Pulse Methylprednisolone Therapy in Type 3 Adenovirus Pneumonia with Hypercytokinemia

IKUKO TAKAHASHI, TSUTOMU TAKAHASHI, SATOKO TSUCHIDA, TAMAKI MIKAMI, HIROYUKI SAITO,¹ CHIAKI HATAZAWA² and GORO TAKADA

Department of Pediatrics, Akita University School of Medicine, Akita, Japan,
¹Akita Prefectural Institute of Public Health, Akita, Japan, and
²Division of Pediatrics, Akita Kumiai Hospital, Akita, Japan

Takahashi, I., Takahashi, T., Tsuchida, S., Mikami, T., Saito, H., Hatazawa, C. and Takada, G. Pulse Methylprednisolone Therapy in Type 3 Adenovirus Pneumonia with Hypercytokinemia. Tohoku J. Exp. Med., 2006, 209 (1), 69-73 —— Adenovirus pneumonia is uncommon but its severe infection has a mortality as high as 10%, and survivors may have residual airway damages, manifested by bronchiectasis, bronchiolitis obliterans, or pulmonary fibrosis. We report a case of adenovirus pneumonia demonstrating fatal respiratory distress. Adenovirus was isolated from pharyngeal specimens using cell culture and typed as serotype 3 by a combination of polymerase chain reaction (PCR) and restriction fragment length polymorphism analysis. The patient characteristically showed hypercytokinemia, characterized by increased levels of lactate dehydrogenase, ferritin, and several cytokines including interferon-γ and interleukin-6. We treated the patient with pulse methylprednisolone therapy (25 mg/kg/day, for 3 days), resulting in the rapid amelioration of respiratory distress. This is the first report describing the treatment of pulse methylprednisolone therapy in fatal adenovirus pneumonia. During the clinical course, serum Krebs von den Lungen-6 (KL-6), which is a marker for the activity of diffuse interstitial lung disease, was elevated, suggesting that serum KL-6 could be available as a marker of pulmonary prognosis in viral pneumonia. ——— type 3 adenovirus; pneumonia; pulse methylprednisolone therapy; KL-6

© 2006 Tohoku University Medical Press

Adenovirus is a well-known cause of acute respiratory infections in infants and children, usually caused by type 1, 2, 3, 5, or 6. Adenovirus pneumonia is uncommon but its severe infection has a mortality as high as 10%, and survivors may have residual airway damages, manifested by bronchiectasis, bronchiolitis obliterans, or pulmonary fibrosis. Any of the respiratory serotypes can cause pneumonia, but severe infection is most likely due to type 3, 5, or 7 (Munoz et al. 1998). We here report a girl with type 3 adenovirus pneumonia showing respiratory distress complicated by virus-associated hypercytokinemia. The patient was treated with intravenous pulse methylprednisolone therapy, resulting in the rapid amelioration of respiratory distress, but residual airway damage was left as the sequelae. We discuss treatment of adenovirus pneumonia, espe-
Adenovirus Pneumonia. We also suggest that serum Krebs von den Lungen-6 (KL-6) could be available as a marker of pulmonary prognosis in viral pneumonia.

**CASE REPORT**

The patient was a term 3,160 g girl uneventfully born to healthy Japanese parents. There was nothing remarkable during her infancy. At the age of 2.2 years, the patient presented to the hospital on 6 December 2003, designated as day 0, with high fever, 40°C, and productive cough. She was hospitalized with pneumonia and treated with antibiotics. After fever initially normalized, she again developed high fever and productive cough with dyspnea on day 6. Over the next 6 days, her fever and dyspnea worsened despite antibiotic treatment and γ-globulin administration. The patient was diagnosed with adenoviral pneumonia by positive immunoreactive detection of adenovirus antigen in her pharyngeal specimens and referred to our hospital on day 12.

On admission, her height and weight were 87.5 cm (+0.7 standard deviation, [S.D.]) and 12.0 kg (+0.48 S.D.), respectively. The patient had an increased respiratory rate of 60 /min and showed dyspneic respiration with nasal alar breathing. Body temperature and heart rate were 38.5°C and 160 beats/min, respectively. The findings of a chest examination were notable for bilateral basilar rales. The findings of a chest X-ray examination were notable for bilateral hilar infiltrations. There was no conjunctivitis, lymphadenopathy, or rash in the patient.

Laboratory tests showed the following: white blood cell count, 9,100/mm³ (normal, 4,900-13,400 /mm³); red blood cell count, 462 × 10³/mm³ (normal, 391-507 × 10³/mm³); platelet count, 462 × 10³/mm³ (normal, 117-329 × 10³/mm³); hemoglobin, 11.3 g/dl (normal, 12.1-16.7 g/dl); C-reactive protein, 1.6 mg/dl (normal, < 0.2 mg/dl); aspartate aminotransferase, 147 U/L (normal, 13-34 U/L); alanine aminotransferase, 70 U/L (normal, 8-41 U/L); lactate dehydrogenase, 1,328 U/L (normal, 124-234 U/L); ferritin, 420.6 ng/ml (normal, < 233.7 ng/ml); Na, 131 mEq/L (normal, 135-147 mEq/L); K, 4.1 mEq/L (normal, 3.5-4.9 mEq/L); Cl, 90 mEq/L (normal, 95-110 mEq/L); prothrombin time, 75.4% (normal, 70-130%); thrombin time, 84.1% (normal, 70-130%); fibrinogen, 411.2 mg/dl (normal, 160-360 mg/dl); fibrinogen degradation product (FDP), 10.72 μg/ml (normal, < 10 μg/ml); antithrombin-III, 121.9% (normal, 75-125%); total cholesterol, 133 mg/dl (normal, 131-253 mg/dl); high density lipoprotein (HDL) cholesterol, 28.8 mg/dl (normal, 36.8-95.3 mg/dl). Routine cultures, including pharyngeal specimens and blood, were all negative. Blood gas analysis under room air condition showed the following: pH, 7.596; pO₂, 89.1 mmHg; pCO₂, 32.3 mmHg; HCO₃⁻, 32.8 mmol/L; Base excess, 9.1. The concentrations of several cytokines were increased as followed: soluble interleukin-2 receptor, 4,620 U/ml (normal, < 1,090 U/ml); interferon-γ, 35 U/ml (normal, < 1.0 U/ml); interleukin-6, 34.4 pg/ml (normal, < 4.0 pg/ml). The levels of lactate dehydrogenase and ferritin in serum were elevated, corresponding to the increased levels of several cytokines in the patient. From these findings, we determined that the pathogenesis of high-grade fever and pneumonia in this case was attributable to hypercytokinemia induced by virus infection. With informed consent obtained from the parents, treatment with intravenous pulse methylprednisolone (25 mg/kg/day) for 3 days was initiated promptly and followed by daily oral prednisolone (1 mg/kg/day). The patient showed rapid amelioration: fever disappeared within 24 hrs, and O₂ requirement and auscultation normalized in 3 days (Fig. 1). Adenovirus was isolated from her pharyngeal specimens using cell culture and typed as serotype 3 by a combination of PCR and restriction fragment length polymorphism (RFLP) analysis (Fig. 2) (Saitoh-Inagawa et al. 1996). During the clinical course, serum KL-6, which is a marker for the activity of diffuse interstitial lung disease, was elevated to 958 U/dl, 1,172 U/dl, 805 U/dl, 611 U/dl, and 590 U/dl (normal, < 250 U/dl) on day 12, 31, 68, 3 months, and 1 year, respectively.

For evaluation of lung damage, radionuclide perfusion imaging with ⁸¹ᵐKr and ⁹⁹ᵐTc and chest computed tomography (CT) scan were per-
formed after 8 months and 11 months, respectively. Both ventilation and perfusion of a left lung were extremely decreased in the images acquired during tidal breathing using $^{81m}$Kr gas and $^{99m}$Tc-MAA (Fig. 3). Decreased ventilation and perfusion were demonstrated as spotty images in the right lung (Fig. 3). On chest CT scan, spotty low-density lesions were scattered in the right lung and predominated in the left lung. Findings of bronchiectasis were also observed in the bilateral lungs (Fig. 4).

**DISCUSSION**

Adenovirus can be associated with severe or fatal infection in both immunocompromised and healthy individuals (Munoz et al. 1998). Our case involved adenoviral pneumonia occurring in a previously healthy child. The patient characteristically showed increased levels of several cytokines, soluble interleukin-2 receptor, interferon-$\gamma$, and interleukin-6. Some abnormal laboratory data, elevated levels of lactate dehydrogenase and ferritin in serum, corresponded to the increased
Adenovirus Pneumonia

There have been a limited number of case reports describing adenovirus pneumonia complicated with hypercytokinemia (Mistchenko et al. 1994; Morimoto et al. 2003; Seidel et al. 2003). In a report describing 38 patients with an acute lower respiratory tract infection due to adenovirus, high serum values for interleukin-6, interleukin-8 and tumor necrosis factor alpha were associated with the severity of adenoviral infection (Mistchenko et al. 1994). Thus, our case was expected to become fatal. There have been some reports that adenovirus pneumonia was successfully treated with intravenous ribavirin (Gavin and Katz 2002). Other reports described successful treatment with a combination of intravenous immunoglobulin and clarithromycin, dexamethasone and cyclosporin A, or intravenous ribavirin and immunoglobulin (Sabroe et al. 1995; Morimoto et al. 2003; Seidel et al. 2003). However, we chose intravenous pulse methylprednisolone therapy as a treatment, because we considered hypercytokinemia to be the predominant pathogenesis of respiratory distress and high fever in our case. Intravenous pulse methylprednisolone therapy provided rapid amelioration and the patient survived. This is the first report that a fatal outcome of adenovirus pneumonia was successfully averted by intravenous pulse methylprednisolone therapy. Unfortunately, the patient had residual airway damage shown on lung CT scan and radionucleotide perfusion imaging with $^{81m}$Kr and $^{99m}$Tc, but intravenous pulse methylprednisolone therapy could be one of the options for treatment of potentially fatal viral pneumonia, especially in cases demonstrating hypercytokinemia.

Serum KL-6 is a well-known marker for the activity of diffuse interstitial lung involvement (Kohno et al. 1989). We sequentially measured serum levels of KL-6 in our patient. Elevated levels of KL-6 were observed on day 12 and continued for at least one year. These data demonstrated that residual pulmonary damage after viral

Fig. 3. Radionuclide perfusion imaging with $^{81m}$Kr and $^{99m}$Tc. Both ventilation and perfusion of the left lung were extremely decreased on images acquired during tidal breathing using $^{81m}$Kr gas (A) and $^{99m}$Tc-MAA (B). Decreased ventilation and perfusion were observed as spotty images in the right lung.

Fig. 4. Chest CT image. Spotty low-density lesions were scattered in the right lung and predominately in the left lung. Findings of bronchiectasis were also observed in the bilateral lungs.
pneumonia might remain active for a long time. There has been also a report describing the usefulness of serum KL-6 to evaluate the pulmonary damage after adenovirus pneumonia (Takahashi et al. 2001). KL-6 may be a useful marker for pulmonary prognosis in children with viral pneumonia.

References


