CASE REPORT

Development of severe thrombocytopenia 3 months after delivery complicated with early-onset preeclampsia: a case report

Ikuno Kawabata, Reiko Nagata, Yoichi Sato, Jun Kakogawa, Masaki Ogawa, Tsutomu Tabata

Perinatal Medical Center, Tokyo Women’s Medical University, Tokyo, Japan

We report a case of preeclampsia with severe organ dysfunction, diagnosed conclusively as antiphospholipid syndrome (APS), following the onset of severe thrombocytopenia 3 months after delivery. A 21-year-old female (gravida 1, para 0) delivered preterm at 31 weeks of gestation due to preeclampsia. During pregnancy, hypertension remained in the mild range (<160/100 mmHg) during the day, but proteinuria (12.5 g/gCr) and thrombocytopenia (51,000/μl) were severe. After delivery, proteinuria and platelet count improved rapidly, but at 3 months after delivery, platelet count fell to 15,000/μl. Diagnostic workup for the cause of thrombocytopenia revealed positive lupus anticoagulants. The patient was diagnosed with APS based on her pregnancy course and positive antiphospholipid antibodies. Long-term follow-up is imperative for patients with early-onset preeclampsia with severe organ dysfunction, even if their clinical symptoms improve.

Introduction

Preeclampsia is a major cause of maternal and fetal mortality and morbidity. It presents as multisystem dysfunction characterized by hypertension, proteinuria, and renal, hepatic, and neurological involvement in pregnant women. Antiphospholipid syndrome (APS) increases the risk of recurrent pregnancy loss, stillbirth, and ischemic placental dysfunction such as severe preeclampsia and fetal growth restriction.1 Women with a history of eclampsia or early-onset preeclampsia should be tested for antiphospholipid antibodies (aPL). However, most women with preeclampsia show improvement in clinical findings as well as laboratory test results within 3 months after delivery. The International Society for the Study of Hypertension in Pregnancy (ISSHP) guidelines recommend that all women with preeclampsia be followed up to 3 months postpartum, as blood pressure, urinalysis, and all laboratory test results should be normalized by this time.2 Patients who fail to show any improvement during this period should be referred to cardiovascular specialists, nephrologists, or hematologists. However, blood pressure measurements, urinalysis, and laboratory tests associated with preeclampsia are often stopped once patients show improved clinical data, before 3 months after delivery.

Here, we report a case of a 21-year-old female who delivered at 31 weeks of gestation due to early-onset preeclampsia with severe organ dysfunction. Her clinical data improved around 1 month after delivery, but she developed severe thrombocytopenia 3 months after delivery. The patient was examined further to determine the cause of thrombocytopenia and was diagnosed with APS.

Case presentation

A 21-year-old (gravida 1, para 0) Japanese female was referred to our perinatal medical center at 29 weeks 0 days of gestation with mild hypertension and proteinuria. Her height and weight were 152.8 cm and 53.5 kg (46.7 kg before pregnancy), respectively, at first visit. The course of pregnancy was normal in the first and early second trimesters.

At the time of evaluation at 29 weeks 0 day of gestation, her blood pressure was 150/93 mmHg, and
her urinary protein as tested with reagent strips was 4+. The estimated fetal body weight by ultrasonography was 1,166 g (−0.9 SD) without fetal growth restriction, the amniotic fluid index was 14.3, and the biophysical profile score was 10/10. At the initial visit, laboratory results were consistent with thrombocytopenia (118,000/μL) and proteinuria (urine protein/creatinine ratio, 2.84 g/gCre). She was admitted for a physical examination and prescribed bed rest.

After admission, the patient’s blood pressure returned to within normal limits during the daytime (systolic blood pressure < 140 mmHg; diastolic blood pressure < 90 mmHg), but increased slightly before bedtime around 9 pm (systolic blood pressure, 140–150 mmHg; diastolic blood pressure, 90–100 mmHg). Proteinuria, creatine, and uric acid levels increased, and platelet count decreased.

Figure 1.
Trends in blood pressure, platelet count, and urine protein/creatinine ratio during the clinical course of the patient after admission. (A) Blood pressure. Gray area represents blood pressure measurements before bedtime (around 9 pm) (B) Platelet count. (C) Urine protein/creatinine ratio.
Cre, creatinine; DBP, diastolic blood pressure; GA, gestational age; SBP, systolic blood pressure.
over the following 2 weeks (Figure 1). Although the estimated fetal weight did not increase, the fetus appeared healthy. At 31 weeks of gestation, blood pressure before bedtime increased to >160/110 mmHg, but she did not complain of hypertensive symptoms such as headache. Her blood pressure often dropped below 160/110 mmHg after recheck a few hours later. Occasionally, when her systolic blood pressure before bedtime was high, she took alpha-methyldopa, an antihypertensive agent. During daytime, her blood pressure naturally declined to within the mild hypertensive range without the antihypertensive agent. The patient gained approximately 2 kg in 1 week, and generalized edema worsened. At 31 weeks of gestation, urinary protein level and protein/creatinine ratio were 10.61 g/day and 12.45 g/gCre, respectively; serum creatinine was 0.76 mg/dl; uric acid was 8.3 mg/dl; serum total protein and albumin were 5.2 g/dl and 2.0 g/dl, respectively; aspartate transaminase and alanine transaminase levels were within normal ranges; platelet count was $5.1 \times 10^4/\mu l$; and activated partial thromboplastin time, antithrombin III, and fibrinogen were 36.6 seconds, 65%, and 305 mg/dl, respectively. Laboratory analysis revealed worsening of proteinuria, renal function, and thrombocytopenia. Organ dysfunction, as indicated by thrombocytopenia and proteinuria, was markedly exacerbated, although no antihypertensive treatment was required for hypertension. Emergency cesarean section was performed at 31 weeks and 3 days of gestation due to worsening of thrombocytopenia and renal function. General anesthesia was administered

![Figure 2.](image)

Trends in platelet count and urine protein/creatinine ratio during the clinical course of the patient after delivery. (A) Platelet count. (B) Urine protein/creatinine ratio.

Cre, creatinine
given the low platelet count, and the patient gave birth to a boy weighing 1,526 g, which is an appropriate weight for the gestational age. The infant’s Apgar scores were 4 and 6 at 1 and 5 min, respectively, and the umbilical arterial blood gas pH was within the normal range at 7.292.

After delivery, maternal blood pressure increased to 160–180/80–100 mmHg. A calcium channel blocker was administered for antihypertensive treatment, resulting in normalized blood pressure; antihypertensive treatment was discontinued one month after delivery. The urine protein/creatinine ratio decreased from 6.75 g/gCre at 1 week after delivery to 1.65 and 1.02 g/gCre at 1 and 3 months, respectively, after delivery (Figure 2). Based on these findings, proteinuria was considered to be due to chronic nephritis. Proteinuria was not detectable at 5 months after delivery. Renal biopsy was not performed due to minimal proteinuria and no decline in renal function. Blood pressure remained in the normal range with no increase.

Conversely, the platelet count, which initially increased to 199,000/μl at 2 weeks after delivery, showed a rapid decrease to 15,000/μl at 3 months after delivery (Figure 2). Petechiae were observed during physical examination; therefore, a full evaluation was performed to determine the underlying cause of thrombocytopenia. Thrombocytopenia was first attributed to idiopathic thrombocytopenic purpura (ITP) given its severity. Levels of platelet-associated immunoglobulin G (PAIgG) and immature platelet fraction (IPF) were higher than normal ranges (510 ng/10⁷ cells and 18.7%, respectively). Bone marrow examination revealed a slightly increased megakaryocyte number, but other hemopoietic lineages were normal. As for disorders associated with platelet depletion, the patient was positive for lupus anticoagulants (LAC) and anti-SSA antibody, but negative for anti-dsDNA, anti-Sm, anti-SSB, ant Necardiolipin antibody IgG, and anti-β2-glycoprotein I antibodies. Laboratory test results excluded other potential causes of thrombocytopenia including viral infection and medications. LAC levels remained positive for 12 weeks. No clinical findings were obtained for systemic lupus erythematosus such as general, cutaneous, articular, cardiovascular, and neurological symptoms. A diagnosis of APS was obtained based on the fact that the patient had early-onset preeclampsia and was LAC-positive at least twice on two separate occasions more than 12 weeks apart. Oral prednisolone therapy (initial dose, 15 mg/day) was initiated prior to a second aPL analysis, with an immediate improvement in platelet count. Prednisolone was tapered slowly and discontinued at 3 months after initial therapy. Currently, the patient is prescribed low-dose aspirin (100 mg/day) for antithrombotic treatment.

Discussion

The Japan Society for the Study of Hypertension in Pregnancy (JSSHP) and ISSHP recently changed the definition and classification of hypertensive disorders in pregnancy, with an increased emphasis on organ dysfunction. Notably, proteinuria is not required to meet the criteria for a diagnosis of preeclampsia according to revised JSSHP guidelines. Moreover, severe preeclampsia is diagnosed independently of proteinuria in pregnant women with de novo mild hypertension after 20 weeks of gestation accompanied by organic dysfunction such as thrombocytopenia, renal dysfunction, liver dysfunction, neurological features, or placental dysfunction. Hypertension and proteinuria usually disappear within 1 to 3 months after delivery in patients with preeclampsia. Some studies have suggested that patients with severe preeclampsia who delivered before 34 weeks of gestation should be followed up for at least 6 months after delivery. Furthermore, history of preeclampsia was associated with a higher frequency of microalbuminuria for up to 5 years after delivery, and consultation with a nephrologist is advised if proteinuria persists for 3 to 6 months postpartum. Hypertension due to severe preeclampsia may take 3 to 6 months to resolve. However, there are few recommendations regarding the length of follow-up for preeclamptic patients with other disorders, such as thrombocytopenia and liver dysfunction.

The differential diagnosis of preeclampsia from new-onset comorbid diseases during pregnancy is challenging. Rolfo et al. suggested that maternal serum levels and the ratio of soluble fms-like tyrosine kinase-1 and placental growth factor could distinguish preeclampsia from de novo chronic kidney disease in pregnancy. Secondary hypertension can be diagnosed based on elevated serum levels of several maternal hormones such as catecholamines, thyroid hormone, and cortisol. In some cases, pheochromocytoma or renovascular hypertension may be confirmed by imaging.

There are several causes of decreased maternal platelet count during pregnancy. Gestational thrombocytopenia (GT) is the most common cause of decreased platelet count, accounting for 60% to 75% of all cases, followed by preeclampsia and hemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome (20%). ITP is a common cause of severe thrombocytopenia during the first and second trimesters of pregnancy and accounts for 3% to 20% of all thrombocytopenia cases during pregnancy. Differentiating between GT and ITP is difficult, and diagnosis is based on exclusion. Medical history prior to conception is important for differentiating between GT and ITP, although this approach is not helpful if thrombocytopenia occurs during pregnancy.
Additionally, it is even more challenging to differentiate between GT, ITP, and preeclampsia, if they are associated with the development of hypertension and/or proteinuria.

In the present case, preeclampsia occurred at 29 weeks of gestation. The patient had severe proteinuria and showed a rapid decrease in platelet count; however, hypertension was mild and only occurred at night. Furthermore, organ dysfunction was serious, but was not proportional to the severity of changes in blood pressure. Given that proteinuria became undetectable 5 months after delivery, proteinuria was thought to be due to preeclampsia and required time to improve. On the other hand, thrombocytopenia improved initially at 2 weeks to 1 month postpartum, then declined precipitously to 15,000/μl at 3 months after delivery. Therefore, preeclampsia was not considered the cause of thrombocytopenia. The additional evaluation of PAIgG and IPF as well as bone marrow examination suggested that severe thrombocytopenia was possibly due to ITP during pregnancy, although ITP is usually diagnosed by exclusion of other diseases. In the present case, LAC levels were positive on two separate occasions. The Sapporo criteria for the classification of APS include presence of thrombosis, pregnancy complications, or both in patients with persistent aPL (LAC, antiphospholipid antibodies, or anti-β2-glycoprotein I antibodies). Our patient developed severe preeclampsia before 34 weeks of gestation, with positive LAC levels at 3 and 6 months after delivery. Her clinical course and autoantibodies test results led to a diagnosis of APS. Continued long-term follow-up supported this diagnosis, despite preeclampsia improving previously.

There is substantial evidence that aPL is associated with recurrent late pregnancy loss, early-onset preeclampsia, placental abruption, and fetal growth restriction. Several mechanisms have been proposed regarding the presence of aPL in association with obstetric clinical manifestations. aPL reportedly causes endothelial and monocyte activations, which lead to thrombotic state in various tissues. In addition, the reactions of aPL inhibit trophoblast invasion associated with decidual natural killer cells. These mechanisms suggest an important association between aPL and preeclampsia. Prado et al. reported in their systematic review and meta-analysis that moderate to high levels of aPL were associated with a higher risk of preeclampsia. Furthermore, some studies have demonstrated frequency of retaining some aPL among women who developed preeclampsia. Heilmann et al. reported that aPL including LAC, antiphospholipid antibody IgG, and anti-β2-glycoprotein I antibodies was positive in 20% and 6% of patients with early-onset preeclampsia (onset at < 34 weeks of gestation) and late-onset preeclampsia (onset after 34 weeks of gestation), respectively. However, other studies could not demonstrate the association between aPL and preeclampsia and thus concluded that routine screening is not indicated for women with a history of preeclampsia. Moreover, the revised JSSHP guidelines do not stipulate that women with early-onset preeclampsia should be tested for aPL after delivery. Yet, the gestational stage when preeclampsia develops, and clinical findings of preeclampsia, may differ between women with aPL and those without aPL. In the present case, organ dysfunction was more severe than hypertension, and this may reflect the pathognomonic condition of those who develop preeclampsia followed by APS onset. Furthermore, some women who developed SLE or ITP have any aPL. As severe thrombocytopenia with a platelet count of < 20,000/μl is rare in women with APS, the clinical conditions observed in the present case may more closely resemble those of ITP. Follow-up examinations should be performed over a long-term period, particularly in these cases, regardless of whether or not patients develop APS or other autoimmune diseases.

In conclusion, long-term follow-up is crucial for the differential diagnosis of the underlying causes of preeclampsia mainly presenting with organ dysfunction such as thrombocytopenia, rather than hypertension.

Funding
This case report received no financial support.

Conflicts of interest
None.

References
Preeclampsia with severe thrombocytopenia 3 months after delivery
