Case report

Adenovirus pneumonia treated with Cidofovir in an immunocompetent high school senior

Hee-Young Yoon, Hyun-Hae Cho, Yon Ju Ryu

Division of Pulmonary and Critical Care Medicine, Department of Internal Medicine, College of Medicine, Ewha Womans University, Seoul, Republic of Korea

Department of Radiology, Ewha Womans University, College of Medicine, Seoul, Republic of Korea

ARTICLE INFO

Keywords:
Adenovirus
Cidofovir
Healthy
Young adult
Pneumonia
Immunocompetent

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 the 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 × 10⁹/L) with increased neutrophil proportion (84.0%) and decreased lymphocyte proportion (9.4%). Hemoglobin was within the normal range (14.0 g/
dL), but mild thrombocytopenia was revealed (126 × 10⁹/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 × 10⁹/L), neutrophilia (84.7%), lymphopenia (9.5%), and thrombocytopenia (121 × 10⁹/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. 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 pneumatic consolidation in both the upper and 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.
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.

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 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.

References

[1] J.P. Lynch 3rd, A.E. Kajon, Adenovirus: epidemiology, global spread of novel serotypes, and advances in treatment and prevention, Semin. Respir. Crit. Care Med. 37 (4) (2016) 586–602.

[2] M.A. Ryan, G.C. Gray, B. Smith, J.A. McKeehan, A.W. Hawkworth, M.D. Malasig, Large epidemic of respiratory illness due to adenovirus types 7 and 3 in healthy young adults, Clin. Infect. Dis. Offic. Publ. Infecti. Dis. Soc. Am. 34 (5) (2002) 577–582.

[3] J.L. Sanchez, L.N. Binn, B.L. Innis, R.D. Reynolds, T. Lee, F. Mitchell-Raymundo, S.C. Craig, J.P. Marquez, G.A. Shepherd, C.S. Polyak, J. Conolly, K.F. Kohlhase, Epidemic of adenovirus-induced respiratory illness among US military recruits: epidemiologic and immunologic risk factors in healthy, young adults, J. Med. Virol. 65 (4) (2001) 710–718.

[4] J.H. Barker, J.P. Luby, A. Sean Dalley, W.M. Bartek, D.D. Erdman, Fatal type 3 adenoviral pneumonia in immunocompetent adult identical twins, Clin. Infect. Dis. Offic. Publ. Infecti. Dis. Soc. Am. 37 (10) (2003) e142–e146.

[5] F.A. Hakim, I.M. Tleyjeh, Severe adenovirus pneumonia in immunocompetent adults: a case report and review of the literature, Eur. J. Clin. Microbiol. Infect. Dis. Offic. Publ. Eur. Soc. Clin. Microbiol. 27 (2) (2008) 153–158.

[6] M.L. Doan, G.B. Mallory, S.L. Kaplan, M.K. Dishop, M.G. Schecter, E.D. McKenzie, J.S. Heine, O. Eldemir, Treatment of adenovirus pneumonia with cidofovir in pediatric lung transplant recipients, J. Heart Lung Transplant. Offic. Publ. Int. Soc. Heart Transplant. 26 (9) (2007) 883–889.

[7] M. Refaat, D. McNamara, J. Teuteberg, R. Kormos, K. McCurry, M. Shullo, Y. Toyoda, C. Bermudez, Successful cidofovir treatment in an adult heart transplant recipient with severe adenovirus pneumonia, J. Heart Lung Transplant. 27 (6) (2008) 699–700.

[8] S.J. Kim, K. Kim, S.B. Park, D.J. Hong, B.W. Jhun, Outcomes of Early Administration of Cidofovir in Non-Immunocompromised Patients with Severe Adenovirus Pneumonia, PLoS One 10 (4) (2015) e0122642.

[9] R. Dolin, M.J. Blaser, John E. Bennett, Douglas Mandell, eighth ed., Bennett’s Principles and Practice of Infectious Diseases vol. 2015, Elsevier/Saunders, Philadelphia, PA, 2015.

[10] S. Khanal, P. Ghimire, A.S. Dhamoon, The repertoire of adenovirus in human disease: the innocuous to the deadly, Biomedicines 6 (1) (2018).

[11] H. Yoon, B.W. Jhun, H. Kim, H. Yoo, S.B. Park, Characteristics of adenovirus pneumonia in military personnel, 2012–2016, J. Kor. Med. Sci. 32 (2) (2017) 287–295.

[12] J.J. Park, B.-J. Kim, E.J. Lee, K.S. Park, H.S. Park, S.S. Jung, J.O. Kim, Clinical Features and Courses of Adenovirus Pneumonia in Healthy Young Adults during an Outbreak among Korean Military Personnel, PLoS One 12 (1) (2017) e0170792.

[13] S. Khanal, P. Ghimire, A.S. Dhamoon, The repertoire of adenovirus in human disease: the innocuous to the deadly, Biomedicines 6 (1) (2018).

[14] T. Lion, Adenovirus infections in immunocompetent and immunocompromised patients, Clin. Microbiol. Rev. 27 (3) (2014) 441–462.

[15] N.M. Ahmad, M.P. Weinstein, S.E. Boruchoff, Life-threatening adenovirus pneumonia in an immunocompetent civilian adult, Infect. Dis. Clin. Pract. 13 (1) (2005) 39–41.

[16] W. Cheungpasitporn, J. Bruminhent, C. Thongprayoon, J. Pupaibool, Severe adenovirus pneumonitis in an immunocompetent patient, Ann. Med. Health Sci. Res. 7 (2017) 222–223.

[17] S.O. Ha, H.S. Kim, S. Park, K.-S. Jung, S.H. Jung, S.J. Han, H.-S. Kim, S.H. Lee, Severe ARDS caused by adenovirus: early initiation of ECMO plus continuous renal replacement therapy, SpringerPlus 5 (1) (2016) 1909.

[18] A. Ortiz, P. Justo, A. Sanz, R. Melero, C. Caramelo, M.F. Guerrero, F. Strutz, G. Muller, A. Barat, J. Egidio, Tubular cell apoptosis and cidofovir-induced acute renal failure, Antivir. Ther. 10 (1) (2005) 185–190.

[19] H. Pelisola, M. Jaakkola, C-reactive protein in early detection of bacteremic versus viral infections in immunocompetent and compromised children, J. Pediatr. 113 (4) (1988) 641–646.

[20] K. Sasaki, I. Fujita, Y. Hamasaki, S. Miyazaki, Differentiation between bacterial and viral infection by measuring both C-reactive protein and Z-S’-oligo adenylate synthetase as inflammatory markers, J. Infect. Chemother. Offic. J. Jpn. Soc. Chemother. 8 (1) (2002) 76–80.

[21] J.-S. Jeon, I. Rheem, J.K. Kim, C-reactive protein and respiratory viral infection, Kor. J. Clin. Lab. Sci. 49 (1) (2017) 15–21.

[22] C. Appenzeller, R.A. Ammann, A. Duppenthaler, M. Gorgievski-Hrisoho, C. Aebi, Serum C-reactive protein in children with adenovirus infection, Swis Med. Wkly. 132 (25–26) (2002) 345–350.

[23] D. Tan, H. Zhu, Y. Fu, F. Tong, D. Yao, J. Walline, J. Xu, X. Yu, Severe Community-Acquired Pneumonia Caused by Human Adenovirus in Immunocompetent Adults: a Multicenter Case Series, PLoS One 11 (3) (2016) e0151199.