. Results of laboratory work-up and Doppler study

Antithrombin activity [% of normal activity level]; 78 (24^{-0/7}), 72 (25^{-2/7}), 86 (27^{-6/7})

AST [IU/L]; 12 (24^{-0/7}), 13 (28^{-3/7}), 16 (PPD 3); LDH (IU/L), 161 (24^{-0/7}), 137 (28^{-3/7}), 190 (PPD 3)

PAC [ng/L]; 124 (24^{-6/7}), 115 (26^{-0/7}); PRA [ng/mL/hour]; 2.8 (24^{-6/7}), 2.7 (26^{-0/7})

TSH; 2.16 μ IU/mL (24^{-6/7}): Free T4; 1.1 ng/dL (24^{-6/7})

NT-proBNP [ng/L]; 992 (26^{-0/7}), 79 (27^{-6/7})

IgA; 147 mg/dL (24^{-2/7}): IgG; 735 mg/dL (24^{-2/7}): IgM; 186 mg/dL (24^{-2/7}):
IgE; 107 mg/dL (24^{-2/7})

C3 *; 95 mg/dL (24^{-2/7}): C4*; 7 mg/dL (24^{-2/7}): CH50*; 31 U/mL (24^{-2/7})

Rheumatoid factor; 0.9 IU/mL (24^{-2/7}): Antinuclear antibody; negative (24^{-2/7})

Anti-cardiolipin antibody; ND (25^{-2/7}): Lupus anticoagulant; ND (25^{-2/7})

Anticardiolipin- β 2 glycoprotein I complex antibody; ND (26^{-1/7})

Umbilical artery pulsatility index; 1.52 (25^{-2/7}), 0.99 (28^{-2/7})

Umbilical artery resistance index; 0.76 (25^{-2/7}), 0.65 (28^{-2/7})

Fetal middle cerebral artery pulsatility index; 1.27 (25^{-2/7}), 1.30 (28^{-2/7})

Fetal middle cerebral artery resistance index; 0.73 (25^{-2/7}), 0.74 (28^{-2/7})

Gestational week at examination is indicated in parenthesis.

PPD 3, postpartum day 3; AST, Aspartate aminotransferase; LDH, Lactate dehydrogenase;

PAC, plasma aldosterone concentration; PRA, plasma renin activity; TSH, thyroid stimulating hormone;

NT-proBNP, N-terminal fragment of precursor protein brain-type natriuretic peptide;

Ig, Immunoglobulin; *, Complement; ND, not detected