

THROMBOTIC THROMBOCYTOPENIC PURPURA: A CASE REPORT AND REVIEW OF LITERATURE

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Abstract: Introduction: Thrombotic thrombocytopenic purpura (TTP) is a syndrome that consists of the pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal disease. Moskowitz was the first who described this syndrome in 1925, finding hyaline thrombi in many organs. The micro thrombi cause tissue ischemia, platelet consumption, and microangiopathic hemolytic anemia. Brain involvement is common and leads to stroke, seizure, confusion, and headache. Renal injury occurs in a minority of patients and it is usually modest.

Case report: We present a 57-year old male who came to our hospital because of weakness, prostration and darkening of his urine, occurring several days before admission. On physical examination we found icteric coloring of his skin and conjunctiva, big hematoma on his right lower leg and he had neurological abnormalities presented as mild headache, disorientation and aphasia. Laboratory tests revealed anemia and thrombocytopenia and the examination of peripheral blood smear showed presence of schistocytes. Direct and indirect antiglobulin test (Coombs) was negative. Emergency treatment was started with plasmapheresis on daily basis, immunosuppressive treatment with high-dose methyl prednisolone and transfusions of red blood cells. The laboratory results and the clinical condition improved within two weeks.

Conclusion: TTP is a medical condition that can be fatal if emergency treatment with plasma pheresis is not initiated presently after suspected diagnosis.

Key words: thrombotic thrombocytopenic purpura (TTP), hemolytic uremic syndrome (HUS), plasma exchange.

INTRODUCTION

Thrombotic microangiopathies are a group of hereditary and acquired syndromes with diverse mechanisms that lead to shared clinico-pathological features:

microangiopathic hemolytic anemia, thrombocytopenia and organ injury (1). Moskowitz was the first who described this syndrome in 1925, finding hyaline thrombi in many organs (2). Classic form of this syndrome consists of the pentad of thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, fever and renal disease. It has been shown that these symptoms are due to decrease of the enzyme ADAMTS13 which is responsible for cleaving large VWF multimers into shorter strands and therefore platelet adhesion and aggregation is promoted (3). In some cases a genetic problem was asserted due to an irregularity in several suspect genes (4). In other cases, the disease appears without other known causes and this is called an “idiopathic” form (5). In acquired TTP, an autoantibody inactivates the ADAMTS13 protease, and there for the VWF multimers remain large and abundant. The multimers bind platelets and form aggregates in the microvasculature that induce thrombus formation. The micro thrombi cause tissue ischemia, platelet consumption, and microangiopathic hemolytic anemia. Brain involvement is common and leads to stroke, seizure, confusion and headache. Renal injury occurs in a minority of patients, and it is usually modest. Fever may develop but it is often due to precipitating infection (6).

Since, patients rarely present with the pentad of symptoms, it is very important to start the treatment promptly. Currently, unexplained thrombocytopenia and microangiopathic hemolytic anemia are the two criteria required to establish the diagnosis. A simple blood test will show shattered red blood cells and a low platelet counts, and it is a definite sigh to initiate treatment (7). Plasma exchange is the standard of care for the initial management of acquired TTP (8) and it should be continued daily until resolution of organ dysfunction and stable normalization of the platelet count. Adjunctive therapy with glucocorticoids as immunosuppressive

treatment should also be initiated in order to decrease the production of inhibitory anti-ADAMTS13 antibodies.

CASE REPORT

We present a 57-year old male who came to our hospital because of weakness, prostration and darkening of his urine, occurring several days before admission. Laboratory tests from local laboratory revealed anemia and thrombocytopenia. He didn't have any similar symptoms in his past medical history, neither his family history was remarkable. On physical examination we found icteric coloring of his skin and conjunctiva, he had big hematoma on his right lower leg and he had neurological abnormalities presented as mild headache, disorientation and aphasia. His temperature was 36.7 °C, his blood pressure was 100/60 mm Hg and his pulse was 82 beats per minute. The physical examination of lungs was normal, his abdomen was not distended and there was not hepatosplenomegaly on palpation. There was no swelling in the legs.

Laboratory findings revealed hemolytic anemia with hemoglobin level 67 g/L; hematocrit 17.3%; reticulocyte count 7%; total bilirubin 70.7 umol/L; (indirect 54.1 umol/l). Aspartate aminotransferase (AST) was 90 U/L, alanine aminotransferase (ALT) 36 U/L, lactate dehydrogenase (LDH) 2170 U/L. There was a significant thrombocytopenia with platelet count $14 \times 10^9/L$. There were also signs of renal damage with blood urea nitrogen 17.0 mmol/l, serum creatinine 146 umol/l, total serum protein 52 g/l, albumin 31 g/l. Urinalysis showed 2+ blood and 3+ protein. Examination of peripheral blood smear revealed 3-4 schistocytes in a field with no erythroblasts seen. White cells were normal with a normal granulation pattern. Direct and indirect antiglobulin test (Coombs) was negative. Blood coagulation tests (prothrombin time, activated partial thromboplastin time and thrombin time) were within normal range.

The genetic panel testing for AHUS was negative.

Emergency treatment was started with plasmapheresis on daily basis and transfusions of red blood cells. Immunosuppressive treatment consists of high-dose methyl prednisolone 2x250mg per day and Mabthera (Rituximab) 375mg/m² once weekly, a total of 4 doses. On hospital day 5 the hemoglobin level improved to 105g/L and the platelet count to $68 \times 10^9/l$, reticulocyte count failed to 3.4%. On the hospital day 12 the hemoglobin level was 122 g/L, the platelet count was $184 \times 10^9/L$, reticulocyte count 1.5%, and total bilirubin failed to 15.9 umol/l. As the serum glycaemia grew progressively, Insulin rapid in low doses was started. The clinical condition improved along with the improvement in laboratory results. After 64 days of hos-

pitalization and 35 plasmaphereses performed, the patient was discharged from the hospital in a good clinical condition with Hb level 124 g/L, WBC 4.8 and Plt 75, Rtc 1.9%. Maintenance therapy with prednisolone 60 mg and Aspirin 100 mg per day was suggested.

One month after discharging from hospital the patient was still in good clinical condition with normal blood tests: hemoglobin level 139 g/L, WBC 14.8, Plt 163, reticulocyte count 3%, and indirect bilirubin in normal range. The treatment was continued with prednisolone 40 mg per day and Aspirin 100 mg per day. Two months after the last dose of Mabthera was completed, we continued a maintenance therapy with Mabthera on two-months' intervals and lower doses of prednisolone 10 mg per day. Now, seven months after the onset of the disease, the patient is still in a good condition with blood tests in normal range: Hb level 149 g/L, WBC 12.3, Plt 298, reticulocyte count below 1%, no schistocytes present in the peripheral blood smear.

DISCUSSION

Our patient presented with weakness, prostration, occurrence of dark urine and neurological abnormalities, symptoms which were initial presentation of TTP. Laboratory findings revealed hemolytic anemia and thrombocytopenia that could be associated with Evans syndrome. However, the negative antiglobulin test (Coombs) and the lack of spherocytosis in peripheral blood smear that are present in cases of Evans syndrome, excluded this diagnosis (9).

Microangiopathic hemolytic anemia warrants consideration when schistocytes are seen in a patient with hemolysis (7). Severe hypertension, disseminated intravascular coagulation, sepsis and cancer can cause microangiopathic hemolytic anemia and thrombocytopenia, but there was no evidence of these conditions in our patient. Hemolytic-uremic syndrome (HUS) is a thrombotic microangiopathy that arises when shiga toxin-secreting strains of *Escherichia coli*, on occasion, *Shigella dysenteriae*, induce endothelial damage that leads to bloody colitis and, subsequently kidney injury; these features were also not present in this case (8). Atypical hemolytic syndrome (aHUS) is considered a complement-mediated form of thrombotic microangiopathy. It is a genetic disease associated with a mutation in CFHR1 (Complement Factor H Related 1) Coding gene. AHUS genetic panel was performed in our patient and the result was negative.

There are two forms of TTP; hereditary and acquired. The hereditary form is caused by mutations of the ADAMTS13 gene. The acquired form may be idiopathic, resulting from autoantibodies against ADAMTS13

metalloprotease or secondary to other conditions such as infections, hematopoietic stem cell transplantation, certain drugs, cancers, other autoimmune diseases (10). An ADAMTS13 activity level that is less than 10% is highly suggestive for a diagnosis of TTP. Three tests are commonly performed to confirm the diagnosis of TTP: assays for ADAMTS13 activity, ADAMTS13 inhibition, and anti-ADAMTS13 antibodies (11). However, these tests are not available in our laboratory.

According to clinical and laboratory findings (four out of the pentad of symptoms for TTP: thrombocytopenia, microangiopathic hemolytic anemia, neurologic abnormalities, and renal disease) a prompt initiation of treatment was started in our patient with plasma exchange and high doses of glucocorticoids, with clinical and laboratory improvement within two weeks.

CONCLUSION

TTP is a medical emergency that can be fatal if not recognized on time. The most important factor in improving patient survival is initiation of treatment as soon as possible. With induction of plasma exchange,

the mortality rate dropped from ninety to nearly twenty percent. Plasma exchange is essential treatment option because it depletes the circulating autoantibody to ADAMTS13 and also the very high molecular weight von Willebrand factor multimers along with replacement of the missing protease.

Abbreviations

ADAMTS13 — a desintegrin and metalloprotease with a thrombospondin type 1 motif, member 13

aHUS — atypical hemolytic syndrome

HUS — hemolytic uremic syndrome

TTP — thrombotic thrombocytopenic purpura

VWF — Von Willebrand factor

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Sažetak

TROMBOTIČNA TROMBOCITOPENIJSKA PURPURA: PRIKAZ SLUČAJA I PREGLED LITERATURE

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Uvod: Trombotična trombocitopenijska purpura (TTP) je sindrom koji se sastoji od pentade: trombocitopenije, mikroangiopatske hemolitičke anemije, neuroloških ispada, povišene temperature i bubrežne bolesti. Moskowitz je bio prvi koji je opisao ovaj sindrom 1925. godine, pronašavši hijaline trombe u mnogim organima. Mikrotrombi izazivaju ishemiju tkiva, potrošnju trombocita, kao i mikroangiopatsku hemolitičku anemiju. Zahvaćenost mozga je česta, što može dovesti do infarkta, epileptičkih napada, i glavobolje. Povreda bubrega se javlja kod manjeg broja pacijenta i obično je umerena.

Prikaz slučaja: Predstavljamo 57-godišnjeg muškarca, koji je primljen u našu bolnicu zbog slabosti, prostracije i tamnog urina. Simptomi se javili nekoliko dana pre prijema u bolnicu. Na fizikalnom pregledu uočena je ikterična boja kože i konjunktiva, veliki he-

matom na desnoj nozi, kao i pozitivan neurološki nalaz koji se manifestovao dezorijentacijom, glavoboljom i afazijom. Urađeni laboratorijski testovi pokazali su anemiju i trombocitopeniju, a pregled razmaza periferne krvi pokazao je postojanje šistocita. Direktan i indirektan antiglobulinski test (Coombs) bili su negativni. Započeto je lečenje primenom plazmafereze svakog dana, imunosupresivnom terapijom sa visokim dozama metilprednizolona i transfuzijom eritrocitima. Laboratorijske analize i kliničko stanje pacijenta su se značajno popravile u okviru dve nedelje.

Zaključak: TTP je stanje koje bi moglo da ima fatalne posledice, ako se ne započne hitna terapija plazmaferezom nakon sumnje na ovu bolest.

Ključne reči: trombocitopenijska purpura TTP, hemolitičko uremijski sindrom HUS, izmena plazma.

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