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□ Case Report □

Multiple extrarenal manifestations in hemolytic uremic syndrome: A case report

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Extrarenal manifestations of hemolytic uremic syndrome (HUS) have increasingly been recognized and may be major determinants of mortality and morbidity. Although microthrombi are often found in the pulmonary and coronary circulation, apparent lung and cardiac involvement are clinically infrequent. We describe here a 10-month-old boy with HUS who developed pulmonary hemorrhage, acute respiratory distress syndrome and dilated cardiomyopathy. Complete renal as well as clinical recovery from these very uncommon complications was achieved by optimum supportive care. **(Korean J Pediatr 2007;50:1261-1265)**

Key Words : Hemolytic uremic syndrome, Cardiomyopathy, Extrarenal manifestations

Introduction

Hemolytic uremic syndrome (HUS) is the most common cause of acute renal failure in infants and young children, which is characterized by microangiopathic anemia, thrombocytopenia, and acute nephropathy[1]. Although microthrombi may be found in a wide distribution of organs, clinically apparent lung and cardiac involvement is rare[2]. Recently, death from acute renal failure has been decreasing due to improved management of renal problems, and extrarenal involvement has become an important factor, not only in death in the acute phase but also in chronic morbidity[2].

We report on an infant who developed pulmonary hemorrhage and acute respiratory distress syndrome (ARDS), dilated cardiomyopathy in the acute stage of HUS.

Case Report

A 10-month-old, previously healthy boy presented with generalized tonic-clonic convulsions with fever. The convulsions lasted for about 5 minutes. For the past week, he had been suffering from watery diarrhea, cough and intermittent fever. On admission, his vital signs revealed a heart rate of 162/min with a blood pressure of 90/60 mmHg, a respiratory rate of 26/min, and a body temperature of 37.5℃. He had periorbital edema, coarse breathing sounds with rales in both lungs, abdominal distention, dry oral mucosa, and decreased skin turgor. His cardiac examination and extremities were unremarkable. His complete blood count showed a white blood cell count of 14,600/mm^3 (53% neutrophils, 11% band forms, 34% lymphocytes), a hemoglobin concentration of 8.5 g/dL, a hematocrit of 25.3%, a platelet count of 278,000/mm^3, which decreased to a hemoglobin concentration of 7.7 g/dL, a hematocrit of 23.1%, a platelet count of 26,000/mm^3 on 3rd hospital day and reticulocyte count of 0.2%. Microangiopathic hemolytic anemia was suggested by marked poikilocytosis, schistocytes and burr cells on microscopy of blood film. The blood biochemical analysis showed BUN and creatinine concentrations of 68 and 2 mg/dL respectively, a sodium concentration of 131 mEq/L, a calcium concentration of 6.6 mg/dL and a fractional Na excretion (FEna) was 10.88%. The blood and throat swab culture was negative. Urinalysis showed many RBC and positive ocult blood. A stool culture obtained at that time was negative for *E. coli0157:H7*, but *Streptococcus pneumoniae* antigen was detected in the urine. C-reactive protein was 23.94 mg/L (normal range: 0-5 mg/L), fibrinogen was normal, 220 mg/dL, complement C3/C4 was 61.34/27.96 mg/dL. The arterial blood gas analysis was as follows: pH 7.18, PO_2 62.9 mmHg, PCO_2 40.9 mmHg, HCO_3 14.8 mmol/L, SaO_2 85.3%. GFR calculated from subsequent 24h urine collection was 16.9 mL/min/1.73m^2. The chest

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radiograph revealed bilateral infiltrations in both lower lungs without evidence of cardiomegaly (Fig. 1). He was moved to the intensive care unit on hospital day 2 due to respiratory distress and a deteriorating general condition. Antibiotics administration and supportive care, including fluid restriction, continued for HUS with pneumonia. On hospital day 5, the patient showed sudden cyanosis, bradycardia of 60/ min and decreased oxygen saturation of 70%. When an endotracheal tube was inserted without trauma, copious amounts of fresh blood were suctioned via the tube. The follow-up chest radiograph showed a diffuse opacification of both lung fields (Fig. 2A), suggesting ARDS following pulmonary hemorrhage, and a ventilator was applied. He had platelet and fresh frozen plasma transfusions due to thrombocytopenia (53,000/mm^3) with a prolonged aPTT (80.6 sec). He showed improvement in his general status and chest x-ray (Fig. 2B). However, on hospital day 10, respiratory distress developed again. His chest x-ray demonstrated cardiomegaly (Fig. 2C) and echocardiography revealed a pattern of dilated cardiomyopathy; global hypokinesia, ejection fraction 39%, E-point to septal separation (EPSS) 10 mm. There was no evidence of hypertension, fluid overload, or electrolyte abnormalities. Angiotensin converting enzyme inhibitor (Captopril) and digitalization were started. He began to show recovery from heart, lung and renal problems and was extubated on hospital day 21 (Table 1, Fig. 2D). The evaluation for other viral or connective tissue disease showed a negative result (*adenovirus, parainfluenza virus, respiratory syncitial virus* culture in sputum, *influenza virus* in nasal *swab, rubella, varicella, ebstein-barr virus* antibody, fluorescent antinuclear antibody (FANA), anti double stranded DNA (dsDNA) antibody, anti-Sm (Smith) antibody). Echocardigraphy on hospital day 34 showed a normal heart. He was in good condition and was discharged on hospital day 40. After then, he is in good health and has had a normal neurodevelopmental examination.

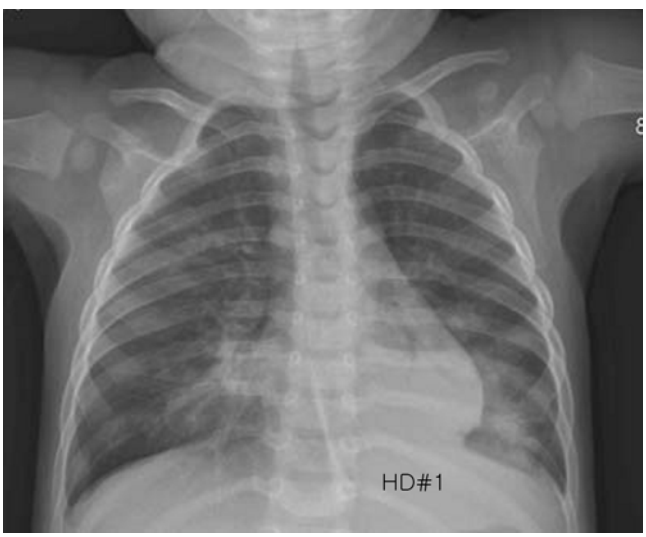

Fig. 1. Bilateral infiltrations in both lower lungs without evidence of cardiomegaly on admission.

Discussion

HUS is associated with diarrheal illness caused by shiga toxin (Stx) producing *E. coli0157:H7* in 90% of childhood cases. However, there is increasing awareness that other organisms, drugs, and conditions, such as bone marrow transplantation, SLE, glomerulonephritis or systemic sclerosis, may also initiate features of HUS[1].

S. pneumoniae is relatively common among non-*E. coli*-mediated HUS[1] and was reported as a cause of HUS in 2-5% of cases in Western countries[1, 2]. Information on its incidence in Asia is scant but invasive pneumococcal infection accounts for a substantial number of cases of HUS in Taiwan[3-5].

Neuraminidase produced by *S. pneumoniae* exposes the cryptic T-antigen on erythrocytes, platelets and glomeruli,

Table 1. Laboratory Results at the Timing of Each Event

	Admission	Pulmonary hemorrhage, ARDS	Dilated cardiomyopathy	Discharge
Hospital day	1	5	10	40
WBC (/mm^3)	14,600	5,400	9800	7,300
Hemoglobin (g/dL)	8.5	7.7	9.5	11.9
Platelet (/mm^3)	90,000	53,000	180,000	374,000
Bun/Cr (mg/dL)	69/2	30/1.1	15/0.5	17/0.5
Na/K (mEq/L)	131/4.9	144/3.2	143/4.2	134/4.6
PT/PTT (s)	11.9/71	12.8/80.6	12.3/40	11.7/45

Abbreviation : ARDS, acute respiratory distress syndrome

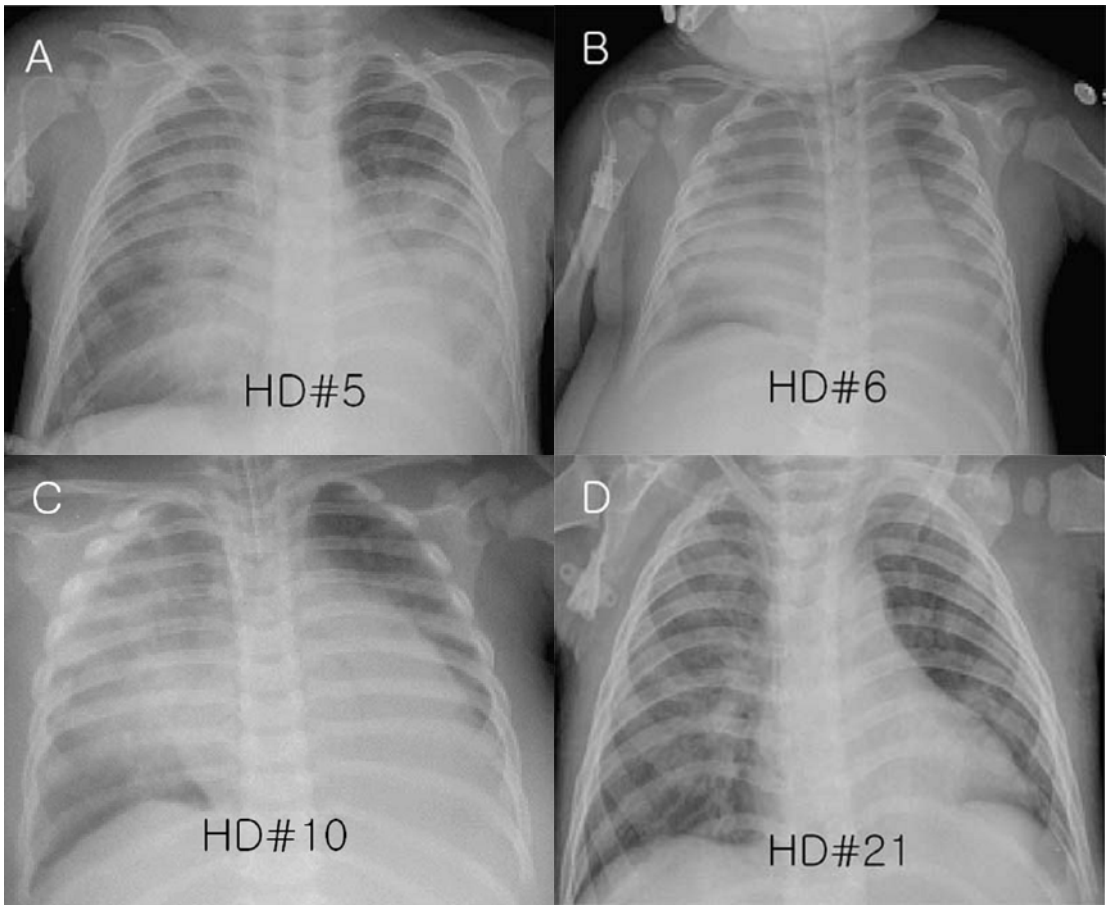

Fig. 2. Serial chest x-rays. (A) A diffuse opacification of both lung fields showing ARDS following pulmonary hemorrhage. (B) An improvement in bilateral haziness. (C) Cardiomegaly (CT ratio 0.64) and pulmonary congestion in dilated cardiomyopathy. (D) An improvement of a chest film along with recovery of cardiopulmonary and general conditions.

which react with anti-T antibodies normally present in plasma. As a result, damaged blood cells and endothelial cells cause glomerular thrombotic microangiopathy (TMA)[1]. The *S. pneumoniae* infection is confirmed by a culture of blood or pleural fluid, and by the *S. pneumoniae* antigen test in pleural fluid or urine[1, 2]. The rate of false-positive test results among febrile children without identified pneumococcal infection is approximately 15%[6]. *Streptococcus pneumoniae* vaccine, nasopharyngeal colonization may cause false positive results in urine test[7]. In our case, the *S. pneumoniae* antigen test was positive in urine. But the blood and throat swab culture was negative. He had not been vaccinated against *S. pneumoniae*.

Some patients with HUS develop extrarenal complications. With regards to gastrointestinal involvement, bowel necrosis resulting from colitis and pancreatic damage may occur. Hepatomegaly and elevated liver enzymes are common but severe dysfunction is rare.

Although it is relatively common to find thrombi in the coronary microcirculation of those who die in the acute stage of HUS, clinically apparent cardiac dysfunction is infrequent[2]. Cardiac dysfunction in HUS results from disturbances of renal failure, including metabolic disorders, volume overload, high blood pressure, anemia[8, 9], and myocardial microangiopathic thrombosis (MAT)[9]. However, cardiac involvement can occur without uremia or MAT[9], suggesting an unknown mechanism. Various factors have been suggested concerning the possible mechanism of myocardial ischemia or damage; the recruitment of microvascular collateral vessels, arrhythmia, hypoxemia, iron and fluid shifts during or following dialysis, myocardial edema, diastolic dysfunction[10], and a direct verotoxin related effect[11]. Reported forms of involvement are myocarditis, congestive heart failure, myocardial infarction, and cardiomyopathy[2, 9, 12-14]. Cardiac manifesta-

tions usually appear in the acute stage, but there is a report of cardiomyopathy developing 4 months after the onset of HUS[9]. Therapy is mostly supportive, and includes the use of digoxin or other inotropic agents[2, 9]. Severe congestive heart failure treated by ECMO (extracorporeal membrane oxygenation) has been reported[15]. However, despite aggressive management, myocardial involvement can be fatal or may lead to ventricular dysfunction for more than one year[2, 12].

Clinically apparent lung involvement, such as pulmonary edema or pulmonary hemorrhage subsequent ARDS is extremely rare in HUS[16, 17]. Pathogenesis is not clear but microvascular damage with a loss of capillary integrity and necrosis of the alveolar wall are considered as possible mechanisms[2, 17]. Experiences in treatment and prognosis are deficient, and reports on mortality vary from fatal cases[2] to those of recovery[16]. Although our patient developed pulmonary hemorrhage when thrombocytopenia with prolonged aPTT was present, the possibility cannot be excluded that HUS itself may have partly contributed to this pulmonary hemorrhage, considering the fact that this laboratory abnormality was not an acute finding but had been present from the first hospital day and that a previous report noted that pulmonary hemorrhage did not occur during severe thrombocytopenia but during the period of recovery from thrombocytopenia[16].

Huang et al.[18] reported that all their *S. pneumoniae*-associated HUS patients had pneumonia and empyema, with the latter known as the most common extrarenal complication in *S. pneumoniae*-associated HUS[19]. Although our patient had pneumonia from the first hospital day, empyema did not develop.

Survivors of the acute stage of diarrhea-associated HUS require a long term follow up because 30-50% may show signs of renal injury or hypertension afterwards[1]. *S. pneumoniae*-associated HUS has a high risk of mortality and morbidity[18] but its long-term prognosis is still controversial [18]. It is important for the pediatrician to be aware that infectious agents other than *E. coli* and that various illnesses can induce HUS[1] and that aggressive supportive therapy for extrarenal complications may contribute to improve the prognosis of HUS. It also means that children with pneumococcal disease and severe hematologic or renal abnormalities should be investigated for evidence of HUS[19].

Our patient, despite having multiple extrarenal involvements including heart, lung and CNS, recovered with conservative therapy and is currently being observed for 3 years without specific health problems. He is in good health and has had a normal neurodevelopmental examination.

한 글 요 약

다발성 신외 증상이 동반된 용혈요독증후군 1례

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김 유 진 · 김 소 영

근래 용혈요독증후군의 신외 증상에 대한 인식이 점점 더 증가하고 있으며 이환률과 사망률의 주요 결정인자가 되고 있다. 용혈요독증후군 환자의 심장동맥순환계에서 미소혈전이 발견되는 일은 흔하지만 실제 임상적으로 명백하게 발현하는 폐 혹은 심장 합병증은 흔하지 않다. 저자들은 용혈요독증후군으로 치료 받던 10개월 영아에서 폐출혈, 급성호흡곤란증후군, 확장심근병증 등이 발생하여 지지요법 후 회복된 1례를 경험하여 문헌고찰과 함께 보고하는 바이다.

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