Concurrent Atypical Hemolytic Uremic Syndrome and Autoimmune Hemolytic Anemia: a case report

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Case Report

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Abstract

Background: Atypical hemolytic uremic syndrome (aHUS) is a life-threatening and scarce disorder characterized by acute renal failure and disease, non-immune microangiopathic hemolytic anemia and thrombocytopenia, leading to end-stage renal failure or death, and consequently maybe accompanying by extra renal manifestations.

Case report: We reported aHUS accompanied by autoimmune hemolytic anemia in a 40-month-old girl with chief complaint of fever and tea-colored urine starting on the morning of the same day. The aHUS was diagnosed based on patient's clinical manifestations, increased serum creatinine, hemolytic anemia, thrombocytopenia and no history of diarrheal disease.

Conclusions: Since the atypical hemolytic–uremic syndrome has a poor prognosis, its death rates is as high as 25% and it progresses to end-stage renal disease in half of the patients. It seems that an upper respiratory infection caused both autoimmune hemolytic anemia (AIHA) and aHUS in our patient.

Key Words: Atypical Hemolytic-Uremic Syndrome, Autoimmune Hemolytic Anemia, Child

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Introduction

Hemolytic uremic syndrome (HUS) comprises of thrombocytopenia, microangiopathic hemolytic anemia (MAHA) and acute kidney injury. HUS can be typical or atypical (aHUS): the typical one caused by Shiga toxin-producing E. coli (STEC) and atypical one caused by dysregulated complement system activation or secondary HUS so that some conditions and diseases such as autoimmunity, transplantation, some drugs, pregnancy or cancer can be coexisted [1]. Unlike typical HUS, the aHUS is a heterogeneous and scarce disorder characterized by acute renal failure, non-immune microangiopathic hemolytic anemia and thrombocytopenia as well as is not usually preceded by diarrhea [2.3]. The aHUS is mainly triggered by a genetic or acquired dysregulation of the complement system and this process is sometimes caused by infections, certain drugs and malignancies [1, 4]. The common pathogenetic features in secondary HUS, aHUS and STEC HUS are concurrent damage to intravascular hemolysis, endothelial cells and activation of platelets, resulting in a formation of microthrombi, tissue damage and procoagulative state [1]. The aHUS firstly affects the renal microvasculature, leading to hypertension, hematuria, increased creatinine, edema, and electrolyte imbalance in both children and adults [3, 5]. For the prognosis is usually unfavorable, 65% of patients die or have renal damage requiring dialysis or transplantation despite supportive care [6]. In this article, a 40-month-old girl with aHUS accompanied by concurrent autoimmune hemolytic anemia (AIHA) is reported.

Case Report

A 40-month-old girl as a second-born child of nonconsanguineous parents was referred to the Emergency Department of Bahrami Children Hospital with chief complaint of fever and tea-colored urine starting on the morning of the same day. She had signs of upper respiratory infection such as dry cough for three days prior to presentation.

On physical examination, the child was conscious and her level of consciousness was normal. She had a blood pressure of 100/60 mmHg, pulse rate of 70/min, respiratory rate of 20/min and axillary temperature of 38°C. She had mild edema of the eyelids and upper and lower limbs. Lung auscultation was normal. No petechiae, purpura and hepatosplenomegaly were detected. The lymph nodes were intact. There was no history of diarrhea during the days prior to admission.

The results of laboratory tests at the time of admission were as follows: WBC count 15900/mm3, hemoglobin 11.4 gr/dl, hematocrit 34%, platelet count 17000/mm3, C-reactive protein (CRP) 22 mg/l, serum urea 59 mg/dl and serum creatinine 1.1 mg/dl. Peripheral blood smear showed helmet cells and schistocytes but no rouleaux formation and polychromasia were found.

Analysis of the urine sample revealed hematuria and proteinuria (red blood cells (RBCs) (6-8/HPF), white blood cells (10-12/HPF), protein (4+), retic (1/3) and granular casts [1, 3]). Random urine protein to creatinine ratio was 62/30.5. No dysmorphic RBCs or cellular casts were reported.

Renal Doppler ultrasound indicated parenchymal involvement of both kidneys. An echocardiogram revealed no significant pathologic finding. Bone marrow aspiration represented a hypercellular marrow with increased megakaryocytes, increased erythroid series, normal bone marrow flow cytometry. Blood culture was negative.

Based on patient's clinical manifestations, increased serum creatinine, hemolytic anemia, thrombocytopenia, no history of diarrheal disease and normal chest x-ray, aHUS was suspected. Further evaluation illustrated normal levels of I, B and H, ADAMTS13- Activity and ADAMTS B -1NH and low levels of C3 and CD46. The diagnosis of these low levels was confirmed and plasma exchange with a daily dose of 20 ml/kg of fresh frozen plasma (FFP) was initiated.

Despite plasma exchange, the patient gradually developed oliguria, generalized edema, tense ascites and loss of consciousness during hemodialysis. Moreover, her hemoglobin level dramatically declined to 3.6 gr/dl. Transfusion of packed RBCs was not possible due to incompatible cross-match. Direct Antiglobulin (DAT) test was positive and AIHA was diagnosed for this girl. Monospecific DAT revealed positive reaction with both anti IgG and anti C3d, and the type of AIHA was warm AIHA. A three-day course of treatment was started for the patient using methylprednisolone pulse and intravenous immunoglobulin (IVIG).

After three sessions of hemodialysis, patient's general status was improved and her urinary output increased to1-1.5 ml/kg/h. Meanwhile, the catheter was removed, and the child developed drowsiness and her O2 saturation was reduced in less than 24 hours. She was diagnosed with pulmonary edema and was subsequently intubated, and finally she underwent respiratory support by mechanical ventilation. Despite the insertion of a peritoneal catheter and immediate peritoneal dialysis, the patient experienced cardiac arrest and expired after unsuccessful attempts of cardiopulmonary resuscitation.

Discussion

Our case was a 40-month-old girl suspected to have aHUS because she developed thrombocytopenia, hemolytic anemia, acute renal failure and following an upper respiratory infection as well as she had no history of diarrhea. Low C3 and CD46 levels and normal ADAMTS13 activity were strongly indicative of aHUS due to the complement overactivation.

The aHUS which is not caused by either streptococci or Shiga toxin producing bacteria constitutes approximately 10% of the hemolytic uremic syndrome.

The HUS is characterized by acute renal failure, thrombocytopenia and microangiopathic hemolytic anemia, and is divided into a) typical or D+ HUS which is more common in children, usually preceded by diarrhea and caused by STEC, and b) aHUS which involves overactivation and dysregulation of the complement system [7, 8].

There are genetic mutations in the proteins of the alternative complement pathway in many aHUS patients [1]. However, the condition is usually triggered by precipitating factors including drugs, infections, pregnancy and autoimmune disorders [2].

In Western countries, aHUS approximately affects 3.3 per million in children and its prognosis is poorer in children than in adults, especially in those with genetic susceptibility [9, 10].

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Despite the initial treatment with FFP, our patient gradually developed oliguria, generalized edema, tense ascites and loss of consciousness during hemodialysis. Based on a recent guideline, the patients who are clinically suspected of having aHUS should receive early plasma exchange and/or plasma infusion [4]. Nevertheless, according to an Italian cohort study, 48% of children and 67% of adults with aHUS died or developed renal failure during the 3-year follow-up after plasma exchange despite the initial favorable response [10, 11].

There are some reports on Streptococcus pneumoniae-associated hemolytic uremic syndrome with positive Coombs test, but our case had no evidence of pneumonia and empyema or any other infections such as meningitis or septicemia [2, 4].

It seems that an upper respiratory tract infection accelerates an antigen-antibody reaction, leading to the AIHA [5].

AIHA is an acquired hemolytic anemia that rarely affects children, results from production of auto-antibodies against RBC surface antigens and is classified as warm or cold based on the temperature at which auto-antibodies react with RBCs [12]. It can be idiopathic or secondary to malignancies, drugs, infections and other autoimmune disorders [13].

In conclusion, in the present case, a rapid decline in hemoglobin level, incompatible crossmatch and positive direct Coombs test resulted in the diagnosis of warm antibody AIHA and subsequent treatment with corticosteroid and IVIG. This process can be stopped by therapeutic complement inhibition in most patients with aHUS, but usually not those with a DGKε mutation and some patients with STEC-HUS or secondary HUS. Therefore, understanding the pathogenesis of the different forms of HUS may prove helpful in clinical practice.

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