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■ Case report ■

A case of atypical hemolytic uremic syndrome as an early manifestation of acute lymphoblastic leukemia

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= Abstract =

Hemolytic uremic syndrome (HUS) is the most common cause of acute renal failure in children younger than 4 years and is characterized by microangiopathic hemolytic anemia, acute renal failure, and thrombocytopenia. HUS associated with diarrheal prodrome is usually caused by Shiga toxin-producing *Escherichia coli* O157:H7 or by *Shigella dysenteriae*, which generally has a better outcome. However, atypical cases show a tendency to relapse with a poorer prognosis. HUS has been reported to be associated with acute lymphoblastic leukemia (ALL) in children. The characteristics and the mechanisms underlying this condition are largely unknown. In this study, we describe the case of an 11-year-old boy in whom the diagnosis of ALL was preceded by the diagnosis of atypical HUS. Thus, patients with atypical HUS should be diagnosed for the possibility of developing ALL. (Korean J Pediatr 2010;53:253-257)

Key Words : Hemolytic uremic syndrome, Acute lymphoblastic leukemia, Acute renal failure

Introduction

Hemolytic uremic syndrome (HUS) is a frequent cause of oliguric acute renal failure in infants and young children [1]. This syndrome is defined by the triad of microangiopathic hemolytic anemia (MAHA), acute renal insufficiency, and thrombocytopenia. Most cases of HUS are associated with a bloody diarrheal prodrome caused by *Escherichia coli* (most commonly O157:H7) or *Shigella dysenteriae* serotype I. Small epidemics of HUS are usually traced to the ingestion of contaminated beef or dairy products[2]. Non-diarrhea-associated HUS is rare in children and, in adults, is most frequently found in association with pregnancy, primary glomerulopathies, acquired immunodeficiency syndrome (AIDS), bone marrow transplantation, malignancy, severe hypertension, drugs, and collagen vascular disease. These atypical cases have a worse prognosis with relapsing episodes[3-5]. There have been rare reports of HUS preceding acute lymphoblastic leukemia (ALL) in children[6-8]. We report here a case of atypical HUS in a child who subsequently developed ALL.

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Case report

An 11-year-old boy was admitted to another hospital with abdominal pain and emesis after having eaten a hamburger. There was no preceding diarrhea, nor had he taken any drug that could cause HUS. Four days later, the boy became oliguric, and the concentrations of blood urea nitrogen (BUN) and creatinine (Cr) increased to 101 mg/dL and 4.4 mg/dL, respectively, which is consistent with acute renal failure. Laboratory findings were as follows: hemoglobin (Hgb) of 7.4 g/dL; white blood cell (WBC) count of 4,000/mm^3; and platelet count of 20,000/mm^3. Urinalysis revealed microscopic hematuria [30-40 red blood cells (RBCs)/high power field (HPF)] but no proteinuia. The patient was transferred to our hospital on his fourth day of hospitalization.

At the time of transfer, physical examination revealed pallor and a marginally palpable liver but not splenomegaly or enlarged lymph nodes. His vital signs were: temperature,

36.8℃; blood pressure, 120/70 mmHg; pulse rate, 90/minute; and respiratory rate, 24/minute. Neurological examination was normal. Mediastinal enlargement was not noted in his chest radiograph. A complete blood count revealed anemia and thrombocytopenia: Hgb 6.9 g/dL [hematocrit (Hct) 19.1%, mean corpuscular volume 80.1 fL, mean corpuscular hemoglobin concentration 36.0 g/dL, red cell distribution width 12.2%, reticulocyte count 0.91%]; platelet 11,000/mm^3; and WBC 4,800/mm^3 (neutrophil 61.8%, lymphocyte 27.1%, monocyte 10.5%, eosinophil 0.3%). A peripheral blood smear showed sporadic fragmented erythrocytes and slight anisocytosis, with no immature cells or blasts (Fig. 1). Direct and indirect Coombs' tests were negative. Serum biochemistry was as follows: BUN 84.6 mg/dL; Cr 4.7 mg/dL; uric acid 26.1 mg/dL; lactate dehydrogenase (LDH) 1,335 U/L; and haptoglobin 93.4 mg/dL (normal 30–200). Coagulation profiles (including prothrombin, activated partial thromboplastin time, fibrinogen, and antithrombin III levels) were normal. Urinalysis revealed microscopic hematuria (20–29 RBCs/HPF) but no proteinuria. The work-up for hematuria including antinuclear antibody (ANA), antistreptolysin O (ASO) titer, C3, C4, IgG, and IgA was normal. Renal ultrasonography revealed parenchymal renal disease and a mild increase in renal size. Although there was no prodrome of enterocolitis, the combination of acute renal failure, thrombocytopenia, and hemolytic anemia suggested a clinical diagnosis of atypical HUS. The patient was treated with urine alkalization and a transfusion of packed red blood cells. After 5 days, azotemia improved (BUN 11.7 mg/dL, Cr 1.1 mg/dL) without any proteinuria or microscopic hematuria, and uric acid and LDH levels normalized. The stool *E. coli* O157:H7 test was negative. No antibiotics or antihypertensive, anticoagulant, or antiplatelet agents were administered. Renal biopsy and bone marrow examination were not performed. At the time of discharge, laboratory findings were as follows: BUN 17.6 mg/dL; Cr 0.9 mg/dL; Hgb 8.8 g/dL; Hct 24.7%; platelet 198,000/mm^3; WBC 4,200/mm^3; and normal erythrocyte morphology.

One month later, the patient developed malaise, easy bruising, petechiae, and hepatosplenomegaly. There was no lymphadenopathy or mediastinal enlargement. Hematological profiles showed leukocytosis and thrombocytopenia: WBC 15,900/mm^3 (neutrophil 2.1%, lymphocyte 59.2%, monocyte 8.5%, eosinophil 0.6%); platelet 36,000/mm^3; and Hgb 10.0 g/dL. A peripheral blood smear showed immature or abnormal cells, and bone marrow aspiration revealed a proliferation of lymphoblasts with L1 morphology (Fig. 2). The immunophenotyping study demonstrated an early precursor B cell type of ALL (HLA-DR, 69.9%; CD10, 90.6%; CD19, 89.9%; CD22, 65.6%; CD34, 90.1%). The patient was treated with a high-risk protocol from the Children's Cancer Study Group until September 2004. To date, he remains in hematological remission with normal renal function, 7 years after diagnosis. There has been no relapse of HUS in the meantime.

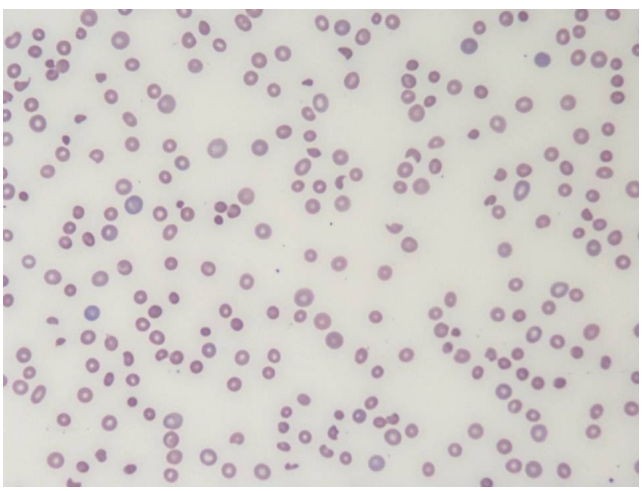

Fig. 1. Peripheral blood smear showing fragmented red blood cells (RBCs) without immature cells or blasts at the time of initial presentation (Wright & Giemsa stain, magnification ×400).

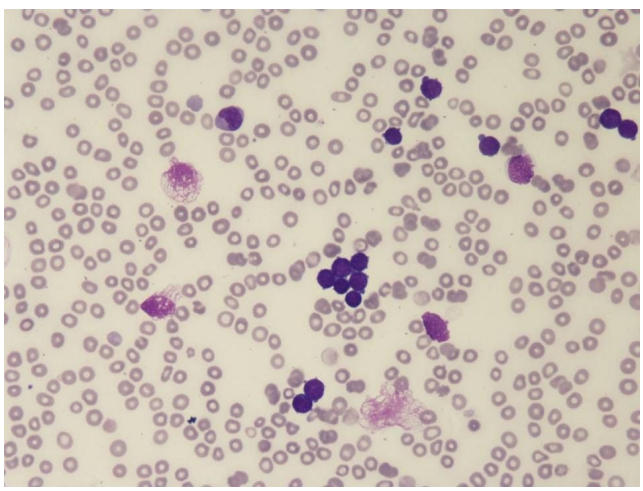

Fig. 2. Bone marrow aspiration performed after 1 month reveale 80–90% small-sized lymphoblasts with scanty cytoplasm (Wright & Giemsa stain, magnification ×400).

Discussion

In 1955, Gasser et al[9] first reported HUS in children who showed MAHA, thrombocytopenia, and acute renal failure. Current thinking divides HUS into two major types, one associated with a prodromal diarrhea (D+HUS) and the other without diarrhea (D−HUS). Most pediatric cases are D+HUS, affecting younger children and generally having a good prognosis[10]. The less common D−HUS (or atypical HUS) is more heterogeneous in nature. D−HUS is generally associated with a higher morbidity and mortality than is D+HUS. Extra−renal involvement is quite common in atypical HUS and may even be the cause of death or sequelae in these patients[11]. Colitis may last for about a week. Pancreatitis has been described in 18.2% of cases, and diabetes mellitus may follow this insult[12]. However, exocrine pancreatic insufficiency is not common. Elevation of transaminases with hepatomegaly may suggest involvement of the liver. Heart involvement may take the form of myocarditis or cardiomyopathy, presenting as congestive cardiac failure. The lungs may develop pulmonary infarct or hemorrhage. CNS dysfunction is seen in up to 50% of the cases, showing drowsiness, agitation, irritability, lethargy, seizures, and/or coma[13]; CT scans may show infarcts or hypodensities, most commonly in the basal ganglia.

Injury to the endothelial cell is the central and likely inciting factor in the sequence of events leading to thrombotic microangiopathy. Other factors, such as loss of physiological thromboresistance, leukocyte adhesion to damaged endothelium, complement consumption, abnormal von Willebrand factor (vWF) release and fragmentation, and increased vascular shear stress may contribute to sustaining and amplifying the microangiopathic process[14]. In our patient, acute renal failure might have been aggravated by leukemia−related mechanisms, such as cytokine release by damaged endothelial cells, leukemic infiltration of the kidneys, or uric acid nephropathy[7]. The level of uric acid is often extremely high (>20 mg/dL) in HUS, so it was difficult to determine whether the hyperuricemia in our patient was the result of catabolism of nucleoproteins from the breakdown of neoplastic cells or the effect of acute primary renal dysfunction in connection with HUS[15]. The renal microcirculation damage with glomerular endothelial lesions might have been induced by chemokines, such as tumor necrosis factor (TNF)−α and interleukin (IL)−1, −6, and −8. These chemokines, which may also be released in neoplastic diseases, are assuming an important role in our understanding of HUS pathogenesis. High levels of TNF−α, IL−6, and IL−8 have been found in urine and occasionally in serum during the acute phase of HUS in children, returning to normal values upon recovery[16]. However, these chemokines may lead to renal microcirculation damage through different mechanisms. TNF−α could act on endothelial cells to induce pro−coagulant activity and on the release of vWF, which produces platelet formation and fibrin thrombi formation. Also, IL−8, a potent activator of white blood cells, could induce the release of tissue−damaging enzymes from the leukocytes[17].

The destruction of RBCs is characterized by increased levels of unconjugated bilirubin, LDH and decreased haptoglobin levels. Both LDH and Hgb are released into the peripheral blood when RBCs are destructed. Free Hgb is converted into unconjugated bilirubin in the spleen or may be bound in the plasma by haptoglobin. The Hgb−haptoglobin complex is cleared quickly by the liver, leading to decreased haptoglobin levels. Haptoglobin is an acute phase protein which may increase in the event of an inflammatory stimulus such as infection, injury, malignancy or non−infectious diseases (diabetes, coronary artery disease, obesity)[18]. Our patient showed a normal level of haptoglobin despite initial hemolytic anemia, which might reflect a compensatory increase as an acute phase reaction secondary to subsequent ALL.

Since 1979, when Krauss et al[19] reported the first case of chemotherapy−related HUS, the association between cancer and HUS has become well established. The common tumors associated with HUS are solid tumors, such as gastric adenocarcinoma, carcinoma of the breast and colon, and small cell lung carcinoma[20]. In addition, HUS can occur in association with cancers of the pancreas, prostate, and ovary, with lymphoma, and, rarely, with leukemia[2]. Chemotherapeutic agents, especially mitomycin C, and infections during the course of the disease have been implicated as causative factors. Very rarely, HUS precedes ALL.

There are 3 previous reports that describe HUS preceding ALL[6−8]. In 1986, Salcedo and Fusner[6] reported a 4−year−old boy who developed ALL 8 months after contracting D+HUS, with the typical histologic features of glomerular involvement. In 2000, Martini et al[7] described an 8−year−old girl with the diagnosis of ALL who had had D−HUS one month earlier. In 2003, Hahn et al[8] reported a 5−year−old

boy who developed ALL 4 months after he was diagnosed with D−HUS. In the case reported by Salcedo and Fusner, there was a rather long interval between the onsets of D+ HUS and ALL. This long interval presents the possibility that the diseases were unrelated.

The other cases, including our patient, showed D−HUS followed by ALL. There are some differences among these cases. The cases of Martini[7] and of Hahn et al[8] presented with gross hematuria and hepatosplenomegaly at the time each was diagnosed with HUS. The presence of hepatosplenomegaly suggests that HUS was the presenting manifestation of the leukemia, which was not yet apparent in peripheral blood or bone marrow aspirates. But our patient did not have hepatosplenomegaly when he was diagnosed with HUS. Martini's[7] patient had oliguria, neurologic involvement, lymphadenopathy, persistent pancytopenia, and an elevated haptoglobin level. In the case reported by Hahn et al[8], leukemic cells were not detected in the initial bone marrow examination. As it was performed unilaterally, it is possible the examination missed patchy bone marrow involvement early in the onset of ALL. Our case was similar to Martini's in that the diagnosis of ALL followed the onset of HUS by one month and the haptoglobin level was not decreased. These findings suggest that HUS may be the presenting manifestation of the leukemia itself.

Although the relationship between HUS and ALL is unclear, this case demonstrates that D−HUS could be the result of subclinical ALL. Therefore, the hematological profiles of such D−HUS patients should be monitored closely, and a bone marrow exam, preferably bilateral, should be performed, if pancytopenia persists or haptoglobin level is increased.

한 글 요 약

비전형적 용혈성 요독 증후군으로 조기 발현한 급성 림프모구성 백혈병 1예

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한동균 · 백희조 · 조영국 · 김찬종 · 신명근* · 국 훈 · 황태주

용혈성 요독 증후군은 미세혈관병성 용혈성 빈혈, 급성 신부전 및 혈소판감소증을 특징으로 하며 4세 미만 소아의 급성 신부전의 가장 흔한 원인이 된다. 설사 연관형 용혈성 요독 증후군은 설사가 전구 증상으로 동반되며, shiga−toxin을 생산하는 *Escherichia coli* O157:H7 또는 Shigella dysenteriae 감염이 원인으로 써 비교적 예후가 좋다. 하지만, 비전형적인 경우는 재발할 수 있으며 더 불량한 예후를 보인다. 소아에서는 용혈성 요독 증후군이 선행된 급성 림프모구성 백혈병은 매우 드물게 보고되며, 이들에서의 임상적인 특징이나 기저 기전은 잘 알려져 있지 않다. 이에 저자들은 11세 남아에서 비전형적 용혈성 요독 증후군 후에 발생한 급성 림프모구성 백혈병 1예를 보고하는 바이며, 이와 같은 비전형적인 경우에는 급성 림프모구성 백혈병의 가능성을 염두해 두어야 할 것으로 사료된다.

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