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■ Case report ■

Thrombotic thrombocytopenic purpura with decreased level of ADAMTS-13 activity and increased level of ADAMTS-13 inhibitor in an adolescent

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= Abstract =

Thrombotic thrombocytopenic purpura (TTP) is a thrombotic microangiopathy characterized by endothelial cell damage, resulting in microangiopathic hemolytic anemia, thrombocytopenia, and various degrees of neurological and renal impairment caused by microvascular thrombi. It is rare in children and frequently follows a fatal course. TTP is divided into 2 types: one is inherited and associated with ADAMTS-13 gene mutations and the other is acquired and associated with anti-ADAMTS-13 autoantibodies. The measurement of ADAMTS-13 activity in plasma, identification of ADAMTS-13 circulating inhibitor, anti-ADAMTS-13 IgG, and ADAMTS-13 gene sequencing are crucial to the diagnosis of TTP. Plasma exchanges are the first-line treatment for acquired TTP, combined with steroids and immunosuppressive drugs. Here, we describe the case of an adolescent patient with TTP, confirmed by decreased level of ADAMTS-13 activity and an increased level of ADAMTS-13 inhibitor, who was successfully treated by plasma exchanges. (Korean J Pediatr 2010;53:428-431)

Key Words : Purpura, Thrombotic thrombocytopenic, ADAMTS13 protein

Introduction

Significant progress in the understanding of the two thrombotic microangiopathies (TMA), thrombotic thrombocytopenic purpura (TTP) and hemolytic uremic syndrome (HUS) has been made over the past decade[1]. Both diseases are due to disseminated thrombi in the microcirculation. Patients present with microangiopathic hemolytic anemia (MAHA) due to the mechanical damage of erythrocytes in the partially occluded microcirculation, and thrombocytopenia due to platelet consumption within the thrombi[2]. These two disorders are distinguished mainly on clinical grounds: HUS is associated with renal insufficiency as the predominant symptom, while TTP with central nervous system (CNS) symptoms[3]. However, there are frequently overlapping clinical symptoms. Immunohistological studies demonstrate abundant von Willebrand factor (vWF) but little fibrin in the thrombotic lesions of TTP, but the opposite is observed with HUS[3, 4]. In addition, TTP but not HUS is associated with a deficiency in vWF cleaving protease[5]. The principal function of a desintegrin and metalloprotease with a thrombospondin type 1 repeats 13 (ADAMTS-13) involves the cleavage of unusually large forms of vWF (ULVWF), thereby preventing ULVWF multimers from accumulating in the circulation; platelet aggregation in TTP is thought to be the consequence of the binding of platelets from ULVWF remaining in the circulation[6]. Plasma exchange, the first line of treatment for TTP, has significantly decreased the mortality from 80-90% to 10-20%[7]. Additional treatment modalities such as corticosteroids, splenectomy, rituximab, and antiplatelet agents have been used, although their benefit is less clear. Most cases of TTP present in adults; fewer than 10% of the cases occur in the pediatric and adolescent age groups[8]. Here we report a case of TTP in an adolescent with a low level of ADAMTS-

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13 activity and high ADAMTS-13 inhibitor, who showed a rapid and marked improvement with plasma exchanges.

Case report

A 12-year-old girl presented with a progressive headache, dysarthria and paresthesia of the right arm and face. The headache continued for 2 weeks and paresthesia developed the morning of presentation. The patient had gastroenteritis symptoms for 2 weeks; there was no history of special food intake. There was no history of previous medical problems and no renal impairment. She complained numbness of the face and right arm. Her temperature was 36.2℃, blood pressure was 110/70 mmHg, and heart rate was 90 beats/min. A complete blood count showed: white blood cell count 4,900/μL (neutrophils 38%, lymphocytes 45%, monocytes 5%, eosinophils 1%); Hgb 4.9 g/dL (reticulocyte count 16.8%, corrected reticulocyte count 6.2%, reticulocyte production index 2.5); platelet 7,000/μL. The peripheral blood smear showed poikilocytosis, schistocytes and nucleated red cells suggestive of MAHA (Fig. 1). Bone marrow aspiration showed erythroid hyperplasia and an increase of megakaryocytes (Fig. 2). Hemolytic markers were as follows: total bilirubin 2.4 mg/dL, direct bilirubin 0.3 mg/dL, lactate dehydrogenase (LDH) 1,597 U/L (normal, 120-330), haptoglobin 7.13 mg/dL (normal, 22-164), and a negative anti-globulin test. The renal function and coagulation profiles were normal. The autoantibody analysis was positive: antinuclear antibodies (ANA) mixed 2+ (homogeneous and nucleolar patterns), anti-Ro and anti-Ro52 antibodies. The serum complements were normal: C3, 98.7 mg/dL (normal, 83-177); C4, 17.9 mg/dL (normal, 15-45); CH50, 42 mg/dL (normal, 23-46). The other autoantibodies and lupus-associated laboratory findings were negative. The urinalysis revealed no proteinuria or hematuria. Urinary protein excretion was normal (10 mg/ 24hr, 0.28 mg/m^2/hr). The stool culture for *E.coli* O157:H7 was negative. The brain MRI with enhancement, MR angiography and diffusion-weighted images showed no abnormal findings. The ultrasound of the abdomen revealed mild splenomegaly. The diagnosis of TTP was made based on the symptoms and laboratory findings. The patient was treated with plasma exchanges for 7 consecutive days from the second to the eighth day after admission, using the CS-3000 (volume, 40 mL/kg). In addition, the patient was treated with two doses of intravenous methylprednisolone, 1 mg/kg/day from the second day of admission. Thereafter she was treated with prednisolone (1 mg/kg/day) tapered over 2 wks. Seven days after the plasma exchanges, the patient had a full hematological and neurological recovery. A serum sample was sent to the Blood center of Wisconsin. It showed a significant decreased level of ADAMTS-13 activity (<5 %, reference range >66%) with an increase of ADAMTS-13 inhibitor (0.9, reference range <0.5) suggestive of acquired ADAMTS-13 deficiency.

Three months later a low platelet count (22,000/μL) developed without hemolytic evidence; the platelet count recovered without treatment. The peripheral blood smear showed bicytopenia without abnormal cells. The serum ANA

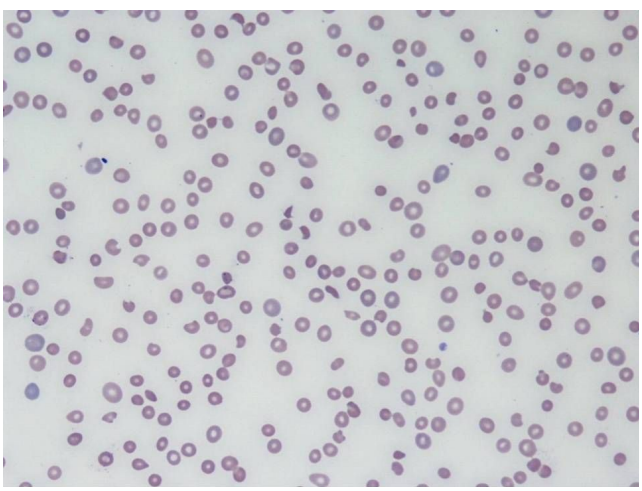

Fig. 1. Peripheral blood smear shows spherocytes, fragmented RBC, nucleated RBC, and thrombocytopenia, suggestive of microangiopathic hemolytic anemia.

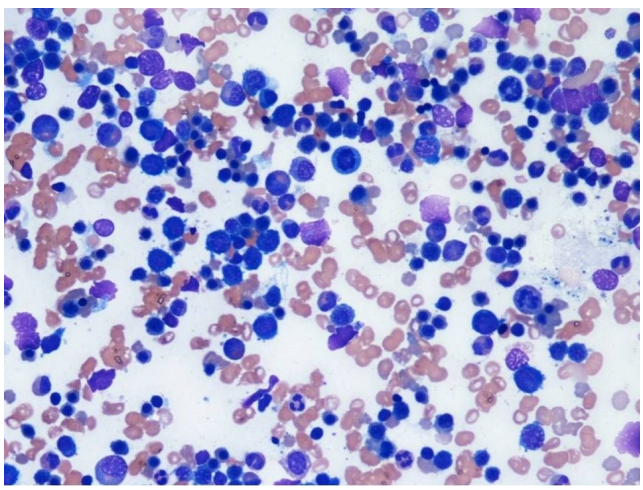

Fig. 2. Bone marrow aspirates show marked erythroid hyperplasia.

titer was 1:400. The indirect Coombs' test was positive, and the direct Coombs' test was weakly positive. Eighteen months later, the patient developed a persistent fever and arthralgia involving multiple areas. The urinalysis showed trace proteinuria. The serum ANA titer was increased compared to the initial level, and the C3 and C4 levels were markedly decreased. Autoantibodies (anti-double-stranded DNA, anti-Ro, anti-Ro52, anti-nucleosome, anti-histone antibodies) and the LE cell test were positive. The patient was diagnosed with systemic lupus erythematous (SLE) with an increased SLE disease activity index of 15 (active >8), and treated with intravenous methylprednisolone for 3 days. Three days later, the symptoms improved, and she continues to have normal hematological and neurological findings on hydroxychloroquine, azathioprine and prednisolone during 6 months of follow-up.

Discussion

TTP is a life-threatening disorder characterized by MAHA and thrombocytopenia as a result of microvascular platelet clumping often accompanied by ischemic organ dysfunctions manifesting as neurological abnormalities or renal insufficiency, and fever. TTP was first described by Moscowitz in 1924; it is a rare condition with an incidence of 3.7 per million in the United States; fewer than 10% of cases occur in children[8]. TTP may develop as an idiopathic disorder or secondary to drugs (such as cyclosporine), infection, malignancy, autoimmune disease or bone marrow transplantation[9-12].

In the 1980's the plasma of patients with chronic relapsing TTP was found to have large multimers of vWF, unlike normal plasma[13]. Since then many investigators have shown that a metalloprotease is required to cleave these large multimers of vWF and this protease is consistently deficient in the plasma of patients with TTP[14]. Normally, vWF circulates in plasma as multimers that allow platelets to adhere to vascular surfaces. When vWF is initially released from endothelial cells, it exists as large multimers, that are more adhesive for platelets than normal. These large multimers are normally cleaved into smaller units by circulating vWF-cleaving metalloprotease, named as ADAMTS-13[2]. In the absence of ADAMTS-13, the large multimers of vWF will eventually become fully unfolded by shear stress to become elongated forms, creating an environment favoring vWF-platelet binding, platelet aggregation, and microvascular thrombosis. Decrease of ADAMTS-13 levels below 10% of normal results in clinically apparent thrombosis and thrombocytopenia[15]. Two types of ADAMTS-13 deficiency have been recognized: the acquired form is caused by circulating autoantibodies, mainly IgG which neutralize ADAMTS-13 activity[16]; a hereditary form, the Upshaw-Schulman syndrome, is due to mutations of the ADAMTS-13 gene resulting in severe deficiency of the ADAMTS-13. Our patient had decreased ADAMTS-13 activity and increased inhibitor, compatible with the diagnosis of an acquired form of TTP.

TTP is associated with a very high mortality rate (>90 %) without treatment. Plasma exchange has been shown to be effective treatment for reducing the mortality[7], which has been attributed to the removal of ADAMTS-13 autoantibodies and the replacement of ADAMTS-13 activity. The American Association of Blood Banks, the American Society for Apheresis, and the British Committee for Standards in Haematology recommend daily plasma exchange with the replacement of 1.0 to 1.5 times the predicted plasma volume of the patient as standard therapy for TTP[9]. Our patient was successfully treated by daily plasma exchange. Corticosteroids are widely used in addition to plasma exchange; however, their efficacy is less clear. In some patients with poor disease control, immunosuppressive therapy is often prescribed in addition to plasma exchange[17].

TTP has been reported in association with SLE. With regard to the sequence of events, TTP may precede or follow SLE, or they may develop concurrently. SLE and TTP share similar clinical symptoms and both have low levels of ADAMTS-13 suggesting a possible common pathway for this disease association[18]. However, the effective treatments for these disorders are different; plasma exchange is the most effective therapy for TTP, whereas its efficacy for SLE is controversial[19]. In SLE-related TTP, standard immunosuppression should be given to control the SLE activity, and patients should also receive plasmapheresis with fresh frozen plasma. The mortality rate may differ according to the sequence of development: the mortality rate of TTP preceding SLE has been reported to be 0%, whereas in patients with simultaneous TTP and SLE it was 33.3%, and in those where SLE preceded TTP it was 40.5 %[20]. Our patient showed a typical TTP followed by SLE, and had a good response to the initial plasmaphereses.

TTP is rare in children and adolescents, and is often

difficult to distinguish from atypical forms of HUS. Measurement of ADAMTS-13 and its inhibitor is often necessary to confirm the diagnosis of TTP. The diagnosis of TTP should be considered in any child presenting with thrombocytopenia, especially in association with MAHA.

한 글 요 약

청소년기에 발생한 ADAMTS-13 활성도 저하와 항체 양성을 보인 혈전저혈소판혈증자색반병 1례

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양은미 · 한동균 · 백희조
신명근* · 김영옥 · 국 훈 · 황태주

혈전저혈소판혈증자색반병은 혈관 내피 세포 손상에 의한 혈전미세혈관병증으로 미세혈관병용혈빈혈, 혈소판감소증과 미세혈관 혈전에 의한 다양한 정도의 신경 및 신장 침범을 보인다. 이는 소아에서는 드물게 발생하며 종종 치명적인 경과를 보일 수 있다. 혈전저혈소판혈증자색반병은 ADAMTS-13 유전자 변이에 의한 결핍을 보인 선천성 그리고 ADAMTS-13 항체들에 의해 발생하는 후천성인 경우로 분류할 수 있다. ADAMTS-13 활성도 및 순환 항체검사, 그리고 항 ADAMTS-13 IgG와 ADAMTS-13 염기서열분석은 이 질환의 진단에 중요하다. 후천성 환자에게는 혈장교환술이 주된 치료이며, 스테로이드제나 면역억제제도 사용된다. 저자들은 청소년기에 발생한 ADAMTS-13 활성도 저하와 항체 양성을 보인 후천성 혈전저혈소판혈증자색반병을 진단 후 혈장교환술로 효과적으로 치료하였던 1례를 보고하는 바이다.

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