

[ CASE REPORT ]

## Therapeutic Plasma Exchange Improved Pregnancy-associated Thrombotic Microangiopathy but not the Pregnancy Outcome in Patient with Systemic Lupus Erythematosus

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### Abstract:

Thrombotic microangiopathy (TMA) is a rare but life-threatening complication of systemic lupus erythematosus (SLE) and is associated with adverse pregnancy outcomes. We herein report a 30-year-old pregnant woman with SLE complicated by TMA. Because her condition was unresponsive to initial corticosteroid and fresh-frozen plasma infusion treatment, we attempted plasma exchange (PE). Although thrombocytopenia and microangiopathic hemolytic anemia gradually improved, fetal death was confirmed at 23 weeks of gestation. This case suggests that PE is an effective therapeutic option but might be insufficient to maintain pregnancy in patients with SLE complicated by TMA.

**Key words:** systemic lupus erythematosus, thrombotic microangiopathy, pregnancy, plasma exchange

(Intern Med 59: 3235-3238, 2020)

(DOI: 10.2169/internalmedicine.4655-20)

### Introduction

Thrombotic microangiopathy (TMA) is a life-threatening condition related to the presence of localized or diffuse microvascular thromboses and is characterized by thrombocytopenia, microangiopathic hemolytic anemia, a fever, neurological signs, and renal involvement. The typical histopathological finding is hyaline thrombi composed of fibrin and platelets that occlude the microvasculature and cause tissue ischemia (1). TMA encompasses the spectrum of classical thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome as well as TMA associated with pregnancy, malignancy, certain drugs, and connective tissue diseases (2). The most common cause of secondary TMA is collagen disease, especially systemic lupus erythematosus (SLE) and scleroderma (3). Although TTP is caused by a

marked decrease in the activity of the von Willebrand factor-cleaving protease ADAMTS13, this decrease is not often observed in SLE-related TMA.

Pregnancy-associated TMA is rare disorder, with an estimated incidence of approximately 1 in 25,000 pregnancies (4), and pregnancy is a known risk factor for precipitating acute episodes of TTP (5). The mainstay of acute TTP treatment during pregnancy is plasma exchange (PE) with fresh-frozen plasma (FFP), and this should be considered if there is any delay in apheresis. Steroids may be used until anti-ADAMTS13 antibody presence is excluded by testing. Rituximab, however, is reserved for emergency situations where this immune-mediated disease is particularly severe or refractory and the mother's life is in danger (6). Both TTP and SLE are associated with a significant risk of adverse pregnancy outcomes (7).

We herein report a pregnant woman with SLE who was

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Received: February 13, 2020; Accepted: June 16, 2020; Advance Publication by J-STAGE: August 12, 2020

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diagnosed with TMA. Her condition was unresponsive to initial treatment with corticosteroids and FFP, highlighting that therapeutic plasma exchange may improve pregnancy-associated TMA but may not guarantee acceptable pregnancy outcomes.

## Case Report

A 30-year-old woman with SLE was admitted to our hospital due to thrombocytopenia at 12 weeks' gestation. She had been diagnosed with SLE 15 years prior based on findings of pericarditis and leukopenia, positive antinuclear antibodies, positive anti-DNA antibodies, and positive anti-Smith antibodies. High-dose glucocorticoid therapy with additional tacrolimus (TAC) improved her condition, and remission was achieved. However, SLE flare-ups were observed during the tapering of glucocorticoid therapy, along with a fever, arthritis, and thrombocytopenia, all of which were relieved by increasing the glucocorticoid dosage. As butterfly rash and arthritis recurred, hydroxychloroquine (HCQ) was added but was discontinued due to side effects. The patient was therefore unable to be weaned from glucocorticoids but had no other abnormal findings except for low complement levels.

She had become pregnant two years earlier, and because TMA was suspected based on her low platelet counts and undetectable haptoglobin at 17 weeks' gestation, prednisolone had been increased to 25 mg/day at that point. Although the platelet counts did recover, intrauterine fetal death was confirmed at 20 weeks' gestation. The platelet counts normalized after the interruption of pregnancy, and there were no further findings associated with SLE disease activity.

Her second pregnancy was recognized while receiving a prednisolone (14 mg/day) and TAC (3 mg/day) regimen for SLE. Thrombocytopenia and renal impairment were observed at 11 weeks' gestation, and the platelet counts dropped to 54,000/ $\mu$ L while creatinine increased to 0.81 mg/dL. Hypocomplementemia had been present prior to pregnancy, but anti-DNA antibodies were not elevated. No fever, hypertension, or skin rash was observed, but the complement levels decreased further. High LDH, low haptoglobin, and the appearance of schistocytes led to a tentative diagnosis of TMA as the cause of thrombocytopenia and renal impairment. An unchanged ADMATS13 activity and low level of both complement component 3 (C3) and complement component 4 (C4) ruled out thrombocytopenic purpura and atypical hemolytic uremic syndrome (HUS). Antiphospholipid antibody syndrome and disseminated intravascular coagulation (DIC) were excluded because Lupus anticoagulant, anti-cardiolipin antibody IgG, and anti-cardiolipin  $\beta$ 2 glycoprotein I antibody were all negative and because there were no abnormal findings in the coagulation system. Although anti SS-A antibody was positive, Sjögren's syndrome was unable to be diagnosed due to the lack of dryness. Accordingly, we considered TMA to have been induced by

SLE exacerbation associated with pregnancy, as the SLE activity had not been sufficiently controlled in our case before pregnancy.

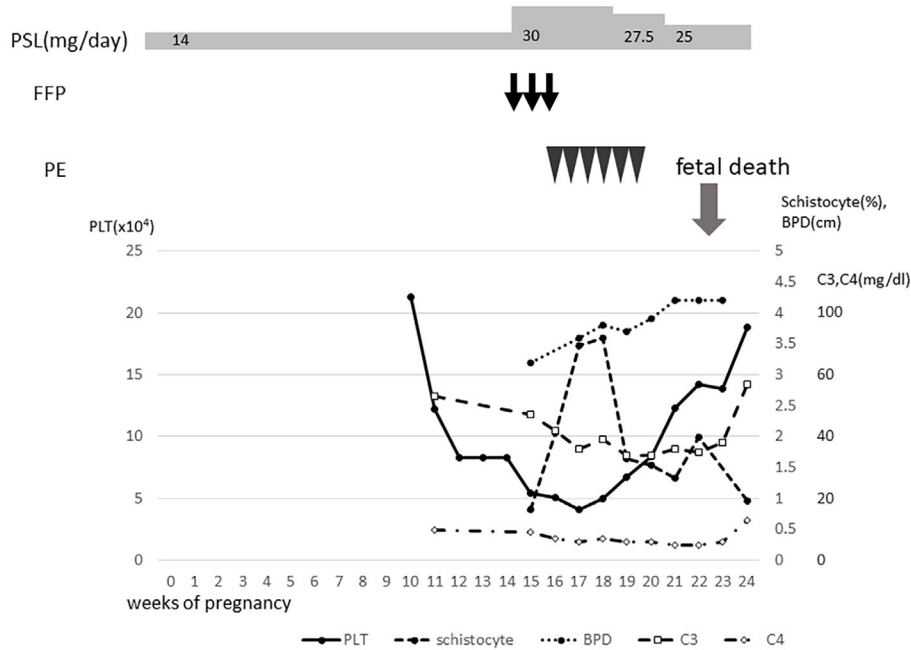
After discontinuing TAC due to possible vascular endothelial damage and platelet aggregation, oral glucocorticoid therapy was started with 30 mg/day of prednisolone (0.6 mg/kg/day) combined with 3 intravenous FFP infusions. However, the platelet count and complement titer decreased further, and the schistocyte counts increased, leading to the need for full PE for TMA resistant to the initial treatment with increased prednisolone and intravenous FFP therapy. After six PEs, the platelet counts had increased, the schistocyte counts had gradually decreased, and the creatinine level had normalized. However, fetal growth retardation, evidenced by a significantly smaller than normal fetal biparietal diameter at 19 weeks' gestation, and the disappearance of the fetal heartbeat at 23 weeks occurred. Placental abruption and dysfunction were not observed during the pregnancy period. The body weight of the nonviable fetus was 250 g (<2 standard deviations). The clinical course is summarized in Fig. 1.

After the interruption of pregnancy, the platelet counts normalized again. A pathological assessment revealed that the immature placenta contained focal villous necrosis and calcification, while the umbilical cord change was unremarkable (Fig. 2). These findings suggest that placental insufficiency might have caused the intrauterine fetal death.

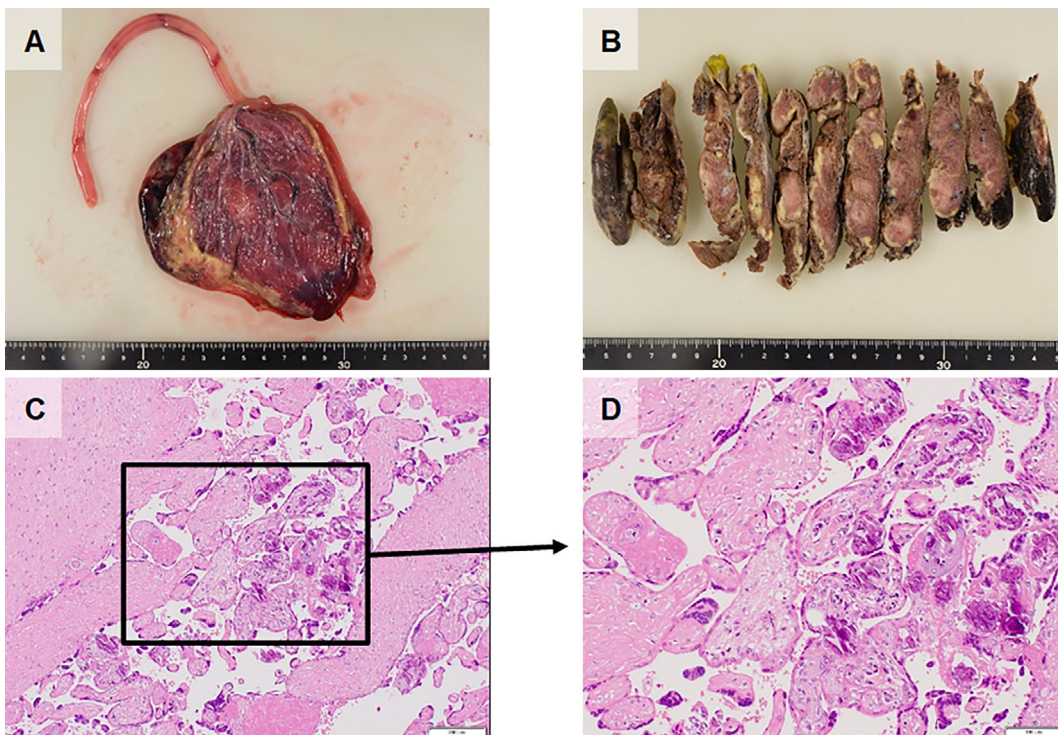
## Discussion

We encountered a case of pregnancy complicated by SLE and TMA that was unresponsive to initial corticosteroid treatment and FFP infusion. After we attempted PE, the thrombocytopenia and microangiopathic hemolytic anemia improved gradually, but fetal growth retardation occurred, resulting in intrauterine fetal death at 23 weeks' gestation. Through our experience with this case, we can make three clinically important observations.

First, our patient did not have elevated anti-DNA antibodies but did have hypocomplementemia, indicating that SLE was poorly controlled during pregnancy. This might have been because our case was treated with steroid monotherapy, as HCQ was contraindicated due to its side effects and TAC had to be discontinued due to thrombocytopenia. As SLE is the most common cause of secondary TMA, the disease activities of both SLE and TMA seem to run a parallel course (3, 8). In addition, pregnancy is a recognized risk factor for precipitating acute TMA (5). Excessive inflammation caused by SLE is reported to trigger placental dysplasia and induce placental ischemia, resulting in vascular endothelial damage mediated by several cytokines and the exacerbation of TMA pathology (9, 10). However, TMA during pregnancy is also caused by fetal loss and placental abruption with or without DIC or by complement abnormality, such as atypical HUS. In the present case, TMA developed more than 12 weeks before intrauterine fetal death, and placental



**Figure 1.** Clinical course. Thrombocytopenia and microangiopathic hemolytic anemia continued to progress during combination therapy of prednisolone and fresh-frozen plasma infusion. Gradual improvement was seen after six plasma exchanges. However, fetal biparietal diameter growth was not observed on ultrasound scans, and the fetal heartbeat was undetectable at 23 weeks' gestation. PSL: prednisolone, FFP: fresh-frozen plasma, PE: plasma exchange, Plt: platelet count, BPD: biparietal diameter, C3: complement component 3, C4: complement component 4



**Figure 2.** Pathological findings of placenta. (A) The placenta weighed 80 g (mean-110 g). (B) Necrotic areas were found on both the maternal and fetal sides. (C) Villous necrosis and calcification as observed in the placenta [Hematoxylin and Eosin (H&E) staining, 20× magnification]. (D) An enlarged view of the boxed area in (C) (H&E staining, 100× magnification).

abruption was not observed during the pregnancy period. There were also no abnormal findings in the coagulation system, so DIC was excluded. In addition, atypical HUS was unlikely to have caused TMA, since our case had already been diagnosed with SLE before pregnancy, and laboratory testing revealed low levels of both C3 and C4 persistently, although low C3 and normal C4 are characteristic of atypical HUS (11). Consequently, we suspect that our patient developed TMA due to pregnancy-induced stress during an uncontrolled state of SLE activity. However, the TMA was refractory to therapy, and the low complement titer failed to respond to the initial treatment of increased prednisolone, so whether or not the SLE activity directly affected the TMA and whether or not our case needed immunosuppressive treatment are unclear.

Our second clinically important observation is that PE had a dramatic effect on the TMA in the present patient. Although the mainstay treatment for acute TTP in pregnancy is PE with FFP (12), its effectiveness for TMA during atypical TTP has not been clearly demonstrated. However, PE may remove cytokines and activated complement while supplementing complement regulators (13). In the present case, we believe that PE saved our patient from life-threatening TMA during a pregnancy complicated by SLE.

The third observation in the present case is the nonviable pregnancy despite improvements in laboratory findings associated with TMA. Pathologically, the placenta had no thrombi or vascular stenoses, but the presence of partial necrosis of the placental villi may have indicated blood flow failure, although we were unable to verify that this occurred before the intrauterine fetal death. The total placental weight was 80 g, which was well below the 190 g that is standard for 23 weeks' gestation (14). Accordingly, we propose that a decreased blood flow occurred before TMA had been sufficiently controlled, resulting in incomplete maturation of the placenta and a poor outcome. Dashe et al. reported that TMA in or before the early second trimester is remarkably severe, refractory to treatment, and causative of a poor pregnancy prognosis (4). Previous case reports regarding TMA complications of SLE before the second trimester indicate that early delivery is needed in order to control treatment-refractory TMA and SLE flare-ups (15-17). Furthermore, the present and previous reports also suggested the possibility that disease flare-ups coupled with high-dose glucocorticoid therapy might correlate with adverse pregnancy outcomes (7). It is therefore important to suppress the SLE activity before pregnancy in order to prevent or delay TMA onset and achieve a successful delivery.

In conclusion, PE is an effective therapeutic option but insufficient to maintain pregnancy in patients with SLE complicated by TMA. Adequate control of SLE activity before pregnancy is therefore important to prevent or delay the onset of TMA.

**The authors state that they have no Conflict of Interest (COI).**

#### Acknowledgement

We thank Dr. Bryan J. Mathis of the Medical English Communications Center, University of Tsukuba, for the critical reading of the manuscript.

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