CASE STUDY

POSTPARTUM RENAL THROMBOTIC MICROANGIOPATHY: A TURN-BASED DIFFERENTIAL DIAGNOSIS

DOI: 10.36740/WLek202201124

Leonid Markin, Kateryna Shatylovych
DANYLO HALYTSKY LVIV NATIONAL MEDICAL UNIVERSITY, LVIV, UKRAINE

ABSTRACT

Pregnancy-associated renal thrombotic microangiopathy is a rare condition with poor maternal outcome. Pregnancy may trigger atypical hemolytic uremic syndrome or thrombotic thrombocytopenic purpura. The article describes the clinical case of a 37-year-old woman who developed acute renal failure following complicated delivery. A turn-based differential diagnosis of atypical hemolytic uremic syndrome was performed. Unwarranted discontinuation of the targeted therapy with Eculisumab led to the development of chronic renal failure.

Pregnancy-associated atypical hemolytic uremic syndrome is a life-threatening condition rarely seen in pregnancy making its early recognition difficult. As thrombotic microangiopathies require urgent treatment, plasmapheresis should be started as soon as they are suspected, followed by Eculisumab after the confirmation of the diagnosis of atypical hemolytic uremic syndrome. This may contribute to reducing maternal morbidity and mortality rates.

KEY WORDS: acute kidney injury, hemorrhage, atypical hemolytic-uremic syndrome

Wiad Lek. 2022;75(1 p.1):128-131

INTRODUCTION

Thrombotic microangiopathy (TMA) is a heterogeneous group of diseases, which in the presence of endothelial damage can lead to thrombosis of small and micro vessels, secondary consumption of platelets, mechanical haemolysis and ischemic end-organ damage [1]. Depending on the vascular systems involved, renal failure, neurological symptoms, cardiac complications, respiratory failure, visual disturbances, pancreatitis, intestinal ischemia, and (less commonly) skin changes may occur [2].

Such characteristic triad of symptoms as acute kidney injury (AKI), microangiopathic hemolysis and thrombocytopenia can also complicate several pregnancy-specific conditions (in particular, severe preeclampsia/HELLP syndrome (hemolysis, elevated liver enzymes, and low platelet count) [3], acute fatty liver of pregnancy (AFLP) [4], and conditions not related to pregnancy, but triggered by it (catastrophic antiphospholipid syndrome (cAPS) [5], lupus flare. All the above makes early recognition of TMA difficult.

Pregnancy itself and its complications (placenta abruption, hemorrhage, intrauterine fetal death) may trigger two types of TMA - atypical hemolytic-uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) [1,2]. However, it is not usually clear whether the coagulopathy accompanying the HELLP syndrome, cAPS, AFLP, TMA can increase the magnitude of *bleeding* and lead to severe AKI or, conversely, whether uterine hemorrhage can initiate or aggravate the TMA and subsequent renal ischemia [6,7]. Their association might represent a peculiar risk of AKI in the *postpartum* period.

This study is designed to show the stepwise differentiated approach to diagnosing the type of TMA causing AKI in the postpartum period and further prescription of/the pathogenetic targeted therapy.

CASE REPORT

A 37-year-old gravida 4 para 4 was admitted to our facility at 27 weeks of gestation with regular contractions and heavy bloody vaginal discharge. At admission, her blood pressure (BP) was 130-140/90 mm Hg, Ps 92' and mild pretibial edema was observed. Her obstetrical history: 3 deliveries at term, the last delivery – 10 years ago. She had no notable gynaecological or social history. Due to uneventful course of this pregnancy the patient did not visit prenatal care centre. After rapid vaginal childbirth a dead newborn 990 g in weight, 37 cm in length was born. Postpartum subtotal placenta abruption was noted. Total blood loss volume was assessed as ≈ 2 L (in the hospital - 800 ml).

After delivery, according to patient's clinical signs (pale skin, BP 110/60mm Hg, Ps 84', respiration rate 19', shock index – 0.76) severe thrombocytopenia, anaemia, and AKI (anuria) were considered as posthemorrhagic. Infusion therapy with crystalloids, fresh frozen plasma, blood transfusion and antianemic treatment were initiated.

During the first 24 hours after delivery laboratory investigation revealed severe anaemia and thrombocytopenia, increased level of serum aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), total bilirubin,

Table I. Laboratory testing results during 24 hours postpartum. HELLP? AFLP? cAPS?

Indices	After delivery	After plasma and blood transfusion		Reference values
		In 12 h	In 24 h	
Hb (g/L)	48↓↓↓	65↓↓	73↓↓	110-160
Platelets ($\times 10^9$ /L)	28↓↓↓	34↓↓	51↓↓	180-320
Total blood protein (g/L)	43↓	43↓	48↓	65-85
Blood creatinine (μmol/L)	84N	187↑	300↑↑	44-176
Blood urea (mmol/L)	7.0N	8.65↑	16.6↑↑	2.5-8.3
Total bilirubin (μmol/L)	27.2↑	30.4↑	39.2↑	4.3-20.5
AST (IU/L)	-	39.7↑	50.0↑	0-37
ALT (IU/L)	-	65.0↑	74.3↑	0-42
aPTT (sec)	39N	34N	31N	23-39
PT (sec)	18N	16N	15N	14-17
PI (%)	83↓	94N	90N	88-107
Fibrinogen (g/L)	1.2↓	1.4↓	2N	2-4

Hb – haemoglobin; AST - aspartate aminotransferase; ALT - alanine aminotransferase; aPTT - activated partial thromboplastin time; PT - prothrombin time; PI - prothrombin index.
N – normal; ↑ - slightly elevated; ↑↑ - greatly elevated; ↑↑↑ - extremely elevated; ↓ - slightly lowered; ↓↓ - greatly lowered; ↓↓↓ - extremely lowered.

serum creatinine, serum urea, and initially prone to hypocoagulation, but subsequently normalized coagulogram indices (table I). HELLP syndrome, AFLP and cAPS were considered as preliminary diagnoses. For suspected cAPS serologies (lupus anticoagulant (LA) and antiphospholipid antibodies (aPL)) were sent to a special laboratory. Anticoagulants were subsequently added to therapy.

On the second postpartum day, the patient's condition was stable but not improved: BP increased up to 140-150/90 mm Hg, swelling of the face and limbs appeared. Despite intensive therapy and absence of bleeding, anuria persisted, liver enzymes increased, severe thrombocytopenia and anaemia progressed (table II).

Ultrasound revealed normal sizes, but striking parenchymal echogenicity, increased parenchymal density, increased renal resistance indices (0.84-0.87) in the interlobar arteries of both kidneys, unchanged liver and spleen, empty urinary bladder. *Chest X-ray* showed lungs pattern without focal and infiltrative shadows.

Placental pathology reported large hemorrhage into the basal layer with the blood spread into the intervillous space, presence of micro thrombi within villous vessels with placental infarct, which is typical to thrombotic vasculopathy.

The patient was transferred to the Intensive Care Unit and then to the Nephrology Department where she was consulted by a multidisciplinary team. All consultants reached a consensus for a diagnosis of probable TMA, although they still did not exclude cAPS.

In order to differentiate types of TMA (TTP from pregnancy associated aHUS (p-aHUS)), the blood sample was sent for the measurement of serum ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif, member 13) and Complement C3 and C4 levels. The woman was initiated on daily plasma-exchange therapy (PE) (30 ml/kg/day (in total - 6 procedures) with unfractionated heparin (70-80 mg/kg of body weight) and concomitant prednisone therapy (1 mg/kg/day).

However, throughout the therapy the patient's condition did not improve: hypertension (BP 160/90 - 170/100 mm Hg), anaemia (Hb 56 - 60 g/L), thrombocytopenia (70 - 80x10^9/L), high LDH values (789 - 1514 U/L) persisted. Due to the lack of resolution of acute renal failure (persisted oligo-anuria and azotaemia (blood creatinine - 416 - 636 μmol/L)) intermittent hemodialysis was performed (in total - 3 sessions).

On days 10-13 negative serology assays (LA and aPL) were received which allowed to rule out the diagnosis of cAPS. When the ADAMTS13 activity level was reported as normal (62%; reference values: 50-140%), the diagnosis of TTP was excluded. Complement tests revealed alternative pathway dysregulation with low plasma levels of C3 (0.68 g/L; reference values: 0.8-1.6 g/L) and low levels of C4 (0.1 g/L; reference values: 0.12-0.36 g/L). A diagnosis of p-aHUS was confirmed and targeted therapy with Eculisumab (a monoclonal antibody that binds complement protein C5 and prevents the activation of a complement terminal complex) was started on 14 day after delivery at a dose of 900 mg intravenously per week [8].

In 2 weeks, the improvement of patient's condition was observed: BP<140/90 mm Hg, regression of peripheral swelling, diuresis recovery. The patient's platelets count was greater than 170x10^9/L with stable Hb levels (99-105 g/L), near-normal LDH (<235 IU/L) and serum creatinine (<170 μmol/L).

Continued therapy (the next 2 doses) and maintenance regimen of Eculisumab (1,200 mg at week 5 followed by 1,200 mg every 2 weeks) was recommended but discontinued by a patient. A woman left the hospital.

10,5 months later this woman was admitted to the Nephrology Department with symptoms of *severe chronic*

Table II. Laboratory testing results during 48 hours postpartum.

Indices	In 36-48 h	Reference values
Hb (g/L)	63-58↓↓↓	110-160
Platelets (x10^9 /L)	51-43↓↓↓	180-320
Single schizocytes (in view field)	4-6	-
Blood creatinine (μmol/L)	412 - 591 ↑↑↑	44-176
AST (IU/L)	101 ↑↑	0-37
ALT (IU/L)	145 ↑↑	0-42
LDH (IU/L)	1096 ↑↑↑	120-246
Potassium (mmol/L)	5.17 N	3.4-5.8
Sodium (mmol/L)	132 N	130-150
Coombs' tests	negative	negative
Shiga toxin in blood	negative	negative

Hb – haemoglobin; AST - aspartate aminotransferase; ALT - alanine aminotransferase; LDH – lactate dehydrogenase.
N – normal; ↑↑ - greatly elevated; ↑↑↑ - extremely elevated; ↓↓ - greatly lowered; ↓↓↓ - extremely lowered.

Table III. Doppler parameters of the main and interlobar renal arteries.

Doppler parameter	Right kidney	Left kidney	Reference values
Main renal artery			
PSV, cm/sec	68.3N	74,4N	60-100
RI	0.79↑	0.86↑	0.6-0.7
Interlobar artery			
PSV, cm/sec	19,7↓	21.4↓	25-45
RI	0.87↑	0.95↑↑	0.6-0.7

N – normal; ↑ - slightly elevated; ↑↑ - greatly elevated; ↓ - slightly lowered.
PSV - peak systolic velocity; RI - resistive index.

kidney injury: hypertension (160/100 to 200/130 mm Hg), oliguria (100-250 ml/day), anemia (Hb 74-80 g/L), persisting azotaemia (blood creatinine – 580 - 844 μmol/L), reduced glomerular filtration rate (GFR) (<15ml/min/1.73 m^2) [9]. The diagnosis was confirmed by kidney ultrasound which showed: reduced kidney sizes, reduced distal renal vascularity (table III), signs of nephrosclerosis - decreased cortical thickness (11-17 mm), increased renal cortical echogenicity, poor visibility of the renal pyramids and the renal sinus [9,10].

Currently, being dialysis-dependent (3 times per week), the patient is receiving supportive antihypertensive and antianemic therapy and awaiting a donor renal transplantation.

The diagnosis of p-aHUS is challenging, as this condition mimics several other diseases that must be ruled out when making a diagnosis. Common features such as acute renal failure, thrombocytopenia, and microangiopathic hemolytic anemia seen in p-aHUS are also observed in severe preeclampsia with HELLP syndrome, cAPS, AFLP and TTP [1,2,11,12].

It should be acknowledged that initially the above listed differentials were considered as posthemorrhagic consequences [13]. Later particular focus was given to HELLP syndrome, AFLP and cAPS. However, HELLP syndrome and AFLP typically resolve after delivery, hemolysis and thrombocytopenia are less severe [3]. In addition, AFLP is characterised by elevated liver enzymes with AST, and ALT 5 to 10 times the upper limit of normal [14]. Absence of history of APS, negative serology results have allowed to rule out the diagnosis of cAPS [15]. Eventually, negative Coombs' tests, progressive anaemia with shizocytosis, increased level of LDH and resistant to therapy anuria *(core symptom)* pointed out the TMA [11,16].

The classic types of TMA are TTP and typical HUS, also known as enterohemorrhagic *Escherichia coli*–associated HUS (EHEC-HUS) [2,12,17]. Pathophysiologically, all forms of HUS have complement-mediated endothelial cell damage, which mainly affects the capillary area of the kidney. If HUS is due to a transient trigger, such as Shiga toxin of enterohaemorrhagic *Escherichia coli*, an infection with *Streptococcus pneumoniae*, or medications, spontaneous remission generally occurs with supportive therapy after the trigger has been removed [12]. However, in the cases of a genetic defect or an acquired dysregulation of the complement or coagulation system, TMA may lead to damage of the affected organs (usually the kidney) even after the trigger (infection, surgical intervention, use of medication) has been controlled or in the absence of a trigger [1,2,16].

Diagnosis of aHUS requires exclusion of both EHEC-HUS (typical HUS, with Shiga toxin detection in stool or blood) and ADAMTS13-mediated TMA (TTP, with ADAMTS13 levels <10%) [3,12]. Absence of bloody diarrhoea and negative Shiga toxin in blood, normal ADAMTS13 level have excluded in our patient the diagnoses of typical

HUS and TTP and confirmed the diagnosis of p-aHUS. It can be assumed that the combination of a premature placental abruption with haemorrhage led to systemic activation of the alternative complement pathway, which induced the development of aHUS.

It is recommended starting PE therapy within 24 hours of diagnosis without waiting for the ADAMTS13 testing or aforementioned testing, as confirmatory testing takes usually weeks before they are available [17]. Nevertheless, despite the initial success of PE, the abnormal pattern of complement activation and TMA are likely to persist with the risk of irreversible organ damage, primarily renal, in the subsequent weeks [18]. Thus, ineffectiveness of PE in our patient can be only partially be explained by the late initiation of therapy (on the third day after delivery).

The treatment of choice for aHUS is the complement inhibitor Eculizumab, a monoclonal antibody against C5. Binding of Eculizumab to C5 disrupts the terminal pathway of complement signaling and thereby reduces endothelial injury [8,19].

In the presented case, the diagnosis of p-aHUS was confirmed on the 13th day, and Eculizumab as a first-line treatment was immediately prescribed. According to some authors, within 1 year of diagnosis, more than 60% of patients with AKI secondary to p-aHUS will progress to end stage renal disease [8,11]. However, taking into account the positive effect of the use of Eculisumab, continuation of this therapy in our case could prevent or at least delay the development of such a negative outcome.

CONCLUSIONS

In conclusion, p-aHUS is a life-threatening condition rarely seen in pregnancy making its early recognition difficult. As TMAs require urgent treatment, plasmapheresis should be started as soon as they are suspected, followed by Eculisumab after the confirmation of the diagnosis of aHUS. This may contribute to reducing maternal morbidity and mortality rates.

REFERENCES

1. George J.N., Nester C.M. Syndromes of thrombotic microangiopathy. N Engl J Med. 2014;371:1847-1848.
2. Shatzel J.J., Taylor J.A. Syndromes of thrombotic microangiopathy. Med Clin N Am. 2017;101:395-415.
3. Kappler S., Ronan-Bentle S., Graham A. Thrombotic microangiopathies (TTP, HUS, HELLP). Emerg Med Clin N Am. 2014;32:649-671.
4. Xiong H.F., Liu J.Y., Guo L.M. et al. Acute fatty liver of pregnancy: over six months follow-up study of twenty-five patients. World J Gastroentero. 2015;21:1927-1931.
5. Collict M., Sciberras B.W., Mercieca C. et al. Catastrophic antiphospholipid syndrome in pregnancy: a life-threatening condition. BMJ Case Rep. 2019;16:e230863.
6. Chien H.P., Liu J., Arend L.J. Acute tubular injury in a woman with placental abruption. Austin J Clin Pathol. 2014;1:1019.
7. Mir M.M., Najar M.S., Chaudary A.M. et al. Postpartum acute kidney injury: experience of a tertiary care center. Indian J Nephrol. 2017;27:181-184.
8. Zuber J., Fakhouri F., Roumenina L.T. Use of eculizumab for atypical haemolytic uraemic syndrome and C3 glomerulopathies. Nat Rev Nephrol. 2012;8:643-657.
9. Yamashita S.R., Castelli von Atzingen A., Iared W. et al. Value of renal cortical thickness as a predictor of renal function impairment in chronic renal disease patients. Radiol Bras. 2015;48:12-16.
10. Gao J., Chevalier J., Auh Y.H. et al. Correlation between Doppler parameters and renal cortical fibrosis in lupus nephritis: a preliminary observation. Ultrasound Med Biol. 2013;39:275-282.
11. Arnold D.M., Patriquin C.J., Nazy I. Thrombotic microangiopathies: a general approach to diagnosis and management. Can Med Assoc J. 2017;189:153-159.
12. Bommer M., Wolfle-Guter M., Bohl S. et al. The differential diagnosis and treatment of thrombotic microangiopathies. Dtsch Arztebl Int. 2018;115:327-334.
13. Jonard M., Ducloy-Bouthors A., Boyle E. et al. Postpartum acute renal failure: a multicenter study of risk factors in patients admitted to ICU. Ann Intensive Care. 2014;4. doi:10.1186/s13613-014-0036-6.
14. Liu J., Ghaziani T.T., Wolf J.L. Acute fatty liver disease of pregnancy: updates in pathogenesis, diagnosis, and management. Am J Gastroenterol. 2017;112:838-846.
15. Hanouna G., Morel N., Huong D.L.T. et al. Catastrophic antiphospholipid syndrome and pregnancy: an experience of 13 cases. Rheumatology. 2013;52:1635-1641.
16. Williams L.A., Marques M.B. Pathology consultation on the diagnosis and treatment of thrombotic microangiopathies (TMAs). Am J Clin Pathol. 2016;145:158-165.
17. Scully M., Hunt B.J., Benjamin S. et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. Br J Haematol. 2012;158:323-335.
18. Saad A.F., Roman J., Wyble A. et al. Pregnancy-associated atypical hemolytic-uremic syndrome. Am J Perinat Rep. 2016;6:125-128.
19. Demir E., Yazici H., Ozluk Y. et al. Pregnant woman with atypical Hemolytic uremic syndrome delivered a healthy newborn under Eculizumab treatment. Case Rep Nephrol Dial. 2016;6:143-148.

ORCID and contributionship:

Leonid B. Markin: 0000-0002-7775-4543^{A,E,F}

Kateryna L. Shatylovych: 0000-0002-8465-0355^{A,B,D}

Conflict of interest:

The Authors declare no conflict of interest.

CORRESPONDING AUTHOR

Kateryna L. Shatylovych

Danylo Halytsky National Medical University

8 Rappoport st., 79000 Lviv, Ukraine

tel: +380 677 672 133

e-mail: shatik2@ukr.net

Received: 21.11.2020

Accepted: 15.08.2021

A - Work concept and design, **B** – Data collection and analysis, **C** – Responsibility for statistical analysis, **D** – Writing the article, **E** – Critical review, **F** – Final approval of the article