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## Thrombotic thrombocytopenic purpura associated with pregnancy - Case report

*Púrpura trombocitopênica trombótica associada à gravidez –  
 Relato de caso*

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### ABSTRACT

Case report of a patient with 37-week gestational age admitted to an obstetric intensive care unit with an altered level of consciousness, related primarily to the pregnancy-induced hypertension. The patient presented a worsening clinical course characterized by, anemia and severe thrombocytopenia, Investigation led to a diagnostic of thrombotic thrombocytopenic purpura after the hematological profile was assessed. The

authors emphasize the importance of the disease recognition as a prognostic marker for obstetric patients, in view of the similarity with other common morbidities during pregnancy and the importance of timely diagnosis and early treatment as determinant factors for the outcome.

**Keywords:** Pregnancy complications, hematologic; Plasmapheresis; Purpura, thrombotic thrombocytopenic; Intensive care; Case reports

### INTRODUCTION

Thrombotic thrombotic purpura (TTP) is a rare etiology in critically ill patients (0.5% of admissions) belonging to an array of diseases classified as thrombotic thrombocytopenia syndromes that also involve the hemolytic uremic syndromes (HUS) and the HELLP syndrome (Hemolysis, Elevated Liver enzymes levels, Low Platelet count). In the absence of treatment, these pathologies present a high rate of mortality.<sup>(1-3)</sup>

TTP is more common in the female gender (3:2), predominantly in black women. According to the Oklahoma TTP-HUS Registry there is an association of TTP with cancer or sepsis in up to 10% of cases.<sup>(3)</sup> Pregnancy is an important cause of TTP due to a significant decrease of endothelial expression of the ADAMTS-13 molecules (A disintegrin and metalloprotease domain with thrombospondin-1 type I motifs 13), a protease responsible for cleavage of the Von-Willebrand factor (fVW).<sup>(4-5)</sup>

The event takes place in 70% of pregnant women over 40 years of age, with a ratio of 1:25000 pregnancies, seldom occurring in the first trimester and more common in periparturient.<sup>(5-6)</sup> It is estimated that events associated to pregnancy are often underdiagnosed or have a delayed diagnosis due to similarity with findings of specific hypertension diseases or HELLP syndrome as well as other well studied clinical etiologies such as sepsis or endocrine metabolic syndromes.<sup>(6-9)</sup>

The clinical case reported illustrates the importance of recognizing pregnancy as an associated factor for triggering TTP, stressing the similar symptomatology with other common events in pregnancy, such as pregnancy-specific

hypertensive disorders (PSHD) with or without HELLP syndrome and signaling need to investigate underlying factors such as infections.

## CASE REPORT

Patient KCFM, 38 years old, primigravida, from the interior of the state was admitted in this maternity ward in the 37<sup>th</sup> week of gestation with a report of malaise associated to epigastric pain and visual change. There was no report of previous hypertension neither in the prenatal follow-up. The companion reported appearance of darkened red spots over the whole body and fluctuating level of consciousness during the last two weeks. At physical exam the patient was pale, in good nutritional status. She was lucid and oriented: arterial pressure (AP) - 180 X110mmHg; respiratory rate – 24breaths/ min and heart rate – 107 bpm.

She did not present with signs of respiratory distress and lung and heart auscultations were normal. Upon examination of the abdomen the uterine fundus was palpable 10 cm from the umbilical scar; fetal heart beats (FHB) were inaudible at fetal heart monitoring. Extremities were adequately perfused without edema. On the anterior face of the chest and inner face of the arms she presented petechia. At neurological examination the patient was lucid and oriented without focal neurological signs or alterations of the surveyed brain stem and osteotendinous reflexes and with normal muscle strength.

The electrocardiogram (ECG) was normal and chest X- ray showed discreet cardiomegaly. Obstetric ultrasound with Doppler flowmetry found fetal death. Laboratory tests are described in chart 1.

Evaluation of the peripheral blood smear showed anomalies compatible with thrombotic thrombocytopenia (anemia, moderate anisocytosis, schizocytes and target shaped and tearshaped erythrocytes) and laboratory tests were compatible with a condition of hemolysis (high levels of lactic dehydrogenase and hemoglobinuria). The patient was submitted to blood transfusion with packed red blood cells and a platelets apheresis as a preparation for a Cesarean section (with the control test showing hemoglobin levels of 9.2 g/dL and platelet count of 90,000/mm<sup>3</sup> and normal prothrombin time (PT) as well as time of activated partial thromboplastin (APT), also, use of dexamethason 40 mg/day due to suspicion of severe antepartum HELLP. She was taken to the obstetric center (OC) for removal of the fetus with report of cloudy amniotic fluid without excessive bleeding. During the procedure the patient evolved to respiratory failure being placed under mechanical ventilation. Because of suspicion of severe

## Chart 1- Laboratory tests upon admission

Hemoglobin 5.5 g/dL
Leukocyte count 27900/mm <sup>3</sup> (3% of Erythroblasts)
Platelets 16000/mm <sup>3</sup>
Glycemia 120 mg/dL
Urine contents Protein++ and Hemoglobin
Urea 64 mg/dL
Creatinine 1.26 mg/dL
Sodium 133 mEq/L
Potassium 4.5 mEq/L
AST 81 U/L
ALT 25 U/L
Bilirubins 1.06 mg/dL
Prothrombin activity 72.8%
Albumin 3.0g/ dL
Lactic Dehydrogenase (LDH) 2300 U/L
Uric acid 7.0 mg/dL
Serum Bicarbonate 10 mmol/L

AST - aspartate aminotransferase; ALT - alanine aminotransferase

sepsis secondary to endometritis, cefepime 6 g/day and metronidazol 2 g/day were administered. At immediate postoperative she evolved with rather high AP (mean AP 130-150mmHg) requiring use of sodium nitroprussiate and other anti-hypertensives.

After these measures she presented improvement of ventilatory parameters, and was uneventfully extubated after 48h.

The following days were characterized by fluctuating level of consciousness, worsening of the renal function and of perfusion parameters (persistent metabolic acidosis, central venous saturation below 70%, CO<sub>2</sub> gap above 6.0 mmol/L) whereupon the antimicrobial regimen was changed to piperacillin and tazobactam, later changed to inipenem and vancomycin (with doses adjusted to clearance of measured creatinine). Due to respiratory worsening with diagnosis of nosocomial pneumonia (hypoxemia, fever, purulent airway secretion and diffuse infiltrates, at chest X-ray), mechanical ventilation was reinitiated and a low dose of vasopressor and inotropic was required.

In parallel, she presented with worsening of the hematological markers, especially persistence of anemia and significant thrombocytopenia (<25,000 platelets/mm<sup>3</sup>) and posterior elevation of lactic dehydrogenase (DHL). Thrombotic thrombocytopenic as the baseline event, decompensated by pregnancy was suspected. An hematology assessment was requested that agreed with the clinical suspicion whereupon a continuous plasmapheresis (exchange of 100mkl of plasma) without use of heparin, to achieve platelets count

above 10,000/ mm<sup>3</sup> and DHK < 600 U/L was implemented. Non-pharmacological prophylaxis against deep venous thrombosis was carried out using elastic stockings.

After implementation of specific management, the renal function improved progressively, while the infection decreased (cure of fever improved of leukocyte count and pulmonary function tests), the seven days antibiotic therapy was completed, with spontaneous ventilation. Hemocultures were negative and qualitative tracheal secretion was positive for *Klebsiella pneumoniae*, a strain producing extended spectrum beta-lactamase (ESBL). At the same time there was an improvement of the hemolysis markers, with counts for discharge from the intensive care unit of 247,000 platelets/mm<sup>3</sup> and DHL of 438 U/L using low-dose corticosteroids.

## DISCUSSION

Pathophysiology of TTP encompasses endothelial changes related to peripheral destruction of the blood cell elements, formation of thrombus in terminal and capillary arterioles and ischemia of target-organs.<sup>(2)</sup> TTP results from the reduced expression or deficient activity of the ADAMTS-13, protein, responsible for cleavage of the Von-Willebrand factor in various monomers. In the disease protein-deficiency fosters formation of Von Willebrand abnormally large multimers, attracting platelets and fibrin-anchors and creating a disseminated process of prothrombotic feedback.<sup>(2-4)</sup> In rare family cases, mutations in the ADAMTS-13 gene were described which are possible triggers for infection (viral, bacterial) or other mechanisms of endothelial injury such as surgery and cancer. However, in the non-familial form of deficiency, TTP occurs exclusively during pregnancy, suggested by the inducing action of proteins at placental levels, stimulating antibody activity against ADAMTS-13, contributing also to recurrence in future pregnancies.<sup>(5)</sup>

Clinical presentation is based upon findings of hemolytic anemia and thrombocytopenia with microangiopathic hemolysis smears and skin purpura. Symptoms are strongly represented by neurological changes, generally of sudden onset, indicating a condition of recurrence and signaling persistence of the disease during treatment. Among the more important laboratory analyses for follow-up of the disease are smear of peripheral blood (evidence of schizocytes and reticulocytes) and measurement of LDH as a marker of tissue ischemia and hemolytic activity, in addition to serum count of erythrocytes and platelets.<sup>(2-3)</sup>

Various authors have reported cases of pregnant women admitted in specialized centers with primary suspicion of hypertension decompensation, pre-eclampsia, HELLP syn-

drome or acquired coagulopathy, however evolving unfavorably as represented by continued thrombocytopenia, hemolytic anemia, renal failure and expressive changes in the level of consciousness, with or without a former history of skin purpura, thus confirming a condition of TTP with the typical findings of thrombotic thrombocytopenia. They highlighted the initial diagnostic difficulty due to similarity of symptoms between diseases.<sup>(6-8)</sup> There is no correlation between severity scores (enhancing neurological symptoms, renal function and hematological changes) and in the long term prognosis involving TTP and HUS in pregnant women, although permitting a later occurrence of new events.<sup>(9-11)</sup>

International associations of blood banks and apheresis and the British Committee for Standards in Hematology have established treatment of TTP based upon daily plasmapheresis stipulated by exchange of 1 to 1.5 times the volemia, until platelet count exceeds 150.000/mm<sup>3</sup>, and LDH at normal levels with a low rate of reported complications. Associated use of steroids in moderate to high doses in idiopathic or refractory cases is recommended, as well as use of immunosuppressive agents,<sup>(3)</sup> or even administration of ADAMTS-13 by plasmapheresis.<sup>(5)</sup> Complete remission of the condition is defined by improvement of the neurological symptoms, gradual increase of platelet and hemoglobin count and normalization of LDH.<sup>(9)</sup>

Finally, the authors stress detection of a scenario of atypical hypertension events in pregnancy and association of hematological events with a strong suspicion for thrombotic thrombocytopenia orienting a multiprofessional treatment (obstetrics, intensive care, hematology and nephrology) directed towards a positive impact on maternal morbidity mortality.

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## RESUMO

A púrpura trombocitopênica trombótica (PTT) é uma entidade rara em pacientes críticos. Relatamos um caso clínico de paciente gestante admitida em unidade de terapia intensiva obstétrica com quadro de alteração de sensório, atribuído inicialmente à doença hipertensiva da gravidez. Evoluiu com piora do quadro geral caracterizada por anemia e plaquetopenia grave, suscitando a investigação diagnóstica de púrpura trombocitopênica trombótica após o reconhecimento do perfil hematológico. Os autores enfatizam a importância do conhecimento da doença como marcador de prognóstico para pacientes obstétricas, em vista da semelhança com outras patologias comuns ao ciclo gravídico-puerperal e o fato do diagnóstico e tratamento precoce serem determinantes para o desfecho.

**Descritores:** Complicações hematológicas na gravidez; Plasmaférese; Púrpura trombocitopênica trombótica; Cuidados intensivos; Relatos de casos

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