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Thrombotic thrombocytopenic purpura in pediatrics. A case report

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ABSTRACT

Thrombotic thrombocytopenic purpura is a rare disease in pediatrics, but it has a high mortality if not managed in an adequate and timely manner. It is characterized by microangiopathic hemolytic anemia associated with neurological, cardiac, abdominal, and less frequently, renal signs and symptoms; it may be accompanied by fever.

In children, diagnosis is based on clinical and laboratory findings. ADAMTS13 activity < 10% supports the diagnosis but does not confirm it and, given its severity, the result should not delay treatment initiation.

Here we describe the case of a previously healthy 15-year-old female patient with neurological signs associated with hemolytic anemia and thrombocytopenia. During hospitalization, she was diagnosed with acquired thrombotic thrombocytopenic purpura.

Keywords: *hemolytic anemia; thrombotic microangiopathies; ADAMTS13 protein.*

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INTRODUCTION

Thrombotic microangiopathies (TMAs) are characterized by the presence of non-immune microangiopathic hemolytic anemia and thrombocytopenia.[1] TMAs include thrombotic thrombocytopenic purpura (TTP), a rare entity in the pediatric age group, potentially fatal and with a low incidence.[2] TTP is caused by a severe deficiency in ADAMTS13 protease activity, defined by a level of less than 10%; however, deficiency alone is not sufficient to trigger it. In children, the clinical presentation of TTP includes multiorgan involvement, neurological and cardiac alterations, intestinal ischemia and, sometimes, renal impairment and fever.[1]

The differential diagnosis of TMAs should include TTP due to its high mortality if not managed adequately.[1]

CASE REPORT

A previously healthy 15-year-old female patient presented with hemiparesis and transient right brachiocrural paresthesia. She later developed vomiting, abdominal pain, and asthenia for 5 days. On admission, she was in good general condition, had a normal weight and height, normal cardiac function, normal respiratory rate, no fever, but had jaundice, generalized petechiae, and a hematoma on the right ankle. Her abdomen was soft, depressible, and non-tender, her splenic pole was palpable, and her neurological examination did not show positive findings.

Her lab tests on admission showed normocytic normochromic regenerative anemia with transfusion requirement (hemoglobin: 5.4 mg/dL, mean corpuscular volume: 88, mean corpuscular hemoglobin: 29, and reticulocytes: 28%) and severe thrombocytopenia (12 800/µL), with normal blood count and differential leukocyte count, associated with an alteration in the liver function test and predominantly unconjugated hyperbilirubinemia, high aspartate aminotransferase (AST) and lactate dehydrogenase (LDH) levels; kidney function test were normal. An abdominal ultrasound, computed tomography, magnetic resonance imaging, and an angio-MRI of the central nervous system were performed, and results were within normal values. In addition, on the one hand, an autoimmune condition was ruled out based on normal immunological lab tests and, on the other hand, associated acute infections were also tested (non-reactive HIV, positive cytomegalovirus IgG, negative hepatitis C virus IgG, negative anti-core hepatitis B virus IgM/IgG, positive herpes simplex 1 and 2 IgG, negative VDRL and Chagas disease). Follow-up by the Department of Hematology for suspected hemolytic anemia started. Ancillary tests also included the Coombs test, which was negative, and peripheral blood smear, which showed schistocytes and signs of microangiopathy. Based on these criteria, TMA was diagnosed and, due to high suspicion of TTP, plasmatherapy and methylprednisolone pulses were started immediately. Previously, ADAMTS13 test was requested, which showed an activity level below 10%; the inhibitor was positive. Autoimmune acquired thrombotic thrombocytopenic purpura was diagnosed.

After receiving 3 pulses of methylprednisolone and plasmatherapy, the patient´s lab values returned to normal. Due to a disease relapse with thrombocytopenia and increased hemolysis parameters despite the first-line treatment, it was decided to continue with a second-line regimen which contained rituximab (4 doses).

Her clinical and blood values improved, so corticosteroid tapering was started. She continues being treated on an outpatient basis to monitor her ADAMTS13 activity.

DISCUSSION

TTP is a rare disease, with a high mortality in the absence of a timely treatment. It has an annual incidence of 0.1 cases per million in children and was first described in 1924.[1,2] It predominates in the female sex.

It is characterized by non-immune microangiopathic hemolytic anemia and consumption thrombocytopenia. The pathophysiology of TTP is based on severe deficiency of ADAMTS13 protease activity. Such involvement may be hereditary or acquired due to the formation of autoantibodies (10% versus 90% of cases, respectively).[3] ADAMTS13 is an enzyme necessary for the proteolysis of von Willebrand factor (VWF) after its secretion by endothelial cells; in the absence of the VWF multimer size regulatory mechanism, microvascular platelet thrombosis occurs, resulting in red blood cell fragmentation and platelet consumption by thrombus formation.[1]

ADAMTS13 deficiency associated with the absence of anti-ADAMTS13 antibodies suggests congenital TTP, especially when it occurs in the neonatal period, in adult women during

pregnancy, or in children or adults with typical presentations associated with triggering events and family history.[4] Diagnosis is confirmed by the identification of the mutation by means of a molecular genetic study. The clinical course of TTP is heterogeneous; it may be severe and chronic requiring monthly prophylactic treatment or mild to moderate with periods of recurrence and remission.[2]

In the case of our patient, we observed the characteristic laboratory findings of hemolytic anemia, with signs of microangiopathy in the smear and an ADAMTS13 activity of less than 10% with IgG antibodies that neutralize the proteolysis activity of ADAMTS13, which is why she was considered to have acquired TTP. The clinical presentation of this variant, which is the commonest one, is acute with a tendency to relapse.[1]

Hematologic alterations associated with systemic involvement are the first key to raise suspicion, although they are not specific. The main organs involved are usually the central nervous system, heart, and kidneys.

In 60% of cases, as in our patient, there are neurological manifestations of variable severity, such as paresthesias, headache, visual disturbances, seizures, sensory impairment, and even coma. There may be cardiac involvement, such as non-specific ECG alterations, tachyarrhythmia, cardiomyopathy, and ischemic syndromes; in this case, our patient had non-specific repolarization disorders in the ECG. Kidney damage is not severe due to a likely protective effect of local ADAMTS13; therefore, if there is a significant decrease in kidney function, other conditions should be ruled out. At a gastrointestinal level, intestinal ischemia may manifest with abdominal pain, vomiting, and bloody diarrhea, and may be confused with hemolytic uremic syndrome.

The diagnostic criteria for TTP include microangiopathic hemolytic anemia and thrombocytopenia without other cause to account for it. In the presence of a compatible clinical condition, a complete blood count with peripheral blood smear and the Coombs test, coagulation profile, liver and kidney function tests, biochemical parameters of hemolysis, cardiac enzymes, and beta-human chorionic gonadotropin (beta-hCG) (if applicable depending on sex and age) should be requested. In addition, viral serologies should be tested and an immunological profile should be performed due to the prevalence of associated autoimmune diseases.

An ADAMTS13 activity of less than 10% supports the diagnosis of acquired TTP, and a critical value of ADAMTS13 is associated with a higher risk of relapse during the course of the disease, but such measurement is not sensitive enough to confirm diagnosis and is not specific enough to exclude patients with underlying diseases.[3,5] The recovery of ADAMTS13 activity confirms the diagnosis of acquired TTP. Also, the presence of a functional ADAMTS13 inhibitor supports, but does not confirm, the diagnosis of acquired TTP.[5]

The patient of our case report met the characteristic criteria related to clinical and laboratory values, peripheral blood smear, ADAMTS13 activity <10%, and presence of ADAMTS13 inhibitory antibodies.

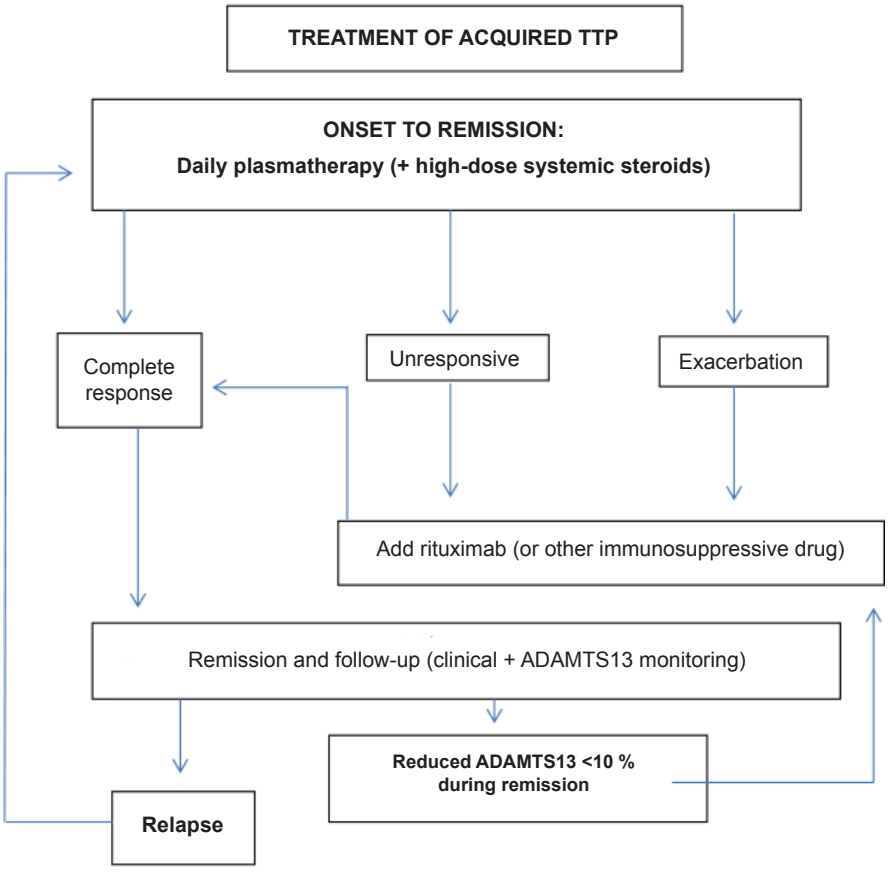
The differential diagnosis of TTP should rule out other thrombotic microangiopathies, such as hemolytic uremic syndrome, hemolytic anemia induced by drugs or infections, complement-mediated thrombotic microangiopathy, hereditary disorders of vitamin B metabolism, and other autoimmune diseases, such as systemic lupus erythematosus.

Treatment is an emergency, and early treatment initiation modifies the prognosis and long-term course. The first-line treatment is plasmatherapy and high-dose corticosteroids (prednisone 1 mg/kg/day or methylprednisolone pulses 30 mg/kg).[1] Before the use of plasmatherapy, mortality in patients with acquired TTP was 90%,[5] so it is necessary to start treatment in any patient with microangiopathic hemolytic anemia without another cause that justifies it. If it is not possible to administer plasmatherapy, infusion of 25–30 mL/kg of fresh frozen plasma should be started until referring the patient to an institution where adequate treatment can be guaranteed.[1]

Once treatment has been started, the course of TTP should be assessed periodically, considering a good response when platelet count increases to 150 000/µL and remains stable for 2 consecutive days, LDH value returns to normal, and neurological symptoms improve or remain stable.[1]

In the absence of a response to first-line measures, alternative therapies should be considered. Rituximab, an anti-CD20 monoclonal antibody, has been successfully used in refractory

Figure 1. Treatment of acquired thrombotic thrombocytopenic



Source: Joly BS, Coppo P, Veyradier A. Pediatric thrombotic thrombocytopenic purpura. *Eur J Haematol*. 2018;101(4):425-34.

and relapsed TTP, with a response rate of 87% and 100%, respectively.[1] Our patient did not show a sustained favorable response over time; therefore, after the initial treatment, she required weekly rituximab, with a good lab test response (*Figure 1*).

To conclude, acquired TTP is a rare disease, with a high mortality and a high risk of sequelae if treatment is not initiated in a timely manner. In the presence of microangiopathic hemolytic anemia and thrombocytopenia with no other cause, treatment should be initiated immediately. ■

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