PREGNANCY ASSOCIATED ATYPICAL HEMOLYTIC UREMIC SYNDROME: CLINICAL CASE AND LITERATURE REVIEW.
Gabija Didziokaite¹, Jelena Volochovici², Ramunė Simkevičiute²
1. Vilnius University, Faculty of Medicine
2. Vilnius University Hospital Santaros Klinikos, Department of Obstetrics and Gynecology

#Corresponding author: Gabija Didziokaite, e-mail: gabija.did@gmail.com, Vilnius University, Faculty of Medicine, M. K. Ciurlionio g. 21, p.o. box 03101 Vilnius, Lithuania, Telephone number: +37069953020

RUNNING TITLE
Pregnancy associated atypical hemolytic uremic syndrome.

KEYWORDS
Pregnancy; Atypical Hemolytic Uremic Syndrome; microangiopathies; ADAMTS13; plasmapheresis therapy

WORD COUNT
2425

CONFLICT OF INTERESTS
no conflicts of interest

ABSTRACT
Pregnancy associated atypical hemolytic uremic syndrome (pa-aHUS) is a rare thrombotic microangiopathy (TMA), fatal in 50-60% of cases. Its typical clinical presentation is a triad of microangiopathic hemolytic anaemia, thrombocytopenia, and acute progressive renal failure. Plasmapheresis therapy is recommended as a specific treatment. Retrospective analysis of medical documentation of a patient, who was treated for the pa-aHUS in Vilnius University Hospital Santaros Klinikos, was carried out. 44-year old 34th-week pregnant woman was admitted to Vilnius University Hospital Santaros Klinikos with signs of preeclampsia. As preeclampsia progressed, caesarian section was performed. The classical triad of aHUS was observed. The most deviant laboratory values were: haemoglobin 61 g/l, lactate dehydrogenase (LDH) 525 U/l, platelets 52×10⁹/l, urea 22.1 mmol/l, creatinine 437 mmol/l. Differential diagnostics between HELLP syndrome, myelodysplastic syndrome, atypical hemolytic uremic syndrome, disseminated intravascular coagulation syndrome and Thrombotic Thrombocytopenic Purpura were carried out. ADAMTS13 activity was 36.4%. Plasmapheresis procedures were initiated, requiring 146 units of fresh frozen plasma for 14 procedures. For the symptomatic treatment, 13 units of red blood cells and 4 units of platelets were used and 6 procedures of hemodialysis were performed. Laboratory signs of hemolysis disappeared and kidney function was restored. Patient was discharged 24 days postpartum. Pa-aHUS requires prompt diagnostics and treatment as well as large expenses of a healthcare institution. A precise differential diagnostics ensures patients the access to the most clinically effective treatment. Timely and complex treatment, including plasmapheresis therapy, significantly improved the outcome of the patient.
emolytic uremic syndrome (HUS) is a rare thrombotic microangiopathy, the typical clinical presentation of which is a triad of microangiopathic hemolytic anaemia, thrombocytopenia and acute progressive renal failure. HUS can be inherited or acquired. Also, this syndrome can be classified into typical and atypical (aHUS) forms. 90% of all cases of HUS are caused by Shiga-toxin-producing Escherichia coli (STEC), type O157:H7, which may be transmitted to humans via different vehicles. Atypical Hemolytic Uremic Syndrome may be related to an abnormal activation of the complement system − complement mediated aHUS. This type of aHUS often results in the end-stage renal disease.

Pregnancy per se may trigger the development of atypical hemolytic uremic syndrome for genetically predisposed women. Pa-aHUS makes about 10 − 20% of all cases of aHUS [1]. This life-threatening condition may develop in the second half of the pregnancy, during delivery or postpartum and especially affects primiparous patients. According to some researchers, aHUS is more frequent within the first 3 months postpartum [2]. Pa-aHUS prognosis is usually poor − mortality rates are from 50 to 60% [3].

The aim of this article is to present the case of pa-aHUS, discuss the differential diagnostics and possible triggers for the development of this pathology.

MATERIAL AND METHODS

Retrospective analysis of medical documentation of the patient, who was treated for the pa-aHUS in Vilnius University Hospital Santaros Klinikos, was carried out.

RESULTS

44-year old 34th-week pregnant woman was admitted to the Vilnius University Hospital Santaros klinikos (VUHSK) with signs of preeclampsia. It was the second pregnancy of the patient as the first pregnancy resulted in an early miscarriage. In 2005, left breast carcinoma pT1N2M0 was diagnosed and treated with chemotherapy (doxorubicin and cyclophosphamide) and radiotherapy. On the 12th week of pregnancy cancer relapse was determined in the left breast (pT1C, G2, EP 40 %, PR 90 %, HER2 3+) and a radical mastectomy was performed. The postoperative period was uneventful and the postpartum radiotherapy was scheduled.

Due to blood pressure elevated up to 175/103 mmHg and proteinuria of 2 g/l, the patient was hospitalised and antihypertensive treatment was initiated. General condition of the patient deteriorated − severe headache occurred, proteinuria increased, progressive anaemia and hypoproteinemia were observed (Table 1). The lower segment caesarian section was performed due to fetal distress and an unstable condition of the patient. A premature male newborn, evaluated 9/9 by Apgar score, was born.

Postpartum the patient was transferred to the ICU, where the signs of acute kidney failure appeared. The progression of anaemia (Hb decreased from 104 g/l to 68 g/l) and thrombocytopenia (52 × 10^9/l), the signs of hemolysis and abnormal clotting parameters were observed in the further laboratory work-ups. The condition was differentiated between HELLP syndrome, myelodysplastic syndrome, aHUS, Disseminated Intravascular Coagulation (DIC) syndrome and Thrombotic Thrombocytopenic Purpura (TTP).

Further diagnostics and treatment of the condition were carried out by a multiprofessional team, composed of obstetricians-gynaecologists, anesthesiologists, transfusologists, nephrologists, vascular surgeons, imaging specialists and chemotherapists. As no significant elevation of liver enzymes was observed, HELLP syndrome was disproved. ADAMTS-13 activity was moderately decreased (36.4 %), Coombs test was negative. Abdominal ultrasonography revealed moderate hepatomegaly, traces of free fluid in the peritoneal cavity, bilateral hydrothorax and alveolar hypoventilation. Chest X-ray also revealed pleural effusion. During echocardiography left ventricular dilatation 1°, relative mitral valve regurgitation and moderate pericardial effusion were observed. The diagnosis of TTP was disproved since no significant neurological symptoms, typical for the clinical presentation of TTP, had been registered.

Evidence gathered from bone marrow trepanobiopsy was insufficient to confirm the diagnosis of myelodysplastic syndrome. After the procedure hematoma emerged on the left thigh and buttocks along with the progression of anaemia. The CT angiography confirmed active bleeding from the deep branch of the left superior gluteal artery, therefore, urgent embolisation was performed.

The condition of the patient deteriorated and the drainage of the left pleural cavity was introduced due to progressive dyspnea − 750 ml of serous fluid was collected. Chest X-ray confirmed the diagnosis of pulmonary edema. Bilateral lower extremity venous duplex scanning revealed local subacute thrombosis in the peroneal vein of the left calf and venous insufficiency in the superficial veins of the left extremity. Disseminated intravascular coagulation was not confirmed since the level of fibrinogen was within the normal range and there was insufficient affirmative data in the blood coagulation parameters to confirm this pathology according to the diagnostic algorithm developed by The International Society for Thrombosis and Haemostasis. As all other possible diagnoses were ruled out and the typical clinical manifestation accompanied by laboratory findings was observed, the diagnosis of aHUS was settled and the specific treatment with plasmapheresis therapy was initiated.

Soon after the initiation of the plasmapheresis therapy and hemodialysis, the condition of the patient significantly improved. For the symptomatic treatment, red blood cell and platelet transfusions were performed. The antibacterial treatment was prescribed due to elevated inflammatory parameters, consequently, thromboprophylaxis was implemented. Antihypertensive treatment and prophylactic anticonvulsant therapy were applied during the hospitalisation.
On the 15th day of hospitalisation the condition of the patient was considered stable and she was transferred to the nephrology department. Complex treatment significantly improved the general condition of the patient: dyspnea resolved, blood pressure was stable, laboratory signs of hemolysis disappeared and kidney function was restored. In total, the patient received 13 units of red blood cells and 4 units of platelets via transfusions, 6 procedures of hemodialysis and 14 procedures of plasmapheresis therapy were performed, requiring 148 units of fresh frozen plasma. The patient was discharged after 27 days of hospitalisation. Afterwards, the condition gradually improved during the outpatient follow-up.

**DISCUSSION**

The atypical hemolytic uremic syndrome (aHUS) includes all possible HUS cases, where the pathogenetic mechanism is not related to Shiga-toxin-producing bacteria, such as Escherichia coli and Shigella dysenteriae. The aHUS may also be divided into two categories: familial and sporadic. Familial aHUS is usually related to genetic mutations which lead to the activation of complement via the alternative pathway [2, 3]. Sporadic aHUS may be associated with non-enteric infections, viruses, malignant tumors (e.g. adenocarcinoma of stomach), chemotherapeutic agents (such as gemcitabin, cysplatin, doxorubicin), post-transplantation state and immunosuppression as well as other medical conditions, such as scleroderma, antiphospholipid syndrome, lupus or pregnancy [3, 4].

Pa-aHUS occasionally develops as a complication of preeclampsia [3] as it was in the case described. Shallow implantation, disrupted development and reduced perfusion of the placenta are characteristic for the pathogenesis of this pathology which leads to the hypoxia. Due to hypoxia the regeneration of endothelium is suppressed as hypoxia leads to the elevated levels of sFlt-1 and sEng which inhibit vascular endothelial and placental growth factors (VEGF, PGF). Moreover, hypoxia stimulates purine catabolism and synthesis of xanthine oxidase which lead to the increased levels of oxygen free radicals. As a result of these processes, the endothelial function is impaired and may lead to the development of aHUS.

When further investigations were carried out for the patients, who had been diagnosed with pa-aHUS, mutations in one or more genes coding for proteins involved in regulation or activation of the alternative pathway of complement had been found frequently [2]. Nowadays there are 10 genes described which, in the case of mutation, may lead to the development of aHUS. The most common mutation, which makes 30% of all cases of aHUS, is the mutation of CFH gene, which is involved in the complement factor H production [5]. Moreover, complement activation during pregnancy may also be stimulated by an immunological conflict between mother and fetus. Postpartum this activation may be stimulated by the labor-associated inflammatory response, fetal cells migration into mother’s circulation, infections and bleeding. Therefore, if there are any mutations in genes, responsible for the regulation or activation of the complement, in the pregnant patient, the uncontrolled activation of the alternative pathway is likely to begin leading to aHUS [2].

In the described case, the patient was diagnosed with left breast carcinoma relapse during pregnancy and treated solely surgically by removal. However, when the patient was first diagnosed with cancer, not only the left breast quadrantectomy was performed but also chemotherapy was applied. While literature mostly associates aHUS with adenocarcinomas of other localisations, the possibility cannot be ruled out that the breast cancer relapse and further treatment could have influenced the development of aHUS for this patient [4, 6]. Moreover, doxorubicin, which was administered as a part of the chemotherapy for the patient, is also mentioned as one of the possible factors to influence the development of aHUS in some publications [4]. What is more, in the case described the patient was diagnosed with preeclampsia, which is also considered to be a possible cause for the development of aHUS [3].

Though morbidity rate of thrombotic microangiopathies (TMAs) is 1 : 25 000 during pregnancy, timely and precise differential diagnostic is crucial to ensure the access to the most clinically effective treatment for the patient [2]. When the clinical manifestation of TMAs is suspected during pregnancy, it is important to consider aHUS, TTP, HELLP syndrome and DIC syndrome in the differential diagnostic.

HELLP syndrome is a thrombotic microangiopathy, characterised by hemolysis, elevated liver enzyme levels and a low platelet count [7, 8]. In the case of aHUS, elevated levels of liver enzymes are not typically observed, however, they may occur if aHUS develops in the late stages of pregnancy and damages the liver – this makes the differential diagnosis highly complicated [9]. Renal function parameters may be of a great help when differentiating between aHUS and HELLP syndrome. A rapidly progressing acute renal failure is likely to be caused by aHUS, the typical clinical triad of which includes renal impairment.

The DIC syndrome is a complex thrombohemorrhagic condition that is always secondary to an underlying disorder [10]. Obstetrical DIC syndrome may occur due to widespread activation of blood coagulation, which is usually associated with pregnancy complications such as acute peripartum hemorrhage, placental abruption, preeclampsia, eclampsia, HELLP syndrome, retained stillbirth, septic abortion and intrauterine infection, amniotic uid embolism and acute fatty liver of pregnancy [11]. DIC is characterised by hypofibrinogenemia, thrombocytopenia, abnormalities of blood coagulation parameters and increased levels of fibrin degradation products (DFPs) in plasma. Similarly to aHUS, in case of DIC syndrome anaemia, thrombocytopenia and elevated levels of D-dimers are observed. Moreover, DIC can affect various internal organs, such as kidneys. When differential diagnosis between aHUS and DIC is carried out, normal levels of fibrin and absence of DFPs in plasma can contribute significantly to disprove the diagnosis of DIC syndrome. Finally, in the case of DIC syndrome schistocytes are absent in the peripheral blood smear, whereas in the case of aHUS they occur due to hemolytic anaemia [10].
TTP is a life-threatening condition which may also develop during pregnancy and is commonly inextricable from aHUS, as it shares the same histopathological phenotype and, therefore, clinical manifestation may also be very similar. TTP is clinically characterised by a group of five symptoms: thrombocytopenia, microangiopathic haemolytic anaemia, fever, neurological alterations and renal failure. The neurological symptoms predominance in case of TTP may be helpful to distinguish this condition from aHUS, where renal failure is usually predominant. However, for the 10% of patients suffering from aHUS neurological alterations may also appear when the condition evolves [12].

While the use of presenting clinical symptoms and findings can be beneficial to differentiate between conditions mentioned previously, the differential diagnostics may still be problematic given their overlapping clinical presentations. Historically, the term TTP/HUS was widely used in situations in which the clinical symptoms did not clearly fit into either category as it was difficult to make a differential diagnosis without a specific test – such as ADAMTS13 activity assay. The ADAMTS13 activity assays are now available for most clinical practices and they are crucial for the diagnosis of TTP and its differential diagnosis from aHUS and other thrombotic microangiopathies [12]. ADAMTS13 is a metalloprotease that disposes of ultra large, highly thrombogenic multimers of von Willebrand factor (VWF) [13]. The normal activity of the ADAMTS13 is considered to be between 40 and 130 %. In case of HELLP syndrome, the activity of this protease is usually within the normal range or, according to some researchers, it can also be moderately decreased [8, 13, 14]. Similarly to the HELLP syndrome, in the case of aHUS the activity of ADAMTS13 may be within the norm or moderately decreased (> 10 %, usually between 30 and 40 %). Contrary to aHUS, in case of TTP a severe deficiency (<10% or <5%, according to different researchers) or a complete absence of this enzyme is observed [8, 12]. In the case presented above, the activity of ADAMTS13 was 36.4 %; therefore, when the absence of a typical neurological symptoms predominance was taken into consideration, the diagnosis of TTP was ultimately disproved.

The complex treatment, combined of specific and symptomatic treatment, is usually applied when the diagnosis of HUS is settled. For the specific treatment, plasmapheresis therapy should be initiated during the first 24 hours for the best outcome [15, 16]. Recently the possibility of molecular biotherapy with Eculizumab became available for the treatment of aHUS [17]. Eculizumab is a monoclonal antibody that is a terminal complement inhibitor and may be future’s first choice for the treatment of such a syndrome.

The symptomatic treatment for aHUS is usually combined with the restoration of fluid, electrolyte balance and renal parameters as well as an antihypertensive treatment. Red blood cell transfusions are usually recommended. The target hemoglobin level is 80–90 g/l. The higher levels may induce cardiac insufficiency, pulmonary edema or hypertension due to higher circulating blood volumes. Platelet infusion is only recommended when the level of platelets is lower than 30 x 10^9/l. It is also indicated in the case of bleeding or when invasive procedures are scheduled.

It is recommended to continue monitoring the numbers of reticulocytes in blood; to perform peripheral blood smears in order to confirm the absence of schistocytes; to determine the levels of creatinine, lactate dehydrogenase, haptoglobin, complement C3 and C4 during regular medical check-ups. Examinations should be carried out once a month during the first year after the patient was discharged and they should be continued to be performed every 3 to 6 months later in life.

CONCLUSIONS
Pa-aHUS requires prompt diagnostics and treatment by a multi professional team as well as large expenses of a healthcare institution. A precise differential diagnostics of thrombotic microangiopathies ensures the access to the most clinically effective treatment for the patients. ADAMTS13 activity assay should be applied whenever possible if a differential diagnosis of TMAs is required. Timely and complex treatment, including plasmapheresis therapy, significantly improved the outcome of the patient.

CITE THIS AS

REFERENCES
9. Batjushin M.M. Atypical hemolytic uremic syndrome

**LIST OF THE TABLES**

Tab. 1. Laboratory values in a chronological order

**TAB. 1. LABORATORY VALUES IN A CHRONOLOGICAL ORDER**

<table>
<thead>
<tr>
<th>Laboratory parameters</th>
<th>Time</th>
<th>The range of normal value for our lab</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>On admission</td>
<td>Before c-section</td>
</tr>
<tr>
<td>PLT (x 10^9/L)</td>
<td>255</td>
<td>251</td>
</tr>
<tr>
<td>Hb (g/L)</td>
<td>104</td>
<td>97</td>
</tr>
<tr>
<td>Urea (mmol/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CR (mmol/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>LDH (U/l)</td>
<td>175</td>
<td>176</td>
</tr>
<tr>
<td>HPT (g/l)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>aPTT (sec)</td>
<td>32.3</td>
<td>-</td>
</tr>
<tr>
<td>PT (%)</td>
<td>163</td>
<td>-</td>
</tr>
<tr>
<td>FBG (g/l)</td>
<td>4.76</td>
<td>-</td>
</tr>
<tr>
<td>D-dimers (mg/L)</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>PIU (g/l)</td>
<td>2 g/l</td>
<td>3 g/l</td>
</tr>
</tbody>
</table>

PLT - platelets; Hb - hemoglobin; CR - creatinine; LDH - lactate dehydrogenase; HPT - haptoglobin; FBG - fibrinogen; PIU - protein in a random urine sample.