CASE REPORT

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Thrombotic thrombocytopenic purpura: a hematological emergency

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Abstract

Thrombotic thrombocytopenic purpura (TTP) is a rare but severe disease characterized by mechanical hemolytic anemia and consumptive thrombocytopenia leading to disseminated microvascular thrombosis that causes signs and symptoms of organ ischemia and functional damage. TTP is diagnosed by the presence of microangiopathic hemolytic anemia and thrombocytopenia in a patient who frequently presents with central nervous system involvement and, to a lesser extent, renal dysfunction. *Case Report*: We present the case of a 23-year-old female with TTP, diagnosed by the presence of the neurological symptoms, microangiopathic hemolytic anemia and severe thrombocytopenia (platelets 4000/μL). During the clinical evolution, the patient presented the hepatic cytolysis syndrome, following disseminated microvascular thrombosis inside the liver, representing an atypical damage. The diagnosis was difficult because it was necessary to make differential diagnosis with other diseases that evolve with microangiopathic hemolytic anemia in a short time to be able to initiate plasmapheresis. Initiation of the plasmapheresis as soon as possible was the goal of our treatment. Following the plasmapheresis combined with administration of corticosteroids was achieved complete resolution of all symptoms. *Conclusions*: TTP is a hematological emergency and diagnostic challenge. The critical determinant of outcome is timely diagnosis and treatment. Once the diagnosis is suspected, life-saving therapeutic plasma exchange therapy is initiated.

Keywords: thrombocytopenia, microangiopathic hemolytic anemia, plasmapheresis.

Introduction

In 1924, Dr Eli Moschcowitz described the case of a 16-year-old adolescent girl with abrupt onset of petechiae, hemolytic anemia, followed by paralysis, coma, and death. Autopsy showed widespread hyaline thrombi in the terminal arterioles and capillaries of various organs. The syndrome described by Moschcowitz is now known as thrombotic thrombocytopenic purpura (TTP) [1].

TTP is a particular form of thrombotic microangiopathy typically characterized by microangiopathic hemolytic anemia, profound peripheral thrombocytopenia, and a severe deficiency of the von Willebrand factor-cleaving protease ADAMTS-13 (acronym for A Disintegrin And Metalloproteinase with ThromboSpondin-1 motifs, 13th member of the family). ADAMTS-13 deficiency is usually severe (<10% of normal activity) and results from autoantibodies directed to ADAMTS-13 (acquired TTP) or from biallelic mutations of the encoding gene. In some cases, acquired TTP occurs in association with specific conditions that must be identified for appropriate management: a HIV infection, a connective tissue disease, a pregnancy, a cancer or a treatment with antiplatelet agents [2].

ADAMTS-13, a 190-kD plasma protease originating primarily in hepatic stellate cells, prevents microvascular thrombosis by cleaving von Willebrand factor (vWF) when the substrate is conformationally unfolded by high levels of shear stress in the circulation. Deficiency of ADAMTS-13, due to genetic mutations or inhibitory autoantibodies, leads to accumulation of superactive forms of vWF, resulting in vWF-platelet aggregation and microvascular thrombosis [3].

Patient, Methods and Results

We present the case of 23-year-old female, smoker, one pack/day, without special medical history reported the beginning of the disease with eight days before admission by the appearance of hyperchromic urine and ecchymosis disseminated on the body. Initially, the patient was presenting in the Emergency Unit for the abdominal pain, back pain, paresthesia and headache and than was hospitalized in the Clinic of Hematology, "Sf. Spiridon" Hospital, Iassy, Romania with the presumptive diagnosis of TTP.

The physical examination revealed the paleness skin, ecchymosis disseminated on the body, the hyperchromic urine and paresthesia.

Laboratory tests revealed the severe thrombocytopenia

[platelets (PLT) 4000/μL, normal range: 15–35×10^4/μL], hemolytic anemia [hemoglobin (Hb) 7 g/dL, high levels – 861 U/L – of lactate dehydrogenase (LDH), normal range: 120–220 U/L, increased total bilirubin and indirect bilirubin, increased serum iron, reticulocytosis]. The serum levels of fibrinogen degradation products (FDP) and D-dimers were elevated +++ (normal range: absent) and 7.07 μg/dL (normal range: <2 μg/dL), respectively, suggesting disseminating intravascular coagulopathy (DIC), the other parameters related to DIC, such as the serum level of fibrinogen, prothrombin time (PT), and activated partial thromboplastin time (aPTT) were normal. Serum creatinine 0.68 mg/100 mL and blood urea nitrogen 50 mg/100 mL. The other biological tests were normal. The blood film featuring evidences the mechanical fragmentation of red blood cells (Figure 1).

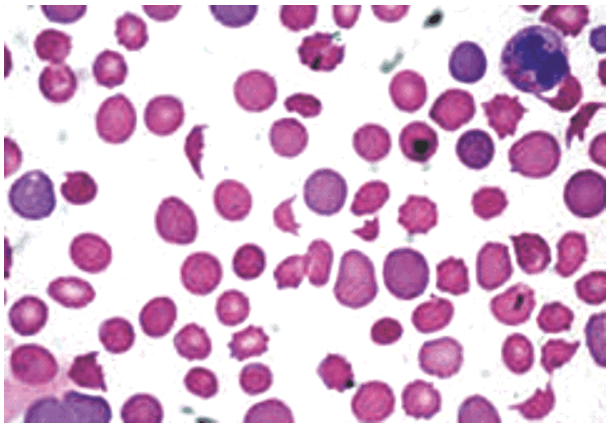

Figure 1 – ***Thrombotic thrombocytopenic purpura. Blood film. The film contains schistocytes that result from the intravascular trauma to the red cells in the fibrin meshwork of the partial thrombotic obstructions in the small arteries and arterioles. HE staining, ×400.***

Direct and indirect Coombs test and antinuclear factor were negative. The anti-DNA antibodies were negative. Urinalysis showed 2+ proteinuria, a moderate number of epithelial cells, 4–6 granular casts, a few epithelial casts, 5–6 red cells and 2–5 white blood cells/high power field, a moderate amount of hemoglobin, and no glucose or acetone.

On admission, the seronegative autoimmune hemolytic anemia with thrombocytopenia (Evans syndrome) hemolytic-uremic syndrome and DIC were considered as possible candidates for her thrombocytopenia with hemolytic anemia. The bacterial cultures from her blood, urine, sputum, and throat swab revealed no signs of any bacterial infections and we subsequently excluded bacterial infection from the diagnosis.

Although she did not have typical symptoms of TTP such as renal dysfunction (only pathological urinalisys, serum creatinine and blood urea nitrogen – normal range) and minor abnormalities of the central nervous system (transitory paresthesia), we diagnosed her illness as TTP. The ADAMTS-13 activity was examined and we found the decreased activity of ADAMTS 13 – 34.2% (normal range: 40–130%). Antigen ADAMTS-13 was normal and antibodies anti-ADAMTS-13 were absent.

The diagnosis of TTP was considered on admission and treatment was initiated with intravenous Dexamethasone (56 mg/day) and fresh frozen plasma transfusion with no treatment response: PLT 21 000/μL, elevated (+++) serum levels of FDP and D-dimers, Hb 5.5 g/dL, schistocytosis, LDH 780 U/L, hepatic cytolysis syndrome with hepatomegaly and pain in the right hypocondrium. After three days of admission, we initiated the plasmapheresis. The therapy was continued for three consecutive days, then, her symptoms and the abnormal findings of laboratory tests completely disappeared. The clinical course of the patient is summarized and illustrated in Table 1.

Table 1 – ***The clinical course of our case. The patient was treated with intravenous administration with Dexamethasone (56 mg/day for three days on the admission). Daily plasma exchange was added on the fourth day. Plasma exchange was performed for three consecutive days and stopped at the sixth day of the admission. Subsequently, peripheral schistocytes diminished, her hemoglobin level and platelet count were improved***

Day after admission	1	3	4 (Plasma-pheresis)	5 (Plasma-pheresis)	6 (Plasma-pheresis)	10
Hemoglobin [g/dL]	7	5.5	7.2	9.7	9.9	9.5
Schistocytosis	++	++	+/-	-	-	
Platelets [×10^4/μL]	4	21	37	57	107	197
LDH	860	780	429	461	275	178
FDP	+++	+++	+++	++	-	-

Differential diagnosis of hepatic cytolysis syndrome was made with an acute viral liver disease because on admission the liver tests were normal. Therefore, we examined the hepatitis B surface antigen (HBsAg), HCV-antibodies and IgM–HAV, which were negative. The abdominal and pelvic ultrasounds revealed the hepatomegaly and homogeneous spleen with the normal size. We finally found that the hepatic cytolysis syndrome is following disseminated microvascular thrombosis inside the liver, representing an atypical damage. All liver symptoms resolved after three sessions of plasmapheresis. After two weeks of complete remission, the patient had a low count of platelets and we administrated Methyl-prednisolone 32 mg p.o/day, two weeks, followed by the gradual dose reduction, and we obtained a normal count of the platelet. At eight weeks after the plasmapheresis, the patient has a normal count of platelets, without corticoids.

Discussion

We reported a case of TTP in a young women. There are relatively few signs/symptoms of organ ischemia related to thrombosis in capillary arteries, thus it was difficult to determine the diagnosis of TTP at presentation. The evaluation of patients with suspected thrombotic thrombocytopenic purpura is difficult because the diagnostic criteria – thrombocytopenia, microangiopathic hemolytic anemia, and no other clinically apparent etiology are not specific [4]. The value of ADAMTS-13 measurements for establishing the diagnosis of TTP and determining the indication for plasma exchange treatment remains uncertain. Although a severe deficiency of ADAMTS-13 activity (<5%) may be an abnormality that is specific for TTP [5], the presenting symptoms of patients with severe ADAMTS-13 deficiency are often

not severe and not distinguishable from many other common illnesses. Patients can have the characteristic presenting features and clinical course of TTP without severe ADAMTS-13 deficiency or even with normal ADAMTS-13 activity (>50%) [6] and also patients can have severe ADAMTS-13 deficiency for many years with no illness [7]. In our case, the patient had presenting features and clinical course of TTP without severe ADAMTS-13 deficiency.

Similar to our case, occasionally is difficult to diagnose TTP, especially in the patients lacking typical clinical signs/symptoms of the disease. Moreover, it may be difficult to distinguish TTP from the other types of TMA (thrombotic microangiopathy).

The possible differential diagnosis and the clinical differences among representative TMA including TTP are summarized in Table 2.

Table 2 – ***Differential diagnosis of hemolytic anemia with thrombocytopenia***

	TPP	HUS	Evans syndrome	DIC
Thrombocytopenia	(+)	(+)	(+)	(+)
Hemolytic anemia	(+)	(+)	(+)	(+–)
Schistocytes	(++)	(+)	(+–)	(+–)
Clinical findings	Mental disorder, renal dysfunction	Diarrhea, renal dysfunction, fever up	Autoimmune reaction	Underlying disease
Specific laboratory findings	Suppression of ADAMTS-13 activity	Positive for Shiga toxin	Positive for Coombs test	Elevation of FDP
Treatment	Plasma exchange	Hydration, plasma exchange	Steroids, immunosuppression therapy	Treatment for underlying disease, anti-coagulant therapy

TTP: Thrombotic thrombocytopenic purpura; HUS: Hemolytic-uremic syndrome; DIC: Disseminating intravascular coagulopathy.

HUS is characterized as renal diseases and usually associated with bacterial colitis (*Escherichia coli* O157: H7 and *Shigella*-toxin-producing strain). HUS can be distinguished from TTP by diarrhea (D+ HUS). The patient had not shown any digestive symptoms; however, diarrhea negative (D- HUS) cases of HUS have been reported [8]. Evans syndrome, which is characterized by autoimmune hemolytic anemia (AIHA) with autoimmune thrombocytopenia, is also considered as one of important differential diagnosis from TTP [8]. The detection of RBC bound immunoglobulin G and complement by the direct anti-globulin test (DAT; Coombs test) is useful in the diagnosis of AIHA [9]. The Coombs test in the patient was negative, although a small number of patients with AIHA have been reported to show a negative DAT [10], probably because of the lower affinity of IgG to RBC [11]. Therefore, the lack of these autoantibodies cannot conclusively exclude AIHA and/or Evans syndrome. Regarding DIC, the patient had an elevation in the serum levels of FDP and D-dimers, suggesting DIC, but the other coagulogram tests were normal and fibrinogen was normal.

The steroid treatment was not sufficiently effective for symptoms of the patient and plasma exchange treatment were performed, and thereafter her clinical and laboratory data were dramatically improved. Daily sessions of therapeutic plasma exchange (TPE) remain the basis of management of TTP. Also, TTP is a rare disease that is fatal if it is not treated. TPE has resulted in excellent remission and survival rates in TTP patients. This aspect is demonstrated by the lots of authors in their articles [12, 13]. Adjuvant therapies include corticosteroids, Rituximab and Cyclophosphamide [14, 15]. In our case, we used corticosteroids with a good therapeutic response.

Conclusions

Thrombotic thrombocytopenic purpura is a hematological emergency and diagnostic challenge. The critical determinant of outcome is timely diagnosis and treatment. Once the diagnosis is suspected, life-saving therapeutic plasma exchange therapy is initiated.

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