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Journal of Clinical Virology 54 (2012) 295–301

Contents lists available at SciVerse ScienceDirect

Journal of Clinical Virology

journal homepage: www.elsevier.com/locate/jcv

Severe community-acquired pneumonia caused by adenovirus type 11 in immunocompetent adults in Beijing

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ARTICLE INFO

Article history:
Received 24 November 2011
Received in revised form 2 April 2012
Accepted 25 April 2012

Keywords:
Adenovirus
Pneumonia
Type
Phylogenetic analysis

ABSTRACT

Background: Severe community-acquired pneumonia (CAP) due to human adenoviruses (HAdVs) in immunocompetent adults has raised concerns.
Objective: To describe the clinical, laboratorial, and radiological characteristics of adenovirus pneumonia and detect the type and diversity of human adenoviruses that caused acute respiratory distress syndrome (ARDS) in Beijing.
Study design: An etiological study of adult community-acquired pneumonia was carried out prospectively at Beijing Chao-Yang Hospital. A total of 18 cases with laboratory-confirmed adenovirus infections in 487 cases with CAP were observed clinically. The viral type and phylogenetic analysis were tested by polymerase chain reaction (PCR).
Results: Patients with adenovirus pneumonia typically reported flu-like symptoms. Some of them developed shortness of breath or severe dyspnea on 6 days after disease onset. The patients with ARDS usually present dyspnea, higher level of serum muscle enzymes and bilateral, mutilobal consolidation and patchy/ground-glass opacities. HAdVs type was detected in 17 samples and all of them belonged to species B (HAdV-11, 7, 3 and 14). Among them, HAdV-11 was most frequently (10/17), followed by HAdV-7 (5/17). Phylogenetic analysis of the partial penton nucleotide confirmed a close relationship with stains circulating in the Beijing region.
Conclusions: Our identification of severe respiratory illness due to adenovirus, especially type 11 may highlight the need for rapid diagnosis and improved surveillance, which may assist with targeted development of antiviral agents or type-specific vaccines.

1. Background

Human adenoviruses (HAdVs) are ubiquitous. The clinical spectrum of disease in humans can vary substantially.[1] Most of these infections are self-limited, with severe or disseminated disease confined to immunocompromised patients.[2,3] Since Ryan et al. reported adenovirus pneumonia-related deaths in two military recruits in 2001,[4] severe adenovirus infections causing significant acute respiratory distress syndrome (ARDS) have raised concerns for immunocompetent adults.[5,6]

To date, 55 different types[7,8] have been identified and grouped in seven different species (A–G) on the basis of distinctive characteristics. Specific types have been linked to distinct clinical syndromes. HAdV-3, and -7 are common causes of severe pneumonia in neonates and young children.[9,10] HAdV-4 are among the most important causes of ARDS in new military recruits.[11,12] Recently, HAdV-11 and -14 associated febrile respiratory diseases outbreaks have been reported in all ages.[5,13]

The clinical features of severe adenovirus pneumonia in immunocompetent adults has been partially reviewed in 2 previous papers,[6,14] but the data came from only sporadic case report, which limits our understanding of clinical features, lab

Abbreviations: HAdVs, human adenoviruses; ARDS, acute respiratory distress syndrome; CAP, community-acquired pneumonia; PCR, polymerase chain reaction; RT-PCR, real-time polymerase chain reaction; SD, standard deviations; IQR, interquartile range; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; CK, creatinine phosphokinase; HBDH, hydroxybutyrate dehydrogenase; ECMO, extracorporeal membrane oxygenation; HRCT, high resolution computed tomography; ORF, open reading frame.

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http://dx.doi.org/10.1016/j.jcv.2012.04.018

findings, radiological characteristics, treatments, and outcomes of adenovirus pneumonia.

2. Objectives

The objective of this study is to detail the clinical, laboratorial, and radiological characteristics of adenovirus pneumonia. The clinical differences in patients with ARDS and non-ARDS were compared for identifying which type of adenovirus is prone to ARDS in Beijing and their virus diversity.

2.1. Study design

From August 2008 to April 2011, a prospective cohort study was carried out for the etiological study of adult community-acquired pneumonia (CAP) (age $\geq$ 14 years) at Beijing Chao-Yang Hospital. A total of 487 community acquired pneumonia cases were enrolled. CAP was defined as the presence of an infiltrate on chest radiograph and at least one of the following signs and symptoms: cough, sputum production, dyspnea, fever, auscultatory findings of abnormal breath sounds, and rales. None of the patients were immunocompromised; patients with HIV infection, neutropenia, or who were receiving immunosuppressive chemotherapy were excluded. In addition, patients from nursing homes or patients who had been admitted to a hospital within the last 30 days were also excluded.

2.2. Data collection at study entry

Data collected at hospital admission or outpatient visit included place of residence, antibiotic treatment prior to admission/outpatient visit, age, gender, comorbid illnesses, and smoking status. Clinical symptoms, vital signs, site of hospital admission/outpatient visit, and antimicrobial treatment were also recorded. Chest radiographic findings were classified as alveolar, interstitial, or mixed infiltrate. Extension (i.e., the number of lobes) involved and bilaterality, and presence of pleural effusion were also recorded. Recorded complications included the following: use of mechanical ventilation, septic shock; and empyema (defined as infected pleural fluid drained by a chest tube). The 30-day mortality rate was also recorded.

2.3. Microbiological evaluation

Throat swabs, sputum, blood, urine, and acute and convalescent serum samples were collected at the clinic and submitted to the Infectious Disease and Clinical Microbiology Laboratory. Microbiological methods were based on the following tests[15]: (1) sputum specimens for Gram stain and cultures considered valid only if microscopy showed >25 neutrophils and <10 epithelial cells per low fold microscopy; (2) urine specimens for *S. pneumonia* and *Legionella pneumophila* antigen rapid detection; (3) blood culture; (4) throat swabs and sputum for virus real-time polymerase chain reaction (RT-PCR) detection, including rhinovirus, influenza A and B, respiratory syncytial virus A and B, Adenovirus, parainfluenza 1–4, Coronavirus OC43 and 229E, and metapneumovirus; (5) throat swabs for *Mycoplasma pneumoniae* PCR detection and culture; (6) acute and convalescent serum samples for *Mycoplasma pneumoniae*, *Chlamydia Pneumoniae* and *Legionella pneumophila* antibody titer determination.

2.4. Typing of human adenoviruses by PCR

The species and types correlated very well with sequence polymorphisms of the genes coding for the primary antigenic determinants, including both the hexon coat protein and the receptor-binding fiber protein. The specie of adenovirus was identified by PCR with species-specific primers. Then, PCR again using type-specific primers targeted the hexon coat protein. The PCR products were sequenced (invitrogen) and then blasted in NCBI database for type of adenovirus. The primers used here were taken from the existing literature and described elsewhere.[16–18]

2.5. Phylogenetic analysis

Multiple sequence alignments and neighbor-joining trees with 1000 bootstrap replicates were generated based on the nucleotide sequences of the PCR products using MEGA 5.0 software.[19]

2.6. Nucleotide sequence accession numbers

Nucleotide sequences obtained in this study have been deposited in GenBank under accession numbers JQ838585–JQ838601.

2.7. Statistical analysis

Continuous variables were summarized as means $\pm$ standard deviations (SD) or medians (interquartile range [IQR]). For categorical variables, percentages of patients in each category were calculated. Differences between groups were assessed using the χ^2-test or the Fisher exact test for categorical variables and the Mann–Whitney *U*-test for continuous variables. All analyses were performed by SPSS software, version 13.0 (SPSS Inc; Chicago, IL). A p value of $\leq$0.05 was considered statistically significant.

3. Results

A total 18 cases were confirmed with adenovirus the only pathogen of pneumonia. Among the 18 confirmed patients, 15 were hospitalized, and 3 were treated as outpatients.

3.1. Clinical characteristics

As shown in Table 1, patients with adenovirus pneumonia usually were young adult and the median age was 28 years (range: 15–55 years), 88.9% were male. Two patients with ARDS had comorbidities, one with poliomyelitis and the other with diabetes mellitus. Patients typically report flu-like symptoms on onset of illness, such as fever, headache, sore throat, cough and little sputum. All patients presented high fever ($39.8 \pm 0.6\,^{\circ}$C) and cough. Duration of fever was 9 days (range: 6–11 days). Some patients presented dyspnea (11/18, 61.1%) and chest paint (4/18, 22.2%). Mean time from onset to dyspnea was 6 days (range: 5–7 days). At this time, patients usually presented respiratory failure or hypoxemia. Dyspnea and chills were significantly more frequent in the ADRS group ($p = 0.05$). Chemistry test desmonstrated serum aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatinine phosphokinase (CK) and hydroxybutyrate dehydrogenase (HBDH) levels were higher in the ADRS group, but only AST level was significantly higher than that in the non-ARDS group ($p = 0.005$). Most patients had a normal leukocyte, thrombocyte count and electrocyte value at presentation, with no difference between the ARDS and non-ARDS groups.

3.2. Radiographic features

In radiographic examinations, 13 patients were examined by high resolution computed tomography (HRCT) scan and 5 with chest X-ray. As shown in Table 2, 55.6% (10/18) of patients had bilateral lung infiltrate, 61.1% (11/18) had $\geq$2 lobars of lung infiltrate. Multiple or single lobar/segment consolidation was the most

Table 1
Comparison of clinical, laboratory and outcomes of patients with Adenovirus pneumonia who developed ARDS and those without.[a]

Characteristic	All cases[a] ($n=18$)	Value		
		ARDS[a] ($n=9$)	Without ARDS[a] ($n=9$)	p-Value
Age (years)	28.1 ± 12.3	29.7 ± 16.2	26.4 ± 7.1	0.59
Male sex (%)	16/18 (88.9)	8/9 (88.9)	8/9 (88.9)	1.00
Type (%)				
HAdV-11	10/18 (55.6)	6/9 (66.7)	4/9 (44.4)	0.63
HAdV-7	5/18 (27.8)	2/9 (22.2)	3/9 (33.3)	1.00
HAdV-3	1/18 (5.6)	0	1/9 (11.1)	
HAdV-14	1/18 (5.6)	0	1/9 (11.1)	
Unknown	1/18 (5.6)	1/9 (11.1)	0	
Any comorbidities (%)[b]	2/18 (11.1)	2/9 (0)	0/9 (22.2)	0.47
Clinical features				
T_{max} (°C)	39.8 ± 0.6	39.8 ± 0.5	39.9 ± 0.8	0.78
Duration of fever, median (IQR) (days)	9 (6–11)	11 (9–13)	6 (6–8)	0.001
Chill	11/18 (61.1)	8/9 (88.9)	3/9 (33.3)	0.05
Cough	18/18 (100)	9/9 (100)	9/9 (100)	1.00
Sputum	15/18 (83.3)	8/9 (88.9)	7/9 (77.8)	1.00
Chest pain	4/18 (22.2)	3/9 (33.3)	1/9 (11.1)	0.26
Dyspnea	11/18 (61.1)	8/9 (88.9)	3/9 (33.3)	0.05
Duration of dyspnea, median (IQR) (days)	6 (5–7)	6 (5–7)	7 (5–10)	0.53
Serum biochemical features				
AST, median (IQR) (U/L)	63 (32–168)	145 (61–311)	30.5 (24.5–58.3)	0.005
ALT, median (IQR) (U/L)	30.6 (23–81)	36 (25–115)	24.5 (20.3–46.3)	0.11
LDH, median (IQR) (U/L)	624 (307–1123)	932 (441–1564)	345 (198–778)	0.06
CK, median (IQR), U/L	537.5 (143.2–114.8)	604 (243–1994)	371 (61–745)	0.28
HBDH, median (IQR), U/L	531 (238–834)	709 (312–852)	233 (149–802)	0.14
Treatment				
Antiviral therapy	10/18 (55.6)	5/9 (55.6)	5/9 (55.6)	1.00
Antibiotics	18/18 (100)	9/9 (100)	9/9 (100)	1.00
Corticosteroids	10/18 (55.6)	6/9 (66.7)	4/9 (44.4)	0.64
Mechanical ventilation[c]	6/18 (33.3)	6/9 (66.7)	0/9 (0)	0.009
ECMO	1/18 (5.9)	1/9 (11.1)	0/9 (0)	1.00
Outcomes				
Length of hospital stay, median (IQR) (days)	12 (8–13)	12 (11–16)	8 (7–9)	0.006
In-hospital mortality	1/17 (5.9)	1/9 (11.1)	0/8 (0)	1.00

ARDS, acute respiratory distress syndrome; IQR, interquartile range; ECMO, extracorporeal membrane oxygenation.
[a] Continuous variables are expressed as medians or mean, and categorical variables are expressed as the no. of patients with the presence of the characteristic.
[b] Comorbidity in patients with ARDS were poliomyelitis and diabetes respectively.
[c] Four patients with ARDS received non-invasive ventilation, one patient with ARDS received invasive ventilation and ECMO, one patient with ARDS received invasive ventilation.

Table 2
Chest radiographic characteristics of patients who developed ARDS compared with those without.

Characteristic	All case patients ($n=18$)	Value		
		ARDS ($n=9$)	Without ARDS ($n=9$)	p-Value
No. of lobar involved ≥2	11/18 (61.1)	8/9 (88.9)	3/9 (33.3)	0.05
Bilateral infiltrate	10/18 (55.6)	8/9 (88.9)	2/9 (22.2)	0.02
Pleural effusion	10/18 (55.6)	6/9 (66.7)	4/9 (44.4)	0.64
Consolidation				
Mutiple lobar or segment	3/18 (16.7)	3/9 (33.3)	0/9 (0)	
Single lobar or segment	5/18 (27.8)	1/9 (11.1)	4/9 (44.4)	
Consolidation and mutifocal patchy/ground glass opacities	7/18 (38.9)	4/9 (44.4)	2/9 (22.2)	
Patchy infiltration (singal lobar)	3/18 (16.7)	0	3/9 (33.3)	
Diffuse ground-glass opacities	1/18 (5.6)	1/9 (11.1)	0/9 (0)	

ARDS, acute respiratory distress syndrome.
Categorical variables are expressed as no. of patients with the presence of the characteristics.

common HRCT finding, followed by ground-glass opacities. The airspace consolidation and ground-glass opacity were often shown at same time. Severe adenovirus pneumonia progressed very quickly within 1 week after onset, especially in patients with ARDS (Fig. 1A–D). HRCT showed that 88.9% (8/9) of patients with ARDS had bilateral and multilobar lung infiltrates (Fig. 2A). In patient without ARDS, single lobar or segment consolidation was more common (Fig. 2B). The radiologic abnormalities usually resolved in approximately 3 weeks.

3.3. Typing of human adenoviruses by PCR

Total 17 (94.4%) strains had type analysis results. All of them belonged to Species B. HAdV-11 was most common (10/17), followed by HAdV-7 (5/17), HAdV-3 (1/17), and HAdV-14 (1/17). Among nine ARDS cases, six cases were HAdV-11 (66.7%), two cases were HAdV-7 (22.2%), and one case was unknown (11.1%). Both HAdV-3 and HAdV-14 were found only in non-ARDS patients. A dead patient was caused by HAdV-11 (Table 1).

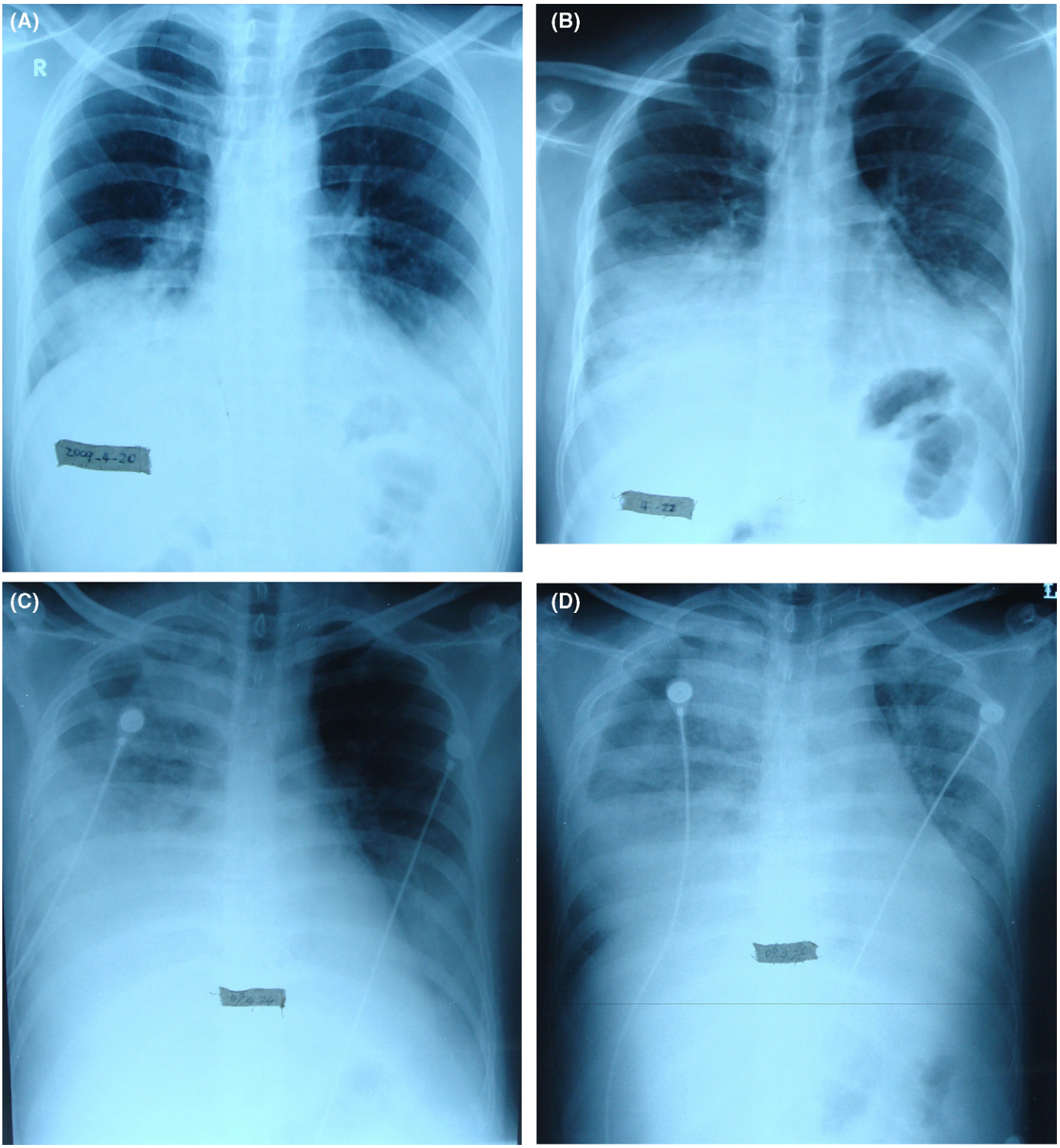

Fig. 1. ARDS due to adenovirus in a 23-year-old male. Chest radiograph showed the infiltrate progressed very quickly in the initial week: (A) bilower lung zones dense patchy infiltrate on Day 3 after onset; (B) light lower lung zones dense infiltrate was progressive on Day 5 after onset; (C) dense consolidations of right lung and left lower lobe are present on Day 7 after onset. The left upper lobe are spared; and (D) extensive bilateral consolidation consistent with ARDS on Day 9.

3.4. Phylogenetic analysis

The phylogeny of HAdV strains were analyzed based on the partial sequences of the hexon gene. Total of ten HAdV-11 strains were closely related with Beijing strains identified primarily in children (GenBank accession numbers EU513203, EU513204 and EU513206), even Japanese HAdV-11 (GenBank accession number AB248459). All HAdV-7 hexon sequences were tightly clustered including those circulating in the Beijing region (GenBank accession numbers JN168838, JN168833 and JN168829), showing high bootstrap support. The same result occurred in HAdV-3 and HAdV-14 (Fig. 3).

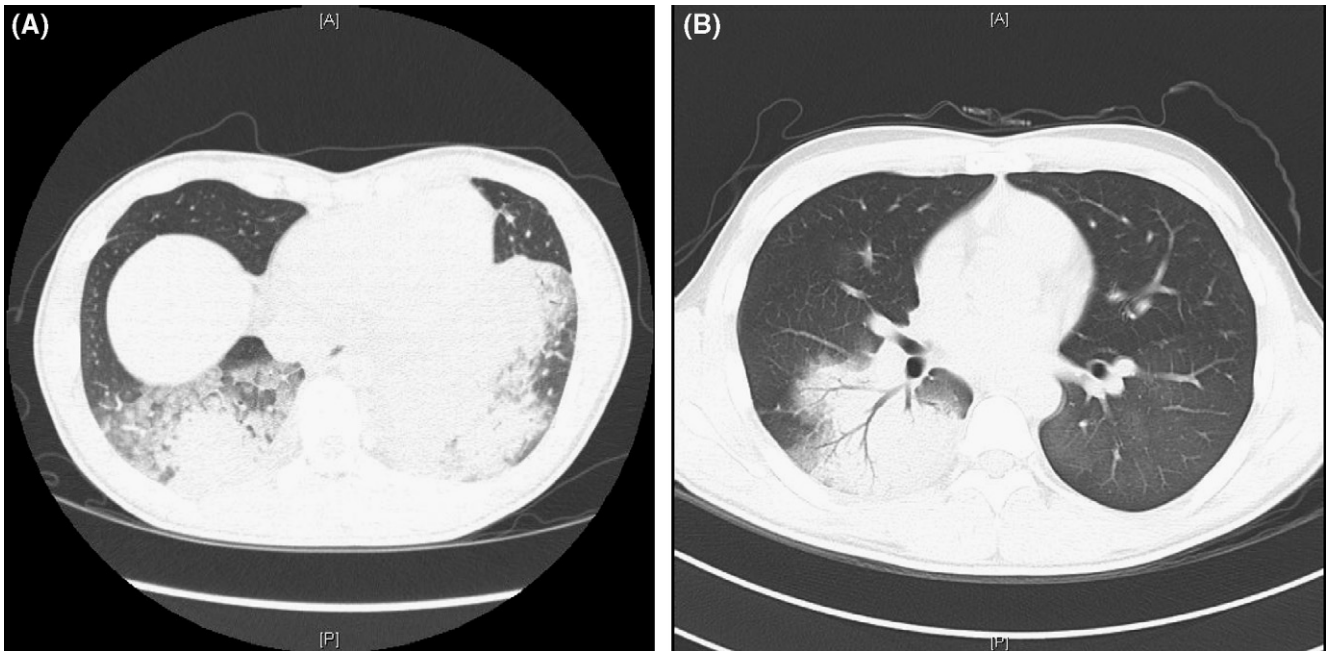

Fig. 2. (A) HRCT scans in a 16-year-old boy with ARDS due to adenovirus which showed bilower lobe consolidation, ground-glass opacity and left pleural effusion; (B) HRCT scans in a 18-year-old boy with adenovirus pneumonia but without ARDS showed right lower consolidation.

3.5. Treatment and outcome

As shown in Table 1, all patients received empirical intravenous antibiotics for 6–10 days. Ten out of 18 (55.6%) patients received corticosteroids, including dexamethasone or methylprednisolone, for 2–9 days. There is currently no formally approved antiviral therapy for the treatment of severe life-threatening adenovirus infections. Acylovir, gancyclovir and ribavirin might be used empirically in China. Our physicians did not know adenovirus type prior to anti-viral treatment. In our study, gancyclovir was most used anti-viral drug ($n = 7$), followed by ribavirin ($n = 2$) and acyclovir ($n = 1$). There is no difference in anti-viral treatment between ARDS patients and those without. More patients with ARDS required mechanical ventilation ($p = 0.009$). In patients with ARDS, four of them received non-invasive ventilation, one received invasive ventilation, and one received extracorporeal membrane oxygenation (ECMO). Two patients with ARDS had hypotension and received fluid resuscitation and dopamine to maintain adequate systemic arterial pressure. The patients' respiratory failure improved over the next 7–10 days after admission. The mean length of hospital stay was 12 days (range: 8–13), and patients with ARDS required a longer hospital stay ($p = 0.006$) than those without ARDS.

A 35-year-old man was transferred to our hospital 8 days after onset with rapidly deterioration after wide-spectrum antibiotics therapy. He presented refractory hypoxemia and septic shock. We collected pleural effusion, bronchoalveolar lavage fluid and serial whole blood for adenovirus detection. High level adenoviral loads 10^6–10^8 copies/ml were detected in all samples. Serial blood adenovirus load remained as high as 10^7–10^8 copies/ml even after gancyclovir therapy for 7 days. He died 1 week after admission even on ECMO support. The patient was infected by type 11 adenovirus.

4. Discussion

Eighteen out of 487 cases were positive for adenovirus up to April 2011, giving an incidence of 3.7%, similar to what Jenninns reported.[20] Most of our cases of adenovirus pneumonia occurred in March and April just after the influenza epidemic. In New Zealand, adenovirus pneumonia primarily occurred in August and September, which partly overlapped with the influenza epidemic.[20] Younger male adults, ranging from 15 to 55 years (average 28.1 years) had the highest prevalence of adenovirus pneumonia. Only two patients with an ARDS complication had underlying comorbidities, poliomyelitis and diabetes, respectively. Typically, patients report flu-like symptoms, such as high grade fever, cough, and little sputum. In addition, some of them develop shortness of breath or severe dyspnea on 6 days after disease onset (range: 5–7 days). Broad-spectrum antibiotics did not work before admission. Hemoptysis, diarrhea, and conjunctivitis were not common in our cases. Three patients presented trace blood sputum. These characteristics are different from that of the 2009 pandemic H1N1 influenza pneumonia, which had a median age of 41 years (range from 14 to 75), and 46.2% severe patients presented with hemoptysis.[21]

Most patients had a normal leukocyte and thrombocyte count at presentation. Relative leukopenia and thrombocytopenia could be found in patients with ARDS. The lowest count of leukocytes and thrombocytes in our patients was 0.9 and 34×10^9/L, respectively. The biochemistry marker for severe disease is elevated serum levels of muscle enzymes. In particularly, higher AST level was better associated with ARDS patients than any other muscle enzyme. In the study, chest HRCT scan showed lobar or segmental air-space consolidation was seen in most patients and small pleural effusion was often found (10/18, 55.6%). Patients with ARDS often presented with multiple lobar or segment consolidation and ground glass opacity. In a recent study by Han et al.,[22] adenovirus pneumonia in children also showed bilateral consolidation in 12 out of 19 patients (63%) and pleural effusion was present in 13 out of 21 patients (62%).

Recently, Guo et al. reported mild acute adult adenovirus infections in Beijing from May 2005 to July 2010. Among them, species B (HAdV-3, -7, -11, and -14) were most common (77.9%),[24] which were similar to our adenovirous type detected in pneumonia. However, HAdV-11 was the most common in our study, especially in

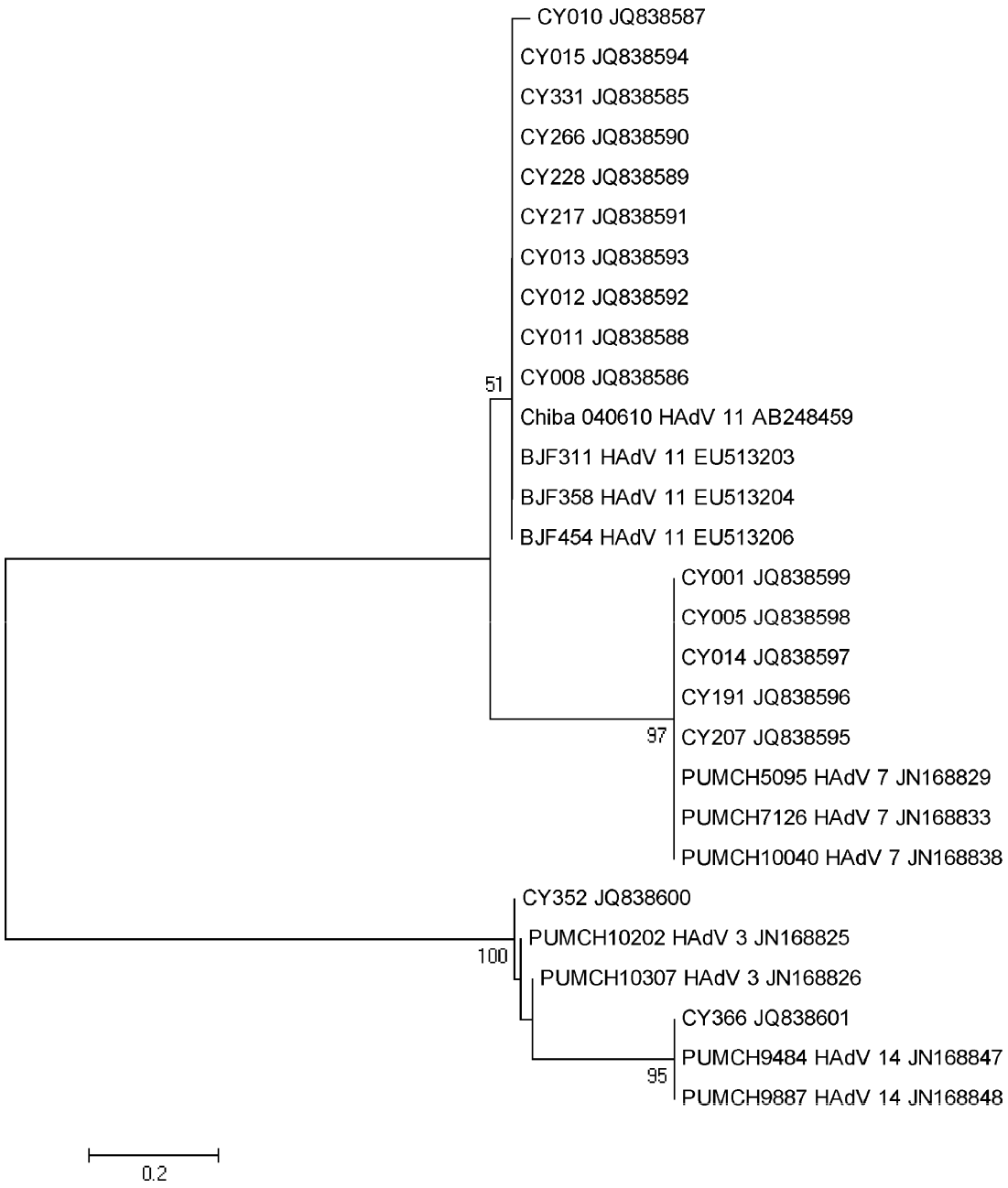

Fig. 3. Phylogenetic analysis of human adenovirus (HAdV) species based on the partial sequence analysis of the hexon gene. The phylogenetic tree with 1000 bootstrap replicates was generated using MegAlign programs in the MEGA 5.0 software package based on the nucleotide sequences of the 17 strains. Each strain from this study is indicated by a specific identification code (CY) followed by the patient number and marked with GenBank accession numbers.

patients with ARDS. Adenovious type 3, 4, 7 and 14 had been reported to be the causative agent of life-threatening adenovirus pneumonia in immnocompetent adult.[6,23] To our knowledge, it is the first report about lift-threatening adenovirus pneumonia caused by HAdV-11. Although little is known about mechanisms of pathogenesis of adenovirus infection, type, mutations or recombinations may result in biological or antigenic changes in the type-specific epitopes in the major viral capsid protein, hexon, which can lead to increased virulence. However, by analyzing the partial hexon nucleotide sequences of HAdVs, we found HAdV-3, -7, -11, and -14 strains from our study have very close relationship with corresponding type stains circulating in the Beijing region. Therefore, to evaluate the real level of variation among stains, full-length genome or open reading frame (ORF) sequencing is necessary.

In addition to gene variation, other host factors, e.g. slow virus clearance and systemic infection with viremia likely play key roles. We identified the systemic infection with high level viremia in a fatal case caused by HAdV-11. Shike et al.[25] also reported a 6-month-old infant with systemic infection by adenovirus type 7 had the high level viremia (1.8×10^8/ml) and showed reduction in viral load paralleling her clinical recovery. Our findings suggested that viremia can appear in severe immnocomplete adult case and consecutive viremia might be a risk factor for mortality in adult.

There is currently no formally approved antiviral therapy for the treatment of severe life-threatening adnovirus infections. Cidofovir is considered the drug of choice for severe infections in immunocompromised patients,[26] but prospective, randomized therapeutic trials have not been done. Cidofovir is not available in most hospitals in China, as well as in our hospital. Our physicians did not

know adenovirus type prior to anti-viral treatment and usually empirically prescribed acylovir, gancyclovir or ribavirin.

Limitations: (1) We did not measure whole blood adenovirus load in all patients with ARDS, so we were not sure about the prevalence of viremia among patients with ARDS. (2) We did not carry out sequential analysis of viral load in respiratory secretions, so we did not clarify the relation between the severe infections and slow virus clearance. (3) Although repeated testing by PCR, we still failed to identify the typing from one strain in a patient with ARDS. We think the main reason may be due to the low virus DNA copies in the specimen (collected by throat swab). (4) Cidofovir was not available in our hospital. So we were not able to analyze the treatment effects of cidofovir.

To conclude, although life-threatening adenovirus pneumonia in healthy adults remains uncommon, it should be considered in the differential diagnosis of severe community-acquired pneumonia, particularly if the patient has no clinical improvement after initiation of broad-spectrum antibacterial agents. The diagnosis should be considered early in the course of illness to avoid unnecessary antibiotics abuse and to apply supportive measures in the ICU setting to improve patient outcome. More work must be done to survey viral variation to better understand the pathophysiology and infectious control.

Funding

This work was supported by Program for New Century Excellent Talents in University (NCET-10-0006) for Dr. Bin Cao.

Competing interest

None competing interests.

Ethical approval

The study was approved by the Beijing Chao-yang Hospital ethics committee and all subjects gave written informed consent.

Acknowledgments

We thank Lili Ren, Shuqiao yang and Jianguo Li for assistance for technical support and Drs Chen Ma, Yudong Yin, Lu Bai, Lin Wu, Ran Li, Yiqun Guo and Bin Sun for collection of clinical data. We also thank Evan Sandel for assistance in careful editing of our manuscript.

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