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Research Article

Clinical Features, Radiological Findings and Risk Factors of an Acute Febrile Respiratory Disease Caused by Human Adenovirus Type 55, and its Variety during COVID-19 Pandemic

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Abstract

Background: *The purpose of this study was to identify the clinical and thin-section CT findings in patients with adenovirus infections occurring at a campus, describe the risk factors for progress in pneumonia. The changes during COVID-19 pandemic were also observed.*

Methods: *From February to April of 2018, clinical data and samples from the patients were collected. We described characteristics of progressed group (n = 97) versus no-progressed group (n = 12) and compared clinic-laboratory between the two groups. From December 2020 to December 2022, all patients with acute respiratory fever on the campus were tested for adenovirus nucleic acid with nasopharyngeal swabs.*

Results: *The main clinical manifestations of acute febrile respiratory caused by B55 adenovirus infection were fever, cough, sore throat and aching muscles which had no significant difference between two groups. The duration of fever (> 5 days) was significantly different between the two groups (p = 0.000). The dynamic changes of neutrophil-lymphocyte count ratio (NLR) in no-progressed patients were lower than those of progressed patients (P = 0.000). The fever duration (≥ 5 days) (OR = 14.628; 95% CI = 0.009 ± 0.508; p = 0.009) and the NLR changes (OR = 0.47; 95% CI = 0.279 ± 0.797; p = 0.005) remained independent factors associated with progressed disease. Four and five adenovirus nucleic acid positive cases were detected in October 2021 and 2022 respectively.*

Conclusion: *Adenovirus infection is associated with the decreased peripheral blood lymphocyte proportion. Proper immunomodulatory treatment may be important for these patients. Hand hygiene, social distance and isolation are import means to control respiratory diseases transmitted by airborne droplets.*

Keywords: *Adenovirus; Neutrophil-Lymphocyte Count Ratio; Clinical Features*

INTRODUCTION

Adenoviruses are non-enveloped viruses with double-stranded DNA genomes, currently comprising more than 50 serotypes which are divided into seven species, designated A to G. It can cause a wide range of clinical manifestations including acute respiratory diseases, gastrointestinal, conjunctivitis and urinary infections [1-8]. Epidemics of adenovirus infections may occur in healthy children or adults in closed or crowded settings (particularly military recruits) [9-11]. Adenovirus infections are a frequent cause of potentially fatal infections in patients after allogeneic human stem cell transplantation or with human immunodeficiency virus infection [12, 13].

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Different serotypes cause different tissue trophisms and relate with clinical characteristics of infection. Adenovirus 55 is a new serotype from the recombinant type 11 and the type 14 gene [5-15]. It is reported that the adenovirus type 55 causes the outbreak of febrile respiratory infection especially a military camp or a colony [9, 10]. Therefore, the purpose of this study was to identify the clinical and thin-section CT findings in patients with adenovirus infections occurring at a campus, describe the risk factors for progress in pneumonia. During the COVID-19, the infection of adenovirus in the same campus was also observed and analyzed.

METHODS

Patients

From February 24 to April 20, 2018, a large number of patients with Acute Febrile Respiratory (AFR) diseases appeared in a campus. Some of these patients were treated in our hospital. The throat swabs were collected for the detection of the respiratory virus by PCR and the serum adenovirus IgM was also tested in all these patients. AFR case was given as an individual with a body temperature over 37.8°C and with at least a respiratory symptom such as cough or sore throat. The diagnosis of adenovirus pneumonia was confirmed when the following findings were present: (i) acute lower respiratory symptoms; (ii) lung infiltration on chest radiography or Computed Tomography (CT); and (iii) evidence of adenovirus infection identified by a respiratory virus PCR test from lower respiratory tract samples such as sputum or bronchoalveolar lavage fluid. When samples obtained from the lower respiratory tract

were considered inadequate, samples from the upper respiratory tract, including oropharyngeal or nasopharyngeal swabs, were obtained.

Laboratory Examination

All patients underwent routine examination of blood routine, liver function, renal function, Mycoplasma pneumona, erythrocyte sedimentation, procalcitonin, chest CT and so on. Blood routine checks once every 3-5 days. The changes of clinical symptoms and signs every day were recorded. Patients still need to be rechecked when an abnormal situation occurs. During the three years, From December 2020 to December 2022, the nasopharyngeal swabs of all patients with acute respiratory fever from this campus were tested for adenovirus and COVID-19 nucleic acid.

Management of the Adenovirus Outbreak

In order to prevent the adenovirus epidemic, patients and dormitories were urged to wash their hands and avoid using public utensils and other public goods. All patients were isolated for 14 days or until symptoms disappeared. Other people on campus should avoid contact with infected patients. All patients were given symptomatic treatment. Severe pneumonia accompanied by hypoxia or shortness of breath were treated with corticosteroids. During the prevalence of COVID-19, hand hygiene, masks, social distance and strict isolation measures were strictly implemented.

Statistical Analysis

Data are presented as medians and interquartile ranges for continuous variables and as numbers and percentages for categorical variables. Data were compared using the Mann-Whitney U-test or Kruskal Wallis test for continuous variables and the x^2 or Fisher's exact test for categorical variables. To assess the predictive factors for the occurrence of progress, univariable and multivariable analyses with a backwards logistic regression model were performed. *P*-value < 0.05 was considered to indicate statistical significance. Statistical analyses were performed using the PASW software program (ver. 18.0; SPSS Inc., Chicago, USA).

Ethics

The study was approved by the human use committee and institutional review board of the general hospital of the central theater command of the People's Republic of China.

RESULTS

Patients Included in the Study Analysis

A total of 258 cases of AFR were treated. 109 cases of adenovirus type 55 were confirmed by PCR and serum IgM. Among them, 12 cases were progressed, and 107 cases had no progress (Figure 1).

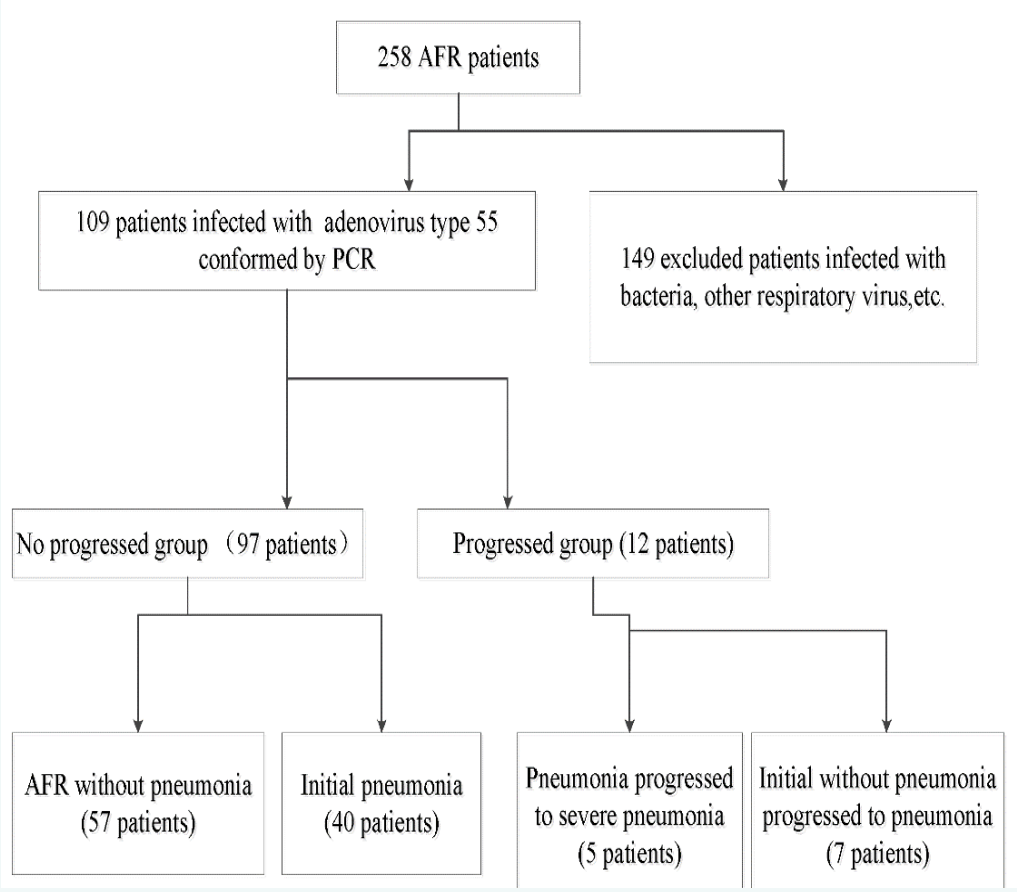

Figure 1 Patients Included in the Study Analysis AFR, Acute Febrile Respiratory.

Table 1: Clinical Manifestations of Human Adenovirus Serotype 55 infectious. Outbreak from February 24, 2018, to April 20, 2018, in Wuhan, China.

	No Progressed		Progressed		
Characteristics	**AFR**	***P***	**Progressed to P**	**P progressed to more P**	***P*-value**
Patients (numbers)	97		12		
Age(years)	24.47 ± 1.68		20.08 ± 0.90		0.432
Clinical Symptoms or signs					
Fever Duration, days (≥ 5 days)	17/97		10/12		0.000
Cough	77/97		9/12		0.727
Purulent Sputum	50/97		6/12		0.920
Sore throat	45/97		5/12		0.758
Myalgia	85/97		10/12		0.676
Diarrhea	10/97		2/12		0.509
Initial Laboratory Findings					
White blood cell count(/ul)	7.56 ± 2.48		8.53 ± 3.71		0.233
Absolute Neutrophils count(/ul)	5.91 ± 2.35		6.25 ± 3.37		0.656
Absolute Lymphocyte count(/ul)	1.10 ± 0.46		1.50 ± 0.59		0.008
Neutrophil-lymphocyte count ratio	6.70 ± 4.96		4.58 ± 2.26		0.148
Platelet count (×103/μL)	212.76 ± 61.52		232.33 ± 38.67		0.285
C-reactive protein, mg/dL	47.20 ± 11.52		48.00 ± 6.90		0.371
Procalcitonin	0.20 ± 0.06		0.20 ± 0.07		0.771

P: Pneumonia; AFR: Acute Febrile Respiratory Illness.

Comparisons between progressed and No-progressed Groups

Most patients had upper respiratory symptoms such asdyspnea, cough, sputum, fever, and myalgia, as shown in (Table1). There was no significant difference between the two groups in the clinical symptoms such as cough, purulent sputum, sore throat, myalgia and diarrhea ($p < 0.05$). However, the duration of fever (> 5 days) was significantly different between the two groups ($p = 0.000$).

We compared the laboratory findings between the progressed and non-progressed patients (Table 1). The white blood cell count, platelet count, absolute neutrophils count, NLR, C reactive protein and procalcitonin was no significant difference between the two groups. The dynamic changes of NLR in no-progressed patients were lower than those of progressed patients ($P = 0.000$). At the same time, there is a significant difference in the absolute lymphocytes in the two groups ($P = 0.008$).

Radiological Findings

Consolidation Ground-Grass Opacities (GGOs), and pleural effusions were the most common findings in adenovirus pneumonia. The parenchymal abnormalities began to absorb about two weeks after illness onset, with no appearances of fibrosis.

Risk Factors for Progress

Univariable analysis comparing progressed patients and those without progressed is presented in (Table 2). Absolute Lymphocyte count (OR = 4.145; 95% CI =1.338-12.844; $p = 0.014$), Fever Duration (≥ 5 days) (OR = 23.529; 95% CI = 0.009-0.212; $p = 0.000$) and NLR changes (OR = 0.435; 95%CI = 0.269 ± 0.702; $p = 0.001$) were statistically significantly associated with progressed disease. The Fever Duration (≥ 5 days), OR = 14.628; 95% CI = 0.009 ± 0.508; $p = 0.009$) and the NLR changes (OR = 0.47; 95% CI = 0.279 ± 0.797; $p = 0.005$) remained independent factors associated with progressed disease in (Table 2).

Effectiveness of Compartmentalization for the Schools

At the end of the epidemic, there were no hospital infection happened. No further infection occurred after returning to campus after discharge. During the epidemic period COVID-19, more than 10 cases adenovirus infection were detected every year. Under strict control measures, no campus adenovirus epidemics were outbreak.

Table 2: Univariate and multivariable analysis with logistic regression model for predicting of Progress in Acute respiratory illness.

	Univariate analysis		Multivariable analysis	
Parameters	**OR (95% CI)**	***p* value**	**Adjusted OR (95%CI)**	***p* value**
Absolute Lymphocyte count(/ul)	4.145(1.338-12.844)	0.014	0.851(0.151-4.797)	0.855
Fever Duration, days (≥5 days)	23.529(0.009-0.212)	0.000	14.628(0.009-0.508)	0.009
NLR changes	0.435(0.269-0.702	0.001	0.47(0.279-0.797)	0.005

NLR: Neutrophil-lymphocyte count ratio; OR: Odds ratio; CI: Confidence interval.

DISCUSSION

The adenovirus has A-G 7 subgroup. Different subgroup may cause the infection of the respiratory tract, the digestive tract, the eye and the myocardium. In 2004, hundreds of people in Turkey were infected and 1 patient died, which were identified as the recombination of adenovirus type 11 and type 14 [5-15]. In 2009, Walsh et al. thought that the recombinant adenovirus was B14 type as the basic framework, inserted part of the B11 type after the complete gene sequence alignment. And it was named B group 55 type, but it did not react with type 11 and type 14 in sera. There have been several reports of epidemic and serious patients were reported [16-19]. Recent researches had been found that patients with severe adenovirus need to use ECMO to support life [20, 21]. In this study, the clinical characteristics, CT manifestations and prognostic factors are summarized, which may help to improve the early diagnosis, treatment and cure rate.

The main clinical manifestations of acute febrile respiratory caused by B55 adenovirus infection were fever, cough, sore throat and aching muscles. However, the significant characteristic of this infection compared with other respiratory viruses is that the fever duration is longer, and

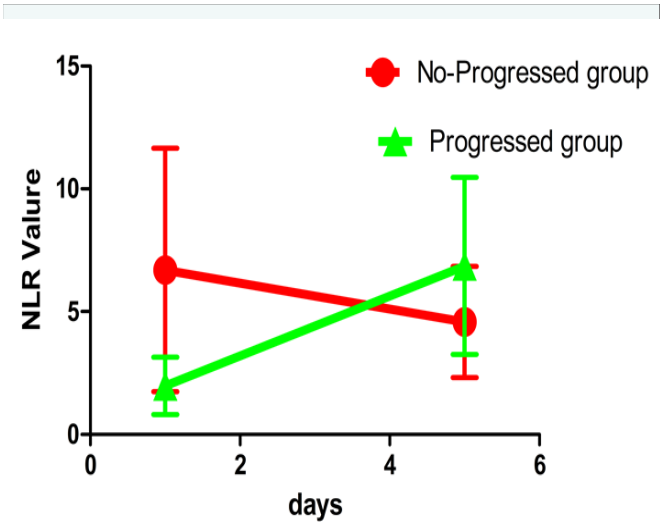

Figure 2: Dynamic Changes of Nlr in In Patients with Adenovirus Type 55 Acute Febrile Respiratory Illness.

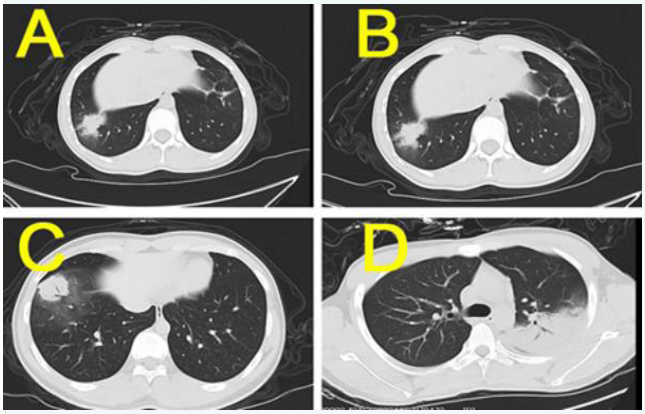

Figure 3: Chest CT Findings in Patients with Pneumonia Caused by Adenovirus Type 55.

A. Initial chest CT scan (day 5 after the onset of illness) shows diffuse ground-grass opacities in a 22 year-old man.

B. Chest CT scan seven days after the onset shows consolidation in a 18 year-old man. (C), Initial CT scan obtained on day 8 shows apparent consolidation with slight patchy ground-glass opacities in 20 year-old man. (D), CT scan obtained on day 10 shows consolidations accompanied by adjacent ground glass opacities and pleural effusions in a 21 year-old man.

the patients with fever duration more than 5 days were more easily progressing. Another feature is the decline in lymphocyte, especially in the progression group.

NLR are the indexes of systemic inflammation and immune status, and are now used in the prognosis of diseases such as cancer and diabetes [22-24]. Studies have shown that adenovirus infection may cause a decrease in lymphocytes and cause a decline in immunity [25-29]. Our study found that the dynamic change of NLR is an independent risk factor for the prognosis of the disease. Therefore, the appropriate use of immunomodulators in the treatment may benefit these patients. In addition, persistent fever is also an independent risk factor for the progression of the disease which suggested that the chest CT should be rechecked at any time in order to find the progress of the disease. The performance of CT is not specific to the pneumonia caused by other pathogens [30-32], but most of patients with severe infiltration without obvious symptoms such as oppression in chest and shortness of breath.

In short, the main manifestations of the patient with the B55 type was that the lymphocytes was destroyed seriously, which directly related with the prognosis. Proper immunomodulatory treatment may be essential for these patients. Since the outbreak of the COVID-19 epidemic, countries around the world had taken strict control measures [33]. Research has found that during this period, the epidemiological characteristics of adenovirus had changed [34-36]. Adenovirus outbreaks often occur in hospitals, schools, or military training bases. Our study found that the control measures can effectively reduce the incidence rate. These effective control measures include hand hygiene, social distance and masks.

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