Thrombotic thrombocytopenic purpura at presentation of juvenile systemic lupus erythematosus patients

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ABSTRACT

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening hematological abnormality characterized by thrombocytopenia and microangiopathic hemolytic anemia, with neurological abnormalities and/or renal disease. TTP has been rarely reported in juvenile systemic lupus erythematosus (JSLE) patients and, to our knowledge, its prevalence in a paediatric lupus population has not been studied. Therefore, from January 1983 to December 2010, we reviewed the charts of 5,508 patients followed-up at the Paediatric Rheumatology Unit of our university hospital. We identified 279 (5.1%) JSLE cases that met the American College of Rheumatology classification criteria. Two (0.7%) of them had TTP, both at JSLE onset, and were described herein. Both patients had fever, microangiopathic hemolytic anemia (with schistocytes in blood smears), and thrombocytopenia. The male patient had hemiparesis and proteinuria and the female patient had persistent headache and hematuria. Both were treated with intravenous methylprednisolone and courses of plasma exchange therapy at TTP diagnosis. After treatment, TTP did not recur and their hematocrit, platelet count, and lactic dehydrogenase remained normal. In conclusion, TTP is a rare and severe manifestation at JSLE onset. The case reports reinforce the importance of early diagnosis and early aggressive treatment for patients with TTP, due to its high morbidity.

Keywords: thrombotic thrombocytopenic purpura, systemic lupus erythematosus, child, plasmapheresis.

INTRODUCTION

Juvenile systemic lupus erythematosus (JSLE) is the prototype of autoimmune disease and may affect multiple organs and systems. Hematologic abnormalities, such as anemia, leukopenia, thrombocytopenia, and clotting defects, are well-known characteristics of this disease.[1]

Thrombotic thrombocytopenic purpura (TTP) is a rare and life-threatening disease. This hematological disorder is characterized by thrombocytopenia, microangiopathic hemolytic anemia, and neurological and/or renal abnormalities.[2–5] Remarkably, it is a microvascular occlusive disorder, with fragmented blood cells and schistocytes in the peripheral blood.[3]

TTP has been rarely reported in JSLE patients.[2–9] This manifestation may occur before lupus diagnosis[2], at presentation,[3,4,6–8] or during the course of the disease.[5,9] However, to our knowledge, the prevalence of this severe manifestation in paediatric lupus population has not been studied.

Therefore, we reviewed our data from January 1983 to December 2010 and included the 5,508 patients of Paediatric Rheumatology Unit, Instituto da Criança, Faculdade de Medicina, Universidade de São Paulo. We identified 279

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(5.1%) cases that met the American College of Rheumatology (ACR)[10] classification criteria for JSLE. Two (0.7%) of them had TTP at presentation of JSLE and were described herein. These case reports were approved by the Local Ethics Committee of our University Hospital.

CASE REPORTS

Case 1

A 10.5 year-old boy had a diffuse petechial rash, oral and nasal spontaneous bleeding, macroscopic hematuria, and hematemesis, in conjunction with high fever for 15 days. Then, the patient had seizures and was hospitalized in our service due to right proportional hemiparesis and dysarthria secondary to stroke on left frontal area. He also had anorexia, photosensitivity, malar and palmar erythema, arthralgia, and hepatomegaly. At that moment, laboratory exams revealed hemoglobin 5.7 g/L, hematocrit 17%, reticulocytes 13%, white blood cell (WBC) count 4,800/mm³ (64% neutrophils, 31% lymphocytes, 2% eosinophils, and 3% monocytes), platelets 8,000/mm³, lactic dehydrogenase (LDH) 4,069 U/L (normal 141–231), negative direct Coombs test, D-dimer 4,632 ng/mL (normal < 500), C-reactive protein (CRP) 13.5 mg/dL (normal < 5), urinalysis with 102,000 erythrocytes and granular casts, urea 40 mg/dL, creatinine 0.45 mg/dL, proteinuria 1.35 g/day, aspartate aminotransferase (AST) 191 IU/L (normal 10–36), alanine aminotransferase (ALT) 50 IU/L (normal 24–49), gamma-glutamyl transpeptidase (GGT) 49 g/dL (normal 14–26), total bilirubin 1.94 mg/dL (normal 0–1), indirect bilirubin 1.37 mg/dL (normal 0.1–1), fibrinogen 241 mg/dL (normal 220–496), normal clotting test, albumin 3.7 g/dL (normal 3.8–5.6), haptoglobin 75 mg/dL (normal 30–200), C3 140 mg/dL (normal 67–149), C4 28 mg/dL (normal 10–38), and ferritin 3,807 mg/mL (normal 36–311). The blood smears showed microangiopathic anemia, with presence of several schistocytes. The von Willebrand factor was 316% (normal 60%–150%). An auto-antibodies analysis revealed positive antinuclear antibodies (ANA) 1/160 (speckled pattern), IgG anticardiolipin 25 GPL, IgM anticardiolipin 7 MPL, and negative anti-double stranded DNA (anti-dsDNA), lupus anticoagulant and anti-Sm antibodies. The carotid ultrasonography was normal and the brain computer tomography evidenced an ischemic brain vascular accident on the left frontal area. Therefore, TTP and JSLE were diagnosed. At that moment, the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K) score was 32.[11] The patient was treated with three intravenous methylprednisolone pulses followed by prednisone (60 mg/day), nine sequential courses of plasma exchange therapy and chloroquine. After that his hematocrit, platelet count and LDH remained normal, and without evidence of antiphospholipid antibodies. However, he had persistent neurological sequelae with hemiparesis and TTP remission for a period of 13 months.

Case 2

A 10.4 year-old girl had pale skin, petechial rash, haematomas, epistaxis, fever, alopecia, vomiting, severe and persistent headache, and arthritis in knees for 10 days. She was hospitalized, and her laboratory exams revealed hemoglobin 6.4 g/L, hematocrit 19%, reticulocytes 18%, WBC count 6,300/mm³ (79% neutrophils, 17% lymphocytes, 0% eosinophils, and 4% monocytes), platelets 10,000/mm³, LDH 2,700 U/L, negative direct Coombs test, D-dimer 1,611 ng/mL, CRP 1.2 mg/dL, urinalysis with 42,000 erythrocytes, urea 53 mg/dL, creatinine 0.48 mg/dL, proteinuria 0.24 g/day, haptoglobin 8 mg/dL, AST 171 IU/L, ALT 212 IU/L, total bilirubin 2.08 mg/dL, indirect bilirubin 1.79 mg/dL, fibrinogen 53 mg/dL, normal clotting test, albumin 3.2 g/dL, ferritin 500 mg/mL, lipase 290 mg/dL (normal 145–226), C3 138 mg/dL, and C4 12 mg/dL. Blood smears showed microangiopathic anemia with several schistocytes. The von Willebrand factor-cleaving protease (ADAMTS-13) activity was < 1% (normal > 5%). Brain computer tomography and echocardiogram were normal. Immunological tests revealed positive ANA 1:1280 (speckled pattern), anti-Sm, anti-RNP and IgM anticardiolipin (17 MPL), being negative for other serum antibodies: anti-dsDNA, anti-Ro, anti-La, IgG anticardiolipin, lupus anticoagulant, anti-nucleosome, and anti-ribosomal P antibodies. Therefore, TTP and JSLE were diagnosed. At that moment, the SLEDAI-2K score was 17.[11] The patient was treated with three intravenous methylprednisolone pulses followed by prednisone (60 mg/day) and 18 sequential courses of plasma exchange therapy. After that, she was treated with azathioprine and chloroquine. Prednisone dose was progressively tapered to 15 mg/day. After six months, her hematocrit, platelet count and LDH remained normal with TTP remission, and without evidence of antiphospholipid antibodies.

DISCUSSION

To our knowledge, this is the first study that evaluated the prevalence of TTP in a large population of JSLE in a tertiary Paediatric University Hospital and evidenced a rare prevalence of this hematological abnormality at lupus onset.

TTP is a severe hematological disorder which is characterized by the involvement of the central nervous system

microangiopathic hemolytic anemia, and thrombocytopenia.[4,5,9] Hemolysis with detection of elevated reticulocyte count and/or decrease of haptoglobin, and elevated LDH levels have also be observed in patients with TTP,[7,8,9] as detected in our cases. The Coombs test is generally negative, as also evidenced herein.[2]

Of note, the TTP involvements are similar to lupus manifestations, especially neuropsychiatric and renal involvements.[2] Recently the two hematological abnormalities (platelets counts lower than 100,000/mm^3 concomitantly with microangiopathic hemolytic anemia with presence of schistocytes in peripheral blood smears) were considered essential to TTP diagnosis, with exclusion of other diseases, such as autoimmune hemolytic anemia, disseminated intravascular coagulation, cancer, drug toxicity, and malignant hypertension.[12]

In addition, TTP is a microvascular occlusive disorder, that may lead to microthrombi and ischemia, particularly in brain and renal glomeruli.[2,9] In fact, neurological features (such as headache,[2,6] seizures, hemiparesis,[2] and transitory mental confusion[4]) and renal abnormalities[2,9] are common clinical manifestations of TTP. Importantly, to our information, the occurrence of ischemic brain vascular accident with neurological sequelae, as evidenced in one of our cases, has not been previously described in paediatric lupus population.

The pathogenesis of TTP is unknown. This abnormality may occur due to some genetic deficiency[13] or due to the acquired form, which is a result of the presence of autoantibody against the protease that cleaves the von Willebrand factor, named ADAMTS-13 (a disintegrin and metalloprotease with a thrombospondin type 1 motifs 13).[9] In fact, the reduction of this protease releases the von Willebrand factor multimers and determines thrombi formation in this disease.[13]

This hematological abnormality can be associated with autoimmune disease, in both adult[6] and paediatric lupus.[2,3] Indeed, TTP associated with JSLE and lupus nephritis[9] has been rarely described, affecting mainly females[2–4,6,9] at disease onset.[3,4,6–8]

The most important differential diagnosis of TTP in lupus patients are: macrophage activation syndrome,[14] disseminated intravascular coagulation, Evans syndrome (autoimmune hemolytic anemia and idiopathic thrombocytopenic purpura),[9] antiphospholipid antibody syndrome, eclampsia, and hemolytic uremic syndrome.[12] In the latter, fever is rarely observed and renal abnormalities are more severe when compared to TTP.[9]

The treatment of TTP in JSLE patients consists of concomitant plasmapheresis and glucocorticoids therapy[2,9] until clinical and laboratory improvement, mainly the normalization of hematocrit, platelets' count and LDH[9], as evidenced in our two cases. The mean number of therapeutic plasma exchange sessions reported in the literature varied from 5–14.[4,6,7,9] Other treatments to refractory or severe TTP associated with lupus included immunosuppressive drugs, such as cyclophosphamide and mycophenolate mofetil,[5] intravenous immunoglobulin[8] and rituximab.[9]

Regarding the outcome, death due to multiple organ failure[8] and reminiscent occasional headache[2] have also been previously described. Our case 1 had a relevant ischemic brain vascular accident with persistent neurological sequelae.

The possible limitation for this study could be the retrospective medical records analysis, and this haematological manifestation could be underestimated. A future prospective and multicentre study is necessary.

In conclusion, TTP is a rare and severe manifestation at lupus onset. The case reports reinforce the importance of early diagnosis and early aggressive treatment for patients with TTP due to high morbidity.

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