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Onset of Hemophagocytic Lymphohistiocytosis during Piperacillin-Tazobactam Therapy in Three Children with Acute Focal Bacterial Nephritis

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Hemophagoytic lymphohistiocytosis (HLH) is a rare life-threatening disorder caused by overactivation of the immune system, associated with infections, autoimmune disorders, and malignancies. The pathological hallmark of HLH is phagocytosis of blood cells and platelets by activated macrophages and histiocytes. In this report, we describe the onset of HLH in three children, aged 2, 5 and 7 years old, during the treatment of acute focal bacterial nephritis (AFBN) with an antibiotic, piperacillin-tazobactam (PIPC-TAZ). AFBN is acute localized bacterial infection of the kidney without abscess formation. PIPC-TAZ was chosen for the treatment of AFBN, because it not only has indications for complicated urinary tract infections, but also covers most of the causative bacteria of urinary tract infections, including β-lactamase-producing *Escherichia coli*. The clinical courses of the three patients were similar, and they were treated with PIPC-TAZ and amikacin (AMK) for AFBN. Fever went down 2 to 5 days later, and AMK was discontinued by day 6. However, fever recurred on 13 to 15 days after introduction of PIPC-TAZ therapy, even though all of the patients had no signs of recurrence of AFBN. The clinical features and laboratory tests of two patients fulfilled the criteria of HLH, whereas the other patient had initiated therapy before fulfilling the criteria. Cessation of PIPC-TAZ combined with corticosteroid therapy improved clinical symptoms. HLH of our patients was probably induced by PIPC-TAZ, as judged by the timing of the onset of HLH and the positivity of the drug-lymphocyte stimulation test. In conclusion, prolonged antibiotic therapy with PIPC-TAZ could be a cause of HLH.

Keywords: acute focal bacterial nephritis; antibiotics; computed tomography; hemophagoytic lymphohistiocytosis; piperacillin-tazobactam
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Introduction

Urinary tract infection (UTI) is one of the most common pediatric infections. It may cause permanent kidney damage. There are two broad clinical categories in UTI: upper UTI and lower UTI (cystitis). Upper UTI is classified as acute pyelonephritis, acute focal bacterial nephritis (AFBN) and renal abscesses. Focal mass lesions, which are not seen in acute pyelonephritis, are observed in AFBN and renal abscess by computed tomography (CT). The focal mass lesions observed in AFBN lack abscess formation. Thus, AFBN is an intermediate condition between acute pyelonephritis and renal abscess.

Hemophagocytic lymphohistiocytosis (HLH) is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes (Ishii et al. 2007; Chandrakasan and Filipovich 2013). It is characterized by clinical signs and symptoms of extreme inflammation, including fever, hepatosplenomegaly, pancytopenia, lymphadenopathy, and skin rash. The pathological hallmark of this disease is phagocytosis of red blood cells (RBC), white blood cells (WBC), and platelets, by activated macrophages and histiocytes, thereby leading to clinical symptoms. HLH is categorized into two groups. Primary or familial HLH is when there is a family history or known underlying genetic defect. Secondary HLH occurs after strong immunologic activation by systemic infection, immunodeficiency, autoimmunity, and malignancy (Chandrakasan and Filipovich 2013). In addition, drugs, such as antiepileptic drugs and anticancer drugs, are known to cause HLH (Lambotte et al. 2002; Yang et al. 2004; Gümüş et al. 2007; Ishii et al. 2007; Eshki et al. 2009; Oda et al. 2012). However, antibiotic-induced

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HLH is rarely reported (Picard et al. 2013; Gauchan et al. 2015). In this report, we present three pediatric patients with HLH that occurred during the treatment of AFBN with an antibiotic, piperacillin-tazobactam (PIPC-TAZ).

Materials and Methods

Piperacillin-tazobactam is a fixed combination medication containing extended-spectrum penicillin, piperacillin and a β-lactamase inhibitor, tazobactam (Sörgel and Kinzig 1993).

Informed consent was obtained from the parents of each child, and this study was approved by the ethics review board at Sendai Medical Center (C29-71).

Case Presentation

Case 1

A 5-year-old girl was admitted to our hospital with a 3-day history of fever. Ten days prior to admission, she had suffered from vomiting, diarrhea, and fever. She did not have a history of recurrent fever. On admission, physical examination revealed positive right costovertebral angle (CVA) tenderness. The laboratory examination revealed leukocytosis (19,800/mm^3) with neutrophilia (15,630/mm^3), elevation of C reactive protein (CRP; 26.9 mg/dl), and mild leukocyturia. A computed tomography (CT) scan showed patchy areas of enhancement in the left kidney (Fig. 1). Involved areas were lower density than normal parenchyma. She was diagnosed with AFBN, and intravenous antibiotic therapy with PIPC-TAZ and amikacin (AMK) was initiated on the first day of admission. *Escherichia coli* (*E. coli*) grew in her urine culture. Two days later, the patient's body temperature was normalized, and AMK was discontinued by day 5. However, on day 13 of admission, fever recurred, and two days later maculopapular rashes appeared on her whole body covering less than 50% of the body surface area. At that point, laboratory studies revealed WBC 6,700/mm^3 (neutrophils; Nt. 45%, eosinophils; Eo 1%, atypical lymphocytes; Aty-L 1%), hemoglobin (Hb) 13.7 g/dl, platelets 12.3 × 10^4/mm^3, aspartate transaminase (AST) 1,639 IU/L, alanine transaminase (ALT) 337 IU/L, lactate dehydrogenase (LDH) 8,406 IU/L, triglyceride (TG) 155 mg/dl, ferritin 108,638 ng/mL, sluble interleukin-2 receptor (sIL-2R) 3,812 U/mL, fibrinogen 173 mg/dL, and activated partial thromboplastin time (APTT) 53.0 seconds, international normalized ratio (PT-INR) 1.63, and natural killer (NK) cell activity 1%. Bone marrow aspirate revealed hypercellular marrow with occasional hemophagocytosis without any evidence of malignancy (Fig. 2). Viral culture of her throat was negative. Serum IgM antibodies against herpes simplex virus (HSV), cytomegarlovirus (CMV), and Epstein-Barr virus (EBV) were all negative. Urine was clear of WBCs and bacteria, and the blood culture was negative. An intensive search for an infectious, neoplastic, or autoimmune cause of the HLH was negative. The patient's constellation of clinical features (fever) and

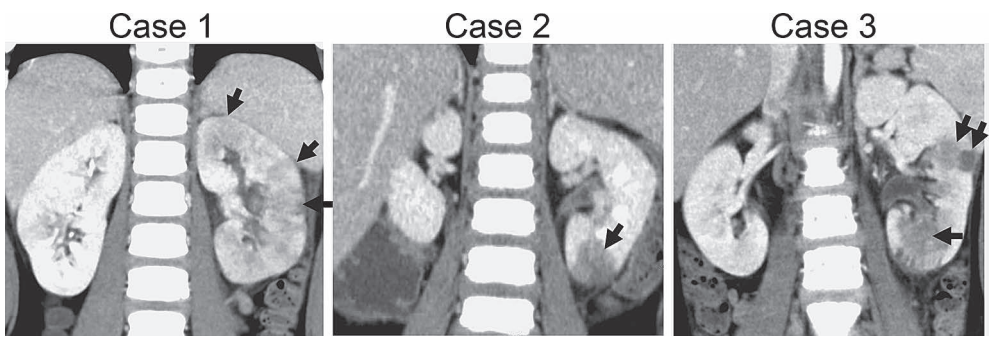

Fig. 1. Computed tomography scan.
Coronal images of enhanced CT demonstrated decreased enhancement areas (indicated by arrows) in the kidneys in all three patients.

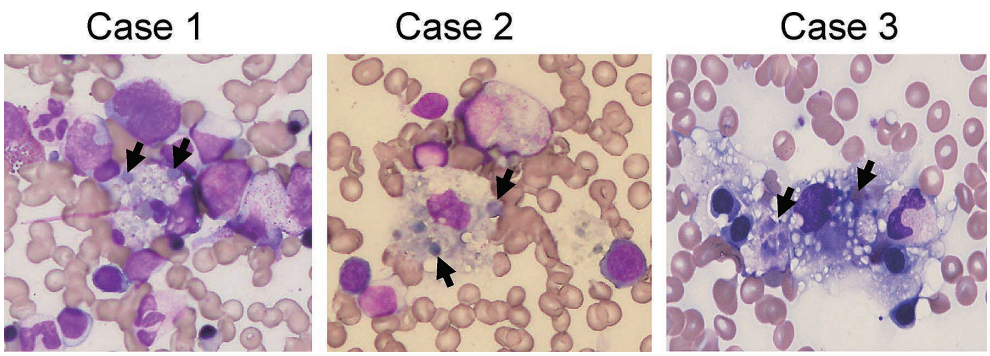

Fig. 2. Bone marrow smear.
Bone marrow smears showing activated macrophages with hemophagocytosis (May-Giemsa staining, original magnification × 400). Arrows indicate phagocyted neutrophils and platelets.

laboratory evaluation (hypofibrinogenemia, elevated ferritin and sIL-2R levels, lack of natural killer cell activity, and hemophagocytosis in the bone marrow) fulfilled the criteria of HLH. The patient was treated with intravenous methylprednisolone pulse therapy (30 mg/kg/day for 3 days) starting on day 15. With this therapy, fever went down and the patient's condition was improved, but itchy skin rash had persisted and the rash was enhanced especially soon after injection of PIPC-TAZ. PIPC-TAZ was discontinued on day 18, and was switched to cefotaxime (CTX). However, fever and skin rash recurred with eosinophilia 4 days later. After discontinuation of CTX, the skin rash was resolved gradually. Drug lymphocyte stimulation test (DLST) using PIPC-TAZ performed 30 months after the onset of HLH, revealed marked lymphocyte proliferation by PIPC-TAZ (stimulation index (S.I.) was 891%).

Case 2

A 2-year-old boy was admitted to our hospital with a 2-day's history of fever together with episodes of febrile convulsion and frequent vomiting. He had suffered from two episodes of fever of unknown origin. On admission, his consciousness was clear and he had tenderness in the right lower abdomen. The laboratory examination revealed leukocytosis (18,000/mm^3) with neutrophilia (14,830/mm^3), elevation of CRP (8.0 mg/dl), and bacteriuria. A CT scan revealed decreased enhancement areas in the left kidney and showed a dilated left ureter (Fig. 1). He was diagnosed with AFBN, and intravenous antibiotic therapy with PIPC-TAZ and AMK were initiated. High dose of intravenous immunoglobulin therapy (IVIG; 400 mg/kg/day for 4 days) was also administered because his condition had deteriorated by the following day along with marked elevation of CRP (21.0 mg/dL). *Enterococcus faecalis* grew in his urine culture. On day 5 of admission, the patient's body temperature was normalized, and AMK was discontinued. However, fever recurred on day 15, and a maculopapular appeared on his whole body with lymphadenopathy and splenomegaly two days later. At that point, laboratory studies revealed WBC 1,800/mm^3 (Nt. 11%, Eo 2%, Aty-L 0%), Hb 11.3 g/dl, platelets 10.3 × 10^4/mm^3, AST 408 IU/L, ALT 107 IU/L, LDH 2,230 IU/L, TG 160 mg/dl, ferritin 20,189 ng/mL, fibrinogen 190 mg/dl, APTT 62.3 seconds, PT-INR 1.21, and NK activity 10%. Bone marrow aspirate revealed hypocellular marrow with severe hemophagocytosis in the absence of monotonous premature cell proliferation (Fig. 2). Viral culture of his throat was negative. Serum IgM antibodies against HSV, CMV, and EBV were all negative. Urine was clear of WBCs and bacteria. The patient's constellation of clinical features (fever and splenomegaly) and laboratory evaluation (cytopenia in peripheral blood, low natural killer cell activity, elevated ferritin and sIL-2R levels, and hemophagocytosis in bone marrow) fulfilled the criteria for the diagnosis of HLH. The patient was treated with intravenous prednisolone therapy (2 mg/kg/day) and IVIG (2 g/kg). Although fever went down by the following day, skin rash and hepatomegaly persisted. In addition, abnormal laboratory data including cytopenia, elevated liver enzymes, hypertriglyceridemia (806 mg/dl), and elevated ferritin levels also persisted. Because the skin rash remained even after intravenous methylprednisolone pulse therapy (30 mg/kg/day for 3 days) on day 17 of admission, PIPC-TAZ was discontinued on day 26, and finally the skin rash disappeared. DLST could not be performed because the patient's family moved far away from our hospital.

Case 3

A 7-year-old girl was admitted to our hospital with a 3-day history of fever with cough followed by frequent vomiting and abnormal behaviors. She did not have an episode of recurrent fever. On admission, her consciousness was clear and there were no signs of meningitis. The laboratory examination revealed leukocytosis (22,200/mm^3) with neutrophilia (19,380/mm^3), elevation of CRP (8.5 mg/dl) and mild leukocyturia. Although the patient received antibiotic therapy with ceftriaxone (CTRX) for 3 days, high fever continued. To search for the cause of the fever, ultrasonography was performed and found an enlarged left kidney. A CT scan revealed patchy enhancement in the left kidney and duplicate renal pelvis on the same side (Fig. 1). She was diagnosed with AFBN, and intravenous antibiotic therapy with PIPC-TAZ and AMK was initiated. On the second day of the therapy, fever went down. Urine culture on admission was negative, and AMK was discontinued by day 6. On day 14 of treatment with PIPC-TAZ, fever recurred. At that point, laboratory studies showed WBC 2,600/mm^3 (Nt. 65%, Eo 0%, Aty-L 3%), Hb 12.9 g/dl, platelets 13.3 × 10^4/mm^3, AST 140 IU/L, ALT 119 IU/L, LDH 999 IU/L, TG 116 mg/dL, ferritin 5,932 ng/mL, sIL-2R 1,756 U/mL, fibrinogen 334 mg/dl, APTT 35.2 sec, and PT-INR 1.10. Viral culture of her throat was negative. Urine was clear of WBCs and bacteria, and the blood culture was negative. Bone marrow aspiration revealed normocellular marrow with proliferation of reactive histiocytes with hemophagocytosis of neutrophils and erythroblasts without evidence of malignant cells (Fig. 2). From our previous experience of Cases 1 and 2, we stopped PIPC-TAZ on day 14 of the antibiotic therapy and started treatment with intravenous prednisolone (60 mg/day), although the patient's clinical features did not fully fulfill the criteria of HLH. With this therapy, fever went down within 2 days and the patient's condition was improved. DLST using PIPC-TAZ performed 6 months after the onset of HLH, revealed marked lymphocyte proliferation (stimulation index was 451%).

Discussion

Secondary HLH is a condition that can occur after strong immunologic activation, such as infections, autoimmune diseases, and malignancies, and is associated with high mortality (Ishii et al. 2007; Chandrakasan and Filipovich 2013). In addition, anti-epileptic drugs and anti-

cancer drugs are known to cause HLH (Lambotte et al. 2002; Yang et al. 2004; Gümüş et al. 2007; Eshki et al. 2009). However, antibiotic-associated HLH is rarely reported (Picard et al. 2013; Gauchan et al. 2015). One reason for this rarity is due to the fact that drug-associated HLH is based on drug hypersensitivity, as reported in previous cases (Lambotte et al. 2002). A severe delayed adverse drug-induced reaction with eosinophilia and systemic symptoms is called DRESS using its acronym. The diagnosis is based on clinical pictures and data including fever, enlarged lymph nodes, eosinophilia, atypical lymphocytes, skin involvement, organ involvement, and negative antinuclear antibodies, blood culture, viral hepatitis, chlamydia and mycoplasma (the regiSCAR criteria for DRESS; Kardaun et al. 2007). HLH and DRESS have similar characteristics, such as activated lymphocytes and hypercytokinemia. However, $CD8^{+}$T-cell activation, which is a hallmark of HLH, is rarely observed in DRESS. Only a few cases develop uncontrolled activation of macrophages, and result in hemophagocytosis in the bone marrow (Picard et al. 2013). In our cases, none had eosinophilia when fever recurred, and only Case 2 was classified as a possible case of DRESS, whereas Cases 1 and 3 were not the case based on the regiSCAR criteria for DRESS. Thus, we speculate that drug-associated HLH is based on drug hypersensitivity but it is not necessarily to be DRESS, a severe form of drug hypersensitivity. It is difficult to distinguish cytopenia as a side effect of drugs from drug-associated HPS because bone marrow examinations are not usually done and corticosteroids are used for the first line drug of drug hypersensitivity. In addition, it is difficult to discriminate bacteria-induced HLH from antibiotic-induced HLH, because bacterial infections themselves can induce HLH (Wada et al. 2003; Hoshino et al. 2007; Ishii et al. 2007; Rouphael et al. 2007; Chandrakasan and Filipovich 2013; Masiá et al. 2014). In our cases, urine was clear of pyuria and bacteriuria when fever recurred, and bacteria were not detected in the blood samples of the two examined cases. Thus, we have concluded that PIPC-TAZ could cause HLH. One report describes ceftazidime-associated HLH in a patient with bacterial meningitis after ventricular drain replacement for subarachnoid hemorrhage in a previously healthy 55-year-old woman (Picard et al. 2013). The other describes amoxillin clavulanate-associated HLH in a patient with upper respiratory tract infection in a previously healthy 24-year-old woman (Gauchan et al. 2015). These two patients exhibited characteristic drug hypersensitivity-related febrile exanthema two weeks after the initiation of antibiotic therapy, and subsequently, developed cytopenia.

In the present study, we reported three patients with HLH associated with PIPC-TAZ, which was used for treatment of AFBN. PIPC-TAZ was chosen for the treatment of AFBN, because it not only has indications for complicated urinary tract infections but also covers most of the causative bacteria of urinary tract infections including β-lactamase-producing *E. coli* (Nowé 1994; Naber et al. 2002). All of our patients showed cytopenia after two-week of antibiotic therapy without any signs of recurrence of AFBN. Although Cases 1 and 2 developed febrile exanthema, only Case 2 was classified as a possible case of DRESS based on the regiSCAR criteria for DRESS. There are many reports on PIPC-TAZ-induced DRESS (Cabañas et al. 2014; González Díaz et al. 2015; Kim et al. 2016). However, to the best of our knowledge, this is the first report on HLH associated with TAZ/PIPC. In addition, we could not find any report on HLH associated with AFBN. Cessation of PIPC-TAZ combined with corticosteroid therapy improved clinical symptoms. From our previous experience, we intentionally stopped PIPC-TAZ and started corticosteroid therapy in Case 3 when febrile cytopenia developed, although the patient did not fulfill the criteria of HLH. The patient recovered from cytopenia promptly. DLST using PIPC-TAZ was performed in Cases 1 and 3, and was positive in both cases. Since we used the commercially available premixed antibiotic PIPC-TAZ for DLST, we could not specify which drug (PIPC or TAZ) was the causative agent. Unfortunately, DLST could not be done in Case 2, because the patient's family had to moved far away. Taken together, HLH of our patients was thought to be a result of prolonged antibiotic therapy of PIPC-TAZ as demonstrated by the timing of the onset, and the positivity of DLST.

Most cases of drug reaction are induced by a single drug. However, patients with drug reaction are known to be at risk for multiple drug hypersensitivity (Cacoub et al. 2011; Daubner et al. 2012). Some patients are sensitized to unrelated drugs during the course of drug reactions to the first causative drug. In case 1, fever and the skin rash recurred even though antibiotics were switched from PIPC-TAZ to CTX. The result suggests that initial drug reaction that was triggered by PIPC-TAZ sensitized the patient to another antibiotic CTX.

In conclusion, we propose that prolonged therapy with PIPC-TAZ could be a cause of HLH. It is, therefore, important to consider HLH when patients requiring long-term antibiotic therapy show febrile cytopenia.

Conflict of Interest

The authors declare no conflict of interest.

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