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Postpartum microangiopathic disorders: A case report and review of the literature

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ABSTRACT

Introduction: Thrombotic microangiopathic disorders (TMA's) consist of five overlapping disorders: severe pre-eclampsia; HELLP (haemolysis, elevated liver enzyme, and low platelet count) syndrome; thrombotic thrombocytopenic purpura (TTP); haemolytic–uremic syndrome (HUS) and systemic lupus erythematosus (SLE). Although several case reports are published on TTP during pregnancy, none of them has described TTP in the postpartum period.
Case presentation: We present a case report that illustrates the clinical difficulties and uncertainties in diagnosing TTP in a peripartum period. After repeatedly borderline ADAMTS13 tests and deteriorating TMA abnormalities in the first 72 h postpartum, treatment with plasma filtration, fresh frozen plasma and prednisolone resulted in a quick clinical and laboratory response.
Conclusion: Treatment for TTP should be strongly considered in case of an on-going TMA more than 72 h after delivery.

1. Introduction

Thrombocytopenia is a common finding during pregnancy. Isolated thrombocytopenia has a vast aetiology, but in most cases it is mild and pregnancy induced. Sometimes thrombocytopenia is accompanied by schistocytes in the blood smear. This is of clinical importance because their presence indicates an endothelial dysfunction, which is referred to as thrombotic microangiopathy (TMA) [1]. The differential diagnosis of isolated thrombocytopenia is quite different from the differential diagnosis of TMA's: 1) severe pre-eclampsia; 2) HELLP syndrome (Coombs-negative haemolysis, elevated liver enzymes and low platelet count) [1]; 3) thrombotic thrombocytopenic purpura (TTP); 4) haemolytic–uremic syndrome (HUS) [1–3] and 5) systemic lupus erythematosus (SLE) [4]. To the concerned physicians these five entities together are a diagnostic challenge in pregnancy because of their overlapping features and the requirement of different treatment regimens.

Here we describe a case of postpartum thrombocytopenia caused by TMA in pregnancy, in which the difficulties in establishing the cause of the TMA are highlighted.

2. Case Presentation

A 27 year old Caucasian woman, gravida 1, was admitted to the hospital for induction of labour because she was nearly post-term (40 + 5 weeks). Cardiotocography (CTG) on admission was non-reassuring with a saltatory pattern. Her blood pressure was 110/70 mm Hg on the day of admission and her medical history comprised erysipelas with lymphangitis, and recurrent sinusitis due to a septum deviation. Her membranes were ruptured artificially and the amniotic fluid was meconium-stained. CTG was optimal during labour, showing no signs of foetal distress. She received 150 mg of pethidine (meperidine) s.c. for pain. The second stage took 45 min and a healthy son was born. He had a birth weight of 3760 g and the Apgar-scores were 7 immediately after birth, and 10 after five insufflations with oxygen. After delivery 10 U of oxytocin s.c. was administered and the placenta was delivered 30 min later. A total blood loss of 300 mL was documented.

Twenty-three minutes later her blood pressure declined to 58/32 mm Hg, the heart rate was 115 bpm and O_2-saturation was 98%. She also felt drowsy and at physical examination the uterus was well contracted. She received oxygen, 20 U of oxytocin s.c., 0.4 mg of naloxone i.v., intravenous infusion with iso-osmotic saline, and plasma replacement fluid (Voluven), which raised the blood pressure to 111/

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62 mm Hg. Laboratory tests showed a haemoglobin of 7.1 mmol/L (normal 7.5–10 mmol/l), and her platelet count was 33×10^9/L (150–400×10^9/L), while platelet count was 154×10^9/L forty-five days before delivery. During the day a total blood loss of 1500 mL was observed, her blood pressure stayed 108/69 mm Hg and her uterus was well contracted, so no action was undertaken. In the next days haemoglobin dropped to 3.5 mmol/L and platelet count to 11×10^9/L. Additional laboratory parameters demonstrated haptoglobulin < 0.3 g/L (0.3–2.0 g/L), creatinine 58 μmol/L (45–84 μmol/L), fibrinogen 3.9 g/L (2.0–4.0 g/L), D-dimer 5.92 mg/L (<0.5 mg/L), APTT 33 s (<32 s), PT 10 s (8–11 s), uric acid 0.39 mmol/L (0.12–0.34 mmol/L), ASAT 64 U/L (<31 U/L), ALAT 39 U/L (<31 U/L), LDH 1487 U/L (<450 U/L) and bilirubin 22 μmol/L (<17 μmol/L) (Table 1). The blood cell differentiation revealed schistocytes and Coombs' test was negative so we concluded that TMA was caused by HELLP syndrome or TTP. She did not complain of abdominal pain, but experienced headache, and a strange feeling of decreased awareness of the things happening around her. She was transferred to the ICU department and prednisone 100 mg/day was started. An abdominal ultrasound was performed which showed no abnormalities except for an enlarged right kidney, due to the recent pregnancy, and a small amount of free fluid in Morrison's space. The ADAMTS13 was 11% (cut-off value of <10% for TTP) which made TTP less obvious and HELLP syndrome remained suspected.

In the ICU department her haemoglobin varied between 3.8 and 4.4 mmol/L, schistocytes were still present, and she received a platelet transfusion which resulted in an increase of platelets from 9×10^9/L to 31×10^9/L. A repeated ADAMTS13 demonstrated a value of 15% (cut-off value of <10% for TTP). Because of deteriorating platelets, lack of spontaneous improvement after delivery as expected in HELLP syndrome and no severe liver enzyme abnormalities, HELLP syndrome was rejected, and a diagnosis of TTP was made. Subsequent plasma filtration and replacement (50 mL/kg) with fresh frozen plasma (FFP) was started on the sixth day after delivery. The following day our patient felt much more aware and the platelet count had increased up to 95×10^9/L. She received plasma filtration and FFP once a day for ten consecutive days and prednisone was continued. Platelet count normalised and haemolysis declined (Fig. 1), so that she could be discharged from the hospital after two weeks in a good clinical condition without any complaints, and without signs of Coombs-negative haemolysis or schistocytes.

As an outpatient the plasma filtration and plasma replacement was given three times a week in the first week and two times a week in the second week after which it was stopped. The prednisone dose was tapered and finally stopped two months after start without signs of relapse of TTP. After 9 months a repeated ADAMTS13 was 25%, which raised a suspicion of the Upshaw–Schulman syndrome.

Table 1
Explorative laboratory tests drawn on day two.

Variables	Value	Unit	Normal value
Hemoglobin	3.5	mmol/L	7.5–10.0
Reticulocytes	3.0	%	0.0–2.5
Haptoglobin	<0.3	g/L	0.3–2.0
Ferritin	329	μg/L	20–150
Vitamin B_{12}	193	pmol/L	130–700
Folate	35	nmol/L	≥5
Platelets	11	$\times 10^9$/L	150–400
APTT	33	s	<32
Prothrombin time (PT)	10	s	8–11
Fibrin	3.9	g/L	2.0–4.0
D-dimers	5.92	mg/L	<0.5
Leucocytes	9.4	$\times 10^9$/L	4.3–10.0
Basophils	0	%	0–1
Eosinophils	0	%	0–5
Rods	3	%	0–5
Segments	72	%	40–70
Lymphocytes	16	%	20–45
Monocytes	5	%	2–8
Schistocytes	++		
ADAMTS13	11	%	<10
Creatinine	58	μmol/L	45–84
Urea	5.4	mmol/L	2.5–6.4
Albumin	21	g/L	35–50
Bilirubin	23	μmol/L	<17
γ-GT	9	U/L	<35
AF	112	U/L	<120
ASAT	64	U/L	<31
ALAT	38	U/L	<31
LDH	1318	U/L	<450
CRP	55	mg/L	0–10

3. Discussion

This case report describes a 27 year old woman with a life-threatening ongoing thrombocytopenia after delivery caused by TTP. The ADAMTS13 level of 25% nine months after delivery is suspicious for the Upshaw–Schulman syndrome. This is congenital TTP caused by a mutation in the ADAMTS gene on chromosome 9q34 [5]. In these patients, pregnancy seems to induce thrombocytopenia in the second or third trimester, often followed by TTP [6].

This case describes a life-threatening thrombocytopenia of pregnancy and peripartum, which is often important to distinguish from milder and physiologic forms of thrombocytopenia. Important in thrombocytopenia of pregnancy is to establish the presence of TMA and in the case of TMA to establish the underlying disorder (Table 2). In this case, the thrombocytopenia was noticed directly after delivery, but a complete evaluation was started on the second day which contributed to a delay in the diagnosis of TTP. Thus we recommend more aggressive evaluation of new onset peripartum thrombocytopenia. The postpartum presentation of severe thrombocytopenia and Coombs-negative haemolytic anaemia was first attributed to an atypical HELLP syndrome. Because of the presence of schistocytes in the blood smear and an ADAMTS13 level of 11%, with a cut-off value of <10%, TTP was discarded at first. A repeated ADAMTS13 revealed a value of 15%, by which no definite diagnosis of TTP could be made. Because of deteriorating platelets and lack of laboratory abnormalities improvement more than 72 h after delivery HELLP syndrome was considered unlikely and treatment for TTP was initiated. Because of rapid clinical and laboratory improvement in the hours following plasma filtration, a diagnosis of TTP was made.

TTP and HUS are rare entities and it is estimated that it occurs in <1:100.000 pregnancies [7]. In a retrospective study between 1955 and 2006 by Martin and colleagues, 166 reports of pregnancy associated TTP were found in the literature [3]. Although TTP mostly presented in the second and early third trimester of the pregnancy (55.5%), in 21 of 166 cases (12.7%) the onset of TTP occurred postpartum. It is estimated that in the era before plasma infusions and plasma exchange maternal mortality was as high as 60% [3]. Nowadays the maternal mortality is 0–15%, which is mainly due to complications of plasma exchange therapy [8]. Furthermore, there is a difference of maternal outcome between patients already known with TTP, and patients who develop TTP for the first time during pregnancy, or in the postpartum period, because of delay in confirming the diagnosis and thus treatment [7]. Pregnancy induced TTP is not only associated with maternal death and morbidity, but also with perinatal loss (17%), perinatal mortality (454:1.000), and preterm delivery [3,7].

The classical features of TTP consist of the pentad: thrombocytopenia, microangiopathic haemolytic anaemia with schistocytes in the blood smear, neurologic abnormalities, fever, and renal failure. The first three symptoms frequently occur together (50–75%), but all five symptoms rarely occur at the same time, and therefore the pentad is considered to be out-dated [7–9]. George and colleagues showed that among eighteen patients diagnosed with TTP, and an ADAMTS13 level of <5% (which is specific for TTP), abdominal pain, nausea, vomiting, and/or diarrhoea were the most presenting complaints [9]. For physicians it is hard to diagnose TTP based on these unspecific symptoms and therefore laboratory results provide the diagnosis. The 'new' diagnostic triad of 1) thrombocytopenia, 2) microangiopathic haemolytic