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【 ORIGINAL ARTICLE 】

Viral Pneumonia Requiring Differentiation from Acute and Progressive Diffuse Interstitial Lung Diseases

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Abstract:

Objective The clinical characteristics and chest imaging findings of viral pneumonia and several interstitial lung diseases (ILDs) overlap, and viral pneumonia may be underrecognized and misdiagnosed as certain ILDs. To clarify the frequency of viral pneumonia among patients with acute progressive clinical courses that required a differential diagnosis between ILDs and pneumonia, and to determine the most frequent ILDs misdiagnosed in cases of viral pneumonia.

Patients and Methods We retrospectively analyzed patients hospitalized from 2010 to 2017 with an acute clinical course (≤30 days) who underwent bronchoalveolar lavage (BAL) for the differential diagnosis of infection and ILDs. We performed a multiplex PCR for respiratory viruses using the patients' preserved BAL fluid. The final diagnosis was made by a multidisciplinary approach and after considering the PCR results. The diagnosis at discharge was compared to the final diagnosis.

Results Among the 109 patients, 53 were diagnosed with viral pneumonia. Viral pneumonia and other diseases showed some differences in symptoms and laboratory data; however, the differences were small or overlapped. Viral pneumonia was misdiagnosed on discharge as acute fibrinous organizing pneumonia, cryptogenic organizing pneumonia, or chronic eosinophilic pneumonia (AFOP/COP/CEP) (n=22), acute interstitial pneumonia (n=5), connective tissue disease-related ILDs (n=3), unclassifiable interstitial pneumonia (n=2), drug-induced ILD (n=1), and pneumonia (n=20).

Conclusion Approximately half of the patients who underwent BAL had viral pneumonia. The most common ILD-related misdiagnoses were AFOP/COP/CEP. Differences in symptoms and laboratory findings between viral pneumonia and other diseases were small, and viral pneumonia should be included in the differential diagnosis when physicians encounter cases in which the abovementioned ILDs are suspected.

Key words: acute lung injury, interstitial pneumonia, organizing pneumonia, viral pneumonia, virus

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Introduction

Community-acquired pneumonia is a leading cause of mortality worldwide. Its diagnosis and treatment have traditionally focused on bacterial pathogens. Recently, nucleic acid amplification testing using polymerase chain reaction (PCR) platforms has greatly improved the diagnosis of respiratory viral infections. Thus, it is now recognized that the rate of viral infection is as high as 27% (1).

Common radiologic patterns of viral pneumonia include patchy bilateral ground-glass opacities (GGOs) and consolidation, which may become confluent. These patterns are not specific for viral pneumonia but overlap with interstitial lung diseases (ILDs) [e.g., cryptogenic organizing pneumonia (COP), acute fibrinous and organizing pneumonia (AFOP), and acute interstitial pneumonia (AIP)]. Patients with the above ILDs complain of progressive dyspnea, which is com-

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monly accompanied by cough and fever, and occasionally by flu-like symptoms, which also overlap with the symptoms of viral pneumonia. Thus, we considered that patients with viral pneumonia may be misdiagnosed with certain ILDs whenever a virus survey is not performed.

The objectives of the present study were to clarify how many patients with viral pneumonia were misdiagnosed with other diseases (including ILDs) and to determine which ILDs were frequently misdiagnosed based on a PCR to detect viruses in bronchoalveolar lavage fluid (BALF).

Materials and Methods

We retrospectively analyzed 109 patients who were admitted to Saitama Cardiovascular and Respiratory Center from January 2010 to December 2017, and whose differential diagnosis included acute progressive (≤30 days) ILDs and pneumonia. All patients had been provided with a diagnosis on discharge. During the hospitalization period, respiratory physicians licensed by the Japanese Respiratory Society performed BAL according to conventional methods (2) on these patients for differential diagnosis. The obtained BALF was transported on dry ice, stored at -70ºC, and used for the detection of respiratory pathogens on a Rotor-Gene Q instrument (Quiagen, Hilden, Germany) with a multiplex, real-time PCR (RT-PCR) using an FTD Resp 21 Kit (Fast Track Diagnostics, Silema, Malta). The kit detects the following respiratory pathogens: influenza A and B viruses; coronaviruses (CoV) NL63, 229E, OC43, and HKU1; human parainfluenza viruses (HPIV) 1, 2, 3, and 4; human metapneumovirus A/B (hMPV); rhinovirus; respiratory syncytial virus (RSV) A/B; adenovirus; enterovirus; human parechovirus (HPeV); bocavirus; and *Mycoplasma pneumoniae*. An EZ1 Virus Mini Kit v2.0 was used for nucleic acid extraction (Quiagen). A threshold cycle value of <33 was considered to be a positive result in the RT-PCR, as indicated in the instruction manual.

Two experienced radiologists (N. T. and T. K.) who were blinded to all clinical information independently reviewed the high-resolution computed tomography (CT) scans. These observers were asked about the presence of 17 findings: consolidation and GGOs (and their distribution), halo sign, inverted halo sign, cavitation, centrilobular nodules, mass, tree-in-bud sign, intralobular reticulation, honeycombing, diffuse bronchial wall thickening, pleural effusion, pneumothorax, mediastinal or hilar lymphadenopathy (minimal diameter ≥10 mm), and cardiomegaly. The pathological findings were reviewed by a pathologist (Y. S). Then, in November 2018, a multidisciplinary diagnosis (final diagnosis) was established based on the laboratory, pathological and radiological findings, PCR results, and the clinical course by a review panel composed of pulmonary physicians (N. T and N. K), radiologists (T. K and N. T), and a pathologist (Y. S). A multidisciplinary diagnosis of viral pneumonia was made based on a positive virus PCR result, a compatible clinical course, and histological and radiological findings. In contrast, we considered that virus colonization had occurred if patients showed findings that were unlikely to indicate viral pneumonia, and an alternative diagnosis was made by a review panel. In the present study, patients with a diagnosis of AFOP, COP, or chronic eosinophilic pneumonia (CEP) were classified into the same category because of their overlapping histological patterns (3). The diagnostic criteria of the established guidelines (3-5) were also considered in the multidisciplinary diagnosis. Causative microorganisms of pneumonia were defined using conventional methods that have been reported previously (6).

As a control, BALF samples of 40 patients with chronic pulmonary diseases [more than several months (or years) from the onset], such as chronic hypersensitivity pneumonitis (n=3), sarcoidosis (n=8), fibrotic non-specific interstitial pneumonia (IP) (n=7), desquamative interstitial pneumonia (n=1), connective tissue disease-related ILD (CTD-ILD) (n=7), recurrent relapse of COP (n=13), or radiation-primed organizing pneumonia (OP) (n=1) without any acute symptoms were analyzed with the virus PCR test. Virus colonization was defined when the result of a virus PCR test was positive in patients with diseases other than viral pneumonia, as diagnosed by a multidisciplinary diagnosis.

Treatment failure was defined as persistence/reappearance of fever and symptoms or hemodynamic instability, the development or worsening of respiratory failure (PaO_2<60 Torr or saturation <90% at an FIO_2 of 0.21), radiographic progression, or the appearance of new infectious foci, as described in a previous report (7), whereas treatment was considered effective based on the improvement of subjective feelings, oxygenation, and chest imaging findings in cases that did not satisfy the definitions of treatment failure. This study was approved by the ethical committee of Saitama Cardiovascular and Respiratory Center.

Statistical analysis

The demographic characteristics and laboratory measurements at the time of presentation were compared between the viral pneumonia and non-viral pneumonia groups using Student's *t*-test for continuous variables and Fisher's exact test for categorical variables. The interobserver reliability of the radiological findings was evaluated using the kappa coefficient (κ) and was defined as poor (κ<0.00), slight (0.00-0.20), fair (0.21-0.40), moderate (0.41-0.60), substantial (0.61-0.80), and almost perfect (0.81-1.00). Two-tailed p values of <0.05 were considered to indicate statistical significance. All statistical analyses were performed using the SAS software program (version 9.4, SAS Institute, Cary, USA).

Results

The diagnoses

The differential diagnoses of the 109 patients on presentation, as considered by the respiratory physicians, included

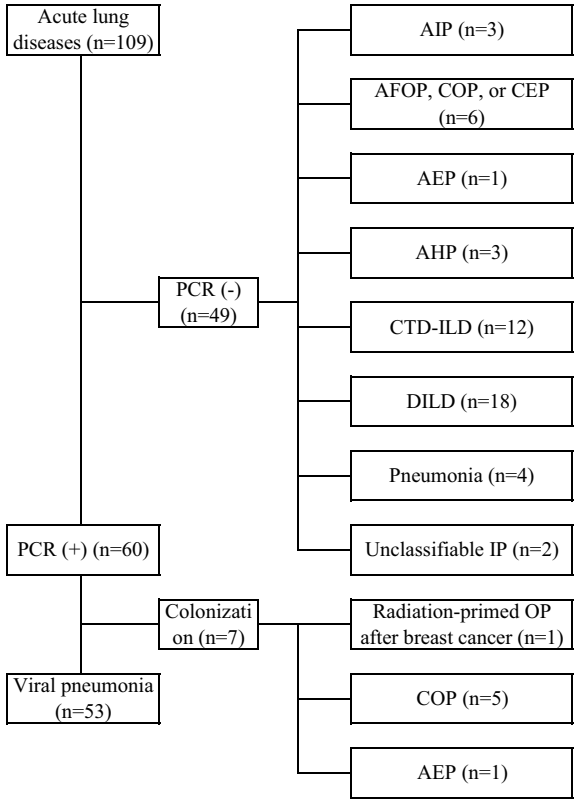

Figure 1. Flow chart of the diagnosis. PCR testing was performed using bronchoalveolar lavage fluid samples from 109 patients. The diagnoses of the 109 patients on discharge included AIP (n=8), AFOP/COP/CEP (n=33), pneumonia (n=24), DILD (n=19), CTD-ILD (n=15), unclassifiable IP (n=4), AHP (n=3), AEP (n=2), and radiation-primed OP (n=1). PCR testing was positive in 60 of the patients, among whom 7 were finally re-diagnosed as having diseases other than viral pneumonia: COP (n=5), radiation-primed OP (n=1), and AEP (n=1). The final diagnosis included viral pneumonia in 53 patients and diseases other than viral pneumonia in 56 patients: unclassifiable IP (n=2); AFOP, COP, or CEP (n=11); radiation-primed OP after breast cancer (n=1); AEP (n=3); AHP (n=3); CTD-ILD [n=12; polymyositis (n=3); dermatomyositis (n=2); amyopathic dermatomyositis with MDA5 antibody (n=2); antisynthetase syndrome (n=5); and rheumatoid arthritis (n=1)], DILD (n=18), and pneumonia due to unknown pathogens (n=4). AEP: acute eosinophilic pneumonia, AFOP: acute fibrinous and organizing pneumonia, AHP: acute hypersensitivity pneumonitis, AIP: acute interstitial pneumonia, CEP: chronic eosinophilic pneumonia, COP: cryptogenic organizing pneumonia, CTD: connective tissue diseases, DILD: drug-induced-ILD, ILD: interstitial lung diseases, IP: interstitial pneumonia, OP: organizing pneumonia, PCR: polymerase chain reaction

pneumonia (n=43), AIP (n=4), unclassifiable IP (n=9), AFOP, COP, or CEP (n=44), acute hypersensitivity pneumonitis (n=9), CTD-ILD (n=11), drug-induced ILD (DILD) (n=21), cryptococcosis (n=1), radiation-primed OP (n=2), and others [*Pneumocystis* pneumonia (n=3), diffuse alveolar hemorrhage (n=1), and tuberculosis (n=1)]. All patients underwent BAL for diagnostic purposes. The diagnoses on discharge included AIP (n=8), AFOP/COP/CEP (n=33), pneumonia (n=24), DILD (n=19), CTD-ILD (n=15), unclassifiable IP (n=4), acute hypersensitivity pneumonitis (HP) (n=3), acute eosinophilic pneumonia (n=2), and radiation-primed OP (n=1).

Sixty of the patients were PCR-positive. Among these patients, 7 were finally re-diagnosed as having diseases other than viral pneumonia (Fig. 1). In six patients, pulmonary shadows relapsed several times with the tapering of corticosteroids during post-discharge follow-up. The histological and radiological findings and clinical courses were compatible with those of OP, and the patients' final diagnoses were COP (n=5) or radiation-primed OP (n=1). BALF eosinophilia (44.6%) was found in one of these 7 patients. The patient's chest CT showed pulmonary consolidation, interlobular septal thickening, and pleural effusion. Several days before the onset of symptoms, the patient was exposed to smoking, and these findings were compatible with acute eosinophilic pneumonia. The final diagnoses included viral pneumonia in 53 patients and diseases other than viral pneumonia in 56 patients [unclassifiable IP, n=2; AFOP, COP, or CEP, n=11; radiation-primed OP after breast cancer, n=1; acute eosinophilic pneumonia, n=3; acute HP, n=3; CTD-ILD, n=12 (polymyositis, n=3; dermatomyositis, n=2; amyopathic dermatomyositis with MDA5 antibody, n=2; antisynthetase syndrome, n=5; and rheumatoid arthritis, n=1), DILD, n=18, and pneumonia due to unknown pathogens, n=4]. Patients with a final diagnosis of viral pneumonia had been diagnosed on discharge as having COP/CEP/AFOP (n=22), AIP (n=5), CTD-ILD (n=3), unclassifiable IP (n=2), pneumonia (n=20), and DILD (n=1). The rates at which a final diagnosis of viral pneumonia was made for each diagnosis at discharge were as follows: AIP, AFOP, and COP, 62.5%(5 of 8 patients); CEP, 66.7%(22 of 33 patients), CTD-ILD, 20%(3 of 15 patients); unclassifiable IP, 50%(2 of 4 patients); pneumonia, 83.3%(20 of 24 patients); and DILD, 5.3%(1 of 19 patients) (Fig. 2).

Among the 40 control BALF samples obtained from patients with chronic lung diseases, 3 (7.5%) patients had positive viral PCR results (HPeV in a patient with sarcoidosis, rhinovirus in a patient with sarcoidosis, and rhinovirus in 1 patient with fibrotic non-specific IP).

The etiologies and frequencies of each viral infection

Five patients were intubated and mechanically ventilated when they underwent BAL. The most frequently detected virus from the 53 patients with viral pneumonia was CoV (n=20, 37.7%), followed by HPeV (n=18, 34.0%), RSV (n=15, 28.3%), rhinovirus (n=14, 26.4%), influenza virus (n=13, 24.5%), hMPV (n=10, 18.9%), HPIV (n=15, 28.3%), and adenovirus (n=3, 5.7%) (Table 1). Combined viral infection was found in 35 (66.0%) patients, which included 2 viruses in 19 (Influenza A virus+CoV, n=2; Influenza A virus+HPIV, n=1; Influenza A virus+RSV, n=1; Influenza A virus+hMPV, n=1; RV+HPeV; RV+CoV; RV+hMPV, n=1; CoV+

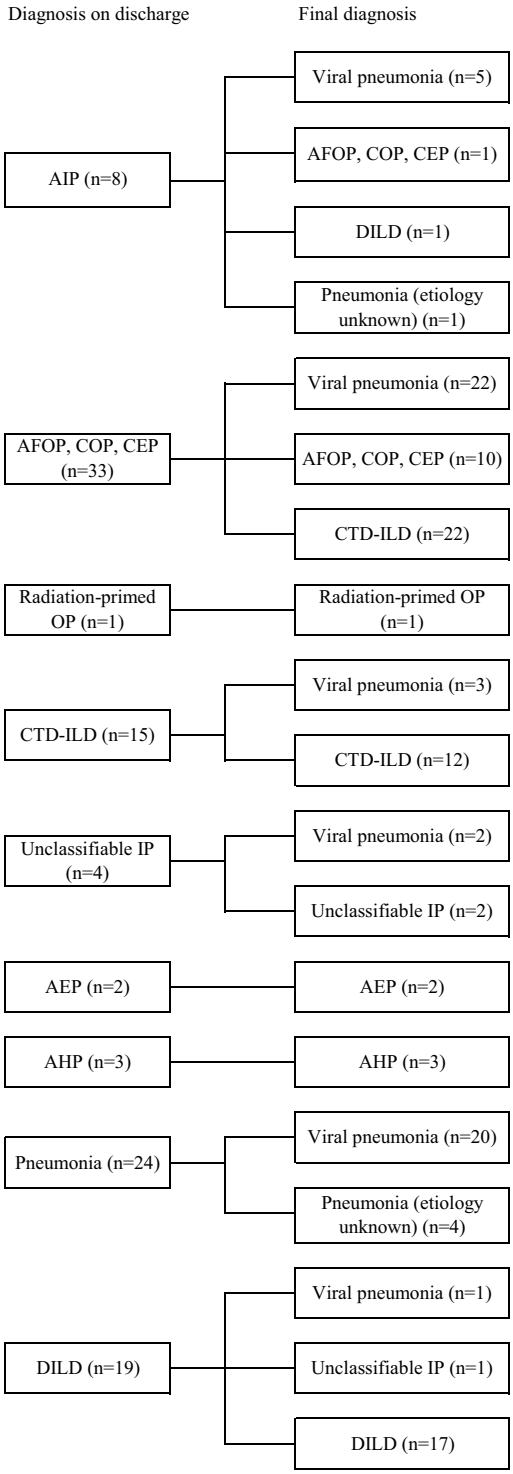

Figure 2. **The correlation between the diagnosis on discharge and the final diagnosis based on the PCR results and the multidisciplinary diagnosis. The panels on the left side indicate the diagnosis at discharge, and those on the right side indicate the final diagnosis based on the PCR results and the multidisciplinary diagnosis. The patients with a final diagnosis of viral pneumonia were diagnosed on discharge as having cryptogenic organizing pneumonia (COP), chronic eosinophilic pneumonia (CEP) or acute fibrinous organizing pneumonia (AFOP) (n=22), acute interstitial pneumonia (AIP) (n=5), connective tissue disease (CTD) -related interstitial lung disease (ILD) (n=3), unclassified interstitial pneumonia (n=2), pneumonia (n=20), and drug-induced ILD (DILD) (n=1).**

Table 1. **Number of Patients with Each of the Identified Viruses in Viral Pneumonia (n=53).**

Virus	n*	(%)
Coronavirus	20	(37.7)
Human parechovirus	18	(34.0)
Respiratory syncytial virus	15	(28.3)
Human parainfluenza virus1	15	(28.3)
Rhinovirus	14	(26.4)
Influenza virus	13	(24.5)
Human metapneumovirus2	10	(18.9)
Adenovirus	3	(5.7)
Influenza B virus	1	(1.9)
Coinfection with bacteria	6	(11.3)

* Indicates number of patients with each detected virus. Thirty-five patients showed mixed viral infection, and thus the sum of * exceeds 53. Bacterial coinfections included *Legionella* sp. (n=2), *Mycoplasma pneumoniae* (n=2), *Chlamydophila psittac*i (n=1), and *Streptococcus pneumoniae* (n=1).

Adenovirus, n=1; CoV+HPeV, n=1; CoV+RSV, n=1; CoV+HPIV, n=1; CoV+hMPV, n=1; RSV+HPIV, n=1; RSV+HPeV, n=1; hMPV+HPeV, n=1; hMPV+HPIV, n=1), 3 viruses in 11 (Influenza A virus+RV+CoV, n=1; Influenza A virus+RSV+HPeV, n=1; RV+CoV+HPeV, n=1; RV+RSV+HPeV, n=1; RV+HPeV+hMPV, n=1; CoV+RSV+HPeV, n=2; CoV+RSV+HPIV, n=1; RV+CoV+RSV, n=1; RV+HPIV+HPeV, n=1; HPIV+RSV+HPeV, n=1), 4 viruses in 7 (Influenza B virus+RV+HPIV+HPeV, n=1; RV+CoV+HPIV+hMPV, n=1; CoV+HPIV+RSV+HPeV, n=1; CoV+HPIV+HPeV+Adenovirus, n=1), and 5 viruses in 1 patient (RV+CoV+HPIV+RSV+Adenovirus). Among the 53 patients with viral pneumonia, 6 were coinfected with *Legionella* sp. (n=2, coinfected with RV+CoV, and with Influenza B virus+RV+HPIV+HPeV, respectively), *Mycoplasma pneumoniae* (n=2, coinfected with hMPV, and with CoV+RSV+HPeV, respectively), *Chlamydophila psittaci* (n=1, coinfected with HPIV), or *Streptococcus pneumoniae* (n=1, coinfected with RV+HPeV). The remaining 48 patients had primary viral pneumonia.

Seasonality of viral pneumonia

The number of cases of virus infection diagnosed each month was higher in the winter months and lower in the summer months (Fig. 3).

Symptoms of patients with viral pneumonia

The median (range) duration from the onset of symptoms to admission of the 53 patients with viral pneumonia was 11.0 (0-30) days. With the exception of 2 patients for whom corticosteroids had been prescribed by local physicians, the clinical symptoms, radiological findings, and laboratory findings were progressive, and 20 of the patients (37.7%) showed respiratory failure. The symptoms experienced by these 53 patients are listed in Table 2. Sore throat and fever

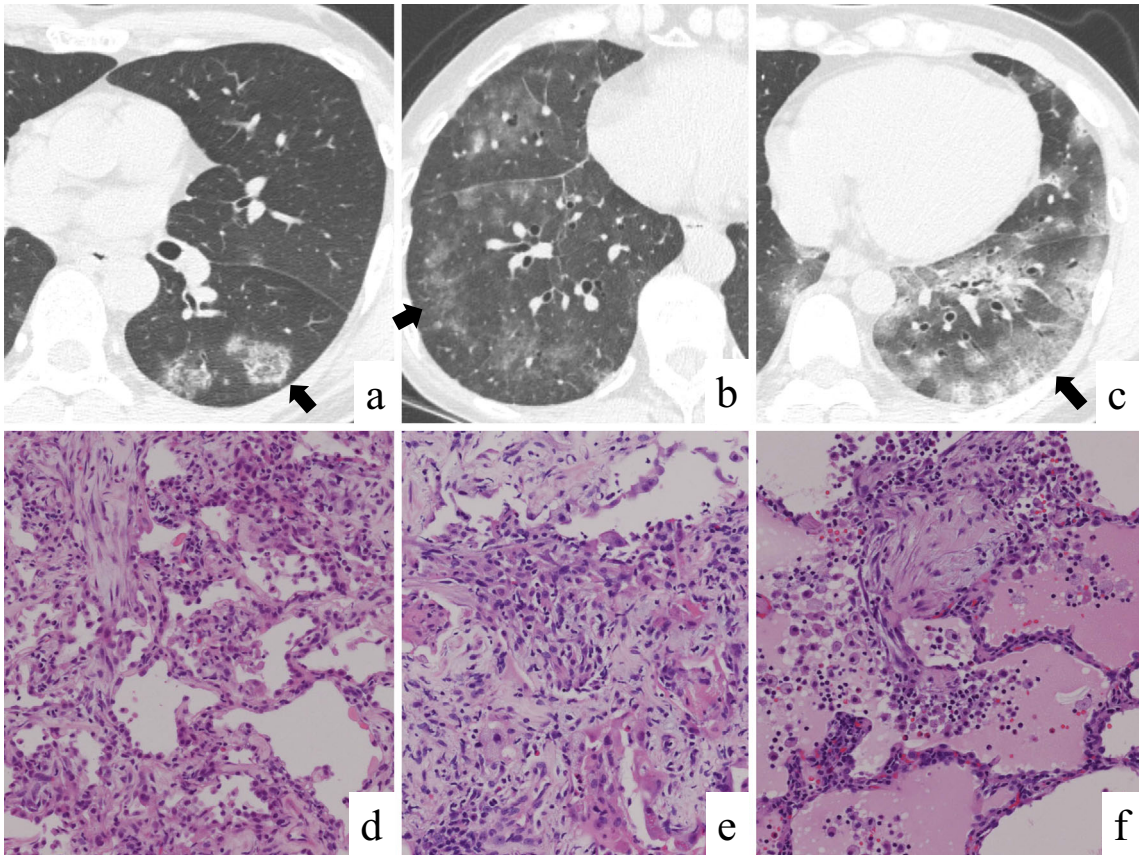

Figure 3. **The chest computed tomography findings and histologic findings of viral pneumonia. Patchy ground-glass opacities (GGOs) and nodules in a 44-year-old man with human parechovirus pneumonia (a). Bilateral GGOs and centrilobular nodules in a 72-year-old woman with mixed viral pneumonia due to respiratory syncytial virus, human parechovirus, and human parainfluenza virus (type 1) (b). Bilateral GGOs and consolidation in a 42-year-old man with mixed viral pneumonia due to influenza A virus, respiratory syncytial virus, and human parechovirus (c). Arrows indicate areas where tissue samples were obtained. Histological findings obtained via transbronchial lung biopsy (d, e) and video-assisted lung biopsy (f) showed organization and swollen pneumocytes. Histological findings obtained via surgical lung biopsy showed organization, swollen pneumocytes, and pulmonary edema (f). The photos of histological specimens in panels d, e, and f respectively correspond to the patients in panels a, b, and c.**

were more frequently found in patients with viral pneumonia than in those with other diseases. The duration from the onset of symptoms to admission and maximum body temperature did not differ between the groups to a statistically significant extent.

The laboratory data of patients with viral pneumonia

The median (range) white blood cell count and C-reactive protein (CRP) value were 9,000 (2,400-27,200)/mm^3 and 9.85 (0.09-46.8) mg/dL. There were no significant differences in the white blood cell counts or serum procalcitonin values between the patients with viral pneumonia and those with other diseases (Table 3). The serum liver transaminase and CRP values were higher in patients with viral pneumonia than in those with other diseases (Table 3). The fraction of eosinophils in BALF was lower in patients with viral pneumonia than in those with other diseases. A nasopharyngeal rapid diagnostic test (RDT) was performed in 10 of the 13 patients with influenza-associated pneumonia, but all tests were negative.

CT findings of viral pneumonia

The chest CT findings revealed that most patients with viral pneumonia showed consolidation and GGOs (Table 4). None of these cases showed cavitation, tree-in-bud appearance, or halo sign. Consolidation and GGOs were bilateral in 58.5% and 84.9% of these patients, respectively (Fig. 4a-c). Consolidation affected 3.1±2.2 lobes, and GGOs affected 4.5±1.6 lobes (Table 4). An inverted halo sign was found in 2 patients.

The interobserver reliability of ratings of radiological findings

The interobserver reliability of CT scans for determining the presence of intralobular reticulation, the distribution of consolidation, and GGOs was poor to slight, but was fair for

Table 2. Clinical Characteristics of the Patients Viral Pneumonia and Other Diseases.

factors		Viral pneumonia (n=53)	Other diseases (n=56)	p value
Sex	Male	39 (73.6%)	28 (50.0%)	0.0177
Age	Mean (SD)	64.8 (13.01)	65.0 (14.66)	0.9383
	Median (min-max)	67.0 (27-84)	67.0 (19-82)	
Age (category)	≤65 yrs	33 (62.3%)	38 (67.9%)	0.5538
Underlying disease				
Pulmonary diseases		13 (24.5%)	12 (21.4%)	0.8205
Diabetes mellitus		9 (17.0%)	9 (16.1%)	1.0000
Hypertension		13 (24.5%)	13 (23.2%)	1.0000
Cardiac disease		12 (22.6%)	10 (17.9%)	0.6351
Neurological diseases		1 (1.9%)	3 (5.4%)	0.6185
Physiatric diseases		2 (3.8%)	3 (5.4%)	1.0000
Chronic kidney disease		4 (7.5%)	2 (3.6%)	0.4294
Chronic liver disease		1 (1.9%)	1 (1.8%)	1.0000
Connective tissue diseases		1 (1.9%)	13 (23.2%)	0.0010
Malignancy		1 (1.9%)	0 (0.0%)	0.4862
None		22 (41.5%)	16 (28.6%)	0.1665
Smoking history		36 (67.9%)	27 (48.2%)	0.0521
Duration from initial symptoms to admission (days)	Mean (SD)	13.9 (9.09)	14.5 (8.55)	0.7504
	Median (min-max)	11.0 (0-30)	14.0 (1-30)	
Duration from initial symptoms to admission (category)	<1 w	16 (30.2%)	13 (23.2%)	.
	1 w≤, <2 w	12 (22.6%)	14 (25.0%)	
	2 w≤, ≤30 d	23 (43.4%)	29 (51.8%)	
Symptoms				
Sore throat		11 (20.8%)	2 (3.6%)	0.0070
Rhinorrhea		2 (3.8%)	1 (1.8%)	0.6112
Cough		39 (73.6%)	41 (73.2%)	1.0000
Sputum		13 (24.5%)	12 (21.4%)	0.8205
Arthralgia, myalgia		5 (9.4%)	5 (8.9%)	1.0000
Dyspnea		20 (37.7%)	28 (50.0%)	0.2476
Dizziness		3 (5.7%)	0 (0.0%)	0.1116
Diarrhea		2 (3.8%)	2 (3.6%)	1.0000
Fever		51 (96.2%)	45 (80.4%)	0.0158
Headache		0 (0.0%)	0 (0.0%)	.
Maximum body temperature	Number	52	56	0.0919
	Mean (SD)	38.08 (1.000)	37.78 (0.833)	
	Median (min-max)	38.00 (36-40.2)	37.90 (36.4-40.4)	
Respiratory failure	Yes	20 (37.7%)	17 (30.4%)	0.4274

determining the other findings (Table 4).

Pathological findings

Twenty-five patients underwent transbronchial lung biopsy (TBLB) and 2 underwent video-assisted lung biopsy. Histological samples showed intraluminal organization (n=21), alveolitis characterized by thickened alveolar septa and infiltration of the inflammatory cells to the alveolar septa (n=26), intraalveolar hemorrhage (n=12), and fibrin exudate (n=3) (Fig. 4d-f).

Treatment of patients with viral pneumonia

Before admission, 31 of the 53 patients with viral pneumonia had received antibiotics. Eleven patients showed early treatment failure with a worsened condition. The other 20 patients showed both early and late treatment failure. Two of these 20 patients received effective corticosteroid therapy before admission. The condition of the other 18 patients became worse after antibiotic treatment. The remaining 22 patients had not received antibiotics or corticosteroids before admission, but they were referred to our hospital after their condition worsened. None of these patients had received neuraminidase inhibitors (NIs) before admission.

After admission, 46 of these 53 patients received antibiotics with β-lactams plus macrolides (n=22, 41.5%), fluoroquinolones with or without other antibiotics (n=16, 30.2%), and others (n=8, 15.1%). Antibiotics were not administered to 7 patients after admission because antibiotic treatment administered by their local physicians had failed.

Six of 13 patients with influenza-associated pneumonia

Table 3. Laboratory Data of the Patients with Viral Pneumonia and Other Diseases.

Factors	Viral pneumonia (n=53)	Other diseases (n=56)	p value
WBC (/mm^3)	9,000.0 (2,400-27,200)	8,100.0 (4,000-19,800)	0.2474
Neutrophils (/mm^3)	7,200.0 (470-25,900)	6,000.0 (2,800-15,700)	0.0722
Lymphocytes (/mm^3)	1,200.0 (400-4,000)	1,300.0 (600-3,300)	0.5126
Eosinophils (/mm^3)	100.0 (0-700)	200.0 (0-10,600)	0.1135
Monocytes (/mm^3)	500.0 (100-1,000)	400.0 (0-1,500)	0.6383
Basophils (/mm^3)	0.0 (0-100)	0.0 (0-100)	0.2857
Hemoglobin (g/dL)	12.90 (10-17.4)	12.45 (8.6-17.6)	0.4030
Platelets (/mm^3)	28.20 (10.8-56)	28.55 (12.9-80.1)	0.4407
AST (IU/L)	31.0 (16-305)	28.5 (10-109)	0.0458
ALT (IU/L)	22.0 (8-205)	20.5 (8-73)	0.0178
LDH (IU/L)	238.0 (136-936)	260.0 (108-719)	0.3099
CRP (mg/dL)	9.850 (0.09-46.8)	3.040 (0.11-23.2)	0.0006
PCT* (ng/mL)	0.090 (0.03-72.41)	0.075 (0-1.28)	0.1789
KL-6* (U/mL)	365.0 (100-1,881)	437.0 (98-3,954)	0.0419
BAL fluid			
Cell numbers* (×10^3/mm^3)	0.530 (0.03-3.77)	0.480 (0.04-8.01)	0.9794
Macrophages* (%)	36.30 (0.5-93.5)	36.30 (6.2-150)	0.5199
Neutrophils* (%)	8.00 (0.3-77)	6.30 (0-90.4)	0.4434
Lymphocytes* (%)	35.90 (2.1-84.8)	34.70 (0.3-88.9)	0.7481
Eosinophils* (%)	2.10 (0-19.2)	2.30 (0-80.9)	0.0135
CD4/8 ratio* (%)	1.400 (0.05-10.57)	1.600 (0.1-14.17)	0.7560

Values are expressed as median (minimum-maximum). *Number of cases with viral pneumonia/other diseases in which PCT, KL-6, and BAL fluid parameters (cell numbers, macrophages, lymphocytes, eosinophils, and CD4/8 ratio), was not 53/56 but 29/28, 51/55, 51/55, 49/55, 49/55, 49/55, 49/55, 48/55, respectively. WBC: white blood cell, AST: aspartate transaminase, ALT: alanine transaminase, LDH: lactate dehydrogenase, CRP: C-reactive protein, PCT: procalcitonin, KL-6: Krebs von den Lungen, BAL: bronchoalveolar lavage, CD: cluster of differentiation

received NIs (from the 5th to 23rd day from the onset of initial symptoms). In three of these 6 patients, both NIs and corticosteroids were started simultaneously, and these patients improved. In 4 of the 6 patients, NIs were started without corticosteroids (from the 5th, 8th, and 11th day after the onset of symptoms). NIs were effective in 2 of 3 patients. In the other patient, however, NI was administered from the 11th day after onset, but the patient showed early treatment failure and was switched to corticosteroid therapy from the 14th day, which was effective. In 7 patients who did not receive NIs, 6 received corticosteroid therapy (which was effective) from the 11th, 19th, 22nd, 23rd, 25th, and 47 th day, respectively, after the onset of symptoms. The pulmonary shadows of the two other patients who did not receive corticosteroids or NIs improved spontaneously during follow-up. Among the 40 patients suffering from viral pneumonia due to non-influenza viruses, corticosteroids with antibiotics were administered to 21 patients from a median of 15 (range, 6-45) days after the onset of symptoms. Two of these patients died. Corticosteroid therapy was effective in one of these patients; however, this patient experienced repeated episodes of aspiration pneumonia causing their condition to deteriorate until their death. The other patient showed early and late treatment failure with corticosteroid therapy, causing the progressive deterioration of the patient's condition until their death. The other 19 patients received antibiotics without corticosteroids and all survived.

Discussion

Viral infection was detected in approximately half of patients with acute progressive lung diseases that required BAL for a differential diagnosis. Surprisingly, more than half of the patients with viral pneumonia were misdiagnosed as having some type of ILD on discharge. Most patients with viral pneumonia had received antibiotics but had responded poorly. The guidelines recommend considering viral pneumonia in non-responders to antibiotics (8); however, respiratory physicians frequently misdiagnosed viral pneumonia as ILD or suspected ILD. Our results suggest the importance of including viral pneumonia in the differential diagnosis of patients with acute and progressive disease suggestive of an ILD.

Several symptoms and laboratory findings have been reported as suggestive of pure viral pneumonia as opposed to bacterial pneumonia: less productive cough, lower peripheral white blood cell counts, lower procalcitonin and CRP levels, and higher serum creatine kinase values (9, 10). Our study compared viral pneumonia and other acute diseases and found that sore throat and fever were observed significantly

Table 4. CT Findings of Patients with Viral Pneumonia and Variability of Radiological Findings from Chest Computed Tomography between Two Observers.

Findings	Number	%	Kappa coefficient (95% confidence interval)
Consolidation	43	81.1	0.638 (0.399, 0.877)
Bilateral	31	58.5	0.849 (0.708, 0.990)
Affected lobes	3.1±2.2		
Subpleural distribution	3	5.7	0.156 (-0.007, 0.319)
Along with bronchovascular bundles	2	3.8	-0.062 (-0.132, 0.008)
Ground-glass opacities	53	100.0	NE
Bilateral	45	84.9	0.554 (0.263, 0.844)
Affected lobes	4.5±1.6		
Subpleural distribution	2	3.8	0.084 (-0.029, 0.197)
Along with bronchovascular bundles	2	3.8	0.174 (-0.182, 0.530)
Halo sign	0	0.0	NE
Inverted halo sign	2	3.8	NE
Diffuse bronchial wall thickening	3	5.7	0.485 (-0.114, 1.000)
Nodule (<3 cm)	9	17.0	NE
Mass (≥3 cm)	2	3.8	NE
Cavity	0	0.0	NE
Centrilobular nodules	11	20.8	0.554 (0.263, 0.844)
Bilateral	9	17.0	0.614 (0.310, 0.918)
Tree-in-bud appearance	0	0.0	NE
Intralobular septal thickening	2	3.8	0.372 (-0.186, 0.929)
Intralobular reticulation	1	1.9	0.195 (-0.134, 0.525)
Honeycombing	2	3.8	1.000 (1.000, 1.000)
Mediastinal or hilar lymph node swelling	16	30.2	0.604 (0.372, 0.836)
Pleural effusion	30	56.6	0.846 (0.702, 0.991)
Bilateral	14	26.4	0.722 (0.514, 0.929)
Pneumothorax	0	0.0	NE
Cardiomegaly	3	5.7	0.307 (-0.060, 0.673)

more frequently in patients with viral pneumonia than in those with other diseases. Laboratory tests showed higher liver transaminase and CRP values, and lower numbers of eosinophils in the BALF of patients with viral pneumonia than in those with other diseases. Our study also showed that it was difficult to distinguish viral pneumonia from acute ILDs or pneumonia due to unknown etiology using procalcitonin alone, although procalcitonin is used as a marker for discriminating between viral and bacterial infections (11).

Conventional diagnostic tests for respiratory viral infection include culture, serology, and direct fluorescence antibody staining; however, these methods are limited by slow turnaround time or insufficient sensitivity. Although PCR techniques are more labor intensive and technically demanding and require specialized laboratory equipment, they have high sensitivity, and our study suggested their usefulness in the detection of viral infection. Nasopharyngeal RDTs in 10 patients with primary influenza viral pneumonia were all negative in our study, which was supported by the low sensitivity of nasopharyngeal RDTs in the 2009 pandemic (12). We did not perform RDTs using BALF; however, PCR tests using BALF were useful and are recommended for the diagnosis of primary influenza viral pneumonia. Some of our study patients had positive PCR results that were considered to indicate colonization. In previous adult studies, viruses were detected in 0.4-4.2% of asymptomatic patients (13-16). Differentiating infection and colonization is still difficult using PCR methods; thus, physicians should not diagnose patients as having a viral infection based on PCR results alone.

In our study, the most frequently detected virus was CoV, which was in line with the findings of a previous report (17). The second most frequent virus in viral pneumonia was HPeV, but it was only isolated in 1 patient among 40 controls. HPeV causes gastroenteritis and respiratory infections in children. Several recent large studies have cast doubt on the role of HPeV as a significant cause of respiratory disease (18); however, our results suggest that HPeV is not rare in adults and has a significant role in viral pneumonia. In immunocompromised patients with pneumonia, the most frequent virus was CoV (32%), followed by rhinovirus (23%) and HPIV (20%) (17).

In the present study, AFOP, COP, and CEP were found to be the most frequently misdiagnosed ILDs. Various influenza-associated pneumonias that show similar CT patterns to COP, AFOP, and AIP have been reported (19), and a previous report focusing on primary influenza suggested the

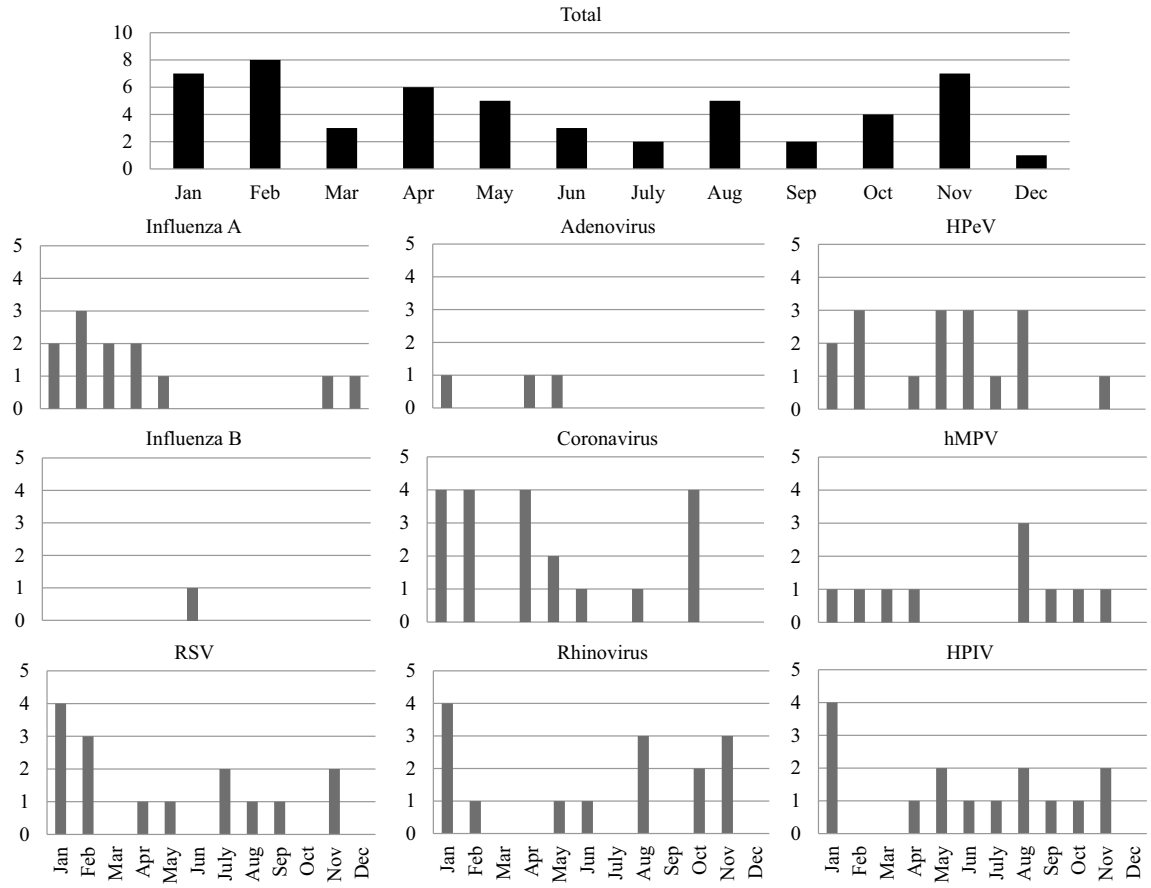

Figure 4. The monthly distribution of the 53 patients with viral pneumonia. The bars represent the number of cases of virus infection diagnosed each month. Higher numbers of cases were diagnosed in winter and lower numbers were diagnosed in summer. RSV: respiratory syncytial virus, HPeV: human parechovirus, hMPV: human metapneumovirus, HPIV: human parainfluenza virus

difficulty of differentiating primary viral pneumonia from the above ILDs (20). Then CT findings in our patients with viral pneumonia were compatible with the diagnosis, but the spectrum of CT findings encountered in viral pneumonia (21-23) is non-specific and is also found in the above ILDs. Physicians should include viral pneumonia in the differential diagnosis of imaging patterns that are suggestive of these diseases. In addition, the histological findings in our patients with viral pneumonia, which were mostly obtained via TBLB, were also non-specific (24), and it was difficult to suspect viral pneumonia on the basis of histological findings alone.

In most patients with viral pneumonia, treatment is mainly supportive care. The efficacy of NIs is partially reported in influenza-associated pneumonia (25), NIs were effective in some of our patients. It is recommended that NIs be administered within 48 hours from the onset of symptoms; however, NIs administered after this 48-h period were effective in some of our patients. Regarding the treatment of viral infections other than influenza virus, immunoglobulin therapy (pegylated interferon-alpha2A) for rhinovirus, the potential efficacy of palivizumab for RSV, ribavirin (a guanosine analogue) therapy for RSV and hMPV, and cidofovir (the nucleoside analogue of cytidine monophosphate) for adenovirus infection have been reported (26). However, the efficacy of these treatments for primary viral pneumonia is unknown. Severe cases require aggressive treatment, including antiviral therapy; however, one problem we found was that viral pneumonia was not infrequently caused by multiple viruses. Similar results have been reported elsewhere (27). It may be useful for physicians to test for multiple viruses simultaneously when considering antiviral therapy.

Most of the patients in the present study received corticosteroid therapy because they were misdiagnosed as having ILDs. The use of corticosteroids for the treatment of viral pneumonia is controversial. Corticosteroids have been reported to be ineffective in the treatment of RSV in children (28). However, some data suggest favorable effects on varicella-zoster virus (in combination with acyclovir) and hantavirus (29) and in influenza-associated pneumonia in some clinical settings (30, 31). In our 13 patients with influenza-associated pneumonia, corticosteroids were administered without NIs to 6 patients, and were effective. Among the patients with viral pneumonia due to non-influenza viruses, corticosteroids were administered to 21 patients, 1 of whom did not survive; however, they were effective in the other 20 patients (95.2%). The significance of corticosteroid

therapy for viral pneumonia should be addressed in future studies.

The present study was associated with several limitations. First, because this is a non-randomized observational study, the level of confidence was reduced. Second, this study was carried out in a single center, and the results may not be applicable to other settings. It is noteworthy that our institution has about 10 specialist physicians licensed by the Japan Respiratory Society. These physicians judged the need for BAL, and thus, there was bias in terms of the patients who underwent BAL. In addition, the requirement for hospitalization was a major criterion for entry into this study. This could potentially induce a spectrum bias in which only the most severe cases were enrolled in the study. Third, there may be incorporation bias in that the review panel determined that the final diagnosis was more likely to classify cases as viral pneumonia when fever and sore throat were present. Fourth, we did not investigate antibody titers against viruses in the acute and convalescent phases; thus, the number of cases of viral pneumonia might have been underestimated (32). Fifth, the multidisciplinary diagnoses were made without video-assisted thoracoscopic surgery in most cases; thus, the pathological findings may not have been fully evaluated. Sixth, some viral infections may have been missed in this study because only a limited number of viruses were screened in the assay. Finally, the possibility of detecting viruses from the upper respiratory tracts cannot be denied when using the BAL technique. To avoid this concern, a well-designed, prospective study is needed in which samples are obtained only from the lower respiratory tract, for example, via intubation or with the use of a protected specimen brush.

In conclusion, we detected viral pneumonia in approximately half of the patients for whom respiratory physicians frequently suspected acute and progressive ILDs. Clinical symptoms and laboratory findings were not diagnostic for viral pneumonia. Our results suggested that significant numbers of patients with viral pneumonia may be misdiagnosed with ILDs, especially AFOP, COP, and CEP. The guidelines recommend considering viral pneumonia in non-responders to antibiotics (8); however, it is important to include viral pneumonia in the differential diagnosis of acute and progressive cases suggestive of ILD.

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