Thrombotic thrombocytopenic purpura in a patient with systemic lupus erythematosus successfully treated with plasma exchange and corticosteroids

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Abstract: Thrombotic thrombocytopenic purpura (TTP) is a rare dynamic life-threatening disease with systemic formation of platelet thrombi in the microvasculature within all the organs. Until recently the mortality in TTP has exceeded 90%. The progress of medical research in the last two decades has significantly improved our understanding of the pathogenesis of TTP and allowed a reduction in mortality. This paper describes a case of a 36-year-old female patient with systemic lupus erythematosus (SLE) who was admitted to our hospital for jaundice and speech disturbances. Laboratory tests revealed hemolytic anemia with a negative Coombs test. Abundant schistocytes were present in peripheral blood smear. During the first day of hospitalization progression of neurological signs was observed – the patient received high-dose corticosteroids (1000 mg of methylprednisolone daily for 5 consecutive days) and underwent plasma exchange therapy. We observed significant improvement of the patient's condition, as well as a complete resolution of clinical and laboratory abnormalities. In the following 24 months there have been no signs of the relapse of TTP. The article contains also a brief update of this unusual disease.

Key words: cell separator, plasma exchange, plasmapheresis, systemic lupus erythematosus, thrombotic thrombocytopenic purpura

INTRODUCTION

Thrombotic thrombocytopenic purpura (TTP) is a life-threatening, dynamically developing disease, where platelet clots are formed in the microcirculation within all organs of the body. This results in a set of symptoms such as thrombocytopenia, microangiopathic hemolytic anemia and symptoms of damage to different organs, especially the brain and kidneys. The syndrome was described for the first time in 1924 by Eli Moschcowitz. Thrombotic thrombocytopenic purpura shows numerous common features with hemolytic-uremic syndrome (HUS), however, according to our current knowledge, due to different pathogenesis, the two diseases should be treated as independent ones. Discoveries of the last two decades of the 20th century not only allowed to understand the TTP pathogenesis, but also brought a dramatic improvement in the treatment results of this life-threatening disease, the mortality of which until the 1990s exceeded 90%.

CASE REPORT

A 36-year-old female patient, chronically treated for 4 years with immunosuppressive drugs (corticosteroids, periodically cyclophosphamide) due to systemic lupus erythematosus (SLE), was referred to the hospital with a history of speech disturbances (sensory motor aphasia type) aggrevating over several hours and jaundice. The patient was taking a 10 mg/d maintenance dose of prednisone (Encorton) orally, and 10 months earlier she completed a treatment with intravenous cyclophosphamide pulses (due to exacerbated SLE).

On admission, the patient was diagnosed neither with circulatory or respiratory failure nor with clinical features of infection. The computed tomography of the head excluded bleeding to the central nervous system (CNS) and showed small ischemic spots within the internal capsule. A peripheral blood count showed anemia and a considerably decreased platelet count (hemoglobin – 7.28 g/dl, leukocytes – 8.8 × 10^9/l, platelets – 4.4 × 10^9/l). Moreover, hyperbilirubinemia (4.3 mg/dl) was found at the normal activity of alanine transferase, asparagine transferase, alkaline phosphatase and gamma-glutamylotranspeptidase, as well as the biochemical signs of intensified intravascular hemolysis – increased plasma free hemoglobin level (84.9 mg/dl), increased reticulocyte percentage (7.1%) and increased lactate dehydrogenase activity (941 U/l). Coombs' test

was negative. On the grounds of suspected microangiopathic hemolysis, a peripheral blood smear was prepared and a considerably increased number of schistocytes (20%) was found. The only coagulant abnormality observed was an increased D-dimer level (405 µg/dl). The international normalized ratio (INR) and the activated partial thromboplastin time were within the reference range. Fibrinogen and antithrombin III levels were normal. The entire clinical presentation, particularly thrombocytopenia, microangiopathic hemolysis and the presence of the CNS symptoms, argued for the TTP diagnosis.

Due to the deterioration in the patient's clinical condition within several hours after admission and the progression of neurological symptoms (complex partial seizures added), a decision was made to carry out the plasma exchange by means of the Fenwal CS 3000 Plus cell separator. Upon the first plasma exchange, the patient's condition significantly improved, neurological symptoms and jaundice subsided completely. Plasma exchanges were repeated daily for the following 5 days and after each procedure the patient was administered intravenous methyloprednisolone in a 1000 mg daily dose. The therapy demonstrated good tolerance and no complications were observed. Control laboratory tests performed upon the completion of the treatment showed the normalization of a platelet number, a reduction in schistocytes and the abatement of hemolysis biochemical features. During the two-year follow-up on an ambulatory basis, no TTP relapse was observed.

In plasma taken from the patient before the therapy, antinuclear antibodies (ANA) Hep-2 at titer of 1:2560 were found, and they showed homogenous and speckled fluorescence (SS-A, SS-B). Anticardiolipin antibody levels were within the reference values (IgG – 0.29 U/ml, IgA – 0.14 U/ml, IgM – 0.13 U/ml), as well as the levels of anti-β_2 glycoprotein-I antibodies (IgG – 0.22 U/ml, IgM – 0.18 U/ml).

DISCUSSION

The coexistence of 5 symptoms, typical of TTP and often cited by textbooks, is not frequent in clinical practice. It is clear from the series of cases that microangiopathic hemolytic anemia and thrombocytopenia occur in 100% of patients and CNS symptoms in 60–88% of cases, whereas renal function disorder (18–76%) and fever (22–86%) are less frequent [1]. Due to systemic activation of the coagulation system, the symptoms may be manifestations of each organ involvement. Among others, acute pancreatitis in the course of TTP and sudden deaths (probably due to cardiac ischemia) were described. Attention should be drawn to the fact that TTP is one of few diseases, where thrombocytopenia is accompanied by clot formation, and that TTP is an absolute contraindication to transfusion of platelet concentrate, unless a life-threatening hemorrhage occurs.

In the differential diagnosis we were considering as follows: disseminated intravascular coagulation (DIC), antiphospholipid syndrome (APS), autoimmunologically mediated platelet and erythrocyte destruction (Evans' syndrome), and HUS. Lack of typical trigger and normal test results of hemostatic system parameters argued against the DIC diagnosis. The clinical presentation could also correspond to a severe form of APS (particularly of catastrophic APS), however, in the light of negative results of determination of anticardiolipin and anti-β_2 glycoprotein-I antibodies, we rejected that diagnosis. Autoimmunological anemia and thrombocytopenia seemed improbable due to the presence of schistocytes and the negative Coombs test. No features of clinically overt renal impairment with the presence of CNS symptoms argued more for TTP than for HUS. A similar group of symptoms can also be found in preeclampsia/eclampsia, HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), sepsis, malignant hypertension and APS.

Discoveries of the last 20 years enable a better understanding of TTP pathogenesis. It is currently thought that ADAMTS13 protease (synthetized mainly in the liver, zinc-dependant metalloprotease of the ADAMTS family) [2] is crucial to its pathogenesis. This enzyme is responsible, among others, for separation of von Willebrand factor (vWF) multimers secreted by endothelial cells. A reduction in ADAMTS13 activity causes accumulation of large plasma vWF multimers, which are directly responsible for platelet adhesion and formation of platelet clots in microcirculation [3]. The presence of clots in the capillary vessels leads to mechanical damage to erythrocytes passing through, i.e. intravascular microangiopathic hemolysis. The exponent of this process activity, apart from thrombocytopenia and biochemical hemolytic indices, is an increased number of so-called schistocytes, i.e. fragmented erythrocytes, which under normal conditions appear in blood in a small proportion (to ~1%).

It is considered that responsibility for the acquired form of TTP lies with antibodies hampering ADAMTS13 activity (mostly directed against other antigens, cross-reacting), whose presence is observed in the course of autoimmunological diseases, as a result of bacterial and viral infections, upon treatment with thienopyridine derivatives (ticlopidine [4] and – far less frequently – clopidogrel [5]), in multiple cancer and after allogenic bone marrow transplant [6]. Determination of activity of ADAMTS13 and antibodies directed against this enzyme is useful in TTP diagnosis and in differential diagnosis [2]. There were also described congenital forms of TTP, related to mutations in the ADAMTS13 gene. Unfortunately, in the presented patient we were not able to determine ADAMTS13 activity or anti-ADAMTS13 antibody titer.

A cause of TTP in our patient is not clear. It seems to be related to the activity of the underlying disease (ANA-Hep-2 antibody titer determined prior to treatment was 1:2560), however, the onset of complaints was sudden, and symptoms characteristic of exacerbated SLE could not be found in the history. According to available data, TTP develops in 1–4% of SLE patients [7].

A method of choice in TTP treatment is the plasma exchange, i.e. replacement of the patient's plasma with fresh frozen plasma. It causes a reduction in the amount of pathogenic antibodies blocking ADAMTS13 protease, elimination of the

excess of vWF multimers and provision of active ADAMTS13 present in the donor plasma [8].

The exchange of plasma radically improves prognosis; a remission is observed in 70–90% of patients [9]. It is recommended to exchange 3–4 liters of plasma daily until remission is reached. If the treatment cannot be administered, it is recommended to transfuse fresh frozen plasma; this, however, is related to significantly increased mortality, lower remission rates and higher risks of complications [10].

Patients with severe anemia should undergo erythrocyte transfusion. Platelet transfusion is contraindicated unless a life-threatening hemorrhage occurs [11,12].

The effectiveness of immunosuppressive treatment with corticosteroids was not assessed in the controlled clinical trials; however, there are numerous reports arguing for this method of treatment. Although there is no full consensus, most authors consider this method acceptable [11,12]. Treatment with antiplatelet agents may be beneficial. However, it is recommended only after an increase in platelet count to a value of $\geq 50 \times 10^9/l$ is reached [11]. All patients should be given folic acid [11].

The recurrences of TTP were observed in 30–60% of patients. Most of the cases took place in the first month after the treatment of the acute episode [13,14]. It is suggested that a gradual reduction in platelet numbers may be a harbinger of recurrence.

In refractory cases or recurrences of TTP, attempts of additional administration of vincristine, cyclophosphamide, cyclosporine A, azathioprine and immunoglobulin infusion were made, although the results were not satisfactory. In those difficult cases splenectomy may be beneficial [15]. Recently, quite promising reports on attempts to treat refractory TTP forms with rituximab have been published [16].

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