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Clinical significance of respiratory virus detection in patients with acute exacerbation of interstitial lung diseases

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ABSTRACT

Background: The impact of viral infections on acute exacerbations in idiopathic pulmonary fibrosis (IPF) and/or non-IPF interstitial lung disease (ILDs) has been scarcely described.
Objectives: To elucidate the frequency of virus infections in patients with IPF or non-IPF ILDs including idiopathic interstitial pneumonia (IIP) or connective tissue disease (CTD)-associated pneumonia, and its influence on their short-term mortality.
Methods: We prospectively enrolled adult patients with acute exacerbation of IPF and non-IPF ILDs who were admitted to the hospital during the last 3 years, and examined the respiratory samples obtained from nasopharyngeal, sputum, and bronchoalveolar lavage fluid.
Results: A total of 78 patients were identified, consisting of 27 patients with acute exacerbation of IPF and 51 patients with non-IPF ILDs (IIP: n = 27, CTD-associated IP: n = 24). Of all patients, 15 (19.2%) had viruses detected in their respiratory samples including the human herpesvirus 7 (HHV7; n = 4) and cytomegalovirus (CMV) plus HHV7 (n = 3). The proportion of virus infections in the IPF and non-IPF ILDs groups was comparable. The Kaplan-Meier survival curves over 60 days revealed a lower survival probability in the virus positive group (n = 15, 60%) than in the virus negative group (n = 60, 83.3%, $p < 0.05$). However, the virus infection itself could not predict the 60-day survival probability using simple logistic regression analysis.
Conclusions: Viral infections, mostly CMV or HHV7, were identified in both patients with acute exacerbation of IPF and non-IPF ILDs, but the clinical significance on short-term mortality or isolation itself from respiratory samples remains to be determined.

1. Introduction

To date, few studies have addressed the etiology of acute exacerbation of idiopathic pulmonary fibrosis (IPF) [1–4], and the impact of infections has yielded mixed results. Furthermore, the significance of viral infections in other types of interstitial pneumonia for triggering acute exacerbation remains to be determined. Therefore, we prospectively examined the relationship between virus infection and acute exacerbation of interstitial pneumonia including IPF, other types of idiopathic interstitial pneumonia (IIP), and connective tissue disease (CTD)-associated interstitial pneumonia.

2. Material and methods

2.1. Patients and study design

We prospectively enrolled adult hospitalized patients having acute exacerbation of interstitial pneumonia admitted at Kyorin University Hospital from August 2012 to August 2015. The definition of acute exacerbation of IIP was based on a previous report [1] as follows: (1)

Abbreviations: BALF, bronchoalveolar lavage fluid; CMV, cytomegalovirus; CTD, connective tissue disease; HHV, human herpes virus; HMPV, human metapneumovirus; HPIV, human parainfluenza viruses; HRSV, human respiratory syncytial virus; HRV, human rhinovirus; ILDs, interstitial lung diseases; IIP, idiopathic interstitial pneumonia; IPF, idiopathic pulmonary fibrosis; PCR, polymerase chain reaction; UIP, usual interstitial pneumonia

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unexplained development of dyspnea within 30 days; (2) presence of new, bilateral pulmonary ground glass abnormalities, consolidation superimposed on a background of a reticular and/or honeycomb pattern on chest computed tomography; (3) acute respiratory symptoms; (4) no pathogenic bacterial in the bronchoalveolar lavage fluid (BALF); and (5) exclusion of alternative causes such as left heart failure and pulmonary embolism. We approved the patients who had no usual interstitial pneumonia (UIP) pattern on their radiological background. Therefore, we also enrolled patients with acute exacerbation of CTD-associated interstitial pneumonia.

Regarding these criteria, only the bronchoalveolar lavage procedure was considered to be not essential for patients to be enrolled in this study. If patients previously or concurrently fulfilled the consensus criteria of the American Thoracic Society/European Respiratory Society for a diagnosis of IPF [5], they were diagnosed with an acute exacerbation of IPF.

2.2. Samples and clinical data collection

The respiratory samples were obtained from sputum or nasopharyngeal swab or BALF within the first 48 h of admission to the hospital. Clinical data were obtained at the day of admission. Disease severity of patients was evaluated by GAP score performed at the timing prior to an acute exacerbation of interstitial lung disease [6].

2.3. RNA extraction and reverse transcription polymerase chain reaction (RT-PCR)

Samples were centrifuged at 3000 × *g* at 41 °C for 30 min. Viral RNA and DNA were extracted from supernatants using the QIAamp Viral RNA Mini Kit (Qiagen, Valencia, CA, USA). Reverse transcription (RT) was performed using PrimeScript™ RT reagent Kit (Takara Bio, Otsu, Japan), according to the manufacturer's instructions. We used polymerase chain reaction (PCR) to detect various respiratory viruses, such as human metapneumovirus (HMPV), human rhinovirus (HRV), enterovirus, human respiratory syncytial virus (HRSV), influenza viruses A, B, and C, human parainfluenza viruses (HPIV), human coronavirus, adenovirus, cytomegalovirus (CMV), human herpes virus (HHV) 6, 7, and 8, human parvovirus B19, varicella zoster virus, and human bocavirus, together with *Mycoplasma pneumoniae* and *Chlamydophila pneumoniae*. The PCR products were purified using MonoFas DNA Purification Kit I (GL Sciences Inc., Shinjuku, Tokyo, Japan).

2.4. Ethical approval

Samples were collected after written informed consent was obtained from the participants or their legal representatives. The study protocol was approved by the Ethics Committee on Human Research of Kyorin University Hospital (H24-021) on July 31, 2012. The protocols were carried out in accordance with approved guidelines.

2.5. Statistical analysis

Statistical comparisons of nonparametric data were performed using the Mann-Whitney test or Wilcoxon signed-rank test. Comparisons of categorical data were performed using Pearson's chi-squared test. All tests were two-sided. A value of $p < 0.05$ was considered statistically significant. Data were analyzed using SPSS version 20.0 software for Windows.

3. Results

3.1. Baseline characteristics: IPF vs non-IPF ILDs group

We examined a total of 78 patients with acute exacerbation of interstitial pneumonia in the study period. The number of patients with IPF was 27 and those with non-IPF ILDs was 51 (Fig. 1) (Table 1). The latter group consisted of 27 patients with IIPs without a usual interstitial pneumonia (UIP) pattern and 24 patients with CTD such as rheumatoid arthritis (n = 20), microscopic polyangitis (n = 3), scleroderma (n = 3), Sjogren's syndrome (n = 2), polymyositis (n = 1), and dermatomyositis (n = 1). The male-to-female ratio and age were

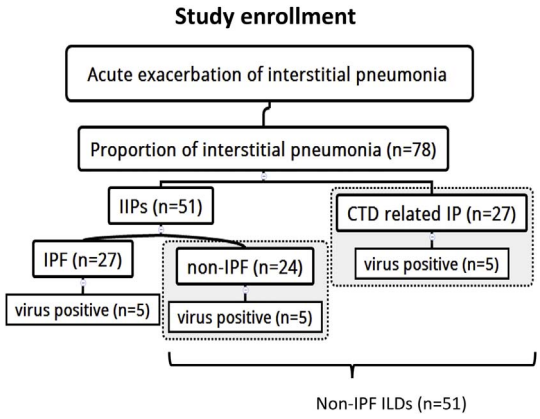

Fig. 1. Study enrollment.
IPF: idiopathic pulmonary fibrosis.
CTD related IP: connective tissue disease related interstitial pneumonia.
Non-IPF ILDs defined as non-IPF patients (n = 24) plus CTD related IP (n = 27).

Table 1
Characteristics of the patients.

	All patients	IPF	Non-IPF ILDs	p value
Number of patients	78 (100)	27	51	
Age	74.5(68.0–82.0)	74.0 (70.0–84.0)	75.0 (67.0–80.0)	0.474
Male	46 (59.0)	18 (66.7)	28 (54.9)	0.229
Smoking status				
Ex or Current	32 (49.2)	16 (59.2)	16 (39.0)	0.041
Never	33 (50.7)	8 (33.3)	25 (61.0)	0.022
Pack-years	0 (0–40.0)	23.5 (0–50.0)	0 (0–20.0)	0.007
Comorbidity				
Asthma	4 (5.1)	1 (3.7)	3 (5.9)	1.0
COPD	10 (12.8)	7 (25.9)	3 (5.9)	0.027
Chronic heart disease	8 (10.3)	1 (3.7)	7 (13.7)	0.25
Old MI or angina	14 (17.9)	3 (11.1)	11 (21.6)	0.357
Diabetes mellitus	14 (17.9)	8 (29.6)	6 (11.8)	0.066
Maintenance hemodialysis	1 (1.3)	0 (0)	1 (2.0)	0.346
Malignancy	11 (14.1)	6 (22.2)	5 (9.8)	0.175
Other lung disease	3 (3.8)	1 (3.7)	2 (3.9)	1.0
Collagen vascular diseases	26 (33.3)	0 (0)	26 (51)	< 0.001
Rheumatoid arthritis	20 (25.6)	0	20 (39.2)	
Microscopic polyangitis	3 (3.8)	0	3 (5.9)	
Scleroderma	2 (2.6)	0	2 (3.9)	
Sjögren's syndrome	2 (2.6)	0	2 (3.9)	
Polymyositis	1 (1.3)	0	1(2.0)	
Dermatomyositis	1 (1.3)	0	1(2.0)	
UIP pattern on HRCT	39 (50)	27 (100)	12 (23.5)	< 0.001
Portion of the retrieved respiratory samples				
Sputum	10 (12.8)	5 (18.5)	5 (9.8)	0.302
BALF	5 (6.4)	0 (0)	5 (9.8)	0.157
Nasal swab	63 (80.8)	22 (81.5)	41 (80.4)	1.0

BALF, bronchoalveolar lavage fluid; COPD, chronic obstructive pulmonary disease; HRCT, high resolution computed tomography; IPF/UIP, idiopathic pulmonary fibrosis/usual interstitial pneumonia; MI, myocardial infarction; UIP, usual interstitial pneumonia.