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Case Reports

Post-partum management in a patient affected by thrombotic thrombocytopenic purpura: case report and review of literature

A.S. Laganà[1], V. Sofo[2], F.M. Salmeri[2], B. Chiofalo[1], L. Ciancimino[1], O. Triolo[1]

[1] Department of Pediatric, Gynecological, Microbiological and Biomedical Sciences. University of Messina, Messina
[2] Department of Environmental Sciences, Safety, Territory, Food and Health. University of Messina, Messina, (Italy)

Summary

Thrombotic thrombocytopenic purpura (TTP) is a rare and potentially lethal syndrome characterized by severe thrombocytopenia, microangiopathic haemolytic anaemia, and aspecific neurologic symptoms. This syndrome is the result of an abnormal intravascular platelet aggregation which induces transient ischemia in various organs, especially in the central nervous system. Platelet aggregation causes also fragmentation of erythrocytes, thus leading to the characteristic anaemia. The exact cause of TTP is unknown, but a large body of evidence suggest that this syndrome might be due to acquired (immunological) or congenital ADAMTS13 deficiency. The dysregulation of ADAMTS13 activity could promote massive release of high molecular weight multimers of von Willebrand factor (VWF) from endothelium and, as a consequence, could cause intravascular platelet aggregation. Pregnancy is commonly associated with numerous metabolic, immunological, and haemostatic changes which could increase thrombotic risk: during pregnancy, in fact, it is generally observed an increase of procoagulant activity and a decrease of fibrinolytic activity; moreover, at the end of pregnancy, it is not rare to find thrombocytopenia. All these reasons lead us to consider pregnancy itself as a triggering event for the onset of TTP. The authors describe a case of TTP occurred during puerperium, in a patient who underwent caesarean section.

Key words: Thrombotic thrombocytopenic purpura; Pregnancy; Plasma exchange; Plasma infusion; Post-partum complications.

Introduction

Thrombotic thrombocytopenic purpura (TTP), as described for the first time by Moschcowitz [1], is a rare and potentially lethal syndrome characterized by severe thrombocytopenia, microangiopathic haemolytic anaemia, and aspecific neurologic symptoms [2]. Patients diagnosed with classical TTP had a severely deficient activity of this von Willebrand factor (VWF) cleaving protease (VWF-cp) (<5% of normal) [3-6]. Two forms of classical TTP are distinguished. Acquired TTP is caused by circulating autoantibodies, mainly IgG, generally neutralizing ADAMTS13 activity [5-7], while hereditary TTP (Upshaw-Schulman syndrome) is caused by severe constitutional deficiency of ADAMTS13 [8-15]. The incidence of TTP is estimated at 4.5 per one million people a year, mean age at diagnosis is 35 years, and is more frequent among women (male/female ratio is 2 : 3) [16]. While at the beginning of the last century TTP's mortality rate was 90%, with the introduction of the plasma-exchange (PE) technique, it fell between 8% and 30% depending on associated diseases [17]. After the first episode, relapses are frequent in the following years [18], especially when the patient undergo pregnancy [19], transplantation of hematopoietic progenitor cells [20], infections [21], metastasis [22], use of ticlopidine, and clopidogrel [23]. This syndrome is the result of an abnormal intravascular platelet aggregation which induces transient ischemia in various organs, especially in the central nervous system. Platelet aggregation causes also fragmentation of erythrocytes, thus leading to the characteristic anaemia. The first indication that VWF was involved in the pathogenesis of TTP originated from the observation by Moake *et al.* [24] of unusually large VWF multimers in the plasma of patients with a chronic relapsing form of TTP. VWF is a multimeric glycoprotein composed of identical disulfide-linked 250 kD subunits synthesized by endothelial cells and megakaryocytes and plays an important role in primary hemostasis by mediating initial platelet adhesion to the subendothelium of the damaged vessel wall at high shear rates. From the storage organelles (Weibel-Palade bodies) of endothelial cells, VWF is secreted in the form of extremely adhesive ultralarge VWF multimers into the circulation, where they are slowly

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Table 1. — *Blood test results at hospital admission.*

Analyte	Measurement unit	Value	Normal Range
Red blood cells	mmc	2080000	Women: 4,000,000 - 4,500,000
White blood cells	mmc	9200	4,500 - 9,000
Haemoglobin	gr%	6.2	Women: 12.0 - 16.0
Hematocrit	%	19	38,0 - 46,0
Platelets	mmc	78000	150,000 - 350,000
Prothrombin time (PT)	%	102.0	70.0 - 120.0
Activated partial thromboplastin time (aPTT)	sec	30.4	21,0 - 35,0
Fibrinogen	mg/dl	217	180 - 350
International normalized ratio (INR)	-	1,03	-
D-Dimer	mg/L	3.37	< 0.50
Antithrombin III (AT III)	%	72	80 - 120
Fibrin degradation products (FDP)	ug/ml	10	0 - 10
Fasting glucose	mg/dl	86	65 - 110
Blood urea nitrogen (BUN)	mg/dl	114	10.0 - 50.0
Creatinine	mg/dl	1.4	0.5 - 1.2
Uric acid	mg/dl	5.0	2.5 - 7.2
Total protein	g/dl	4.2	6.0 - 8.2
Albumin	g/L	31	34 - 48
Total Bilirubin	mg/dl	1.3	0.0 - 1.2
Aspartate aminotransferase (AST)	U/L	30	0 - 42
Alanine aminotransferase (ALT)	U/L	23	0 - 50
Lactate dehydrogenase (LDH)	U/L	1170	150 - 460
Cholinesterase	U/L	5992	4,500 - 14,500
Sodium	mmol/L	142	130 - 148
Potassium	mmol/L	3.7	3.5 - 5.2
Calcium	mg/dl	7.98	8.2 - 10.4

but constantly attacked by plasma protease(s) and degraded into multimers ranging in size from 500 to ~20‘000 kD [25]. Proteolytic cleavage occurs physiologically between the tyrosine residue at position 842 and the methionine residue at position 843 within the A2 domain of the mature VWF subunit [26]. The multimeric structure of VWF is strictly regulated by a VWF-cp, a new member of the ADAMTS (a disintegrin and metalloprotease with thrombospondin type 1 motifs) family of metalloproteases, denoted as ADAMTS13 [27] and to locate the gene to chromosome 9q34 [28]. Levy *et al.* [8], performing a genome-wide linkage analysis in patients with hereditary TTP which displayed severe VWF-cp deficiency and their family members, detected the same gene, ADAMTS13. They identified several different mutations presumably responsible for the severely deficient protease activity and hereditary TTP in homozygous or double heterozygous carriers of mutated alleles. On the contrary, patient’s family members with a heterozygous mutation had about 50% of protease activity and were clinically asymptomatic [29]. Numerous hypotheses regarding the aetiology and pathogenesis of TTP have been put forward over the years [27, 30-32]. Endothelial injury, decreased prostacyclin production, reduced fibrinolytic capacity of the vessel wall, anti-endothelial cell, and -platelet autoantibodies, specifically antibodies toward glycoprotein IV (CD36) [33, 34], and capacity of plasma of TTP patients to induce apoptosis of microvascular endothelial cells [35] have been proposed as pathogenetic factors. Moreover, a 37-kDa protein [36] and a 59-kDa protein or a calcium-dependent cysteine protease (calpain) [37, 38] were identified in serum or plasma from patients with acute TTP and suggested to be responsible for *in vivo* platelet aggregation. TTP acquired form could be also due to a massive endothelial damage which causes releasing of VWF multimers in blood vessels. If these multimers overcome their physiological degradation rate, they could trigger severe microvascular thrombosis [24]. TTP diagnosis is based on the presence of schistocytes at peripheral blood smear [16] and blood tests, which show decrease of haemoglobin and haptoglobin, increase of haemolysis indexes, lactate dehydrogenase (LDH) and unconjugated bilirubinemia, negative Coombs test, severe thrombocytopenia with normal prothrombin time (PT) and activated partial thromboplastin time (aPTT). Another test which can be performed is the enzyme-linked immunosorbent assay (ELISA) immunoassay for IgG anti-ADAMTS13 [39], although its specificity is low. In fact, it has been observed that about 5% of healthy individuals and 13% of patients with systemic lupus erythematosus (SLE) result positive to this immunoassay, nonetheless showing normal activity of ADAMTS13 in plasma [40]. The risk of recurrence after the first episode depends on ADAMTS13 activity rate or anti-ADAMTS13 level at onset. When ADAMTS13 activity rate is <10% the risk of relapse is 40%, while when it is >10%, the risk decreases to 4% [41]. The differential diagnosis must include

haemolytic uraemic syndrome (HUS), disseminated intravascular coagulation (DIC), anti-phospholipid syndrome (APS), pre-eclampsia and haemolysis, elevated liver enzymes, and low platelet count (HELLP) syndrome [42]. Physiological changes and complications during pregnancy or puerperium can determine risk factors to trigger acute episodes of TTP, especially in women with family histories of thrombophilia or ADAMTS13 deficiency [27]. The authors describe a case of TTP occurred during puerperium, in a patient who underwent caesarean section.

Case Report

The authors report a case of a 50-year-old female who was admitted to our obstetric emergency unit on the third day postpartum. She was sent to the authors' observation from another hospital with the suspect diagnosis of TTP. She had a twin pregnancy obtained with eggs donation and subsequent in-vitro fertilization (IVF) procedure, delivered with caesarean section at 34th week for gestational hypertension unresponsive to medical therapy (nifedipine and methyldopa). Both newborns were admitted to neonatal intensive care unit, without reporting any subsequent complication. At admission, the patient was informed in a comprehensive and complete way about clinical condition and procedures that the authors were going to perform, and signed an informed consent to allow the data collection for research purposes. A subsequent approval by the Hospital's Ethic Committee was obtained before initiating the report. During the admission procedure, the patient had treatable abdomen, valid peristalsis, and first passage of flatus, uterus in regular puerperal involution and physiological lochia. The vital parameters were normal, except for the high blood pressure (155/90 mmHg). She complained of mild headache. Family anamnesis showed that a sister was affected by SLE; obstetric history highlighted unexplained infertility, and for this reason she underwent two IVF procedures hesitated in both cases in early miscarriages at fifth week; personal medical history was negative for other disease. Blood tests showed anaemia, thrombocytopenia, high levels of blood urea nitrogen (BUN), LDH, creatinine, and total bilirubin; low levels of antithrombin III (AT III), total proteins, albumin, calcium; PT, aPTT, international normalized ratio (INR) were in normal range (Table 1). Moreover urine test evidenced massive proteinuria and high level of urobilinogen (2.0 mg/dl; normal range 0.0 ÷ 1.0 mg/dl), and 40-50 erythrocytes were present at urinary sediment analysis. Routine and available in the laboratory autoimmunity tests, including antinuclear antibodies (ANA), antiDNA antibodies (nDNA), extractable nuclear antigens (ENA), antimitochondrial antibodies (AMA), anti-smooth muscle antibody (ASMA), anti-meutrophil cytoplasmic antibody (ANCA), IgG and IgM anti-cardiolipin antibodies, were negative. The peripheral blood smear analysis, performed by haematologist, showed the presence of schistocytes (10%). Neurological exam was negative, as well as brain CT scan. Considering all these findings, the authors confirmed the diagnosis of TTP. In full agreement with the haematologist, nephrologist and neurologist, they decided to administrate therapy with nifedipine 30 mg/die per os, methyldopa 500 mg/die per os, Dexamethasone sodium phosphate four mg/die i.m., methylprednisolone hemisuccinate 20 mg/die e.v., acetylsalicylic acid 1g/die e.v., enoxaparin sodium 4,000 UI/die s.c.; additionally, on the basis of daily blood tests, the patient underwent treatment with calcium folinate 25 mg/die i.m., AT III 1000 UI/die e.v., albumin 20% e.v. when required. Moreover, she was treated daily with PE procedure, and multiple plasma infusion (PI) or blood transfusion when required. Nevertheless, on the seventh day of post-partum, the authors noticed a severe bleeding from the caesarean section scar and found a massive subfascial hematoma: therefore, they performed a revision of laparotomic incision, in order to drain the hematoma. Besides this complication, the clinical condition and the results of blood tests progressively improved following the medical treatment and PE procedures, and patient was discharged home on the 13th post-partum day.

Discussion

TTP is a life-threatening systemic illness of abrupt onset and unknown cause(s) which can occur also during pregnancy or puerperium. When it occurs during pregnancy, it could cause fetal death for placental infarction due to thrombotic occlusion of the decidual arteries. More specifically, pregnancy itself can be considered a triggering event for the onset of TTP. Pregnancy is commonly associated with numerous metabolic, immunological, and haemostatic changes which could increase thrombotic risk. During pregnancy, in fact, an increase of procoagulant activity and a decrease of fibrinolytic activity occur [43, 44], and at the end of pregnancy it rare not rare to find thrombocytopenia (prevalence between 6.6 and 11.6%) [45]. According to the Oklahoma TTP-HUS registry, pregnancy-associated TTP accounts for 13% of all cases of TTP [43] and is related to high rates of obstetric complications [46,47]. Some authors [48, 49] suggest that delivery could resolve TTP, although this point of view is not universally shared in literature. In the present reported case, the delivery did not resolve the pathology but it was the triggering event. Nowadays the treatment of this syndrome with PE and PI, together with corticosteroid administration, reduces the mortality and morbidity rate and improves the medium- and long-term maternal-foetal outcomes [50]. This is what occurred in the present patient who improved her condition in one week. PI is effective both in immune-mediated form, because it removes the anti-ADAMTS13 antibodies, as well as in congenital ADAMTS13 deficiency, because it replaces the lacking protease [51]. Although the authors could not perform any dosage of anti-ADAMTS13 antibodies or ADAMTS13-activity, they hypothesized that this reported case is not due to congenital ADAMTS13 deficiency, because the patient had no previous episode of TTP and personal medical history was negative for other related diseases. Since TTP is rare and shares some common features with other more frequent obstetric diseases as pre-eclampsia, eclampsia and HELLP syndrome, the authors suggest that accurate differential diagnosis be mandatory in order to commence treatment as soon as possible and avoid adverse outcomes.

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Address reprint requests to:
A.S. LAGANÀ, M.D.
Department of Pediatric, Gynecological,
Microbiological and Biomedical Sciences
University of Messina
Via C. Valeria 1, 98125 Messina (Italy)
e-mail: antlagana@unime.it