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Maternal Death Due to Refractory Thrombotic Thrombocytopenic Purpura (TTP) Associated With Superimposed Preeclampsia, Sepsis, and Intracranial Hemorrhage: A Case Report

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ABSTRACT

Thrombotic Thrombocytopenic Purpura (TTP) is an acute, rare, potentially life-threatening disorder presenting with thrombocytopenia, hemolytic anemia, and clinical consequences of microvascular thrombosis caused by a deficiency of ADAMS13 [1, 2]. The incidence of acquired TTP is approximately three cases per one million adults per year, based on the Oklahoma TTP-Hemolytic uremic syndrome (HUS) Registry [3]. Here, we present a case of TTP with persistent severely deficient ADAMS13 activity and recurrent relapses. She had a refractory relapse in the third trimester of pregnancy, complicated with superimposed severe preeclampsia and sepsis, and finally expired due to intracranial hemorrhage (ICH).

Introduction

Thrombotic Thrombocytopenic Purpura (TTP) is an acute, rare, potentially life-threatening disorder presenting with thrombocytopenia, hemolytic anemia, and clinical consequences of microvascular thrombosis, caused by a deficiency of ADAMS13 [1, 2]. The incidence of acquired TTP is approximately three cases per one million adults per year, based on the Oklahoma TTP-Hemolytic uremic syndrome (HUS) Registry [3]. TTP divides into acquired and hereditary syndromes

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due to autoantibody against ADAMS13 and ADAMS13 gene mutations.

A variety of presentations includes unexplained anemia or thrombocytopenia, unexplained neurologic findings, or other acute illness. Multiple organs may be involved in micro-thrombosis (central nervous system (CNS), gastrointestinal (GI), heart, kidney, pulmonary involvement). We should exclude systemic disorders that manifest these findings. A good history and physical examination guide selected lab tests, especially as many available are not highly sensitive for a single diagnosis. Diagnosis is based on clinics (based on PLASMIC score) and then confirmed by ADAMS13 activity. The first step is to ensure the presence of Micro-Angiopathic Hemolytic Anemia (MAHA) and thrombocytopenia by examining the Peripheral Blood Smear (PBS).

Despite recent advances in diagnosis and treatment, TTP presents a challenge to health care providers and patients. Treatment options are Plasma Exchange (PEX), glucocorticoids, rituximab, and Caplacizumab. Pregnancy can precipitate TTP [4]. Differentiation from preeclampsia (HELLP) is essential in pregnancy because of different treatments.

We present a case of TTP with persistent severely deficient ADAMS13 activity and recurrent exacerbations and relapses. She had a refractory relapse in the third trimester of pregnancy, complicated with superimposed severe preeclampsia and sepsis, and finally expired due to intracranial hemorrhage (ICH).

Case Presentation

A 27-year-old woman, gravida 1, 33 weeks of gestation, presented with neck ecchymosis and was referred to our center with platelet 20,000. She was a known case of TTP. The first attack was five years before this admission with a presentation of weakness, neck ecchymosis, low platelet, anemia, and then coma. In the first attack, she had hemoglobin 12 mg/dl, which dropped to 8mg/dl in admission, platelet 10,000, severely deficient ADAMS13 activity (<10%), and high titer of ADAMS13 inhibitor autoantibodies and normal bone marrow biopsy, normal rheumatologic tests, and folate and vitamin B12 levels.

During the first admission, she received a platelet transfusion with a diagnosis of ITP that progressed to COMA after platelet transfusion. She was treated with plasma exchange (PEX) and rituximab, and corticosteroids after a delayed TTP diagnosis and had a delayed response to treatment. Also, she had recurrent attacks of exacerbation after discontinuing plasma exchange. She was in COMA for one month, and finally, she was discharged with platelet 150,000 and oral corticosteroids after three months of admission.

She was symptom-free after that and had normal lab tests in follow-up. The second attack was six months before pregnancy (interval to first attack: 4 years), presented with neck ecchymosis and low platelet and anemia, and neurologic symptoms which progressed to COMA. She was admitted with a diagnosis of TTP relapse and treated with rituximab, corticosteroids, and plasma exchange. She was in COMA for two weeks, and after one month, she was discharged with normal platelet (160) on oral glucocorticoids. In the second admission, also she had episodes of exacerbation after continuing plasma exchange. She had persistent severely deficient ADAMS13 activity in follow-up but normal platelet. She had an unwanted pregnancy three months after TTP remission.

In early pregnancy, she had normal hemoglobin and platelet but severely deficient ADAMS13 activity, and she was symptom-free. In serial lab tests, she had hemoglobin 12-13 and platelet >200,000. Her blood pressure was normal during pregnancy, and she had gestational diabetes on a diet. Her corticosteroids were tapered in early pregnancy, and she was not on any medication at the end of the first trimester. She presented with neck ecchymosis at 33 weeks of gestation, one day before admission. She had a hemoglobin of 11 and a platelet of 20,000, so she was referred to our center with a TTP relapse diagnosis. She had no history of headache, nausea, vomiting, blurred vision, or respiratory symptoms. On arrival, her reading was 15/15, as measured on the Glasgow Coma Scale (GCS), her blood pressure was expected, and she was afebrile.

In the general examination, she had neck ecchymosis beneath her necklace. In our center, lab tests showed: WBC: 14* 10 9 (75% PMN, 17% lymph), hemoglobin: 10.6 mg/dl, MCV: 85, platelet: 18,000, LDH: 716, corrected reticulocyte count: 5%, uric acid: 6.3, peripheral blood smear (PBS): low platelet and 3% schistocyte, direct and indirect Coombs tests (DCT, ICT) : negative, coagulation profile (PT, PTT, fibrinogen level): normal, total bilirubin: 1 and direct bilirubin: 0.3, electrolytes: normal, LFT: normal (AST: 27, ALT: 17), Creatinine: 0.6, urine 24 hours: 1000 mg protein, C3,C4: normal and ANA, Anti-ds-DNA, APS lab tests: negative. COVID-19 PCR was negative. Fetal growth was normal in ultrasound. She was admitted to ICU. A hematologist visited her and diagnosed her with TTP relapse, plasma exchange, and corticosteroids

(IV methylprednisolone 1000 mg/day for three days and then prednisolone 1 mg/kg/day) was started for her. Her PLASMIC score was 7. The diagnosis was confirmed by severely deficient ADAMS13 activity and a high titer of inhibitor antibodies 72 hours after admission.

Due to normal blood pressure and normal LFT, preeclampsia was not the diagnosis. In serial lab tests, we had hemoglobin drop to 8 mg/dl and platelet to 5,000, and creatinine to 1.6 in 48 hours, but after ten days of plasma exchange and treatment with corticosteroids, we have hemoglobin: 8 mg/dl and platelet: 156,000 and creatinine: 0.7. The hematologist discontinued plasma exchange after two days of normal platelet, but she had exacerbation 48 hours later (platelet drop to 50,000). So plasma exchange started again, but the platelet trend descended to 18,000. She did not have signs and symptoms of sepsis, so refractory TTP was the first diagnosis.

Two weeks after admission at 35 weeks of gestation, she presented with headache, blurred vision, a crisis of blood pressure to 160 mmHg, and terminated with a diagnosis of superimposed severe preeclampsia with cesarean section after controlling blood pressure. Brain imaging (MRI) was normal. Platelet before the cesarean section was 14, and hemoglobin was 8 mg/dl. Due to a history of COMA after platelet transfusion and no abnormal bleeding during the operation (under general anesthesia), we did not transfuse the platelet. The blood loss was 1300 cc during the operation. One packed cell was transfused for her. Her baby had an excellent APGAR score and weighed 2500 grams.

After a cesarean section, her blood pressure was controlled without medication, and her symptoms (headache and blurred vision) disappeared. Her hemoglobin was 7.9, and her platelet was 18,000 after cesarean section, but there was no increase in her platelet count due to refractory TTP. A hematologist visited her, and plasma exchange and corticosteroids continued. Forty-eight hours after the operation, she had a low-grade fever (38˚C) so rituximab was not started, and broad-spectrum antibiotics were infused. Her fever stopped. She had mild dyspnea, tachycardia, and bloody sputum 3 days after the Cesarean section. The spiral chest CT scan was normal, no thrombo-emboli was detected, and lung parenchyma was normal without lesion or hemorrhage. Her echocardiography showed an average ejection fraction but pulmonary hypertension (pulmonary artery pressure: 47 mm/Hg).

Five days after the operation, she presented with fever, platelet drop to 4,000, and neurologic findings (headache, agitation). She expired after recurrent seizures before the brain CT scan (30 minutes after CNS findings). The autopsy showed massive intracranial hemorrhage. The diagnosis was refractory TTP associated with sepsis complicated by status seizure and intracranial hemorrhage.

Discussion

TTP is a rare, life-threatening disorder characterized by MAHA and thrombocytopenia often associated with renal failure and neurologic manifestations [5]. TTP is thrombotic microangiopathy caused by severely reduced activity of the von Willebrand factor-cleaving protease ADAMS13. It is characterized by small vessel platelet-rich thrombi that cause thrombocytopenia, MAHA, and organ damage. TTP is a medical emergency that is almost always fatal if appropriate treatment is not initiated promptly. Previously, survival rates for patients with TTP were 10%. However, with the intervention of plasma exchange, it has now increased to >80% [6]. Acquired TTP may also present in patients with other autoimmune disorders such as SLE. Organ involvement in TTP often affects the CNS and gastrointestinal (GI) systems. Renal involvement is seen on renal biopsy, but acute kidney injury is uncommon. Other organs such as the heart may also be affected. Pulmonary involvement is rare [7]. Low platelet is not preventive for pulmonary emboli in TTP. In our case, the pulmonary hypertension was chronic and probably due to recurrent attacks of TTP. Neurological findings are common in TTP, especially confusion and headache. Brain imaging is often normal and may show changes consistent with small silent infarction or with PRES.

Our patient had CNS involvement in the first and second attacks. Renal insufficiency can be seen, but acute renal failure is rare. Urine analysis may be normal or shows mild proteinuria, about 1-2 grams per day and few cells or casts. In our case, urine 24 hours showed 1 gram proteinuria. Complements increased in pregnancy and TTP during acute episodes, and decreased levels indicative of complement consumption occurred in 15 % of acute TTP patients [8].

In our patient, complement levels were normal. Pentad of TTP (MAHA, thrombocytopenia, fever, acute renal failure, severe neurologic findings) is rare (<5%) in cases of TTP because of early diagnosis and treatment of TTP with PEX. Therefore, the use of pentad for diagnostic purposes has become obsolete. Severely reduced ADAMS13 activity (generally <10%) during an acute episode is a hallmark of acquired TTP. TTP should

be suspected when a patient presents with MAHA and severe thrombocytopenia, with or without organ involvement symptoms and without another clinically apparent etiology. Diagnosing TTP and initiating therapy with PEX, if appropriate, is urgent. The finding of MAHA with thrombocytopenia in the proper clinical setting is sufficient for a presumptive diagnosis of acquired TTP and therapy initiation.

A presumptive diagnosis based on clinical features and initial laboratory testing is incorporated into the PLASMIC score. For patients with a presumptive diagnosis, initiating PEX, glucocorticoids, and rituximab is potentially life-saving therapy. Although it is well established that pregnancy may predispose to TTP, little is understood regarding pregnancy outcomes in women with a history of acquired TTP who subsequently become pregnant [9]. Hematologists caring for these women are often asked to estimate the risk of recurrence of TTP during pregnancy and the negative impact on the pregnancy.

Because this is a rare disorder and few studies have been conducted on pregnant women with a TTP history, physicians have limited anecdotal studies to consult when advising these patients [10]. Women with acquired TTP also have a high risk of recurrence in a subsequent pregnancy [11]. It has been proposed that specific proteins found in the placenta circulation serve as antigens that trigger maternal antibody production against ADAMS13.

TTP associated with pregnancy accounts for 12% to 31% of all TTP cases and is associated with high rates of obstetrics complications [5, 12, 13]. Given the increased risk of recurrence in pregnancy, women with a previous history of TTP should be monitored closely to develop TTP. In women with a history of TTP contemplating pregnancy, we measure ADAMS13 activity before conception. If activity is below 10%, the patient should receive rituximab to raise ADAM13 action, and monitoring the activity during pregnancy is essential. Still, no PEX or immunosuppressive therapy is needed without symptoms or thrombocytopenia [14].

Additionally, CBC should be obtained at each prenatal visit, or there are symptoms suggestive of relapse. Unfortunately, our patient had an unwanted pregnancy on severely deficient ADAMS13 activity. In patients with a history of TTP, the risk of preeclampsia is higher [14]. Also, the risk of pregnancy loss, fetal demise, and fetal growth restriction increases [14]. Differentiation between TTP and HELLP syndrome is critical and challenging (due to the overlap of several features) as treatments are different. The treatment of HELLP is the termination of pregnancy. Features that may help distinguish TTP include renal dysfunction, significantly reduced platelet count (less than 20,000), fever, and fluctuating neurological symptoms [5, 15, 16].

In our case, normal blood pressure and normal LFT were against the diagnosis of HELLP syndrome. Besides, very high elevations of LDH with only moderate elevations of AST resulting in an elevated LDH to AST resulting in an elevated LDH-to-AST ratio suggest TTP [16]. Although reduced ADAMS13 activity and ultra-large vWF levels can be seen in HELLP syndrome, a severe reduction in ADAMS13 activity and an increase in ultra-large vWF multimers usually suggest TTP [17, 18]. Differential diagnoses are systemic disorders (DIC, systemic infections, systemic malignancies, HELLP, systemic rheumatic disease), drug-induced thrombotic microangiopathy (TMA), complement-mediated TMA, PNH, severe vitamin B12 or folate deficiency.

In our case, a bone marrow biopsy in the first attack was done and was normal. SLE lab tests and folate and vitamin B12 levels were normal. When we have more of the following, the patient is at high risk: neurological abnormalities, decreased LOC, elevated serum troponin level, and other critical illness signs. High-risk patients should receive high-dose corticosteroids, IV methylprednisolone 1000 mg daily for three days, and then prednisolone 1 mg/kg/day, like in our case. Rituximab is an initial therapy in all TTP cases because it reduces the risk of exacerbation and relapse [19, 20]. It is not safe during pregnancy, so we did not use this medication in our case. Also, it is contraindicated in infections.

In our patient, in the postpartum period, we did not use it due to suspicion of sepsis. Unfortunately, we do not have Caplacizumab in our country (Iran). There is no information about the safety of Caplacizumab during pregnancy. Clinically important bleeding is rare in TTP despite severe thrombocytopenia. We do not use platelet transfusion to correct thrombocytopenia (due to the risk of arterial thrombosis) unless clinically significant bleeding occurs or unless an invasive procedure is required that may cause significant blood loss.

We did not transfuse the platelet in our patient due to no abnormal bleeding during the operation. Long-term complications of TTP are minor cognitive impairment, major depression, hypertension, abnormal kidney function, and development of SLE [21]. So, follow-up is needed in these patients. We rechecked SLE lab tests in our patient, and they were negative. Overall, our case had persistent

ADAMS13 deficient activity, presented with refractory TTP relapse in the third trimester of pregnancy, and then complicated with severe superimposed preeclampsia and sepsis unresponsive to therapy and finally status seizure and ICH, and unfortunately ultimately death.

Conclusion

TTP is a rare and life-threatening disease requiring highly clinical suspicion and needs urgent therapy with plasma exchange, glucocorticoids, and rituximab. Following recovery from acquired TTP, most pregnancies are successful [4, 21]. Good counseling is crucial in cases with a TTP history, and ADAMS13 activity should be corrected before pregnancy. Severe ADAMS13 deficiency is not an absolute contraindication of pregnancy, but the patient may have a higher relapse and pregnancy complications, as in our case. However, we advise patients about the risks of relapse and preeclampsia and the need for more intensive monitoring.

Ethical Considerations

Compliance with ethical guidelines

There were no ethical considerations to be considered in this research.

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Conflict of interest

The authors declared no conflict of interest.

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