RANZCOG Annual Scientific Meeting 2023

Thrombotic Thrombocytopenic Purpura in Pregnancy

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Introduction

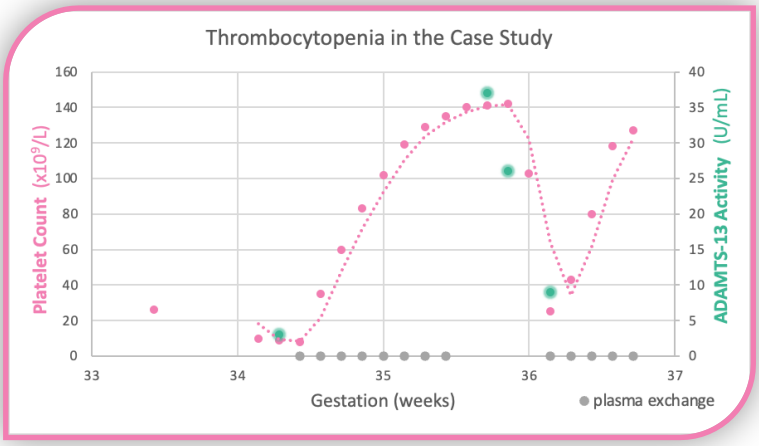
Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disorder involving widespread microthrombi formation secondary to an acquired or congenital deficiency of the von Willebrand factor (VWF) cleaving metalloproteinase ADAMTS13. Historically associated with the clinical pentad of microangiopathic haemolytic anaemia (MAHA), thrombocytopenia, renal dysfunction, neurologic abnormalities, and fever. In pregnancy it is associated with risk of preeclampsia, preterm birth, fetal growth restriction and fetal demise.[1] Pregnancy is a recognised risk for TTP, albeit a rare clinical phenomenon, with TTP occurring in less than 0.005% pregnancies.[2] Despite rare occurrence, it is associated with significant maternal and neonatal morbidity and mortality.

Case Study

A 28-year-old G3P2 female presented at 34 weeks with asymptomatic acute onset thrombocytopenia (platelets 23 x 10^9/L) associated with normocytic anaemia (Hb 107g/L). In the context of systemic lupus erythematosus (SLE), well-controlled with azathioprine, prednisolone and hydroxychloroquine. Past obstetric history included preeclampsia (PE) with haemolysis, elevated liver enzymes, low platelet (HELLP) syndrome in her first pregnancy.

Physical examination was unremarkable and secondary investigations revealed normal hepatorenal function but elevated lactate dehydrogenase (357U/L) and mild red cell fragmentation. Soluble tyrosine kinase /placental growth factor (sFLT/PIGF) ratio was normal, lupus anticoagulant and antiphospholipid antibodies were negative. ADAMTS13 activity was reduced (3U/dL) and a low titre of ADAMTS13 inhibitor was detected (0.7 BU). Acquired TTP was diagnosed, and prednisolone was up titrated without effect. The patient was admitted for plasma exchange via a Permacath, to increment platelets and enable safe delivery.

At 36 weeks, labour was induced, and a healthy female was born. Given TTP was refractory to corticosteroids, the patient was dependant on plasmapheresis postpartum. However, was successfully treated with four cycles of intravenous rituximab (375mg/m2).



Isolated Thrombocytopenia

Physiological	Pathological	Pseudo Thrombocytopenia
- Gestational Thrombocytopenia	- Drug Induced Thrombocytopenia - Immune Thrombocytopenia	- In vitro platelet clumping

Thrombotic Microangiopathies

Platelets <100 x 10^9/L
Haemoglobin <100 g/L
Lactate Dehydrogenase 1.5 times upper limit
Serum haptoglobin undetectable
Negative direct erythrocyte antiglobulin test
Schistocytes on blood smear or TMA features on end-organ on biopsy

Obstetric Specific Pathologies

Pre-eclampsia
Hypertension after 20 weeks, with organ dysfunction

Eclampsia
Preeclampsia with seizure activity

HELLP Syndrome
Haemolysis, elevated liver enzymes, low platelets

Other Haematological Pathologies

Thrombotic Thrombocytopenic Purpura
ADAMTS13 activity <10% or <10U/dL
-> Immune: ADAMTS13 inhibitor assay negative
-> Congenital: ADAMTS13 inhibitor assay positive

Complement mediated TMA
Formally haemolytic uraemic syndrome.
Associated severe acute kidney injury.

Other:
- Systemic Lupus Erythematosus
- Antiphospholipid Syndrome
- Disseminated Intravascular Coagulopathy

Discussion

Thrombotic microangiopathies (TMA), involving both thrombocytopenia and MAHA can appear similar and occur concomitantly, making diagnosis highly challenging. Differentials include pregnancy-specific TMA like PE, and pathologies not limited to pregnancy, like TTP or complement mediated TMA. Additionally, conditions like SLE can present with thrombocytopenia and MAHA due to platelet aggregation with immune complexes. This case raises the diagnostic challenge posed by the analogous presentation of PE, SLE and TTP in pregnancy.

Thus, a high index of suspicion and low threshold for use of diagnostic tests, such as ADAMTS13 activity assay, is crucial to confirm TTP.[3] Where ADAMTS13 assay are not rapidly available, modern clinical prediction tools, such as French TMA scores, may be of use in determining the pre-test probability of TTP. Our case was particularly atypical in initial presentation. Despite lacking the classic presentation of fever, renal dysfunction or neurologic sequalae, given her concomitant SLE with positive ANA, degree of thrombocytopenia at presentation and normal renal function, her French TMA score had an 85% positive predictive value for TTP.[4]

French TMA Criteria [4]	
Platelet	<30 x 10^9/L
Creatinine Level	<2.26 mg/dL
ANA	Positive

The key to management is placing a strong emphasis on initiating plasma exchange. Prior to plasmapheresis becoming a commonplace haematological therapy, fetal mortality secondary to TTP approached 80%.[5] Other mainstay therapeutic options include corticosteroids and rituximab. While delivery is not a treatment for TTP, it may facilitate use of further immunosuppressive therapy, when maternal or fetal compromise is evident. It may also help treat obstetric aetiologies in the undifferentiated TMA patient.

Relapses occurs in approximately 50% of acquired TTP survivors, which is likely attributed to the physiological propensity for ADAMTS13 deficiency and VWF factor excess in later gestations.[6] Identifying TTP is complicated by the infrequency and variability of presentation, particularly in pregnancy. Thus, clinicians should maintain a high index of suspicion, especially in patients with pre-existing autoimmune disease.

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