평소 건강하였던 소아에서 아데노바이러스 감염으로 유발된 혈구탐식성 림프조직구증: 증례 보고 및 문헌 고찰

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Adenovirus-induced Hemophagocytic Lymphohistiocytosis in a Previously Healthy Boy: A Case Report and Literature Review

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A 3-year-old previously healthy boy was admitted because of a 1-week history of fever, abdominal pain, vomiting, and diarrhea. The initial laboratory tests showed hepatic dysfunction with disseminated intravascular coagulation. There was a large amount of pleural effusion, periportal edema, minimal ascites, and splenomegaly. He was initially managed with broad spectrum antibiotics with transfusion. Despite 2 days of treatment, the fever persisted and the results of the laboratory tests had worsened. Bacterial cultures from the blood, urine, pleural effusion, and ascites were all negative. He was finally diagnosed with hemophagocytic lymphohistiocytosis (HLH) based on the diagnostic criteria. Adenovirus was detected in the initial diarrhea and nasal swab specimens using polymerase chain reaction-based method. One year after chemotherapy with dexamethasone, cyclosporine, and etoposide, he is now healthy without evidence of disease recurrence. This is the first Korean case report of adenovirus-induced HLH in a previously healthy child.

Key Words: Adenovirus, Hemophagocytic lymphohistiocytosis, Immunocompetent, Infection-associated hemophagocytic syndrome

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Introduction

Hemophagocytic lymphohistiocytosis (HLH) is a severe disease category with a high mortality rate and associated with a variety of bacterial, viral, fungal, or parasitic infections. Many viruses, such as the Epstein-Barr virus (EBV), cytomegalovirus (CMV), human immunodeficiency virus, parvovirus, or hepatitis viruses are known to cause infection-associated HLH [1]. Adenovirus infection in immunocompetent host generally causes benign and self-limited disease. On the other hand, adenovirus can cause very severe illness including enterocolitis, pneumonia, encephalitis, and even HLH in immunocompromised patients [2-5].

Here we introduce the first Korean case report of fulminant and disseminated HLH caused by adenovirus infection in a previous healthy boy with no evidence of immune deficiency, primary HLH, or malignant disease. Additionally, we have reviewed the published literatures concerning adenovirus-associated HLH in immunocompetent children.

Case Report

A 3-year-old boy was transferred to our hospital because of a 1-week history of prolonged fever and aggravated abdominal pain. He also had vomiting, loose stool, and poor oral intake. He was previously healthy and there was no specific family history.

Initial laboratory tests showed hepatic dysfunction and disseminated intravascular coagulation (DIC) (platelets, 4×10^9/L [reference range, 130-400$\times10^9$/L]; aspartate aminotransferase (AST), 433 U/L [normal rage, 0-34 U/L]; alanine aminotransferase (ALT), 186 U/L [reference range, 10-49 U/L]; albumin, 2.8 g/dL [reference range, 3.2-4.8 g/dL]; prothrombin time (PT) 47.5 sec [reference range, 10-14 sec], international normalized ratio (INR), 4.35 [normal value, 1]; fibrinogen 163.9 mg/dL [reference range, 200-400 mg/dL]; antithrombin III, 52% [reference range, 75-125%]; D-dimer, 3.85 μg/mL [reference range, <0.4 μg/mL]; and C-reactive protein, 11.35 mg/dL [reference range, <0.5 mg/dL]).

A large amount of pleural effusion was on the chest x-ray which was managed with pig tail catheter insertion. On the abdominal x-ray, there was gaseous dilatation of the bowel (Fig. 1). On the abdominal ultrasonogram, there was fluid collection in the subphrenic space, both paracolic gutters, and pelvic cavity. The contrast-enhanced computed tomography of the abdomen showed edema of periportal area, pericystic area, gallbladder, and whole bowel area. Splenomegaly and minimal ascites were also found (Fig. 2).

He was initially managed with broad spectrum antibiotics including vancomycin, meropenem, and metronidazole. Fresh frozen plasma, cryoprecipitate, and antithrombin III were infused to correct the DIC. Intravenous immunoglobulin was also infused. Despite 2 days of treatment there was no improvement of the fever, thus we suggested a diagnosis of HLH. In addition, there was no evidence of bacterial infection on cultures grown from the blood, urine, pulmonary effusion, or ascitic fluid.

The follow up laboratory tests showed aggravated bicytopenia (hemoglobin, 9.0 g/dL and platelet, 3×10^9/L), coagulopathy (anti-prothrombin time [aPTT], 97.6 sec and fibrinogen 106.5 mg/dL), and hepatic dysfunction (AST, 1,338 U/L and ALT, 963 U/L). The ferritin level had increased to 1,810 ng/mL (reference range, 22-322 ng/mL) and the bone marrow aspirate showed hemophagocytic histiocytosis (Fig. 3). Soluble CD25 (IL-2 receptor) was increased at 4,745 U/mL (reference range, 122-496 U/mL). No pleocytosis was noted

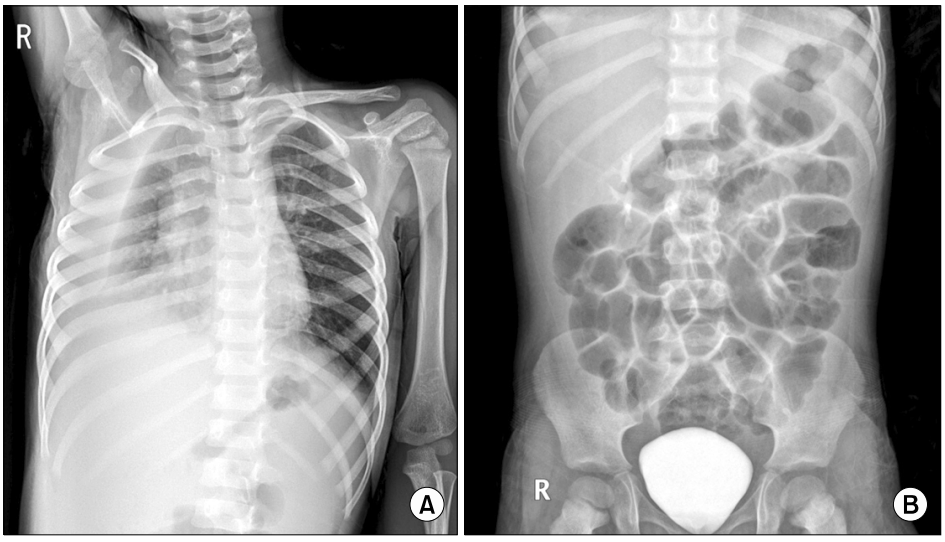

Fig. 1. Simple radiologic findings in a previously healthy boy with hemophagocytic lymphohistiocytosis due to adenovirus infection. (A) Right decubitus chest x-ray showing a massive pleural effusion. (B) Supine abdomen x-ray showing severe gaseous dilatation and some ascites.

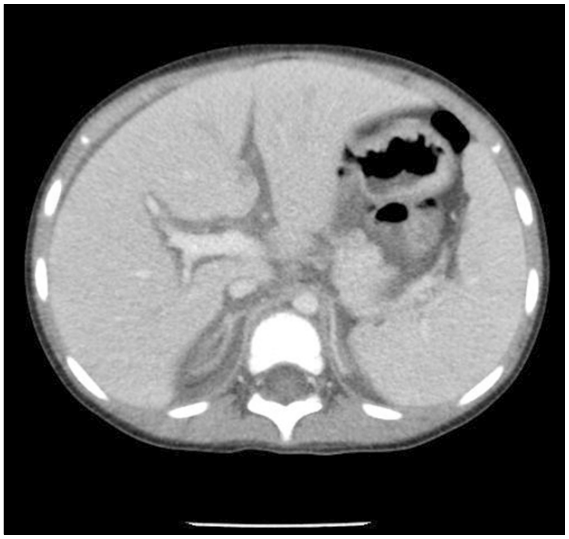

Fig. 2. Contrast-enhanced abdominal computed tomography in a boy with enteric adenovirus-induced hemophagocytic lymphohistiocytosis. There was edema of the periportal area, pericystic area, gallbladder, and whole bowel area. Splenomegaly and minimal ascites were also found.

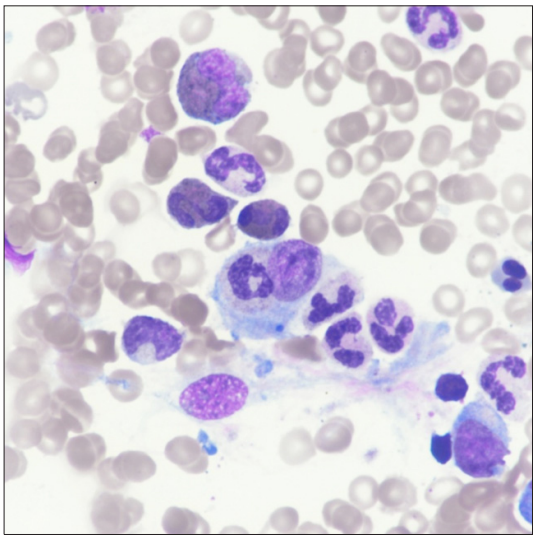

Fig. 3. Bone marrow aspiration smear of a boy with adenovirus-induced hemophagocytic lymphohistiocytosis. The slide showed histiocytes which contained neutrophils (Wright stain ×1,000).

following a lumbar puncture. Chemotherapy based on the HLH-2004 protocol was initiated and continued for 2 months. The treatment protocol consisted of intravenous dexamethasone (10 mg/m^2/day and taper off), oral cyclosporine A (6 mg/kg/day), and intravenous etoposide (150 mg/m^2/day, twice a week for 2 weeks, and 150 mg/m^2/week after).

Polymerase chain reaction (PCR) analysis for the virus potentially causing diarrhea using the initial stool sample detected enteric adenovirus (detectable viruses: Astrovirus, Group A rotavirus, enteric adenovirus, norovirus GI, norovirus GII). In stool bacterial PCR, no bacteria was detected (detectable bacteria: *Vibrio*, *Campylobacter*, *Shigella*, *Salmonella*, *Clostridium difficile* Toxin B, *Yersinia enterocolitica*, *Aeromonas*, *E. coli* O157:H7, Verotoxin-producing *E. coli* [VTEC], *Clostridium perfringens*). In PCR of the nasal swab checking for respiratory viruses, adenovirus was also detected (detectable viruses: adenovirus, rhinovirus, influenza virus A/B, parainfluenza virus, respiratory syncytial virus A/B, bocavirus, coronavirus, and metapneumovirus). Futher classification of adenovirus was not made. The genetic test for primary HLH (*PFR1*, and *UNC13D*) was negative. Thus, he was finally diagnosed with adenovirus-induced HLH. After 2 months of initial chemotherapy, HLH has been resolved and continuation therapy was not initiated. From then, the patient is visiting our out-patient-clinic regularly for 1 year, and is healthy now with no evidence of disease recurrence.

Discussion

HLH is an uncommon, life-threatening hyperinflammatory state caused by severe hypercytokinemia with excessive activation of lymphocytes and macrophages due to a highly stimulated but ineffective immune process [1]. It is classified as familial (primary) or acquired (secondary). Acquired HLH is associated with several viral, bacterial, fungal, parasitic or infections, in addition to autoimmune diseases or malignancy.

The Histiocyte Society presented the first diagnostic guidelines for HLH in 1991 [6]. Since then, many studies have been performed, and in 1994 the first international treatment protocol (HLH-94) was introduced [7]. The cumulative experiences from HLH-94 and other studies have led to the new treatment protocol, HLH-2004 [8]. HLH can be diagnosed with the presence of at least five of the next eight diagnostic criteria, including fever, bi- or pancytopenia, splenomegaly, hypertriglyceridemia or hypofibrinogenemia,

Table 1. Literature review of adenovirus-induced fulminant hemophagocytic lymphohistiocytosis in previously immunocompetent children

Reference	Sex and age of patient	Clinical manifestation	Specimen (Method)	Treatment	Alive or dead
Seidel, 2003 [11]	Male 2 years	Gastroenteritis, pneumonia, encephalopathy	Stool and pharyngeal smear (PCR)	IV immunoglobulin (2 g/kg)	Alive
Morimoto, 2003 [12]	Female 12 years	Pneumonia, pleural effusion	Biopsied lung tissue (PCR)	Oral dexamethasone (10 mg/m^2/day), IV cyclosporine A (3 mg/kg/day)	Alive
Odièvre, 2011 [13]	Male 15 months	Gastroenteritis, pneumonia	Bronchoalveolar fluid (PCR and culture)	Conservative management	Alive
Hoşnut, 2014 [14]	Male 11 months	Pneumonia, pleural effusion, encephalopathy	Serum (anti-adenovirus IgM, IgG, and PCR)	IV immunoglobulin (1 g/kg)	Alive
Present case	Male 3 years	Gastroenteritis, pleural effusion	Stool and pharyngeal smear (PCR)	HLH-2004 protocol	Alive

PCR, polymerase chain reaction; IV, intravenous.

hyperferritinemia, elevated sCD25 (sIL-2 receptor), low natural killer cell activity, and demonstration of hemophagocytosis in tissues [6-8]. In our patient, 1) fever, 2) splenomegaly, 3) bicytopenia, 4) hemophagocytosis on bone marrow aspiration, 5) hyperferritinemia, 6) elevated sCD25 (sIL-2 receptor), and 7) hypofibrinogenemia were found, leading to a diagnosis of HLH.

Viral infections (predominantly EBV and CMV) form the most common cause for acquired (secondary) HLH [1,9,10]. Adenovirus can cause upper respiratory tract infection, conjunctivitis, enteritis, pneumonia, exanthema, and rarely, encephalitis, myocarditis, mesenteric lymphadenitis, and hemorrhagic cystitis. Typically, severe systemic sickness, including HLH, from adenovirus is usually observed in immunocompromised patients (e.g., primary immunodeficiency disease, during chemotherapy, after splenectomy, or after stem cell transplantation) [2-5].

In a literature review, only four case reports of adenovirus-associated HLH in healthy children worldwide were found [11-14]. To the best of our knowledge, the presented patient is the Korean first case report of adenovirus-induced HLH in a previously healthy child. The patients' characteristics, major clinical manifestations and treatment are described in Table 1. Referring to the five cases, including ours, male patients are more frequent than female (4:1). Gastroenteritis, pneumonia, or pleural effusion, and encephalopathy were the characteristic manifestations. Three children resolved following only conservative management or intravenous immunoglobulin. In our case, his clinical manifestations and laboratory test results worsened despite intravenous immunoglobulin treatment, so we prescribed HLH-2004 chemotherapy.

The reason of rare case reports of adenovirus induced HLH comparing with other virus infection is not certain. We suggest the diagnostic modality could influence the frequency of virus. In all cases, including our patient, the PCR method helped to confirm the existence of adenovirus. Despite of the rarity, as we reviewed above, adenovirus can be trigger of HLH in immunocompetent patient, and result in severe multi-organ failure.

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