



Severe adenovirus infection in children

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During the period from July 1, 1999 to September 30, 2000, 9 children with severe adenovirus infection were treated at Chang Gung Children's Hospital. The mean age was 22 months (range, 5-50 months). All of them had lower respiratory tract infections, which manifested as lobar or segmental pneumonia and pleural effusion. Eight (88.9%) of the 9 patients required intensive care and 4 of them required mechanical ventilation. Abnormal laboratory findings included leukocytosis, elevated C-reactive protein, anemia, and prolonged prothrombin time and partial thromboplastin time. Extrapulmonary complications included hepatitis (6 cases), encephalitis (3), conjunctivitis (3), periorbital ecchymosis (1), and coagulopathy (2). One patient died, resulting in a mortality rate of 12.5%. Follow-up at 3 months postdischarge, 5 patients (62.5% of survivors) had bronchiolitis obliterans and/or organizing pneumonia. Seven patients were infected by serotype 3 adenovirus, 1 patient by serotype 2, and another by serotype 11. In conclusion, the clinical, laboratory, and radiographic features of severe adenovirus infection may mimic bacterial infection. Rapid progression of the clinical course despite antibiotic therapy and the presence of unusual extrapulmonary symptoms are important clinical clues in the diagnosis of severe adenoviral infection.

Key words: Adenovirus, lower respiratory tract infection, children

Adenoviruses are non-enveloped icosahedral DNA viruses. They frequently cause acute respiratory diseases that range in severity from mild upper respiratory tract infection to serious lower respiratory tract infection or severe, disseminated life-threatening disease [1-2]. Adenovirus infections occur primarily in infants and children less than 5 years of age, accounting for 2% to 5% of the pediatric respiratory illnesses and 4% to 10% of childhood pneumonias [1]. Various clinical syndromes may result from infection depending on the viral serotype that causes disease and the immunologic status of the host. These are usually acute and self-limited but can be fatal [1,2].

In Taiwan, adenoviruses are endemic and can be isolated throughout the year. Data from a surveillance report by the Center for Disease Control in Taiwan showed an increase in the number of isolates positive for adenovirus throughout the country, from about 2% to 12%, during March 1, 1999 to July 1, 2000 [3]. Similar observations were also made in a study in

southern Taiwan during the winter of 1999 [4]. These findings prompted us to review the clinical presentations, laboratory and radiographic findings, treatment and outcome of 9 cases of severe adenovirus infection in previously healthy children treated at Chang Gung Children's Hospital (CGCH).

Materials and Methods

From July 1, 1999 to September 30, 2000, a total of 7178 viral culture specimens were processed in the Virology Laboratory of CGCH. Of these, 2149 (29.9%) were positive for viruses, among which 617 (28.7%) were adenoviruses. Adenoviruses comprised 24% (199/831) of the positive cultures in 1997, 13.2% (224/1693) in 1998, 24.4% (335/1372) in 1999, and 23.7% (394/1660) in 2000 (1998 vs 1999 and 2000, respectively, both $p < 0.05$). An increasing trend in the number of adenovirus isolates was observed compared with the previous 18-month period (Fig. 1).

Children with severe adenovirus infection hospitalized at CGCH were enrolled in the study. The diagnosis of adenovirus infection was based on a positive culture from specimens related to the patient's clinical signs and symptoms. Severe infection was defined as the involvement of at least one organ system

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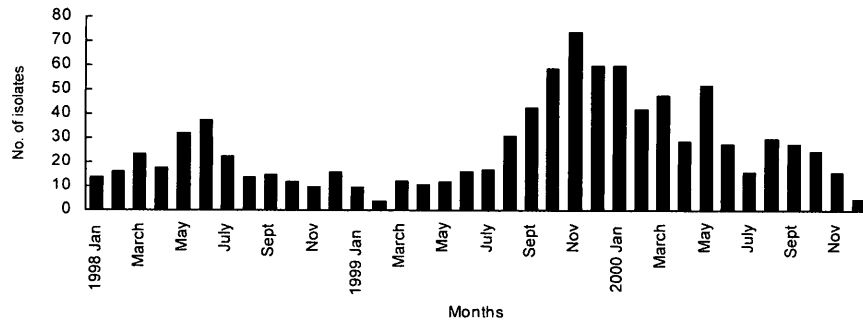


Fig. 1. Monthly distribution of the adenovirus isolates from Chang Gung Children's Hospital 1998-2000.

in a patient with a lower respiratory tract disease. Specimens were obtained from nasopharyngeal swabs, bronchoalveolar lavage, and stools. All specimens were collected in viral transport media. Five different tissue culture lines (HEP2, MRC5, MK2, MDCK, RD) were used for inoculation of respiratory specimens, while 4 (A549, MRC5, MK2, RD) were used for inoculation of anal specimens. The cultures were incubated at 37°C and examined every 2 days for cytopathic effect. The shell vials were stained after 2 days. The staining procedure was also used for examination of cytopathic effect in isolates recovered by conventional methods. Four of the 16 adenovirus isolates derived from the 9 patients were recovered from shell vial assay after 48 h of incubation. Twelve of the adenovirus isolates were recovered from conventional culture. The isolates were sent to Center for Disease Control, Taiwan for serotyping (by neutralization with type-specific antisera). Serologic study by complement fixation using paired sera with an interval of 2 weeks was done. Data on clinical manifestations, laboratory findings, chest radiographs, treatment and outcome of the patients with severe adenoviral infections were collected and analyzed.

Results

Severe adenoviral infection was diagnosed in a total of 9 patients during the study period. Five of these patients were boys. Their mean age was 22 months (range, 5-50 months). All patients were previously healthy, except for one Down syndrome patient with tracheomalacia and another patient with cerebral palsy. All of the patients had fever and cough, which progressed to respiratory distress. The median duration of fever was 12 days (range, 6-24 days). Clinical and radiographic findings were consistent with bronchiolitis in 2 patients, multilobar consolidation in 6, and pleural effusions in 2. The clinical and laboratory data of the patients are summarized in Table 1. The median duration of

hospitalization was 22 days (range, 9-76 days).

Hepatic involvement, characterized as hepatomegaly and/or elevation of aspartate aminotransferase and alanine aminotransferase twice the upper limit of normal value, was seen in 6 (66.7%) children. Encephalitis presenting as altered consciousness and seizure was observed in 3 children. Three children had conjunctivitis and one of them had an extensive subconjunctival hemorrhage extending into the periorbital area. Two children had coagulopathy (prolonged prothrombin and partial thromboplastin time), and one of them died.

Laboratory tests on admission showed a mean white blood cell count of $15.4 \times 10^3/\text{cmm}$ (range, $2.3\text{-}26.5 \times 10^3/\text{cmm}$). Four patients had leukocytosis ($>15 \times 10^3/\text{cmm}$), and one had leukopenia ($<5 \times 10^3/\text{cmm}$). The mean value of C-reactive protein (CRP) obtained at admission was 68.3 mg/L (range, 8-196.7 mg/L). Eight patients had elevated CRP ($>10 \text{ mg/L}$), but no bacterial causes of infection identified. Blood cultures were negative in all cases. Viral studies done in 4 patients were negative for respiratory syncytial virus, influenza A and B, and parainfluenza 1, 2, and 3. Mycoplasma serology tests done in 5 patients were negative. Paired sera were done in cases 1, 2, 8, and 9. There was a rise in the antibody titer in 3 patients (cases 1, 8, and 9). In case 2, the antibody response at admission was 1:2 and remained at that titer on follow-up 2 weeks after admission. Tests for Epstein-Barr virus (EBV) and herpes simplex virus (HSV) types 1 and 2 serology were negative in this case.

Eight patients were admitted to the pediatric intensive care unit, and 4 of them required mechanical ventilation. Antibiotics were initially given to 8 patients. Intravenous immunoglobulin was administered in 3 cases because of a prolonged and disseminated course. One patient with interstitial pneumonia, hepatitis, encephalitis, and disseminated intravascular coagulopathy had a rapidly fatal course and died 2 days

Table 1. Demographic data, chest radiographic findings, extrapulmonary manifestations, isolate sites, serotype, and outcome of severe adenovirus infections

Patient no.	Age	Sex	Underlying condition	Chest radiograph	Extrapulmonary manifestations	Site	Serotype	Outcome
1	2y8m	F	None	RML pneumonia	Hepatitis	NP	2	Survived
2	1y3m	F	None	LLL pneumonia with pleural effusion	Hepatitis, encephalitis	NP, R	11	Survived BO
3	1y8m	M	None	Bronchiolitis	Coagulopathy, anemia, encephalitis, hepatitis	NP, R	3	Died
4	11m	F	None	RUL, RML pneumonia	Conjunctivitis	NP, BAL	3	Survived
5	3y	M	Down syndrome, tracheomalacia	RML, RLL, LLL pneumonia	Hepatitis	NP, BAL, R	3	Survived BO
6	5m	F	None	RUL pneumonia	Anemia, hepatitis	NP	3	Survived BO
7	5m	M	None	Bronchiolitis	Hepatitis, conjunctivitis	NP, R	3	Survived
8	4y2m	M	Cerebral palsy	Pneumonia with pleural effusion	Hemorrhagic conjunctivitis with periorbital ecchymosis, encephalitis	NP, R	3	Survived BO
9	2y3m	M	None	LUL, LML pneumonia with pleural effusion	Coagulopathy, hepatitis	NP	3	Survived BO

Abbreviations: RML = right middle lobe; LLL = left lower lobe; RUL = right upper lobe; RLL = right lower lobe; LUL = left upper lobe; LML = left middle lobe; NP = nasopharyngeal swabs; R = rectal swabs; BAL = bronchoalveolar lavage; BO = bronchiolitis obliterans

after admission. Follow-up at 3 months postdischarge, 5 (50%) patients had chronic pulmonary sequelae of bronchiolitis obliterans, characterized clinically by cough and persistent respiratory distress. High resolution computed tomography scan of the chest showed multiple areas of consolidation and ground-glass appearance, representing obstructive pneumonitis in these patients.

Discussion

Adenovirus infections are common in children between 6 months and 5 years of age. Severe, overwhelming disease has been associated with newborns, malnutrition, environmental crowding, or a preceding viral disease [1]. The incidence of disseminated disease in immunocompetent children usually caused by serotypes 3, 7, and 21 is about 1% to 1.5% [5]. In this series, all children with severe adenoviral infections predominantly had lower respiratory tract involvement, including severe multilobar pneumonia and pleural effusions. The clinical course in all patients was usually acute, and characterized by fever, cough, and increasing respiratory distress. The most common extrapulmonary manifestations were hepatitis and encephalitis. Previous studies have reported that coagulopathy is associated with a poor outcome and is usually fatal [5,6,15]. Patient who had coagulopathy on presentation in this series died within 48 h after admission despite aggressive treatment.

The white blood cell count and CRP in our patients varied markedly, from leukopenia to leukocytosis and

from normal to elevated CRP, respectively, making it difficult to distinguish adenoviral disease from a bacterial disease [7,8]. Chest radiographic findings in these patients included bilateral diffuse infiltrates, multifocal lobar or segmental pneumonia and pleural effusion. These findings are compatible with a previous study by Han *et al* [9]. These features make it difficult to differentiate adenovirus from bacterial pneumonia by hematologic and chest radiographic features. Permanent pulmonary sequelae are reported in 14% to 60% of cases following adenovirus pneumonia [1]. Abnormal findings on follow-up chest radiographs included diffuse interstitial infiltrates, hyperlucent areas, or segmental atelectasis [10]. The typical computed tomography scan usually shows areas of low attenuation and decreased vascularity or multiple peripheral areas of consolidation and ground-glass attenuation, or bronchial wall thickening and dilatation [11]. Findings in this series are in agreement with earlier reports that 50% of patients had chronic pulmonary sequelae during the follow-up period [10].

The reasons for increased severity in some adenovirus infections are not clear. Children with immunodeficiency, malnutrition, or a preceding viral illness are considered more susceptible to the development of a severe disease [1,12,13]. All patients in this series were previously healthy, and this relationship could not be investigated because only one patient had a complete immunologic study, which was normal.

The diagnosis of adenovirus infection is based on either serology or isolation of the virus. Two to 8% of healthy children had adenovirus in the throat and anal samples [7]. Complement fixation test is convenient for diagnosis, but may fail to detect the antibody response in some cases [14]. Recovery of certain serotypes such as 3, 7, and 21 from respiratory secretions is probably more indicative of an etiologic involvement [2]. Most patients in this series had an adenovirus infection caused by serotype 3. Case 1 had a serotype 2 virus isolated, and showed an antibody response to the virus. Serotype 2 has been reported to cause disseminated disease in the immunocompromised patients [5], as well as epidemics of severe lower respiratory tract infections in young children in Korea [15]. In this study, Case 2 had a clinical course compatible with disseminated adenovirus infection and had a serotype 11 virus isolated. Electroencephalogram of this patient showed periodic lateralizing epileptiform discharges, which is a common feature in encephalitis caused by herpes simplex virus, but is rare in the cases of adenoviral encephalitis. Other viral studies (EBV and HSV types 1 and 2) done in this case did not show any evidence of acute infection. Although there was no seroconversion in this case, the clinical manifestations including encephalitis have been recently reported to be closely associated with adenovirus infection [16]. Serotype 11 was reported as the cause of a civilian outbreak of acute respiratory disease in the United States [17].

There is no specific therapy for adenovirus disease. The role of ribavirin as well as intravenous immunoglobulin in the therapy of severe adenoviral infection remains unclear. Ribavirin has been used in transplant recipients, immunocompromised patients, as well as newborn infants with anecdotal evidence of success [18,19].

In conclusion, we observed a clustering of severe cases, presenting with lower respiratory tract infection and extrapulmonary involvement caused mostly by serotype 3 in this study. Severe adenovirus infection may mimic bacterial infection in its clinical, laboratory, or radiographic features. Progression of the clinical course despite antibiotic therapy and the presence of extrapulmonary manifestations are important clues suggesting the possibility of adenovirus infection. Appropriate viral investigation should be done and aggressive intensive supportive care is the mainstay of treatment for such patients.

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