

An Unusual Patient with Atypical Hemolytic Uremic Syndrome Who Developed Hemophagocytic Lymphohistiocytosis

Hemofagositik Lenfohistiositoz Gelişen Bir Atipik Hemolitik Üremik Sendrom Olgusu

ABSTRACT

Hemolytic uremic syndrome (HUS) is characterized by the triad of microangiopathic hemolytic anemia, thrombocytopenia and acute renal failure. Atypical HUS is characterized by the absence of antecedent diarrhea, tendency to relapse, a positive family history and poor therapeutic outcome. Here we report an 8-year-old boy who presented with atypical HUS and did not have antecedent diarrhea or infection. He developed prolonged fever unresponsive to broad-spectrum antibiotics with markedly elevated liver enzymes and hepatosplenomegaly. There were phagocytized macrophages in his bone marrow aspiration. Based on these observations and other laboratory findings, he was diagnosed with hemophagocytic lymphohistiocytosis. He was successfully treated with plasma exchanges and low dose oral steroids. To our knowledge, this is the first case of atypical HUS in the literature associated with hemophagocytic lymphohistiocytosis.

KEY WORDS: Hemolytic uremic syndrome, Acute renal failure, Histiocytosis

ÖZ

Hemolitik üremik sendrom (HÜS) mikroanjiyopatik hemolitik anemi, trombositopeni ve akut böbrek yetmezliği ile karakterize bir tablodur. Atipik HÜS'te başlangıçta diare olmayabilir, hastalığın tekrarlama eğilimi vardır, ailede benzer olgular olabilir ve prognoz kötüdür. Burada 8 yaşında atipik HÜS tablosu ile gelen 8 yaşında bir olgu sunuldu. Hastalığın seyrinde belirgin hepatospleneomegali ile birlikte karaciğer enzimlerinde belirgin artış ve geniş spektrumlu antibiyotiklerle düşmeyen ateş tablosu gelişti. Kemik iliğinde fagositoz yapmış makrofajlar görüldü. Diğer laboratuvar bulguları ile birlikte hasta hemofagositik lenfohistiositoz tanısı aldı. Hastaya düşük doz oral steroid tedavisi ile birlikte plazmaferez tedavisi uygulandı. Bu olgu atipik HÜS ve hemofagositik lenfohistiositozun son derece nadir birlikteliğini vurgulamak amacı ile sunuldu.

ANAHTAR SÖZCÜKLER: Hemolitik üremik sendrom, Akut böbrek yetmezliği, Histiositoz

INTRODUCTION

Hemolytic uremic syndrome (HUS) is a clinical syndrome consisting of hemolytic anemia, thrombocytopenia and acute renal insufficiency (1-3). It is the most frequent cause of acute renal failure in childhood (1). It can be divided into two main groups according to the clinical presentation and outcome (1, 4). Classical or diarrhea (+) HUS occurs almost exclusively in childhood and is caused by bacteria releasing shiga-like toxins. The disease starts with signs of enteritis, generally initiated by *Esherichia coli*

strains, mainly O157, and has a good prognosis (2, 3). Atypical HUS or diarrhea (-) HUS may be idiopathic, familial or due to a variety of conditions such as therapeutic drug usage (ovulation inhibitors, immunosuppressive agents), various diseases (malignancies, systemic lupus erythematosus), pregnancy and infections (4, 5). It can occur at any age including newborns and it has a frequently recurrent course and poor renal prognosis (1, 4, 5).

Familial occurrence of atypical HUS may be transmitted in either autosomal

Sare Gülfem AKYÜZ¹
Abdurrahman KARA²
Aysun ÇALTIK YILMAZ¹
Mehmet BÜLBÜL¹
Özlem ERDOĞAN¹
Gülay DEMİRCİN¹
Nilüfer ARDA³

- 1 Dr. Sami Ulus Children's Hospital, Department of Pediatric Nephrology, Ankara, Turkey
- 2 Dışkapı Training Hospital, Department of Pediatric Hematology, Ankara, Turkey
- 3 Dr. Sami Ulus Children's Hospital, Department of Pathology, Ankara, Turkey



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Correspondence Address:

Sare Gülfem AKYÜZ

Dr. Sami Ulus Çocuk Hastanesi, Pediatrik Nefroloji Bölümü, Ankara, Turkey

Phone : +90 312 305 62 57

E-mail : saredr@gmail.com

dominantly or autosomal recessively which is more frequent in children (1-4). In some families, the affected individuals exhibit decreased plasma levels of C3, indicating defective complement control and suggesting a role of complement regulators for the disease process (2, 3). Membrane cofactor protein (MCP=CD46) mutations, factor I deficiency and anti-factor H autoantibodies are also responsible for familial HUS (2, 3, 5).

Extrarenal manifestations of HUS include gastrointestinal symptoms, neurological abnormalities, cardiac, respiratory and hepatic involvement. Mild jaundice is sometimes present at admission and the liver is frequently enlarged (1). This may be due to fluid overload and cardiac failure; but in some patients a hepatitis-like picture is observed with elevated liver enzymes and enlarged tender liver (1, 6). Here we report a patient in whom prolonged fever and hepatic involvement was prominent during the illness and the disease was accompanied with hemophagocytic lymphohistiocytosis.

CASE REPORT

An 8-year-old boy was admitted to the hospital because of vomiting, fever and halitosis. He was previously healthy and had no family history for a known disease. Physical examination revealed a well-developed boy with the weight, height and blood pressure percentages in normal ranges. He was afebrile. He was pale in appearance, had a systolic murmur of 2/6 degree on the mesocardiac area and splenomegaly of 2 cm.

Laboratory examinations showed hemoglobin (Hb): 5.7 g/dl, white blood count (WBC): 18,100/mm³, platelet count: 113,000/mm³, and reticulocyte count: 9%. Peripheral blood smear revealed predominant polymorphonuclear leukocytes with schizocytes,

spherocytes, normoblasts and fragmented erythrocytes (Figure 1). Direct and indirect Coombs tests were negative. Haptoglobin was <5.38 mg/dl (N: 36-95 mg/dl), and lactate dehydrogenase was 1402 U/L (N:150-500 IU/L). Erythrocyte sedimentation rate was 130 mm/h; C- reactive protein 7.3 mg/L, prothrombin time (PT) 10.3 sec, and partial thromboplastin time (PTT) was 25 sec. Blood urea nitrogen (BUN) was 97 mg/dl, serum creatinine 3.42 mg/dl, uric acid 16.4mg/dl and plasma aspartate transaminase was 100U/L. Arterial blood gases were normal and urinalysis revealed (+) proteinuria with eumorphic red blood cells and granular and red blood cell casts. Plasma C3 level was initially low (0.67 g/L), which returned to normal levels during the following examinations and C4 level was normal (0.226 g/L). Antinuclear antibody (ANA), anti-ds DNA, p- and c-anti neutrophil cytoplasmic antibodies (ANCA) were negative. Chest radiograph and echocardiography were normal. Abdominal ultrasonography revealed splenomegaly and hyperechogenic kidneys with normal size.

A diagnosis of haemolytic uremic syndrome was made on the basis of microangiopathic haemolytic anemia, thrombocytopenia and acute renal failure. Besides supportive therapy for renal failure, he was started on fresh frozen plasma transfusions (10 cc/kg twice daily) and erythrocyte transfusion when necessary. He was clinically well for the first five days of the treatment and serum creatinine level decreased to 2.23 mg/dl. On the sixth day of his admission, he developed a fever with an elevation of CRP and ESR. After samples for bacterial cultures and serological tests for bacterial, viral and parasitic infections were obtained, broad spectrum antibiotics were started. Despite the antibiotic therapy, his fever persisted on the fifteenth day and his renal functions deteriorated (serum creatinine: 5.51 mg/dl; BUN: 124

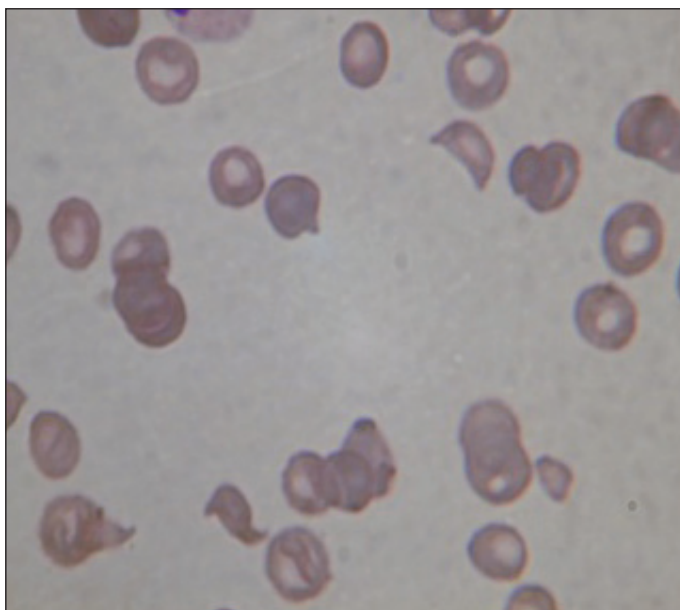


Figure 1: Schizocytes on peripheral smear.

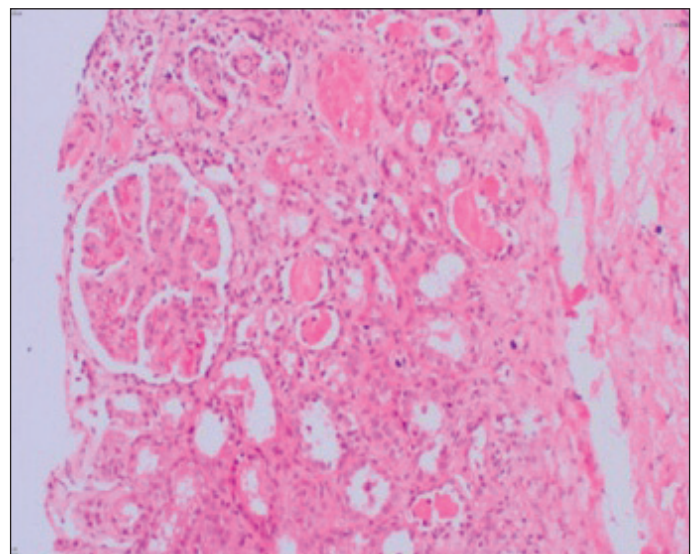


Figure 2: Renal biopsy specimen: the lumen of the capillaries are full of erythrocytes in the glomeruli; there is intimal thickening in the adjacent intimal wall. There is also thyroidisation in the tubuli.

Table I: Laboratory parameters during follow up.

| | Admission | Before plasma exchange | On the second week of therapy |
|------------------------------|-----------|------------------------|-------------------------------|
| Hgb (mg/dl) | 5.7 | 8.1 | 9.6 |
| PLT (/mm ³) | 113000 | 70000 | 166000 |
| WBC (/mm ³) | 18100 | 1600 | 6400 |
| BUN (mg/dl) | 97 | 75 | 50 |
| Creatinine (mg/dl) | 3.42 | 4.1 | 1.64 |
| PT (second) | 11.8 | 11.9 | 13 |
| APTT (seconds) | 17.8 | 69 | 24 |
| AST (IU/L) | 100 | 689 | 112 |
| ALT (IU/L) | 24 | 464 | 110 |
| T. bilirubin (mg/dl) | 1.5 | 16.7 | 1.7 |
| Conjugated bilirubin (mg/dl) | 0.5 | 5.9 | 0.9 |

mg/dl) and hepatic transaminase levels increased (AST: 309 U/L, ALT: 359 U/l; GGT: 624 U/l) with elevation of alkaline phosphatase to 616U/L, total plasma bilirubin to 2.4 mg/dl, conjugated bilirubin to 1.3 mg/dl and PTT to 69 sec. His PT was normal (11. sec). He also developed pancytopenia with Hb: 7 mg/dl, WBC: 3500/mm³, and platelet count: 99.000/mm³, but his bone marrow aspiration was normal. Because of the prolonged PTT, renal biopsy could not be performed. He was started on hemodialysis and fresh frozen plasma infusions were continued. On the twenty-fifth day of admission, he was treated with GM-CSH because of his persistent fever and leukopenia (WBC: 600 /mm³). However on the twenty-eighth day, his clinical state worsened more with further enlargement of liver and spleen, progressive jaundice and persistence of fever, pancytopenia (hgb: 8.1 mg/dl, PLT: 70.000 /mm³, WBC: 1600 /mm³), elevated liver enzymes (AST: 689 IU/L, ALT: 464 IU/L, GGT: 758 U/L), and elevated serum bilirubin levels (t. bil: 16.7 mg/dl, conjugated bilirubin: 5.9 mg/dl). Serum ferritin (4682 ng/ml), fibrinogen (575 mg/dl), cholesterol (465 mg/dl) and triglyceride (684 mg/dl) levels increased with prolongation of PT and PTT. (Table I) All bacterial cultures including bone marrow aspiration and serological tests for various bacterial, viral and parasitic infections were found to be negative.

Bone marrow aspiration was performed again and revealed four macrophages that phagocytized erythrocytes. According to these laboratory and clinical findings, he was diagnosed with hemophagocytic lymphohistiocytosis and plasma exchange therapy was initiated with three sessions in the first week, two sessions in the second week and once in the third week. On the second week of exchange therapy, his clinical picture improved and laboratory parameters returned almost to normal ranges. Renal biopsy was performed demonstrating findings compatible with HUS (Figure 2). After six sessions of plasma exchange

therapy, his complete blood count, renal functions and bilirubin levels were normal with slightly elevated AST and ALT levels and he was discharged with prednisolone therapy at a dose of 1 mg/kg/day.

DISCUSSION

Hemolytic uremic syndrome (HUS) is a common cause of acute renal failure in children, leading to substantial morbidity and mortality (2, 4, 9). The disease shares similar clinical features and pathology with thrombotic thrombocytopenic purpura (TTP) (1, 8). The underlying pathology is thrombotic microangiopathy (TMA), a microvascular occlusive disorder of capillaries, arterioles and less frequently, arteries. In TTP, microvascular aggregation causes ischemic lesions mainly in the brain, whereas in HUS platelet-fibrin thrombi mostly affect the kidney (1). Typical HUS, which represents 90% of cases, occurs in infants and young children and has a good outcome. In contrast, atypical HUS occurs at any age including the newborn and has a frequently recurrent course and a poor renal prognosis (2, 3 5). It may be idiopathic, or familial, or may be associated with many etiological factors. These factors include different bacterial, viral or parasitic infections, chemotherapeutic agents especially anti-cancer drugs and total body irradiation (1). It is also associated with systemic diseases such as systemic lupus erythematosus, metabolic disorders such as cobalamin C disease, pregnancy, malignancies, organ transplantations and rarely primary or secondary glomerulonephritis (1, 11).

Although most cases are sporadic, familial cases of atypical HUS have been described. In these cases, both autosomal dominant and recessive modes of inheritance have been reported (7). Deficiency in von Willebrand factor cleaving (vwf-cp) activity, and intrinsic abnormalities of the complement system have been detected in families with atypical HUS. These include

mutations in complement factor H (FH), membrane cofactor protein (MCP) and complement factor I, presence of antifactor H autoantibodies, or combinations of mutations for FH and MCP (2). Several studies have reported mutations in the factor H gene in among 10% to 22% of atypical HUS patients. Although factor H mutations were reported in both familial and sporadic forms of HUS, CD46 mutations were restricted to familial HUS, and factor I mutations were only observed in cases of sporadic HUS (12). In a previous report, mutations in factor H gene were found in 13.4% of the patients; anti-factor H antibodies were found in 1.7% and decreased serum factor H levels in 5.9% (4). In the same report; vwf-cleaving protease deficiency was found to be 8.4%; membrane cofactor protein abnormalities 4.2%, abnormalities due to factor I were found to be 5%. 10.1% of cases were related to pneumococcal infection; and 0.8% was associated with membranoproliferative glomerulonephritis (MPGN) (4). Mutations in factor B were also recently described in two families (13). Mutations in C3 itself have also been described in a selected group of atypical HUS patients with low C3 concentrations in their plasma but without mutations of FH, MCP, FI or FB (14). Our case presented with the clinical and laboratory findings of atypical HUS without any evidence of diarrhea or other infections. He did not have any systemic disease or a history of drug usage. There was no family history of HUS. He had a transient hypocomplementemia 3 suggesting an abnormality in the complement cascade. However, since we could not study the mutations or investigate the presence of autoantibodies, we could not show the main defect underlying HUS in this patient. During the follow-up period, the patient showed an unusual progress with persistent fever unresponsive to broad-spectrum antibiotics, progressive deterioration of renal and hepatic functions, significant jaundice and pancytopenia. Despite regular plasma infusions and hemodialysis for renal failure, his clinical status did not improve and examination of second bone marrow aspiration demonstrated erythrophagocytosis. Together with other clinical and laboratory findings, a diagnosis of hemophagocytic lymphohistiocytosis was made which has not been reported before in association with HUS.

Extrarenal manifestations may be seen in HUS. Pancreas, intestines, central nervous system, myocardium, muscles and liver may be involved (1, 6, 15). The most common extrarenal manifestation site is the central nervous system affecting up to 20% of cases (1). Jaundice occurs in 35% of patients and a mild transient increase in plasma concentrations of liver enzymes occurs in 40% (1). This may be due to focal ischemic damage or ongoing haemolysis (1, 6). Jaundice usually occurs in the early phase of the disease and cholestatic jaundice occurs occasionally. Cholestasis may be due to cholelithiasis, which might be related to hemolysis during the acute phase of HUS; or it might be related to the use of parental nutrition (6). Our patient had markedly elevated liver enzymes and severe jaundice with conjugated hyperbilirubinemia but there were no risk factors including gallstones and parental nutrition. Infectious and malignant

factors were also excluded and conjugated hyperbilirubinemia, pancytopenia, hepatosplenomegaly were attributed to HLH.

Hemophagocytic lymphohistiocytosis is a clinical syndrome caused by excessive activation and proliferation of well-differentiated macrophages. This condition occurs in a heterogeneous group of diseases, ranging from infections to hematological conditions and rheumatic disorders (16). Persistent fever, lymphadenopathy, and hepatosplenomegaly are the characteristic features of the syndrome (16, 17). Profound depression of one or more blood cell lines, low erythrocyte sedimentation rate (ESR), raised liver enzymes and abnormalities of clotting profile commonly occur (16). The most characteristic feature of the disease is seen on bone marrow aspiration: numerous well-differentiated macrophages actively phagocytic hemopoietic elements (16, 17). Hemophagocytic activity may not be detectable at the time of presentation, thus serial marrow aspirates may also be helpful (18,19). Although our patient had no evidence of infections, malignancies or rheumatoid disorders; he fulfilled diagnostic criteria of HLH (19) (with fever, splenomegaly, pancytopenia, hypertriglyceridemia, hypofibrinogenemia and no evidence of malignancy) and to our knowledge this is the first case in the literature accompanying HUS.

Treatment of D (-) HUS is primarily supportive and plasma infusions and/or plasma exchange are usually recommended although the benefit of their use is not based on evidence. Especially in the familial and recurrent form of HUS, plasma infusion therapy once every two or four weeks is recommended (2, 4, 5). Plasma exchange can be administered if infusion is not sufficient or tolerated (5). It is also important in the treatment of vwf-cp deficiency and in the presence of factor H autoantibodies. Our patient was dialysed, plasma infusions were given and he was administered plasma exchange when his clinical status worsened and he developed HLH. His clinical status dramatically improved on the second week of plasma exchange therapy and this was attributed to the elimination of circulatory autoantibodies and cytokines due to primary condition and also HLH.

Early and aggressive immunosuppression is important in HLH and high doses of steroid and cyclosporin (for steroid resistant patients) are recommended (16, 19). In a report by Marie-Agnes Dragon Durey et al (5), oral steroid therapy was also given to two patients with atypical HUS preventing the development of relapse for about two years. After six sessions of plasma exchange therapy, our patient was also given low dose steroid treatment for HLH and he was completely well on the 45th day of treatment.

In conclusion, atypical HUS is a rare but severe disease and jaundice and mild elevations of the liver enzymes may be observed in some patients. However, markedly elevated liver enzymes and conjugated hyperbilirubinemia must be monitored

by the physician and HLH should be excluded with repeated examinations when other clinical and laboratory findings suggesting this disorder appear. To our knowledge, this is the first case of HLH accompanying hemolytic uremic syndrome in the English literature.

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