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HELLP syndrome as an interdisciplinary problem: A clinical case

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ABSTRACT

Thrombotic microangiopathy (TMA) is a hazardous pathology that induces thrombosis of capillaries and arterioles caused by damage to the endothelium. Patients with suspected TMA should be under the supervision of not only an obstetrician-gynecologist but also related specialists. The main types of TMA in pregnant women include thrombotic thrombocytopenic purpura, catastrophic antiphospholipid syndrome, atypical hemolytic uremic syndrome, preeclampsia (PE), and hemolysis, elevated liver enzymes, and low platelet (HELLP) syndrome. The HELLP syndrome, which is a complication of severe PE in 10–20% of cases, is the most common type of TMA.

This article presents a clinical case of HELLP syndrome development in a 32-year-old multiparous woman with severe preeclampsia and demonstrates the differential diagnostic features of TMA with predominant kidney damage. The origins of HELLP syndrome and its treatment were analyzed. This article discusses modern approaches for diagnosing a group of thrombotic microangiopathies in obstetric practice. An interdisciplinary approach involving specialists such as a hematologist, nephrologist, clinical pharmacologist, cardiologist, therapist, and blood transfusiologist is extremely important for the differential diagnosis of HELLP syndrome in patients with severe PE, which offers positive results from timely and well-chosen therapy. This approach resulted in the reduction in both maternal and perinatal mortality.

Keywords: HELLP syndrome; preeclampsia (PE); thrombotic microangiopathy (TMA); atypical hemolytic uremic syndrome (aHUS); thrombotic thrombocytopenic purpura (TTP); plasma exchange.

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HELLP-синдром как междисциплинарная проблема (клиническое наблюдение)

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АННОТАЦИЯ

Тромботическая микроангиопатия (ТМА) — серьёзная патология, приводящая к тромбозу капилляров и артериол из-за повреждения эндотелия. Пациентки, у которых заподозрена ТМА, должны находиться под наблюдением не только врача акушера-гинеколога, но и смежных специалистов — гематолога, нефролога, кардиолога, терапевта и др. Основные виды ТМА, встречающиеся у беременных женщин, — тромботическая тромбоцитопеническая пурпура (ТТП), катастрофический антифосфолипидный синдром (КАФС), атипичный гемолитико-уремический синдром (аГУС), преэклампсия (ПЭ) и HELLP-синдром. К наиболее распространённым типам ТМА, по данным мировой литературы, относится HELLP-синдром, который, в свою очередь, в 10–20% случаев является осложнением тяжёлой формы преэклампсии.

В данной статье мы рассмотрели клиническое наблюдение развития HELLP-синдрома у повторнородящей женщины 32 лет с тяжёлой формой преэклампсии, продемонстрировали особенности дифференциального диагноза в рамках ТМА с преимущественным поражением почек. Нами проанализированы вопросы происхождения HELLP-синдрома и методы проведённого лечения. В данной статье рассмотрены современные подходы к диагностике группы тромботических микроангиопатий, встречающихся в акушерской практике. Междисциплинарный подход с привлечением таких специалистов, как гематолог, нефролог, клинический фармаколог, кардиолог, терапевт и гемотрансфузиолог, крайне важен для дифференциальной диагностики HELLP-синдрома у пациенток с тяжёлой формой преэклампсии, что позволяет получить положительный результат от своевременной и грамотно подобранной терапии. Конечным результатом при этом становится снижение как материнской, так и перинатальной смертности.

Ключевые слова: HELLP-синдром; преэклампсия (ПЭ); тромботическая микроангиопатия (ТМА); атипичный гемолитико-уремический синдром (аГУС); тромботическая тромбоцитопеническая пурпура (ТТП); плазмообмен.

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INTRODUCTION

The term "HELLP syndrome" (H = Hemolysis, EL = Elevated Liver Enzymes, and LP = Low Platelets) or its variants (ELLP, HEL) was first proposed by L. Weinstein in 1982 as a form of severe preeclampsia. The diagnosis of HELLP syndrome is based on the presence of hemolytic anemia, elevated liver enzyme levels, and thrombocytopenia [1-2]. These clinical manifestations can lead to renal, hepatic, and respiratory failure. In the classical course, HELLP syndrome is often complicated by subcapsular hepatic hematoma and DIC.

According to the international literature, HELLP syndrome affects 10–20% of pregnant women with severe preeclampsia [3]. It is more common in patients over the age of 25; 30% of cases are observed in the third trimester of pregnancy, and 70% during the first week after delivery [4]. In the study by Paulino Vigil-De Gracia (1995–2008), 304 (67.1%) patients with severe eclampsia developed HELLP syndrome resulting in death [5]. Sibai et al. described the development and progression of acute renal and respiratory failure in patients with HELLP syndrome during the postpartum period [4, 6-7]. Several authors reported acute renal failure (ARF) already in the third trimester of pregnancy in 60–65% of cases [1, 8].

Another complication of HELLP syndrome is subcapsular hepatic hematoma. According to the international literature, maternal and perinatal mortality in subcapsular hepatic hematoma is 16.4% and 41%, respectively [9-10]. In the study by Gupta et al., hepatic hematoma was reported in only 1 of 150 pregnant women with severe preeclampsia, but the diagnosis of HELLP syndrome was not confirmed for various reasons [10].

Other specialists, more often hematologists, nephrologists, hepatologists, and internists, consider HELLP syndrome to be the most common form of thrombotic microangiopathy (TMA) in the obstetric practice, with the incidence of approximately 1:100 pregnancies [11]. "Obstetric" TMA is one of the main causes of advanced acute kidney injury and usually progresses to multi-organ failure [12]. TMA is a clinical and morphological syndrome characterized by the following classic triad: thrombocytopenia, hemolytic anemia due to microvasculature pathology, and end organ damage, where kidneys (with acute and chronic renal failure), CNS, gastrointestinal tract, lungs, and other organs are affected. According to the statistics, obstetric TMA accounts for 8–18% of all cases of TMA [13].

In this article, we present a clinical case of a pregnant woman with severe preeclampsia complicated by HELLP syndrome with acute renal failure, which raised many clinical questions for a number of specialists.

CASE REPORT

Patient S., a 32-year-old woman, first presented to the Department of Diagnostics and Treatment of the Snegiryov Clinic of Obstetrics and Gynecology of the Sechenov University on October 26, 2020, at 38–39 weeks of pregnancy, to conclude a contract for childbirth. She did not have any active complaints.

Medical history (according to the medical record): chickenpox, influenza, acute respiratory infections, mild myopia (OD: –1.5; OS: –2), chronic gastritis in remission. The patient did not have COVID-19 and was not immunized. Gynecologic history was unremarkable. The patient was pregnant twice. The first pregnancy occurred in 2016 and ended with spontaneous labor at full term without complications. A live girl was born (body weight 4,030 g, body length 52 cm).

This was the patient's second pregnancy, which occurred spontaneously. In the first trimester, the patient was diagnosed with placenta previa based on ultrasound findings, with no clinical manifestations or complaints. All clinical and laboratory parameters were within the normal range. The second and third trimesters were unremarkable; clinical and laboratory parameters (according to the medical and economical standards) were within the normal range. In the third trimester, at 32 weeks, ultrasound detected a transverse lie of the fetus. At 37–38 weeks, candida vulvovaginitis was detected and treated. During the entire pregnancy, the patient was followed up at a maternity clinic at her place of residence in Moscow.

On presentation: the condition is satisfactory; BP 150/100 (on both arms); no headache, no vision problems; pulse 106 bpm; body temperature 36.8 °C; SpO2 97%. Skin is clean and pink. On auscultation, heart sounds are clear and regular. Vesicular breathing in all parts of the lungs, no rales. The volume of the abdomen is increased due to the uterus, corresponding to a full-term pregnancy. The uterus is not excitable on palpation. Fetal movement is felt well. The fetal lie is longitudinal, with cephalic presentation and the fetal head anterior to the pelvic inlet. Fetal heart rate (FHR) is clear, regular, up to 140 bpm. There is swelling of the shins and feet. Stool and urine are normal, according to the patient. Vaginal examination: external genitalia are developed correctly; vagina of a parous woman. The cervix is deviated to the back, 2 cm long, partially softened. The cervical canal is passable for 2 fingers. The amniotic sac is intact, and the fetal head is located above the pelvic inlet. The promontory is inaccessible, there are no exostoses in the pelvis.

Considering the presence of hypertension and edema, an urgent urine test for protein was taken. The concentration of protein in the urine was 0.13 g/L.

Ultrasound: fetal biparietal diameter (BPD): 87 mm (36–37 weeks), fetal occipito-frontal diameter (OFD): 0, head circumference (HC): 319 mm (36–37 weeks), abdominal circumference (AC): 291 mm (33–34 weeks), femur length (FL): 70 mm (36–37 weeks); fetal heart rate (FHR): up to 167 bpm. The placenta is located along the posterior wall, with a transition to the bottom of the uterus; the thickness of the placenta corresponds to the term, placental maturity is Grade 3. There is a reduced amount of amniotic fluid. The umbilical cord has

3 vessels; there is a single, not tight umbilical cord entanglement around the neck of the fetus. Conclusion: 38 weeks of pregnancy, cephalic presentation, fetal growth retardation (FGR), moderate oligohydramnios.

Doppler ultrasound of the uteroplacental blood flow: umbilical artery resistance index (RI): 0.64; middle cerebral artery pulsatility index (PI): 1.4; right uterine artery RI: 0.48; left uterine artery RI: 0.52. Conclusion: Doppler ultrasound is within the normal range. Cardiotocography (CTG): within the normal range.

Diagnosis: 38–39 weeks of pregnancy; cephalic presentation; moderate preeclampsia; FGR; moderate oligohydramnios; candida vulvovaginitis; mild myopia; chronic gastritis in remission.

Due to moderate preeclampsia (PE), the patient was admitted to the Department of Pregnancy Pathology for further monitoring and decision on delivery. In the department, additional blood tests were taken: hemoglobin (HGB) 112 g/L; white blood cells (WBC) 16.6×10^9/L; platelets (PLT) 311×10^9/L; alanine aminotransferase (ALT) 252 U/L; aspartate aminotransferase (AST) 237 U/L; albumin 30 g/L; total protein 55.4 g/L; total bilirubin 37.1 μmol/L; creatinine 133 μmol/L; alkaline phosphatase 536 U/L. *Coagulation tests:* Quick's prothrombin 65%; ADP-induced platelet aggregation 40%; collagen-induced platelet aggregation 97%; activated partial thromboplastin time (aPTT) 1.09 s; international normalized ratio (INR) 1.53; prothrombin time (PT) 17.5 s; fibrinogen 1 g/L. *Urinalysis*: specific gravity 1,008 g/L; protein 0.13 g/L; ketone bodies: detected; WBC 30–35; unchanged erythrocytes: single in the preparation.

The evening rounds: no complaints. Fetal heart rate (FHR) 140 bpm. CTG at 10:00 PM: within the normal range.

October 27, 2020: no complaints at the morning rounds. Edema persisted. *CTG of October 27, 2020*, at 10 AM: indeterminate type of tracing. Follow-up CTG (2 times a day), blood tests, coagulation tests, and urine tests were prescribed.

Clinical and laboratory parameters of October 27, 2020: *Complete blood count* (CBC): hematocrit (HCT) 29.4%; HGB 107 g/L; WBC 19.3×10^9/l; RBC 4.73×10^{12}/L; PLT 301×10^9/L. *Blood chemistry*: ALT 276 U/L; AST 241 U/L; albumin 27 g/L; total protein 51.7 g/L; total bilirubin 39.8 μmol/L; glucose 2.9 mmol/L; iron 12.4 μmol/L; % iron saturation 12%; transferrin 4.09 g/L; potassium 4.3 mmol/L; creatinine 131.9 μmol/L; sodium 139 mmol/L; alkaline phosphatase 532 U/L. *Coagulation tests:* Quick's prothrombin 61%; ADP-induced platelet aggregation 44%; collagen-induced platelet aggregation 95%; aPTT 1.09 s; INR 1.51; PT 16.7 s; fibrinogen 1 g/L. *Urinalysis:* specific gravity 1,004 g/L; pH 5; WBC 30–35; protein 0.070 g/L; ketone bodies: detected; unchanged erythrocytes: single in the preparation.

The patient was consulted by the head of the department and the attending physician; edema persisted. Vaginal examination showed an improvement. The cervix was along the conductive axis of the pelvis, soft, up to 1.5 cm long. The cervical canal was freely passable for 2 fingers. The amniotic sac was intact, and the fetal head was located above the pelvic inlet. Considering the clinical and laboratory parameters, indeterminate type of CTG tracing, full-term pregnancy, mature cervix in a parous woman with moderate preeclampsia, FGR, and oligohydramnios, a decision was made to schedule delivery in the morning of October 28, 2020.

However, at the evening rounds on October 27, 2020, at 8:30 PM, the fetal heartbeat was not heard. Urgent Doppler ultrasound of uteroplacental blood flow was performed: no HR, umbilical artery RI 0; middle cerebral artery PI 0; right uterine artery RI 0; left uterine artery RI 0. *Conclusion: 38 weeks of pregnancy; intrauterine fetal death; cephalic presentation.*

Due to intrauterine fetal death, the patient was transferred to the delivery room for emergency delivery by amniotomy. At 2 AM on October 28, 2020, a dead premature girl was born (bode weight 2,690 g, body length 49 cm). The placenta was separated and expressed; on examination of the placenta, the lobules and membranes were intact. The uterus was dense, well contracted. The total blood loss during labor was 200 mL. Thirty minutes after the delivery, the patient was lethargic, poorly answering questions, with no headache or vision problems, pulse 72 bpm, BP 105/70 mm Hg. Urgent CBC showed a decrease in hemoglobin to 76 g/L.

Abdominal ultrasound: the uterus is well-contracted, the uterine cavity is closed. No signs of intraabdominal hemorrhage. There is moderate bloody discharge from the vagina.

Considering the worsening of the patient's condition, it was decided to transfer her to the ICU for further monitoring and treatment. CBC of October 28, 2020 showed significant worsening of the anemia (HGB 76 g/L), elevated ALT/AST (ALT 225 U/L; AST 127 U/L), elevated LDH up to 690 U/L, hypoalbuminemia (23 g/L), hyperbilirubinemia (total bilirubin 55.5 μmol/L), and elevated creatinine up to 158 μmol/L.

Coagulation tests: Quick's prothrombin 57%; ADP-induced platelet aggregation 35%; aPTT 69.3 s; INR 1.66; PT 17.6 s; fibrinogen 0.93 g/L. Urine protein 0.085 g/L; diuresis 40 ml/h by the urinary catheter.

A multidisciplinary team meeting was held, including a transfusiologist, in the ICU.

Clinical diagnosis: First day after the second induced full-term labor with a dead fetus. Severe preeclampsia. HELLP syndrome.

Conclusion of the multidisciplinary team: transfusion of albumin (20% 100 mL), fresh frozen plasma (2 doses of 510 mL), and cryoprecipitate (4 doses of 160 mL) for hypoalbuminemia, hypoproteinemia, hypofibrinogenemia, and hypocoagulation. Subcutaneous Clexane 0.4 mL QD was prescribed for the prevention of thromboembolic complications (TEC).

October 29, 2020: The patient's condition was severe. There was edema of the calves, feet, and hands. Pulse 87 bpm, BP 112/64 mmHg, body temperature 36.7 °C, SpO_2 93%. The uterus was 2 cm below the umbilicus; there was no discharge from the genital tract. Diuresis: from 1:00 PM

to 2:00 PM, 10.0 mL of light-colored urine by the urinary catheter; from 2:00 PM, anuria.

Laboratory findings of October 29, 2020: *CBC*: HCT 22.6%; HGB 66 g/L; WBC 35.3×10^9/L; RBC 2.9×10^{12}/L; PLT 190×10^9/L; RDW 19.9%; anisocytosis ++; hypochromia +.

Blood chemistry: albumin 30.5 g/L; ALT 109 U/L; AST 41 U/L; total protein 51.7 g/L; total bilirubin 41.5 μmol/L; glucose 6.5 mmol/L; creatinine 257 μmol/L; LDH 338 U/L; C-reactive protein 11.3 mg/L. *Immunologic blood tests:* complement component C3 0.56 g/L (normal range 0.6–1.26); complement component C4 0.15 g/L (normal range 0.17–0.37). *Coagulation tests:* Quick's prothrombin 62%; INR 1.45; PT 15.8 s; fibrinogen 0.94 g/L. *Urinalysis:* pH 6.0; specific gravity 1,028 g/L; bacteria: moderate; protein 0.04 g/L; bilirubin, glucose, fungi in the urine: negative; WBC: many; altered RBC 30–35. *Hormonal tests (serum):* procalcitonin 1.51 ng/mL; presepsin 2,462 pg/mL.

Due to the progressive deterioration of the patient's condition, an extended multidisciplinary team meeting was held on October 30, 2020, including a nephrologist, hematologist, clinical pharmacologist, transfusiologist, internist, and cardiologist.

Conclusion of the multidisciplinary team: according to the laboratory findings (decrease in hemoglobin in the CBC from 107 g/L (October 27, 2020) to 66 g/L (October 29, 2020) in the absence of hemorrhage, high levels of liver enzymes since October 28, 2020: AST 127 U/L, ALT 225 U/L), AKF with anuria (creatinine 158 μmol/L, anuria), signs of inflammatory changes (procalcitonin 1.51 ng/mL, presepsin 2,462 pg/mL), systemic inflammatory response syndrome (SIRS) and thrombotic microangiopathy as a cause of multiorgan failure could be suspected in the patient with HELLP syndrome. This case was unusual due to the absence of thrombocytopenia, but there was a 25% (from 311,000 to 190,000) decrease in the platelet count, which is a diagnostic criterion. Considering the complement component C3 level (0.56 g/L, slightly below normal), it was possible to assume the presence of complement-mediated mechanism of hemolysis (atypical hemolytic-uremic syndrome).

The multidisciplinary team decided to assess the level of metalloproteinase ADAMTS-13 for differential diagnosis with thrombotic thrombocytopenic purpura (TTP). It was also decided to continue venous hemofiltration, antibiotic therapy, transfusions of fresh frozen plasma (FFP) with transition to plasma exchange, cryoprecipitate, and washed packed red blood cells, and to start magnesium sulfate therapy with BP control.

During follow-up, the patient's condition was stable, but severe due to hypertension, worsening anemia without signs of hemorrhage, criterial decrease in the platelet count, development of edema (hydrothorax and ascites with persistent anuria), confusion, BP within 135/87–145/92 mmHg, pulse within 78-95 bpm, body temperature 36.7–37.5 °*C,* and SpO2 93–97%.

According to the clinical and laboratory findings, signs of intravascular hemolysis (positive Baxter's test in a venous blood sample, hemoglobinuria) persisted despite therapy. To remove the products of hemolysis, fibrin degradation products (fibrinogen), proinflammatory cytokines, and products of inflammatory reactions from the vasculature, plasma exchange of 2,500–3,000 mL/day was performed. Therapy with quarantine FFP (2 doses of 880 mL) and 20% albumin solution, cryoprecipitate (4 doses of 160 mL), washed packed red blood cells (560 mL), and antibiotics (ertapenem IV drip 0.5 g/day, linezolid IV drip 600 mg BID, fluconazole 400 mg IV once on Day 1, then 200 mg IV drip QD) was continued.

Laboratory findings of October 30, 2020: *CBC*: HCT 25.3%; HGB 77 g/L; WBC 29.57×10^9/L; RBC 3.67×10^{12}/L; PLT 188×10^9/L; anisocytosis ++; hypochromia +, schizocytosis +. *Blood chemistry*: urea nitrogen 11.5 mmol/L; albumin 31.2 g/L; ALT 67 U/L; AST 26 U/L; total protein 52.9 g/L; total bilirubin 44.5 μmol/L; glucose 5.1 mmol/L; iron 9.3 μmol/L; creatinine 206.8 μmol/L; LDH 690 U/L; sodium 132 mmol/L; potassium 4.2 mmol/L; alkaline phosphatase 400 U/L; CRP 8 mg/L. *Coagulation tests*: Quick's prothrombin 67%; D-dimer 16.7 μg/mL; INR 1.37; prothrombin time 15.2 s; fibrinogen 1.3 g/L, procalcitonin 0.752 ng/mL.

Ultrasound of the chest, abdomen and pelvic organs. In the abdominal cavity, there is up to 1,200–1,400 mL of fluid with suspension. Visualization is difficult due to pronounced flatulence; decreased intestinal peristalsis. Liver: medium echogenicity; the structure is homogeneous; the capsule is unremarkable; signs of insignificant diffuse changes. Renal collecting systems are not dilated; there is a decrease of renal hemodynamic parameters on Doppler ultrasound. In the pleural cavities, there is fluid up to the level of the 5th-6th rib on both sides. The uterine body is 155×85×155 mm; the uterine cavity is up to 5 mm; some blood and blood clots are seen.

A second consultation with a nephrologist and hematologist was performed. Conclusion: TMA (HGB 77 g/L, LDH 690 U/L, schizocytosis); kidney (AKF: anuria, hypercreatininemia, hyperhydration) and lung (respiratory failure, saturation 90%, ultrasound finding) damage were confirmed. This case was unusual due to the absence of thrombocytopenia, but there was a 25% (from 311,000 to 190,000) decrease in the platelet count, which is a diagnostic criterion. SIRS and DIC (leukocytosis, increased procalcitonin, presepsin, decreased fibrinogen) could be suspected as a cause of TMA. As a result of a session of prolonged veno-venous hemofiltration and initiation of antibiotic therapy, an improvement was observed in the form of clearing of consciousness (the patient was lethargic), as well as reduction of leukocytosis (from 37×10^9/L to 29×10^9/L) and procalcitonin level (from 1.5 to 0.752 ng/mL). It was recommended to continue the antibiotic therapy, magnesium sulfate (with BP control), and plasma therapy. To rule out catastrophic antiphospholipid syndrome (CAPS), considering intrauterine fetal death, it was recommended to test for IgM and IgG antibodies to cardiolipins, antibodies to beta-2-glycoprotein, lupus anticoagulant, antibodies to DNA, and antinuclear factor. As of November 2, 2020, anemia

(82 g/L) persisted; there was a further decrease in the platelet count to 118,000/μL and D-dimer to 2.48 μg/mL; proteinuria persisted (protein 0.085 g/L).

On November 3, 2020, the patient's condition was stabilized. Peripheral edema decreased. After transfusion of washed red blood cells, the signs of anemia decreased. CBC showed moderate hypochromic microcytic anemia; mild thrombocytopenia persisted. Coagulation tests showed positive changes (the fibrinogen level returned to normal, and the D-dimer level decreased).

Laboratory findings of November 3, 2020: HGB 78 g/L; WBC 10.6×10^9/L; PLT 134×10^9/L; anisocytosis: moderate; microcytes: moderate; ALT 37 U/L; AST 556 U/L; LDH 421 U/L; albumin 36 g/L; total protein 57 g/L; total bilirubin 53.1 μmol/L; creatinine 98 μmol/L; D-dimer 2.14 μg/mL; fibrinogen 1.85 g/L. *Immunologic tests:* ADAMTS-13 72%; anti-nuclear antibodies **:** ANF (Hep2) 1:320; type of fluorescence: granular (++); antibodies (IgG) to β-2 glycoprotein 0.7 U/mL, antibodies (IgM) to β-2 glycoprotein 0.7 U/mL; anti-dsDNA antibodies 10.51 IU/mL, which did not confirm the autoimmune etiology of the disease. Diuresis was 4.95 L; minute diuresis by the Reberg test 3.44 mL/min.

Follow-up ultrasound of pelvic and abdominal organs. The uterine body is 120×75×110 mm. The uterine cavity is up to 4 mm. Dilation of myometrial veins. The volume of free fluid in the pelvis and abdominal cavity is up to 300 mL. Intestinal peristalsis is detected in all sections. Liver: medium echogenicity; homogeneous structure; the capsule is unremarkable; there are signs of insignificant diffuse changes. No pathology is detected in both kidneys; renal collecting systems are not dilated.

Chest CT: CT picture of bilateral hydrothorax, more prominent on the right; compression atelectasis of adjacent parts of both lungs. Compaction of pulmonary parenchyma in the central parts of both lungs may correspond to edema.

During therapy (plasma exchange, antibiotic therapy), an improvement was observed in the form of resolution of acute kidney injury (creatinine returned to normal, from 257 μmol/L (October 29, 2020) to 98 μmol/L (November 3, 2020); there was an increase in diuresis), a decrease in acute-phase reactant levels (CRP, leukocytes), and a decrease in severity of consumption coagulopathy. However, signs of microangiopathic hemolysis persisted (decreased hemoglobin and platelets; increased LDH). Therefore, it was decided to continue therapy with FFP until hematological parameters returned to normal within 3 days.

Considering the improvement of clinical and laboratory parameters, the patient's clinical condition, and the additional instrumental test findings, the extended multidisciplinary team decided *to transfer the patient to the obstetric department. Antibacterial therapy was discontinued.*

The presence of ascites, hydrothorax, and peripheral edema was considered by a hematologist and nephrologist as a consequence of increased vascular permeability due to TMA, renal dysfunction, and hypoalbuminemia.

On November 6, 2020, the patient was in satisfactory condition and was transferred to the obstetric department for further follow-up. Hypotensive, anticoagulant, and anti-inflammatory therapy was continued. On physical examination, there was no peripheral edema. BP was within 115/80–135/85 mm Hg. Pulse 70–76 bpm. Body temperature 36.7 °C, SpO2 95–97%. Diuresis was normal. *CBC*: HGB 91 g/L; WBC 9.6×10^9/L; PLT 181×10^9/L; anisocytosis: moderate; hypochromia: insignificant; microcytes: insignificant. *Blood chemistry*: ALT 66 U/L; AST 56 U/L; LDH 599 U/L; albumin 35.2 g/L; total protein 63 g/L; total bilirubin 34.9 μmol/L; creatinine 84 μmol/L. *Coagulation tests:* D-dimer 2.18 μg/mL; aPTT 0.9 s; INR 1.22; fibrinogen 2.06 g/L. *Urinalysis*: normal.

By November 13, 2020, the laboratory parameters returned to normal, so the patient was discharged under follow-up in the maternity clinic, as well as by a nephrologist, hematologist, and internist at the place of residence. The patient was recommended to continue hypotensive therapy with enalapril 5–10 mg/day and amlodipine 5–10 mg/day due to persisting hypertension.

In 2021, the patient had her third spontaneous pregnancy. She was followed up in the Snegiryov Clinic of Obstetrics and Gynecology of the Sechenov University. All trimesters of the pregnancy were unremarkable; laboratory parameters were within the normal range. In April 2022, there was a full-term spontaneous labor with a cephalic presentation. A live full-term boy was born (body weight 3,910 g, body length 55 cm). On Day 5 after delivery, the patient and the baby were discharged in satisfactory condition.

DISCUSSION

TMA is a complex pathology which includes multiple clinical entities. The suspicion of TMA requires a rapid differential diagnosis between aHUS, TTP, PE, HELLP syndrome, CAPS, DIC, and acute fatty liver of pregnancy to determine treatment tactics for these life-threatening conditions. These are the so-called exclusion diagnoses based on their key markers (Table 1).

Microangiopathy is an important cause of acute renal failure during pregnancy and after delivery. It remains relevant from the position of statistics on maternal and perinatal mortality. At the same time, there are well-known risk factors for HELLP syndrome, which include first pregnancy, older age, a history of PE or HELLP syndrome in previous pregnancies (the risk of recurrence after a previous HELLP syndrome is 12.8%), multiple pregnancies, polyhydramnios, family history of PE, diabetes mellitus, and hypertension. The presence of one or several of these risk factors should be taken into account during patient management.

We performed a comparative analysis with another clinical case of TMA with aHUS in a patient during her third pregnancy [15], who was admitted to the Norilsk Maternity Hospital with a diagnosis of 32 weeks of pregnancy, severe PE, and placental abruption. Laboratory parameters: HGB 105

Table 1. Differential diagnosis of thrombotic microangiopathy [14]

Pathology	Laboratory signs	Symptoms	Diagnosis	Treatment
HELLP syndrome	RBC: negative Coombs test Platelets: <100,000/μL AST/ALT: >2 ULN Creatinine: >1.1 mg/dL	Epigastric and right upper quadrant pain, nausea, vomiting, headache, visual disturbances	Resolved within 48–72 h after delivery	Delivery
Atypical HUS or pregnancy-associated HUS	RBC: negative Coombs test Platelets: <150,000/μL AST/ALT: limited data Creatinine: often >2.0 mg/dL	Nausea, vomiting, abdominal pain, headache, altered mental status	Other etiologies must be ruled out	Eculizumab
Autoimmune hemolytic anemia	RBC: MAHA, positive Coombs test Platelets: <150,000/μL AST/ALT: limited data Creatinine: normal	Fatigue, shortness of breath, palpitations	Positive direct antiglobulin test; presence of spherocytes in the blood smear	Glucocorticoids
Thrombotic thrombocytopenic purpura (TTP)	RBC: negative Coombs test Platelets: frequently <30,000/μL AST/ALT: normal Creatinine: <1.1 mg/dL	Fever, confusion, altered mental status	ADAMTS-13 activity <10%	Plasmapheresis
Acute fatty liver of pregnancy	RBC: normal Platelets: <150,000/μL AST/ALT: <ULN Creatinine: >1.1 mg/dL	Nausea, vomiting, abdominal pain, malaise, jaundice	Possible hypoglycemia, increased ammonia levels, coagulopathy	Supportive

Note. ADAMTS-13 — disintegrin-like metalloprotease with a thrombospondin 1 motif; ALT — alanine aminotransferase; AST — aspartate aminotransferase; HELLP — hemolysis, increased content of liver enzymes, thrombocytopenia; HUS — hemolytic-uremic syndrome; MAGA — microangiopathic hemolytic anemia; VPN is the upper indicator of the norm.

g/L, platelets 118×10^9/l, AST 40 U/L, ALT 65 U/L, proteinuria 3.58 g/day. Urgent cesarean section was performed with ligation of the uterine vessels on both sides and application of uterine compression sutures. Amniotic fluid was green, with admixture of blood; the placenta was located along the posterior wall, with a transition to the bottom and areas of detachment. Total blood loss was 900 mL: 300 mL before the surgery and 600 mL during the surgery. In the early postoperative period, negative changes were observed: platelets 74×10^9/L; hemoglobin 75 g/L; AST 115 U/L; ALT 105 U/L; LDH 4,000 U/L; urine protein 3.58 g/day. Hypertension up to 160/90 mmHg. The condition was initially considered as HELLP syndrome. Hypotensive therapy and plasmapheresis were performed. On the following day, the patient's condition worsened, and negative changes in laboratory parameters were observed (hemoglobin 87 g/L; platelets 66×10^9/L; total protein 47 g/L; albumin 28 g/L; LDH 3,170 U/L; creatinine 410 μmol/L; schizocytes 2%). The multidisciplinary team diagnosed the patient with TMA, and then differential diagnosis with other conditions was made according to ADAMTS-13, antibodies to beta-2-glycoprotein, lupus anticoagulant, homocysteine, and Coombs' test. After obtaining negative results for APS, CAPS was ruled out; TTP was ruled out based on the ADAMTS-13 level of 53%; Coombs' test was negative. By ruling out other forms of TMA, the diagnosis of aHUS was made.

In our clinical case, plasma transfusion significantly improved the patient's general condition and laboratory parameters, which did not allow us to make the diagnosis of aHUS despite a very small decrease in complement components C3 and C4.

The obtained values of ADAMTS-13 level, antibodies to beta-2-glycoprotein (IgG), and antibodies to beta-2-glycoprotein (IgM) allowed us to rule out TTP and CAPS.

In terms of pathogenesis, HELLP syndrome is a result of disseminated microangiopathy due to a defect in trophoblast implantation. Delayed invasion of cytotrophoblast leads to hypoxia of uteroplacental complex tissues and, consequently, to vascular endothelial damage due to imbalance of expression of vasoconstrictors and vasodilators, which causes microcirculatory disorders [8, 16]. Our patient had low placentation in the first trimester based on ultrasound findings. It is possible to assume that this was the cause of the pathology in quastion.

Currently, the role of genetic mechanisms of PE, HELLP syndrome, and other forms of TMA in pregnant women is widely discussed in the literature. However, some authors do not confirm their significance in the pathogenesis of TMA. Certainly, some aspects are of interest, such as genetic polymorphism of the hemostasis system, angiotensin-converting enzyme (ACE), and several other systems that contribute to the development of endothelial dysfunction in the

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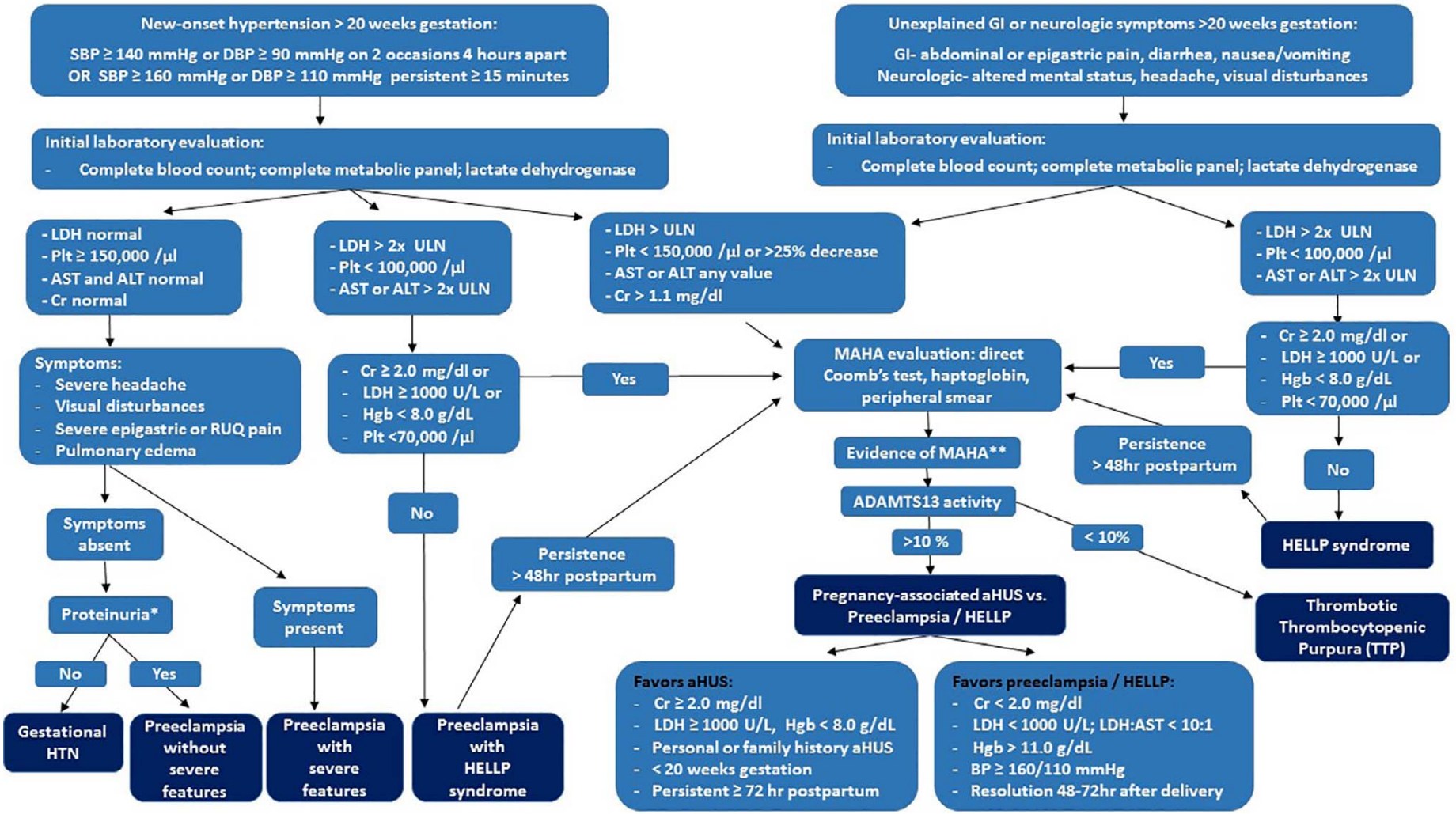

Fig. 1. Algorithm for the diagnosis of thrombotic microangiopathy during pregnancy [14].

*Proteinuria: daily urine protein ⩾300 mg/dl or protein/creatinine ratio in urine ⩾0.3 mg/ml. **МАГА confirmation: negative direct Coombs test, lower-normal haptoglobin or schizocytes in peripheral blood smear. ADAMTS-13 — disentegrin-like metalloprotease with a thrombospondin-1 motif; аГУС — atypical hemolytic uremic syndrome; АЛТ — alanine aminotransferase; АСТ — aspartate aminotransferase; HELLP — hemolysis, elevated liver enzymes, trobocytopenia; ВПН — the upper norm; Hb — hemoglobin; АГ — arterial hypertension; АД — blood pressure; САД — systolic blood pressure; ДАД — diastolic blood pressure; ЛДГ — lactate dehydrogenase; МАГА — microangiopathic hemolytic anemia; ЖК — gastrointestinal.

uteroplacental complex and other locations, causing a systemic vascular immune-mediated process [17-18].

In our case, repeated pregnancy with a combination of certain factors may have led to the realization of a genetic predisposition, elements of which, although not specified (thrombophilic markers), can be discussed.

All this determines the necessity to follow practical guidelines if TMA is suspected. The simultaneous use of the maximal amount of differential diagnostic tests for complement level, ADAMTS-13, and defibrinization products, as well as immunological, genetic, and several other studies, will allow an early diagnosis of TMA in obstetric practice, followed by extensive and, in some cases, targeted therapy (Fig. 1).

CONCLUSION

The described clinical case of HELLP syndrome is unusual due to the development during the second pregnancy, despite the first pregnancy having a normal course.

It is possible that the initial disruption of trophoblast implantation with subsequent formation of an angiogenic pathology and an immune response to fetal antigens could have triggered the process. However, the reason why the patient developed HELLP syndrome during the second pregnancy remains unknown. Apparently, in this case some more complex factors of genetic predisposition have not been clarified, which warrants further research of this essentially multidisciplinary problem.

ADDITIONAL INFO

Authors' contribution. All authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Consent for publication. The patient who participated in the study signed an informed consent to participate in the study and publish medical data.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. Все авторы внесли существенный вклад в разработку концепции, проведение исследования и подготовку статьи, прочли и одобрили финальную версию перед публикацией.

Финансирование. Авторы заявляют об отсутствии внешнего финансирования при проведении исследования.

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

Информированное согласие на публикацию. Пациентка, участвовавшая в исследовании, подписала информированное согласие на участие в исследовании и публикацию медицинских данных.

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