



Case report

Adenovirus pneumonia treated with Cidofovir in an immunocompetent high school senior

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ABSTRACT

Most adenovirus infections are self-limiting in immunocompetent individuals. Here, we report a case of adenovirus pneumonia in a 17-year-old immunocompetent male. He was admitted to our emergency room complaining of a febrile sense, cough, and diarrhea for four days. Crackles in the left lung and a high fever (40.7 °C) were revealed. Initial chest X-ray and computed tomography images showed consolidation in the left lung. We immediately started empirical antibiotic treatment, but his clinical symptoms and pneumonic consolidation in radiography had not improved by hospital day three. Because adenovirus was detected in his sputum using RT-PCR, he was administered Cidofovir. After 24 h of Cidofovir treatment, the symptoms and fever subsided, and the consolidation in his X-ray was significantly reduced by hospital day nine. The early administration of Cidofovir could be beneficial for the treatment of adenovirus infection in immunocompetent patients.

1. Introduction

Adenoviruses typically cause minor infections in the upper and lower respiratory tract, conjunctiva, and gastrointestinal (GI) tract. Adenovirus infection mainly occurs in children younger than 4 years, and more than 80% of those infections result from immature humoral immunity [1]. Outbreaks of adenovirus infection are occasionally reported in young adults in closed settings, particularly the military, despite their normal immune status [2,3]. On the other hand, the cases of severe community acquired-adenovirus infection in the outside closed setting have been also reported [4]. The clinical course of adenovirus in immunocompetent patients is mostly self-limiting, and typically anti-viral treatment is not required [2,5]. Several studies have reported that early treatment with Cidofovir is beneficial not only in immunocompromised patients [6,7], but also in immunocompetent patients with a progressive clinical course [8]. Here, we report the case of a 17-year-old, male, high school senior with combined adenovirus pneumonia and gastroenteritis who showed rapid improvement after early treatment with Cidofovir. This study was approved by the Institutional Review Board of Ewha Womans University Hospital (ECT 2018-07-010).

2. Case report

A 17-year-old immunocompetent male visited our emergency department with a high fever, cough for four days previous, and abdominal pain, vomiting, and diarrhea (5–6 times per day) for two days previous to admission. He also complained of a sore throat, purulent sputum, and rhinorrhea, as well as a headache and dizziness at admission. He had a history of meningitis at the age of seven, and his 12-year-old brother had also complained of an upper respiratory infection for the previous three days. He was a senior in high school, and as an athlete (Taekwondo), he had been staying in an athlete's village for the previous two months with other student athletes training for an upcoming competition. He denied a history of smoking or alcohol.

His initial vital signs included blood pressure of 141/56 mmHg, heart rate of 114 beats/min, respiration rate of 22 breaths/minute, and a temperature of 40.7 °C. On physical examination, bilateral tonsillar hypertrophy with pharyngeal injection was identified. Coarse crackles were auscultated in the left lung field, and tenderness was revealed in left lower quadrant of the abdomen. There was no evidence of nuchal rigidity or impaired neurologic signs. Laboratory exams showed a normal total white blood cell (WBC) count ($5.01 \times 10^9/L$) with increased neutrophil proportion (84.0%) and decreased lymphocyte proportion (9.4%). Hemoglobin was within the normal range (14.0 g/

Abbreviations: GI, gastrointestinal; WBC, white blood cell; PSI, Pneumonia Severity Index; CRP, C-reactive protein; CT, computed tomography; RT-PCR, real-time reverse transcriptase polymerase chain reaction

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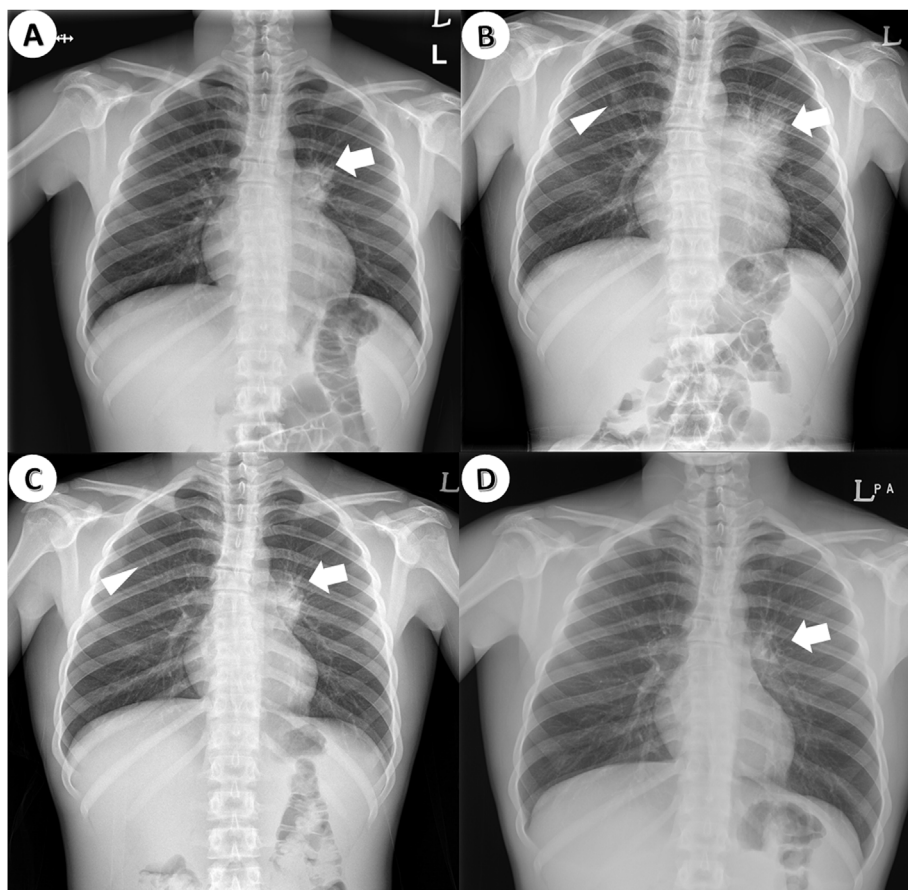


Fig. 1. Serial chest radiographs of a 17-year-old high school male with adenovirus pneumonia. (A) Radiograph at admission showing a dense consolidation (arrow) in the left upper and lower lung. (B) Extent of left lung consolidation progressed (arrow), with newly developed patchy consolidation in the right upper lung (arrow head) on hospital day three. (C) Consolidation in the left lung (arrow) was improved, and another right upper lung lesion (arrow head) had almost completely disappeared on hospital day nine. (D) Presumed pneumonic consolidation in both the upper and left lower lung zones (arrow) improved without definite residual lesions in chest radiographs two weeks after the initial study (after discharge).

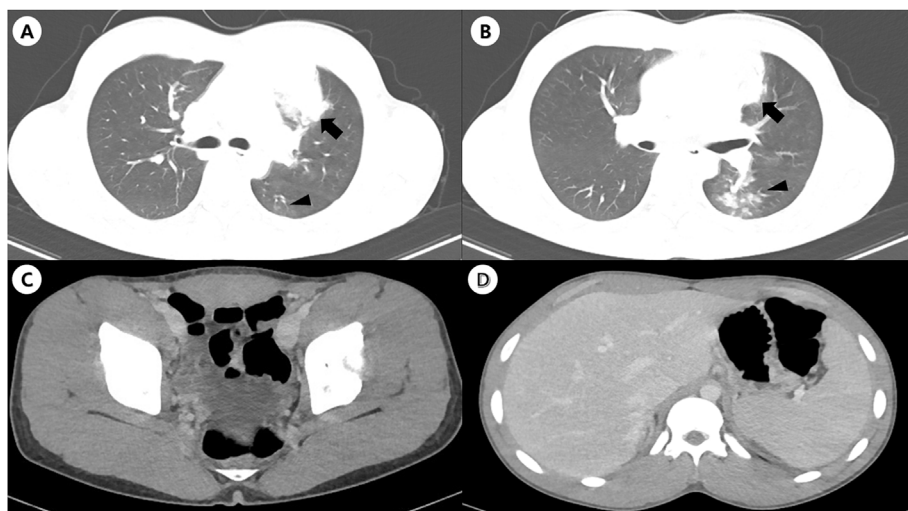


Fig. 2. Chest and abdominopelvic computed tomography (CT) images of a 17-year-old male high school student with adenovirus pneumonia and gastroenteritis. (A) Dense consolidation with infiltration was revealed in the left upper lung (arrow) on the chest CT. (B) In the superior segment of the left lower lung (arrow head), patchy consolidation and centrilobular nodules are shown. (C) On the abdominopelvic CT scan, diffuse wall thickening and mucosal enhancement are noted in the rectosigmoid colon, suggesting the possibility of proctocolitis. (D) Mild hepatosplenomegaly was also noted.

dL), but mild thrombocytopenia was revealed ($126 \times 10^9/L$). Hypochloremia (96 mEq/L) and hyponatremia (133 mEq/L) were observed with elevated C-reactive protein (CRP, 8.65 mg/dL; reference range: 0–0.3 mg/dL) and procalcitonin (0.88 ng/mL; reference range: 0–0.05 ng/mL). His community-acquired Pneumonia Severity Index (PSI) and CURB-65 scores were 31 and 1, respectively. An initial chest X-ray and computed tomography (CT) confirmed dense consolidation and centrilobular nodules in the left upper and lower lungs (Fig. 1-A, Fig. 2-A, B). An abdomen X-ray and CT showed diffuse bowel wall swelling, mucosal enhancement of the rectosigmoid colon, and mild hepatosplenomegaly (Fig. 2-C, D).

The patient underwent blood, urine, and sputum Gram stain/culture

tests and began empirical antibiotic treatment with a third-generation cephalosporin and a macrolide under an initial diagnosis of community-acquired pneumonia combined with severe extrapulmonary symptoms. On the third hospital day, the patient still showed a high fever and complained of a cough, vomiting, and diarrhea. His chest radiography showed infiltration and rapid progression in the left upper and lower lung fields and a newly developed consolidation in the right upper lung field (Fig. 1-B). Although his total WBC counts were still in the normal range ($4.43 \times 10^9/L$), neutrophilia (84.7%), lymphopenia (9.5%), and thrombocytopenia ($121 \times 10^9/L$) were sustained, and his CRP increased from 8.65 to 10.90 mg/dL. Multiplex real-time reverse transcription polymerase chain reaction (RT-PCR) for respiratory viruses in

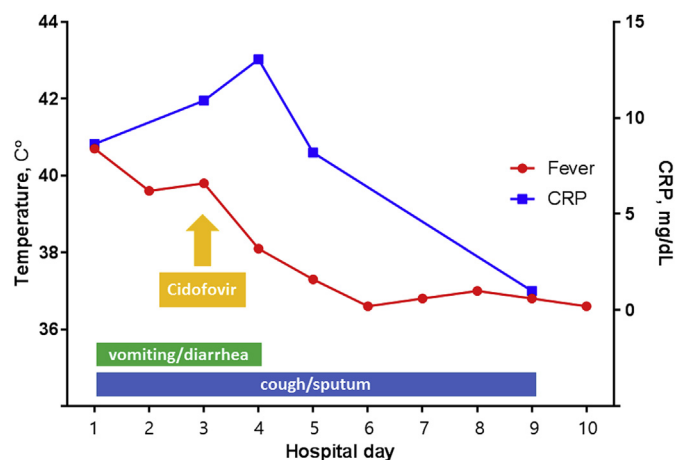


Fig. 3. Clinical course from admission to discharge of the 17-year old patient. HD, hospital day; CRP, C-reactive protein.

his initial sputum specimen was positive for adenovirus, whereas other microbiological tests, including mycoplasma antibody-PCR, acid-fast bacilli, fungus, and mycobacterium tuberculosis-PCR, were all negative. After observing the overall clinical findings, we diagnosed him with combined pneumonia and gastroenteritis caused by systemic adenovirus infection and administered Cidofovir (5 mg/kg per week) with probenecid for a progressive clinical course.

His fever subsided after 24 h of Cidofovir administration, and his other clinical symptoms also improved rapidly (Fig. 3); however, his radiologic and laboratory findings, including CRP (13.05 mg/dL) and platelet ($139 \times 10^9/L$) levels, did not improve until hospital day five. On hospital day nine, he complained of only a mild cough and showed significant improvement in the chest X-ray (Fig. 1-C) and normalization of laboratory markers such as CRP (1.0 mg/dL), platelets ($478 \times 10^9/L$), neutrophil (55.9%), and lymphocyte (29.5%) fraction (55.9%). In addition, abnormal renal function was not identified in follow-up laboratory tests after Cidofovir. He was discharged at hospital day 10, and an outpatient visit was scheduled to monitor further complications. After discharge, we confirmed that adenovirus was cultured in his sputum sample from the initial visit. The patient showed complete improvement of residual pneumonic consolidation in follow-up chest X-rays taken two weeks after discharge (Fig. 1-D).

3. Discussion

Adenoviruses typically cause mild and self-limiting infections, but they can show a severe course with high mortality even in healthy individuals. The transmission of adenovirus is mainly through the respiratory droplet or fecal-to-oral pathways, and closed contact in community settings such as military training camps or schools is considered a cause for the wide spread of the virus [9]. South Korea, China, and Malaysia are regions in which outbreaks occur frequently [10]. Particularly in the Korean military, numerous adenovirus infections have been documented in young patients (mean age: 20–22) [11,12]. In our case, we presumed that adenovirus spread to a high school student in close contact with others at an athletic training camp, which is a similar environment to the military; however, other colleges at the same training camp did not experience adenovirus infection.

Among military patients, the most frequent presenting symptoms are cough (83–98%) and fever (83–98%), with diarrhea presenting only rarely (12–20%). Our patient was younger (17 years) and complained of severe extrapulmonary GI symptoms due to combined gastroenteritis [11,12]. Adenovirus pneumonia typically shows accompanying symptoms of lethargy, diarrhea, and vomiting, unlike other community-acquired forms of pneumonia. In addition, certain adenovirus subgroups and serotypes are common agents of viral gastroenteritis in infants and

young children, along with rotavirus and norovirus [13]; however, it is rare for adults to have a severe disease course. Our young student, an immunocompetent patient, experienced mainly respiratory and gastrointestinal symptoms due to concurrent adenovirus infections of the GI tract and lungs.

In immunocompromised adults or children, adenovirus infection often shows a fatal course, but immunocompetent young adults mostly have mild symptoms [14]; however, severe adenovirus infection disease courses that lead to acute respiratory distress syndrome and require intensive care, intubation, and extracorporeal membrane oxygenation, have also been reported in immunocompetent individuals [15–17]. Thus, adenovirus infection should not be overlooked in healthy individuals. Although our patient did not show high PSI and CURB-65 score or respiratory failure, we decided to administer Cidofovir because he had experienced no improvement in clinical symptoms and rapid progression in radiological findings as of hospital day 3.

Few data are available on the treatment and timing of treatment for adenovirus, particularly in healthy individuals. Although Cidofovir has shown efficacy in treating adenovirus infections in transplant recipients, the use of Cidofovir for all adenovirus infections, even in immunocompetent patients [1,8], remains controversial because of the high risk of nephrotoxicity [18]. In our case, the patient showed remarkable improvement with early administration of Cidofovir and probenecid (before respiratory failure) because of persistent clinical symptoms (Fig. 3). A previous study on the early administration of Cidofovir in immunocompetent patients was consistent with our findings [8]. Although Kim et al. reported that complete improvement of symptoms and radiographic findings occurred a median of 12 and 21 days, respectively, after Cidofovir administration in non-immunocompromised patients, our patient show more rapid improvement [8]. In addition, Ortiz et al. suggested that the tubular cell apoptosis induced by Cidofovir was prevented by concurrent administration of probenecid [18]. Impaired renal function was not observed in our patient after the simultaneous administration of Cidofovir and probenecid.

In our patients, the serum level of CRP was elevated from the time of initial admission and decreased with the improvement of clinical symptoms after Cidofovir administration (Fig. 3). The elevated CRP is generally known to be used in the differential diagnosis of viral and bacterial infections due to its association with acute bacterial infection [19,20]. However, Jeon et al. report that initial elevated CRP is accompanied by a 61.3% (n = 3608) of respiratory virus infections including adenovirus and associated with the lengths of hospital stays [21]. Appenzeller et al. also demonstrate that in children with adenovirus infections (n = 87), CRP is significantly raised without the evidence of secondary bacterial infection [22]. Given that there was no evidence of other bacterial infections and that CRP level had decreased as clinical symptoms following Cidofovir administration, the increased level of CRP in our patients was likely to be derived from adenovirus infection itself, not a secondary bacterial infection.

This is a case report of a severe adenovirus infection in a 17-year-old high school student that resolved with Cidofovir treatment. The immediate administration of Cidofovir may be credited for the dramatic improvement in the disease course, symptoms, and laboratory findings. Several reports have indicated that severe adenovirus infections can cause high mortality in immunocompetent patients [14,23]; thus, Cidofovir could be an important treatment option to prevent disease progression in non-immunocompromised patients despite its nephrotoxicity. Patients with community-acquired pneumonia or colitis should be tested for adenovirus infection and treated appropriately early after detection.

Conflicts of interest

The authors declare no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.rmcr.2019.01.015>.

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