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Cyclosporine-induced thrombotic microangiopathy in pregnant women: A case report and literature review

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Abstract

Cyclosporine A (CsA) is a commonly used immunosuppressant, but its association with thrombotic microangiopathy (TMA) is rarely reported. In recent years, CsA has been used in pregnant women with autoimmune diseases or previous immune-related adverse pregnancies. Our case involves a 34-year-old female who developed typical laboratory indicators of TMA while using CsA to improve pregnancy outcomes. After discontinuing CsA, the TMA markers gradually normalized. To our knowledge, this is the first report of CsA-induced TMA during pregnancy. We also reviewed previous case reports of CsA-induced TMA and summarized the possible mechanisms, characteristics, and risk factors, as well as methods to identify this rare adverse effect of CsA in pregnant women.

Keywords

Cyclosporine A, thrombotic microangiopathy, pregnancy

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Introduction

Since its FDA approval in 1983 for preventing transplant rejection, cyclosporine A (CsA) has become a key immunosuppressant.[1] In recent years, it has also been increasingly used to treat immune-related recurrent miscarriages and pregnant women with underlying autoimmune conditions.[2] Thrombotic microangiopathy (TMA) refers to a heterogeneous group of conditions characterized by microangiopathic hemolytic anemia, reduced platelet count, and organ damage from microvascular clot formation.[3,4] CsA-induced TMA is uncommon and primarily reported in transplant patients.[3–5] To our knowledge, this is the first report of CsA-induced TMA in a pregnant woman without transplantation. The possible mechanisms, characteristics, and risk factors were reviewed to help clinicians understand and identify this rare adverse drug reaction (ADR) in pregnant women.

Case report

A 34-year-old woman with three previous molar pregnancies and four immune-related miscarriages underwent follicular monitoring and conceived naturally. Due to her adverse pregnancy history and a connective tissue disorder, she was prescribed a preconception regimen including low-dose aspirin (LDA), enoxaparin sodium, low-dose glucocorticoids, and hydroxychloroquine (HCQ). CsA was added during follicular monitoring, with a daily dose of 100 mg, administered in two divided doses orally. Throughout her pregnancy, she developed progressive anemia, diagnosed at $12+^{2}$ weeks with a hemoglobin (Hb) level of 106 g/L (Figure 1). Despite iron supplementation, her Hb concentration decreased to 68 g/L at $22+^{6}$ weeks, indicating severe anemia. Laboratory tests revealed hemolytic anemia, with elevated reticulocyte count and ratio at $20+^{3}$ weeks, fragmented erythrocytes in peripheral blood smears, increased lactate dehydrogenase (LDH) level (282 U/L), decreased haptoglobin level (0.19 g/L), and

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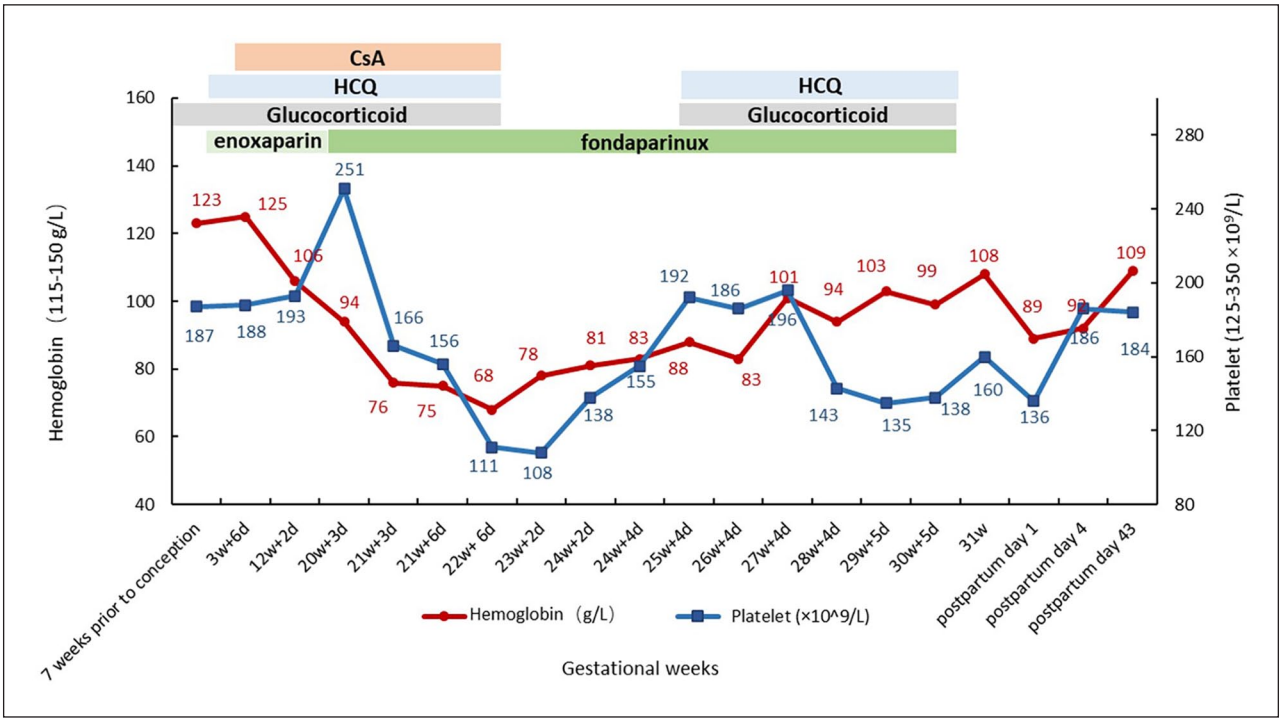

Figure 1. Timeline of Hb and platelet level during pregnancy.
CsA: cyclosporine A; Hb: hemoglobin; HCQ: hydroxychloroquine.

shortened red blood cell life span (RBCS) (56 days) at $21+^{6}$ weeks. Platelet counts showed a downward trend, though not reaching pathological levels. Negative Coombs test result at $21+^{6}$ weeks ruled out immune-mediated hemolysis. Traditional coagulation function tests (prothrombin time, INR, aPTT, TT, and D-dimer levels) remained normal. These findings aligned with the laboratory characteristics of TMA.[3,4] We excluded pregnancy-related TMA (including preeclampsia/eclampsia and HELLP syndrome) and primary TMA (such as thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS)) due to the absence of corresponding clinical manifestations.[4,6,7]

The discovery that CsA-induced TMA was unexpected. Due to a COVID-19 infection at 23 weeks, three immunosuppressants (CsA, HCQ, and glucocorticoids) were discontinued. Surprisingly, her Hb level increased from 68 g/L at $22+^{6}$ weeks to 83 g/L by $24+^{4}$ weeks. Concurrently, platelet and haptoglobin levels also rose above their pre-discontinuation levels. After recovering from COVID-19, glucocorticoids and HCQ were reintroduced, while CsA was withheld due to concerns about maternal secondary infections. Her Hb level continued to rise and eventually stabilized around 100 g/L. Her RBCS extended to 86 days at $28+^{4}$ weeks, significantly longer than the 56 days measured at $21+^{6}$ weeks. At $5+^{5}$ weeks and $14+^{6}$ weeks, CsA trough concentrations were 35.2 ng/mL and 59.6 ng/mL, respectively, indicating non-toxic levels. Using the WHO Uppsala Adverse Events scale, her hemolytic anemia was assessed as an ADR attributed to CsA, with a probable correlation. An emergency cesarean delivery was performed at $31+^{1}$ weeks due to suspected fetal compromise and oligohydramnios. During surgery, an estimated blood loss of 500 mL led to a decline in her Hb level from 108 g/L to 89 g/L. Forty-three days postdelivery, her Hb concentration recovered to nearly normal levels, reaching 109 g/L. A female infant, weighing 1040 g at birth, was admitted to the neonatal intensive care unit and discharged after a successful 79-day stay in excellent health.

With the occurrence of CsA-related TMA, her coagulation-related tests also presented distinctive features (Figure 2). Throughout pregnancy, traditional coagulation function tests consistently returned normal results. From $14+^{2}$ weeks to $21+^{6}$ weeks, a persistently rising trend in thrombin–antithrombin complex (TAT) indicated an in vivo prothrombotic state.[8,9] Despite increasing the enoxaparin dose (from 4000 to 8000 AXaIU/day) and switching to fondaparinux, the hypercoagulable state persisted. At 19 weeks, antithrombin-III levels were within the normal range, and genetic testing ruled out inherited thrombophilia. Thrombomodulin (TM) levels also showed a rising trend, indicating endothelial injury.[8,9] Thromboelastography (TEG) revealed a low clotting index, suggesting hypocoagulability under ex-vivo conditions due to anticoagulants and LDA. Following CsA withdrawal, the abnormally elevated TAT and TM levels steadily declined toward normalization, suggesting alleviation of the in vivo hypercoagulability and endothelial dysfunction.

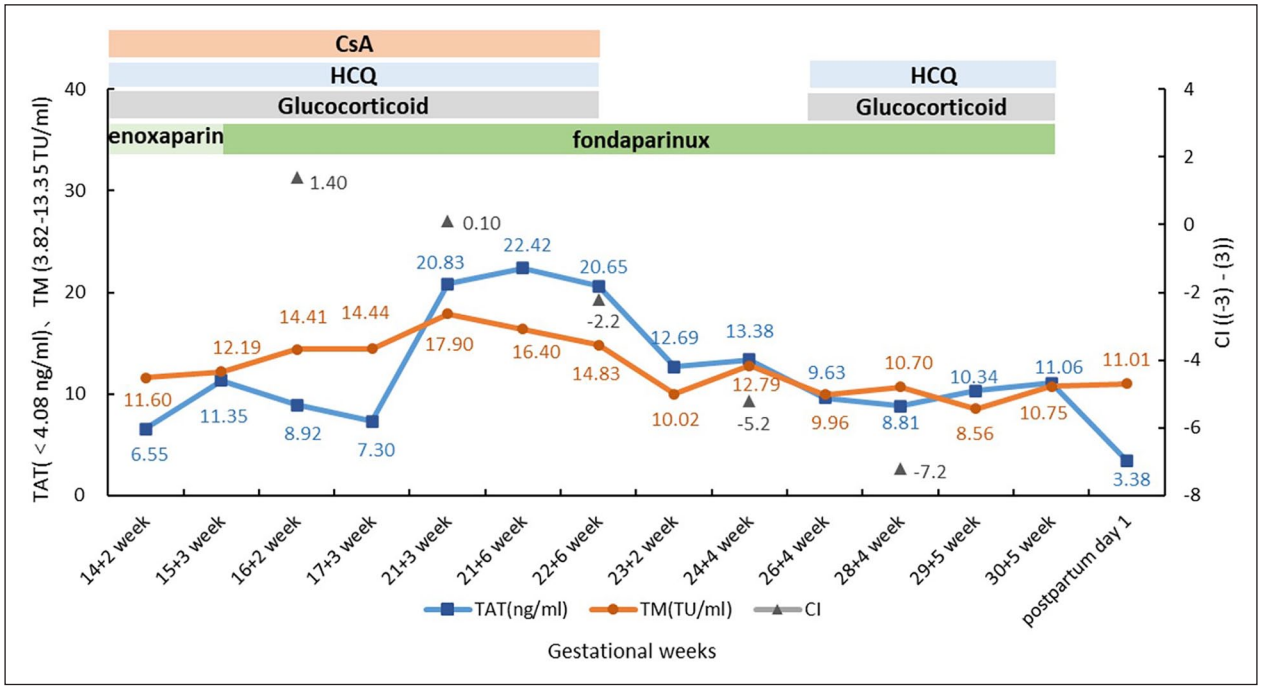

Figure 2. Timeline of TAT, TM, and CI parameters during pregnancy.
CI: clotting index; CsA: cyclosporine A; Hb: hemoglobin; HCQ: hydroxychloroquine; TAT: thrombin–antithrombin complex; TM: thrombomodulin.

Discussion

Drug-induced TMA is a subset of secondary TMA, with a 2015 review identifying 22 medications linked to TMA.[4,10] CsA-induced TMA is believed to result from cumulative toxicity due to excessive dosage or prolonged use.[10,11] The decline in Hb levels from 125 g/L to 68 g/L over 19 weeks in this case reflects the chronic nature of CsA-induced TMA. Pathophysiologically, CsA-induced TMA is linked to an imbalance in vasoactive peptides, leading to vessel constriction and endothelial injury.[12–14] In addition, CsA triggers microparticle release and activates the alternative complement pathway.[14] TM, which has anti-inflammatory and anticoagulant properties, increases during endothelial injury, making it a reliable marker of damage.[8,9] In this case, TM levels rose concurrently with declining Hb and platelet levels during CsA treatment. After discontinuing CsA, TM levels normalized, confirming the role of endothelial dysfunction in CsA-induced TMA.

Beyond medications, other secondary factors capable of triggering TMA include malignant hypertension, pregnancy, infections, cancer, autoimmune diseases, transplantation, disseminated intravascular coagulation, and metabolic disorders.[4,15] CsA-induced TMA is predominantly reported in solid organ or hematopoietic stem cell transplantation.[16–21] Only two non-transplantation cases have been reported: An 11-month-old boy with primary nephrotic syndrome and a 71-year-old patient with stage 4B angioimmunoblastic T-cell lymphoma.[22,23] In these cases, CsA-induced TMA occurred alongside additional risk factors such as transplantation, immune-mediated diseases, and cancer.[16–23] Similarly, our case involved CsA use due to a connective tissue disorder and a history of immune-related adverse pregnancy outcomes. Based on this evidence, we speculate that for individuals using CsA to experience this rare ADR, multiple conditions might be met, including underlying diseases that can cause endothelial cell injury (e.g., transplantation, tumors, and severe immunological conditions) and long-term or high-dose CsA use.

Given the increasing use of CsA in pregnant women, obstetricians should be aware of this rare ADR.[2] The pregnancy-induced hypercoagulability may increase the risk of CsA-related TMA.[12,14,24] Furthermore, the lack of established therapeutic ranges for treating immune-related adverse pregnancy outcomes, combined with frequent long-term use, contributes to the development of CsA-related TMA. When a pregnant woman using CsA presents with laboratory findings such as reticulocytosis, thrombocytopenia, elevated LDH, decreased haptoglobin, and a negative Coombs test, TMA should be considered.[4] Pregnancy-related TMA, including preeclampsia/eclampsia and HELLP syndrome, is well-known to obstetricians. Preeclampsia/eclampsia is diagnosed by hypertension, proteinuria, edema, and abnormal liver function, while HELLP syndrome, a severe form of preeclampsia, is characterized by hemolysis, elevated liver enzymes, and thrombocytopenia.[6,15] TTP or HUS, although rare, can also occur during pregnancy.[6] TTP is characterized by neurological features,

while HUS is defined by renal dysfunction.[4,5] Diagnosis of TTP relies on ADAMTS13 activity testing, whereas HUS depends on the presence of Shiga toxins or complement dysregulation.[4–6,15] After excluding pregnancy-related TMA and initial TMA forms (HUS and TTP), typical laboratory evidence of TMA suggests the possibility of CsA-related TMA. In this case, CsA-induced TMA manifested as a chronic toxic response with typical laboratory abnormalities without overt organ dysfunction. Clotting-related tests, including TAT, TM, and TEG, can help identify CsA-induced TMA. While TAT and TM levels gradually rise during pregnancy, CsA-related TMA is associated with disproportionately elevated TAT and TM levels.[8,9] When patients are treated with anticoagulants, TEG and TAT may reveal a paradoxical juxtaposition of in vitro hypocoagulability alongside in vivo hypercoagulability. The detrimental effect of CsA on endothelial function can explain this disparity.[12–14] When TMA is suspected to be CsA-induced, discontinuation of CsA should be prioritized, with laboratory parameters typically improving thereafter.[4,19,22,23]

Conclusion

CsA-related TMA is a rare adverse reaction often associated with conditions predisposing to TMA, such as transplantation or immunological disorders, and typically involves long-term or high-dose CsA use. Coagulation assays, such as TAT, TM, and TEG, are invaluable tools in identifying CsA-related TMA. With the increasing use of CsA in pregnant women, this rare adverse event demands serious attention.

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Author contributions

S.Z. wrote the manuscript; S.Z., H.H.Z., Z.X.Z., and Q.Q.W. were responsible for the entire treatment of the patient; P.H. and S.X.L. conducted the literature review. All authors reviewed and confirmed the content of the article.

Declaration of conflicting interests

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Ethics approval

This research has been approved by the Ethics Committee of Zhejiang Provincial People's Hospital (ZJPPHEC 2023O(088)).

Informed consent

Written informed consent was obtained from this patient for her anonymized information to be published in this article.

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