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Successful management of recurrent pregnancy-related thrombotic thrombocytopenia purpura: case report and review

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Summary

Thrombotic thrombocytopenic purpura (TTP) is a rare but potentially devastating complication of pregnancy. The authors report a case of a successful treatment of recurrent TTP complicating pregnancy. A review of the literature shows that recurrent TTP complicating pregnancy is uncommon and fresh frozen plasma exchange is important treatment; if the patient was treated properly, the pregnant showed favorable prognosis.

Key words: Thrombotic thrombocytopenic purpura; Pregnancy, Plasmapheresis.

Introduction

Thrombocytopenia during pregnancy is common, and an asymptomatic reduction in platelets count is found near term in about 5% of normal pregnancies [1]. However, thrombotic thrombocytopenic purpura (TTP) is a serious and rare complication of pregnancy, the incidence of is only one in 25,000 pregnancies [2] and it was associated with a high maternal and fetal mortality which approached 80% without a proper treatment [3].

The authors report a 26-year-old pregnant woman who presented initially with severe thrombocytopenia in the 36^{th}+1 week of gestation. Her past medical history included thrombocytopenia and neurologic dysfunction during last delivery five years ago and plasma exchange therapy was successfully used. Immediate plasmapheresis treatment was initiated in this case, then immunoglobin and dexamethasone infusions, followed by platelet infusion. A male neonate was delivered by cesarean section in the 36^{th}+4 week of gestation with uncomplicated postnatal development. After delivery, this patient's platelet count increased to normal values. This case shows interesting aspects of TTP during pregnancy and a close cooperation between obstetricians, nephrologists, and pediatricians is necessary for a favorable outcome of the pregnancy.

Case Report

A 26-year-old pregnant woman was transferred to the tertial perinatal care center of The First Affiliated Hospital of Sun Yat-sen University for termination of the pregnancy due to the diagnosis of a severe thrombocytopenia without obvious bleeding in the 36^{th}+1 week of gestation. Initial laboratory studies demonstrated severe thrombocytopenia (10×10^9/L), proteinuria (7.122 g/L/24 hours), and mild hemolytic anemia (hemoglobin 92 g/L). In her early stage of pregnancy, there were documented normal hemoglobin, platelet values, and normal urine test result.

Past medical history revealed a similar event occurring during last pregnancy five years ago. She was transferred to the present hospital after cesarean section due to persistent thrombocytopenia, postnatal bleeding, and neurologic dysfunction. Platelet and plasma infusion did not work. The findings of bone marrow puncture were consistent with TTP and then, plasmapheresis, plasma, and immunoglobin infusion were given. Cyclosporine and prednisone treatment followed and her platelet count recovered to normal values. After that she had her blood checked routinely every year and the result was normal. There were no other illnesses in the past.

Upon physical examination, the patient was sane and well cooperative. Her skin and mucosa were pale, and multiple petechiae were seen in her right leg. The patient had no fever or edema and blood pressure was normal. The remaining physical examination findings were unremarkable. Obstetrical ultrasound showed an appropriate for gestational age developed fetus without signs of structural abnormality, normal amniotic fluid, and fetal echocardiography. Additional laboratory examinations revealed a negative Coombs test, antinuclear (ANA) double stranded DNA-antibodies and normal levels of complement C3, C4 and CH 50. Blood smear showed 2.5% schistocytes and lactate dehydrogenase (LDH) was 1410 U/L. Detailed laboratory tests results showed in Table 1. A working diagnosis of TTP was made.

This case was presented at Medical Grand Rounds joined with plasma experts, then, termination of pregnancy, plasmapheresis, immunoglobin, and glucocorticoid steroid were recommended to the patient. Emergency plasmapheresis therapy with substitution of fresh frozen plasma or albumin (50 ml/kg body weight) and immunoglobin (0.4 g/kg body weight), and prednisone (60 mg) infusions was started before the delivery.

However, after two days of treatment, her platelets remained at a very low level ($9\text{-}12 \times 10^9$/L) and hemolytic anemia was aggravated (hemoglobin dropped from 92 to 72 g/L). Then, a de-

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Table 1. — *Laboratory tests results.*

Variables (normal values)	Before admission	On admission	Day 2	Day 3	Day 4 (prepartum)	Day 4 (postpartum)	Day 5	Day 6	Day 7
Hb (g/L) (110-150)	92	96	90	72	68	97	82	88	95
PC ($\times 10^9$/L) (100-300)	10	12	9	12	53	93	101	153	211
Sr. bil. (umol/L) (22-30)		30.7		35	13	15.4	9.1		
Direct bil. (umol/L) (6–19)		30.7		35	13	15.4	9.1		
AST (U/l) (1–37)	66	56		34	26	28		32	
ALT (U/l) (1–40)	37	26		24	18	22		43	
ALP (U/l) (0–110)	104	99		46	62	77		59	
Sr. urea (mmol/L) (2.9–8.6)	5.3	5.6		6.0	4.6	4.4	4.9	5.5	
Sr. creat. (umol/L) (53–115)	62	55		58	59	54	57	69	
PTT (seconds) (14-21)		17.5	17.1	18.5	17.5	15.8	17.5	16.9	
INR		1.08	1.03	1.10	1.03	0.88	0.93	0.82	
FDP (μg/ml) (<10)		9.1							
d-Dimer (mg/dl) (<0.5)		353							
Fibrinogen (mg/dl) (2–4)		2.34	2.76	1.29	1.48	2.21	2.0	2.22	
LDH (U/l) (114-140)	1410	853		582	295	435		307	
Proteinuria	++		+++	7.122		+			

PC: platelet count, Hb: hemoglobin, AST: aspartate aminotransferase, LDH: lactate dehydrogenase, ALT: alanine aminotransferase, ALP: alkaline phosphatase, sr. bil.: total serum bilirubin, sr. creat: serum creatinine, NA: not available, PTT: partial thromboplastin time, INR: international normalized ratio, FDP: fibrin degradation products.

cision of platelet infusion (one unit) was made to try to avoid peripartum bleeding especially cerebral hemorrhage. Once the platelets value increased to 50×10^9/L, cesarean section was carried out. During operation, the patient received four units of packed red blood cells, 400 ml fresh frozen plasma, and one unit of platelets. The total blood lost was 400 ml and the patient's vital signs were stable during perioperative period. A male neonate weighing 2.54 kg was delivered and Apgar score was 5, 8, 9, at one, five, and ten minutes. The child had a normal blood routine test result and no other complication. After operation the patient was transferred to SICU for postoperative observation. Her platelet value recovered to 93×10^9/L soon after delivery without any other special treatment and 101×10^9/L next morning. Her proteinuria decreased dramatically from 3+ prepartum to 1+ postpartum. She was then transferred to general postnatal ward two days later and discharged three days after delivery with a stable normal value of platelets ($153\text{-}211 \times 10^9$/L). This patient and her baby both were in good condition in postpartum follow up of six weeks and three months.

Discussion

TTP is a spectrum of syndromes characterized by thrombocytopenia and microangiopathic hemolytic anemia, manifested by an elevated blood LDH concentration and red blood cell fragments. It is one of the few hematologic emergencies. Untreated, most patients will die, however prompt and appropriate treatment allows most patients not only to survive but to recover, with favorable long-term outcome. It classically occurs in patients with a hereditary or acquired lack of ADAMTS13, a metalloproteinase that cleaves large multimers of von Willebrand factor. Other TTP-like syndromes, including TTP associated with pregnancy, organ transplantation, and certain medications, likely have different underlying causes and may require different treatment.

TTP is rare. The estimated annual incidence of all TTP syndromes is about 11 cases per million in the general population [4]. However, patients who have experienced one episode of pregnancy-related TTP are at increased risk in future pregnancies. In many large series, 20% or more of the included patients developed disease during pregnancy or the immediate postpartum period [5]. This is one of few cases of a successful treatment of a patient with recurrent TTP related to pregnancy. Despite the satisfactory outcome, the case raises a number of questions that are discussed.

TTP is classically characterized by the pentad of microangiopathic hemolytic anemia (MAHA), thrombocytopenia, neurologic dysfunction, fever, and renal disease. However, due to the importance of initiating therapy promptly for this disorder, any patient with MAHA and thrombocytopenia that is otherwise unexplained should be considered to have TTP. Of the other clinical manifestations, neurologic dysfunction is most common in classical TTP. Involvement of organs such as the pancreas, heart, and others are demonstrable pathologically, and may lead to complications such as pancreatitis, myocardial infarction, and cardiac arrythmia. TTP may be difficult to discern from other disease such as preeclampsia, HELLP (hemolysis, elevated liver enzymes, and low platelets) syndrome, HUS (hemolytic uremic syndrome), and acute fatty liver. Thus, the differential diagnosis in a pregnant patient presenting with such manifestations is complex, and, in some cases, achieving a definitive diagnosis may not be possible.

In this case, the patient had thrombocytopenia and anemia, an elevated blood LDH concentration, and blood smear showed 2.5% schistocytes; no blood pressure change; ALT and AST levels were normal; no obvious de-

Table 2. — *Comparison of articles regarding recurrent pregnancy-related TTP.*

No.	Study and year	Patient no.	No. of TTP episodes related to pregnancy	Main treatments	Outcome of pregnancy	Obstetric complication	Outcome of patient
1	Nikolaou M., *et al.* [11], 2012	1	3	Fresh frozen plasma exchange	Termination of pregnancies	Not mentioned	Survived
2	Keiser SD., *et al.* [12], 2012	2	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Not mentioned
3	Raman R. [13], 2011	1	2	Fresh frozen plasma exchange	G1: IUFD G2: preterm live birth	Preeclampsia	Survived
4	Richter J. [14], 2011	1	2	Tinzaparin treatment and octaplas infusions	G1: SA G2: term live birth	Preeclampsia	Survived
5	Lam K. [15], 2010	1	2	fresh frozen plasma exchange	G1: IUFD G2:	G1: preeclampsia G2: fetal distress	Survived
6	Stella C.L. [16], 2009	2	4	Plasmapheresis	Live birth	Not mentioned	Survived
7	Kato R. [17], 2009	1	4	Fresh frozen plasma exchange	G1-G3: IUFD G4: live birth	G1: HELLP syndrome and placental abruption	Survived
8	Scully M. [18], 2006	2	4	Low-dose aspirin, low molecular weight heparin and fresh frozen plasma exchange	G1: Second-trimester foetal losses G2: live birth	Not mentioned	Survived
9	Vesely S.K. [19], 2004	19	30	Fresh frozen plasma exchange	Live birth at last pregnancy	Not mentioned	Survived
10	Ducloy-Bouthors A..S [20], 2003	1	2	Fresh frozen plasma exchange	Not mentioned	Not mentioned	Survived
11	Ezra Y. [21], 1996	2	5	Aspirin, dipyridamole	G1-3: IUFD Last pregnancy: live birth	Not mentioned	Survived
12	Natelson E.A. [22], 1985	1	2	Evacuation of the uterus	Recovery soon after evacuation	No	Survived

G: gestation; IUFD: intrauterine fetal death; SA: spontaneous abortion; HELLP: hemolysis, elevated liver enzymes, and low platelets.

teriorated renal function and coagulation function. Furthermore, she had a previous history of pregnancy-related TTP. Therefore, although there was no neurologic dysfunction and no fever, she was considered as recurrent pregnancy-related TTP and was treated promptly to avoid progression to other important organs such as kidney or heart.

Why is the incidence of TTP is increased in pregnancy uncertain? Some studies suggest that TTP usually presents prior to 24 weeks; however, pregnancy-associated TTP can occur in the third trimester or during the postpartum period as well [6]. Patients with pregnancy-associated TTP are at increased risk for the development of recurrent TTP in subsequent pregnancies just like this case. The mortality rate from thrombotic microangiopathies during pregnancy has significantly improved since plasmapheresis therapy has become the standard treatment. In a review of 166 cases of pregnancy-associated TTP between 1955–2006, a maternal mortality of 26% was described [7].

Plasmapheresis the primary treatment for TTP and sometimes plasma infusion (PI) is effective, too. Comparison of plasmapheresis and PI in the treatment of TTP was carried out by the Canadian Apheresis Study Group [8], which reported that plasmapheresis was superior to PI. They performed a randomized trial in which 102 patients with TTP received either plasmapheresis or PI. Patients who received plasmapheresis had a better initial response, a higher survival rate, and a lower rate of relapse than patients receiving PI. The Japanese TTP Study Group [9] made a therapeutic protocol in which a smaller volume of fresh frozen plasma (FFP) was used in the treatment with PI. The efficacy of plasmapheresis and PI was similar. These findings established plasmapheresis as the treatment of choice for TTP. TTP is different from other autoimmune diseases such as idiopathic thrombocytopenia purpura, in which the primary treatments are immunosuppressive agents. Some evidence exists for treating TTP with immunosuppressive agents [10], but the primary treatment should be plasmapheresis.

The management of TTP during pregnancy is much like common patients, with plasmapheresis yielding a very high response rate. The role of corticosteroids in the management of TTP has not been determined through randomized studies and corticosteroids used alone is not recommended. Periodic plasma infusions appear to be helpful, but a specific protocol has not been developed and treatment must remain empiric. Importantly, unlike preeclampsia and the HELLP syndrome, termination of pregnancy does not induce remission of TTP, however, it is suggested to deliver after fetal lung maturation because of the high mortality of the disease.

Treatment of TTP in pregnancy with plasmapheresis can produce similar outcomes to that of non-pregnant population as pregnancy does not impair the response to plasmapheresis. Untreated TTP not only results in poor maternal outcomes, but also fetal death and intrauterine growth restriction due to placental infarcts. Successful treatment can result in the delivery of a normal sized infant, and successful pregnancies have occurred in women receiving maintenance plasma infusions preconception. Delivery is recommended only for patients who do not respond to plasmapheresis. Guidelines have been developed for the optimal plasmapheresis regime, and these include recommendations for diagnosis and treatment of TTP in pregnancy.

The present authors reviewed some articles about recurrent pregnancy-related TTP (Table 2). Recurrent TTP complicating pregnancy is relatively rare and fresh frozen plasma exchange is crucial treatment for life saving; if the patient was treated promptly and properly, the pregnant outcome was always favorable.

Conclusions

In conclusion, this case shows that prompt and proper management of recurrent pregnancy-associated TTP is possible with a good outcome and the close cooperation between obstetricians, nephrologists, and pediatricians yielded the successful outcome of the pregnancy. Pregnancy is a risk factor for manifestation and relapse of severe TTP.

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