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Original Article

Clinical data analysis of 19 cases of community-acquired adenovirus pneumonia in immunocompetent adults

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Abstract: The aim of this study was to investigate the characteristics of clinical manifestations, laboratory tests and imaging changes of community-acquired adenovirus pneumonia in immunocompetent adults. A retrospective study was performed on 19 adult community-acquired adenovirus pneumonia cases in Yantai, whereby the clinical data were collected and analyzed. Of 19 cases, 14 (73.68%) had fever and 17 (89.47%) had cough symptoms. Moreover, 14 cases (73.68%) had normal white blood cell counts, while 11 cases (57.89%) exhibited a reduction in lymphocyte proportion. Among the 19 cases, 17 cases exhibited lesions in a single lung, while 2 cases involved bilateral lungs. The lesions predominantly exhibited ground glass-like changes. The clinical manifestations of adult community-acquired adenovirus pneumonia patients with normal immune functions were mild, with such presenting symptoms as fever, cough, and sputum; most patients did not exhibit high levels of white blood cells or low lymphocyte counts, and the imaging features (ground glass-like effusion) were indicative of single-lung involvement.

Keywords: Community-acquired pneumonia, adult, normal immune functions, adenovirus

Introduction

Community-acquired pneumonia (CAP) refers to the pneumonia acquired outside a hospital or in a long-term care institution, and has an annual incidence rate of around 2% [1]. The potential pathogenic causes of CAP are varied, but often include *Streptococcus pneumoniae* and *Mycoplasma*, according to research from many domestic and foreign scholars. Because it lacked a suitable means of detection, the position of the CAP virus had always been overlooked [2, 3]. However, with the rapid development of nucleic acid detection technologies, as well as the outbreak of Severe Acute Respiratory Syndromes (SARS), H5N1 influenza virus and H1N1 in 2009, the virus became the focus as the pathogen of CAP.

The proportions, types, and epidemic seasonality of the CAP virus have been previously studied by many domestic and foreign scholars. Lieberman et al. [4] performed a one-year CAP survey and found that 346 cases of viral CAP were more common in spring and winter. In addition, de Roux et al. [5] detected the paired serology of 338 CAP patients and found that the first four viruses were the influenza virus, parainfluenza virus, respiratory syncytial virus, and adenovirus. Ruuskanen et al. [6] summarized 10 studies that used the PCR method to identify adult patients with viral CAP, and the following viruses were detected (in descending order): the influenza virus, rhinovirus, human coronavirus, respiratory syncytial virus, parainfluenza virus, and adenovirus. These findings highlight the importance of viral CAP as well as the need to use the survey as a tool for understanding the etiology of CAP in developing countries. Shin [7] pointed out that if a clinician did not consider the position of the CAP virus, he probably would not consider the diagnosis of viral pneumonia; antibiotic overuse would be inevitable, the appropriate time for viral treatment would be lost, and patient prognosis would be affected. In Beijing, China, Liu et al [8] suggested from her recent studies of adult CAP pathogens that viruses accounted for the first place in CAP pathogens, about 32.2%, among

which the adenovirus pneumonia accounted for a large proportion.

Unfortunately, studies focusing on the clinical features and imaging findings of viral CAP-both domestic and international studies (except those on influenza A virus)-are rare. Furthermore, research regarding the adenovirus pneumonia that accounted for a larger proportion was mostly restricted to studies of infants; as such, related domestic studies of adults with normal immune function were rare. This retrospective study was undertaken by collecting clinical data of 19 diagnosed adenovirus pneumonia immunocompetent patients for analysis, to provide help for clinicians to learn more about the performance of adenovirus pneumonia in immunocompetent adults.

Materials and methods

Subjects

Nineteen ACCAP patients that were treated in our department from January 2013 to January 2014 and those meeting the inclusion criteria were selected. This study was conducted in accordance with the declaration of Helsinki. This study was conducted with approval from the Ethics Committee of Yantai Yuhuangding Hospital. Written informed consent was obtained from all participants.

Inclusion criteria

The inclusion criteria were as follows: 1) age was >18 years; 2) the diagnostic criteria of CAP issued by the American Thoracic Society and Infectious Diseases Society of America in 2007 were met [9]; 3) pharyngeal swab PCR confirmed the presence of adenovirus, while the hemagglutination inhibitor experiment and the indirect immunofluorescence assay were performed, and the double serum antibody titers between the acute period and the convalescent period (2-4 weeks) were detected as four-fold or more; and 4) the mycoplasma detection and bacteriological test results were negative.

Exclusion criteria

We excluded the following patients: 1) those who presented with lung diseases such as lung abscess, aspiration pneumonia, and obstructive pneumonia; 2) those who were HIV infected or under an immunosuppressed state; 3) those who had clinical symptoms for more than 1 week from onset; 4) those who were pregnant or lactating; 5) those who were hospitalized within the prior 90 days (hospital stay longer than 2 days); and those who 6) lived in a nursing home or rehabilitation center.

Multiplex PCR

The pharyngeal swabs (167KS01, Guangzhou, China) of initially diagnosed CAP patients were sampled and placed into 2 mL virus-transporting media (167KS01, Guangzhou, China) that were placed into specimen boxes (maintained at 2-8°C) for transportation. After transportation, the samples were stored at -80°C. The collected swabs were then shocked for 5 s and centrifuged at 3000 r/5 min, and the precipitate was then extracted the total viral RNA by QIAamp Viral RNA Mini Kit (QIAGEN) (Cat. No. 52906, Qiagen, Hilden, Germany). Using the RevertAidTM First Strand cDNA Synthesis kit (Fermentas), the total RNA was reversed to cDNA. Subsequently, the respiratory virus 15-combination multiple PCR kit (Neuro-Hemin Biotech Co, Ltd, Hangzhou, China) was used (according to the operating manual), and the AB17500 instrument was used to detect the viruses in the specimens.

The reaction system was as follows: 3 μl cDNA template, 4 μl 5 × RV15 A/B/C primer, 3 μl 8-Mop Solution, and 10 μl 2 × Multiplex Master Mix. The reaction procedures were as follows: 94°C for 15 min for denaturation; 94°C for 30 s, 60°C for 90 s, and 72°C for 90 s (40 cycles); and 72°C for 10 min. The kit determination series included the adenovirus; human metapneumovirus; influenza A virus; influenza B virus; parainfluenza virus types 1, 2, 3, 4; respiratory syncytial virus type A and B; coronavirus types 229E/NL63 and OC43/HKU1; rhinovirus; bocavirus; and enterovirus.

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Immunofluorescence assay and antibody neutralization tests were performed to detect the serum adenovirus-specific antibodies. Testing of serum adenovirus IgM antibody performed in the acute period yielded positive results; for serum adenovirus-specific IgG antibodies performed between the acute and convalescent periods, the titers were revealed to be four-fold or more [10-12].

Table 1. The basic information of all the patients involved in this study

No.	Gender	Age	Weight (Kg)	Underlying disease
1	Male	23	65	None
2	Female	42	57	None
3	Female	69	63.5	None
4	Female	56	52	None
5	Female	20	48	None
6	Female	68	67.5	None
7	Male	81	73.5	Hypertension
8	Male	27	64	None
9	Male	48	80	None
10	Male	45	78	None
11	Female	43	69	None
12	Female	51	59	None
13	Male	33	78.5	None
14	Female	45	57.5	None
15	Female	69	67.5	None
16	Male	54	73	None
17	Male	16	63	None
18	Male	33	81.5	None
19	Male	80	90	Coronary heart disease

Results

Clinical manifestations

Among the 19 cases, 14 were febrile, accounting for 73.68%, with an average temperature as 38.6°C ± 0.6°C; of these, 4 cases were low-fever, 7 cases were moderate-fever, and 3 cases were high-fever grade. The fever duration was 1-7 days, with an average of 4.14 ± 1.70 d. Seventeen cases had cough, accounting for 89.47%. Coughing symptoms typically lasted 1-7 days, with an average of 4.76 ± 1.82 d; 7 cases were accompanied with expectoration, accounting for 41.18%, among which 6 cases had yellow sputum and 1 case had white sputum. Two cases were accompanied with mild chest pain, and one 80-year-old patient simultaneously experienced mild breathing difficulties. None of the 19 cases had any symptoms of gastrointestinal tract or nervous system.

The basic information of all the patients

Among the 19 patients, including 10 males and 9 females (the male/female ratio was 10:9), the average age was 47.5±19.6, and there were 2 patients suffered from hypertension and coronary heart disease, respectively (**Table 1**).

Laboratory testing data

Laboratory testing data are shown in **Table 2**. Among the 19 patients, 14 patients (73.68%) had normal white blood cell counts (range, 4.15-8.93 × 10^9 cells/l; average range, 6.64 ± 1.59 × 10^9 cells/l); 5 patients (26.32%) exhibited leukocytosis (range, 9.58-15.68 × 10^9 cells/l; average range, 12.90 ± 2.49 × 10^9 cells/l). Eleven patients (57.89%) exhibited a reduction of lymphocytes. All patients exhibited mildly elevated CRP, about 19-55 mg/l, with an average of 32.9 ± 8.4 mg/l. Two patients exhibited elevated ALT levels, while 1 patient exhibited increased AST. Eight cases had LDH elevation, with a range of 206-415 IU/l, while the average range was 259.3 ± 66.9 IU/l.

Imaging changes

Among the 19 cases, 17 cases (89.47%) exhibited single-lung involvement, among which 2 cases involved the right upper lung; 4 cases, the right lower lung; 3 cases, the left upper lung; and 8 cases, the left lower lung. Only 2 cases exhibited bilateral-lung involvement. The lesions mostly exhibited ground glass-like changes (**Figure 1**); only one case showed a parenchymal change.

Percentage of virus types

Among the 19 cases, the adenovirus type 55 accounted for 10 cases (52.6%); adenovirus type 7 had 3 cases, accounting for 15.8%; adenovirus type 3 had 2 cases, accounting for 10.5%; adenovirus type 50 had 2 cases, accounting for 10.5%; adenovirus type 2 had 1 case, accounting for 5.3%; and adenovirus type 14 had 1 case, accounting for 5.3%.

Monthly distribution of adenovirus

Adenovirus was detected from January 2013, peaking in February and March.

Discussion

The adenovirus series originated from a double-stranded DNA virus, cultured and separated from human proliferated somatic cells in 1953, with a diameter of 70-100 nm, icosahedral symmetry, and non-enveloped characteris-

Table 2. Laboratory testing data of 19 patients

White blood cells ($3.5\text{-}9.5 \times 10^9$/l)	Lymphocytes (20-50%)	ALT (9-50 IU/L)	AST (15-40 IU/L)	Lactate dehydrogenase (90-205 IU/l)	C-reaction protein (< 10 mg/l)	Virus types
4.69	32.8	18	14	244	19	50
7.73	20.2	23	22	217	29	3
7.18	18.2	29	24	185	35	55
8.6	9.5	43	35	156	33	14
5.69	23.7	11	21	244	27	7
5.79	24.2	19	24	154	32	55
9.58	14.8	16	20	186	29	55
8.5	12.1	48	34	186	36	7
4.87	18.1	24	31	415	23	55
15.68	12.9	83	63	196	47	55
8.93	15.9	13	15	234	26	2
5.64	43.3	18	31	187	27	50
13.1	17.2	17	17	231	55	55
11.34	14.6	19	24	283	34	55
5.95	25.4	20	23	206	37	55
4.15	34.9	122	38	162	33	55
7.18	18.7	32	19	188	35	7
14.8	32.8	18	26	180	27	3
8.12	16	39	29	187	42	55

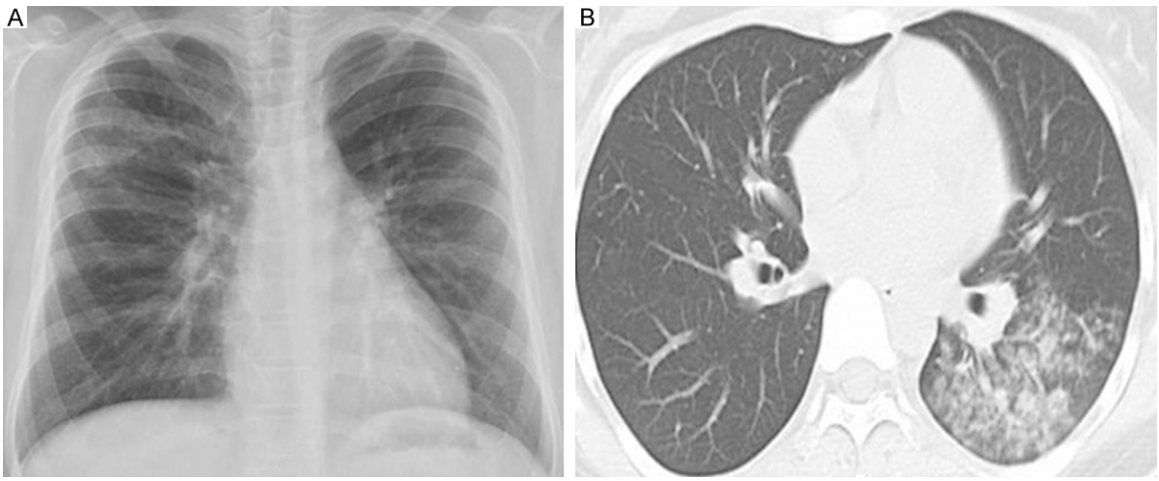

Figure 1. Typical of the imaging appearances of adenovirus pneumonia. A. Ground-grass opacity in X-ray. B. Multifocal consolidation in CT.

tics, belonging to the adenovirus family. These particles could infect humans, mammals, and birds; thus far, the adenoviruses that have potential to infect people can be divided into at least 55 serotypes [13].

Adenovirus pneumonia (AP) often occurs in infants of 6 months to 2 years of age, and is considered the main pathogen of pneumonia. The probability of AP occurrence in adults with normal immunity is low [14]. Presently, research on AP in adults with normal immune function is limited to severe cases [15-18]; the mechanisms of AP in this demographic remains unclear, including an understanding of the types of patients that might progress to severe AP. Foreign study groups have found that the progression and prognosis of AP are related to the

virus classification and host's immunity. Findings show that the adenovirus serotypes 3 and 7 could lead to severe pneumonia in newborns and children [19, 20], which might be related to the fact that they could easily damage host cytokines and T cell functions [21, 22]. We did not investigate critically ill patients in this study, which could be attributed to the patients' younger age and normal immune function.

We found that the adenovirus type 55 was more prevalent (52.63%) compared to previous domestic studies. The reasons for this might be related with the community outbreak of adenovirus type 55 during the data collection. Cao et al. found the adenovirus type 55-induced outbreak of CAP, which accounted for 43.8% [23], which is consistent with our study results. In addition, adenovirus type 55 was the chimera of adenovirus types 14 and 11, thus if the serotypes were identified using PCR, it was possible to mistake adenovirus type 55 as type 11. This created the need for further gene sequence analysis. The clinical symptoms of most of these 19 patients were mild; 18 patients were treated as inpatients, and only one 80-year-old patient was in a critical condition and was hospitalized for 14 d. The patient was eventually discharged after conditions improved, while the review of lung imaging showed incomplete absorption. Our patients with adenovirus types 3, 7, and 14 did not present with severe viral pneumonia, which might be associated with the patients' lack of disease, younger age, and better immune function, but the exact causes would be difficult to analyze. We prepared to measure the humoral immune functions and T cell subsets in the next observation to understand the relationship between the disease state changes and other related factors.

The onset of AP was rapid, and more often than not, accompanied by fever. Among the 19 cases in our study, 14 cases were febrile, with the average temperature being 38.6°C. Most patients had cough symptoms, while phlegm discharge amount and signs of pulmonary distress were minor. The laboratory examinations revealed that 14 patients (73.68%) had normal white blood cell counts; 11 cases (57.89%) exhibited a reduction of lymphocytes, consistent with the previous research [24].

The imaging findings of these 19 cases found that the single-lung lesion accounted for 89.47%, and occurred in the majority of cases, different from that of Kevin who found that the lesions were involved in both lungs, to a proportion of about 40% [25]. The lesions predominantly exhibited fusion-oozing-like and ground glass-like changes, consistent with the Miller group [26].

The shortcomings of our study are as follows: 1) we used PCR for viral detection, therefore, the detected viruses might only be the colonized pathogens. Our next study will set healthy controls to reduce error; and 2) the sample size of this study was small, the scope was limited, and some results were insufficient to draw firm conclusions.

In short, this study summarized the clinical manifestations, laboratory tests and imaging features of 19 CAP cases in Yantai, providing us preliminary understanding about AP, as well as the particular significance of future CAP empirical treatment. The adenovirus typing, combined with the clinical manifestations, could provide us with potential tools for understanding the development and outcome of outpatient-suspected CAP patients. Those who might develop severe pneumonia could be treated early, which will help reduce the associated mortality rate.

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Disclosure of conflict interest

None.

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