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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

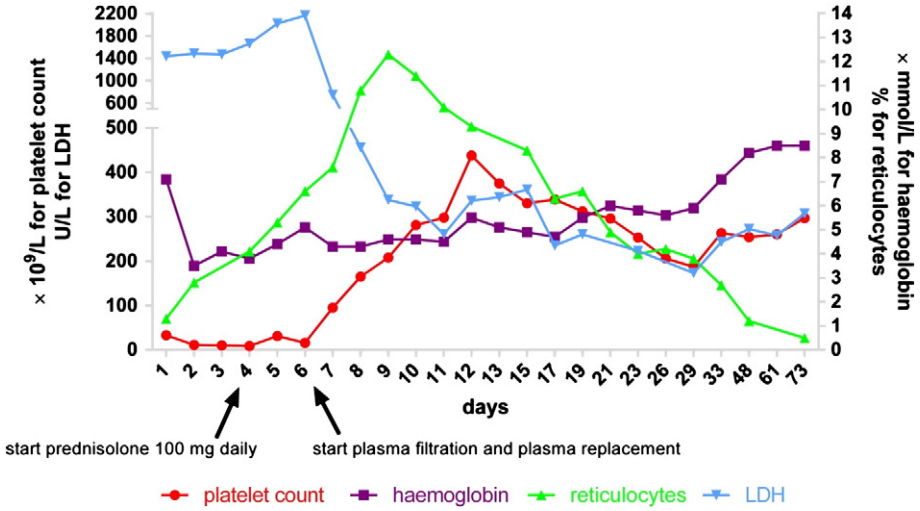

Fig. 1. Graph of the course of the haemoglobin, platelet count, LDH and reticulocytes.

anaemia, and 3) no alternative aetiology is sufficient to diagnose TTP [8,9]. This allows physicians to diagnose TTP rapidly, which can be of life-saving importance. A negative Coombs' test may support the diagnosis together with a low haptoglobin level [10,11]. Neurologic symptoms are difficult to diagnose and are usually vague [7].

TTP is caused by a deficiency of the thirteenth member of a disintegrin-like and metalloprotease with thrombospondin type 1 motifs 13 (ADAMTS13), which normally cleaves the plasma glycoprotein Von Willebrand factor (VWF) [1–3,7,12]. In TTP VWF is not cleaved which results in ultra-large VWF-multimers that cause platelet aggregation, thrombocytopenia and Coombs-negative haemolysis (TMA). A plasma ADAMTS13 activity level of <5% or <10%, depending on the assay, is specific for TTP [2,9]. However, George and colleagues concluded that only a cut-off value of <5% is highly specific for TTP [9]. A cut-off value of <10% included less false negatives (especially relapses of TTP), but logically also more false positives (e.g. severe sepsis or disseminated malignancy). Deficiency of ADAMTS13 in TTP can be a result of genetic mutations (e.g. Upshaw–Schulman syndrome), autoimmune disorder or acquired inhibitors [2,9,10,13]. The measurement of ADAMTS13 activity can be helpful in case of TTP occurrence in pregnancy, although decreased ADAMTS13 levels are associated with normal pregnancy and with HELLP syndrome [12,14]. Hulstein and colleagues found a significant decreased ADAMTS13 in patients diagnosed with HELLP syndrome ($n = 14$) when compared with patients with a normal pregnancy ($n = 9$) [14]. Other studies show that ADAMTS13 activity between 10 and 50% is compatible with a near term of normal pregnancy and that from week twelve of gestation there is a significant decrease in activity compared to non-pregnant women [9,12].

Schistocytes are fragmented erythrocytes that are injured by damaged endothelium [11]. It is important to use a threshold of 0.2–0.5% for schistocytes before suspecting TTP. Furthermore, microscopic determination lacks standardization and remains highly observer dependent [15]. However, schistocytes not only are present in TTP, but may be encountered in other TMA's as well, including SLE [4].

Table 2
Differential diagnosis of severe pre-eclampsia/HELLP syndrome, reproduced from Sibai (2009) [7] with permission, and with slight modifications.

- Acute fatty liver of pregnancy
- Thrombotic thrombocytopenic purpura
- Hemolytic–uremic syndrome
- Exacerbation of lupus erythematosus
- Catastrophic antiphospholipid syndrome
- Systemic viral sepsis (disseminated herpes)
- Systemic inflammatory response syndrome (SIRS)
- Disseminated intravascular coagulation

Martin and colleagues performed a prospective study which included eighteen women diagnosed with HELLP syndrome [16]. These women were treated with plasma exchange postpartum because of 1) persistent evidence of atypical HELLP syndrome >72 h after delivery ($n = 9$) or 2) evidence of worsening HELLP syndrome at any time postpartum in association with single- or multiple-organ injury ($n = 9$). Only patients with class 1 HELLP syndrome (platelet count $\leq 50 \times 10^9$/L; ASAT or ALAT ≥ 70 U/L; LDH ≥ 600 U/L) and progressive anaemia with abnormal red blood cell forms were included. Two out of nine patients from the second arm (with worsening HELLP syndrome) died despite the therapy. All patients in the first arm responded well to plasma exchange. An earlier study recommended that in case of doubt between ongoing HELLP syndrome and TTP after delivery, one should wait at least 72 h before considering plasmapheresis [17]. McMinn & George support the '72-hour policy' [18]. They provide additional clinical features for starting with plasma treatment, especially in pregnant or postpartum women who are more likely to have TTP-HUS. They recommend to start with plasma therapy if:

- Severe thrombocytopenia and microangiopathic haemolytic anaemia progress for more than three days following delivery.
- There are normal coagulation parameters, or resolving disseminated intravascular coagulation (DIC).
- There are mental status abnormalities (such as confusion, disorientation, stupor, coma).
- There are focal (neurologic) abnormalities (such as aphasia, dysarthria, or focal motor deficits).
- There are seizures (in association with progressive postpartum thrombocytopenia and microangiopathic haemolytic anaemia).
- There is oliguric acute renal failure (in association with progressive postpartum thrombocytopenia and microangiopathic haemolytic anaemia).

TTP that occurs during pregnancy carries the risk of relapse after delivery as well as in subsequent pregnancies. Patients should be instructed about recognizing symptoms and reporting them immediately to a physician [7]. Relapses are common among those with congenital ADAMTS13 deficiency (approximately 40% will relapse), but very rare among patients without congenital ADAMTS13 deficiency. Most of the relapses of non-congenital TTP occur within the first year and are a single event. Relapses after four years are rarely seen [9].

4. Conclusion

New onset thrombocytopenia during pregnancy should have a thorough work-up, including a peripheral blood smear to look for schistocytes, to exclude thrombotic microangiopathy's (TMA's). Also treatment for TTP should be strongly considered in case of an ongoing TMA more than 72 h after delivery.

Conflict of Interests

The authors declare that they have no conflicts of interests.

Authors' Contributions

C.H. Wessel: first draft, drafting, conception, revising, literature search, and final approval. C.E. Andreescu: drafting, revising, treating physician, and final approval. S. Rombout-De Weerd: drafting, revising, attending gynecologist, and final approval. M-D. Levin: drafting, revising, supervision, attending internal medicine physician, and final approval.

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