

[ CASE REPORT ]

## Two Cases of Primary Human Parainfluenza Virus 1 Pneumonia in Which Bronchoalveolar Lavage Fluid Yielded Human Parainfluenza Virus 1

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### Abstract:

Two patients, a 76-year-old woman and 66-year-old woman, presented to our hospital with symptoms of lower respiratory tract infection. Both patients showed chest imaging findings of bilateral ground-glass opacities and consolidations. We initially suspected these patients of having influenza-associated pneumonia and cryptogenic organizing pneumonia, respectively, and performed bronchoalveolar lavage, but only human parainfluenza virus-1 infection was detected by multiplex polymerase chain reaction testing. These findings suggest that pneumonia due to human parainfluenza virus-1 should be included in the differential diagnosis of such cases.

**Key words:** human parainfluenza virus, viral pneumonia, multiplex PCR, corticosteroid

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### Introduction

Human parainfluenza viruses (HPIVs) are single-stranded, enveloped RNA viruses belonging to the *Paramyxoviridae* family. Compared with findings in studies of HPIV infection in children, less is known about these infections in adults. In previous studies, 0.2 to 11.5% of hospitalized patients with pneumonia were found to have HPIV infection (1, 2); however, the characteristics of primary viral pneumonia due to HPIV are not well known. We recently experienced two cases of pneumonia in which HPIV-1 was isolated from bronchoalveolar lavage (BAL) fluid and confirmed by a multiplex polymerase chain reaction (PCR) test (Fast Track Diagnostics Resp 21 Kit, Silema, Malta), which detects the following respiratory pathogens: influenza A and B viruses; coronaviruses NL63, 229E, OC43, and HKU1; human parainfluenza viruses 1, 2, 3, and 4; human metapneumovirus A/B; rhinovirus; respiratory syncytial virus A/B; adenovirus; enterovirus; human parechovirus; bocavirus; and *Mycoplasma pneumoniae*. We herein report these cases and

review the clinical and radiological features.

### Case Reports

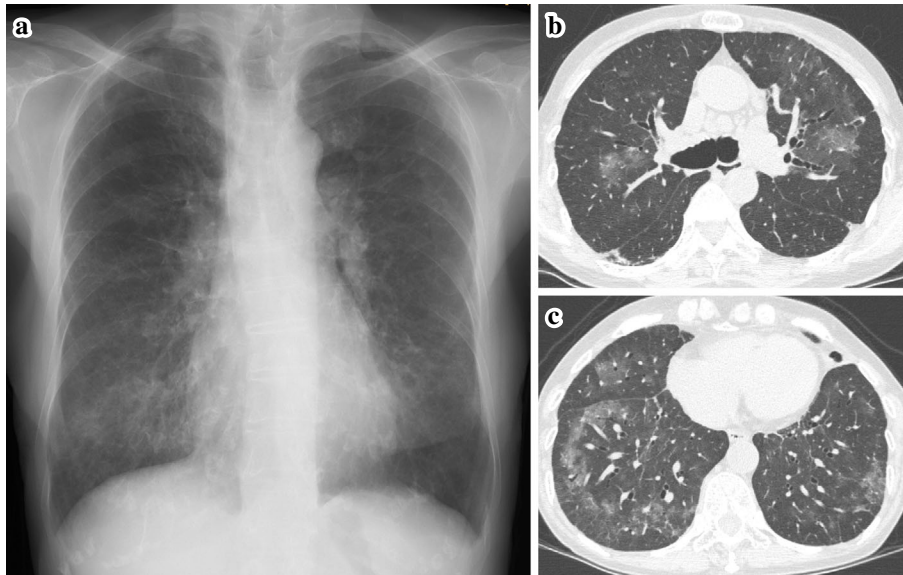
#### Case 1

A 76-year-old woman presented to our hospital with appetite loss and fever in March. On the first day of illness, she initially developed appetite loss, and on the second day, she developed a fever of 37.7°C. On the fourth day, she developed dyspnea, sore throat, and cough, and on the fifth day, she presented to a local physician who found abnormal shadows on chest X-ray and referred her to our hospital. She had no noteworthy past history. She was a never-smoker and was never exposed to dust. On admission, her vital signs included a body temperature of 37.8°C, respiratory rate of 20/min, systolic blood pressure of 119 mmHg, and heart rate of 90 beats per min. Chest auscultation showed bilateral coarse crackles. An arterial blood gas analysis under O<sub>2</sub> of 4 L/min by nasal canula showed a pH of 7.49, partial pressure of carbon dioxide in arterial blood (PaCO<sub>2</sub>)

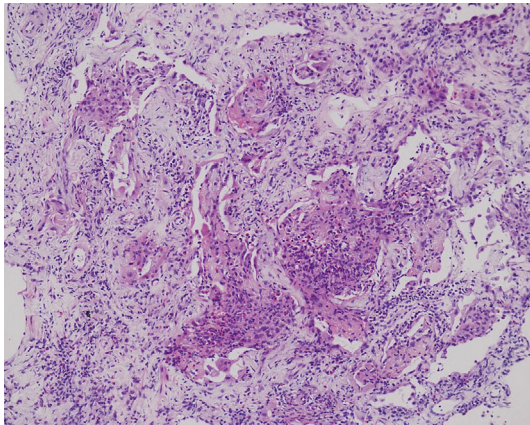
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**Figure 1.** Chest imaging of Case 1. Chest X-ray showed bilateral ground-glass opacities (GGOs) and consolidations (a). Chest computed tomography (CT) showed bilateral GGOs (b, c).



**Figure 2.** Histological findings of Case 2. Transbronchial lung biopsy showed an infiltration of macrophages, neutrophils, and lymphocytes. Exudates of fibrins and mild alveolitis were also found, which indicate alveolitis.

of 31.6 Torr, partial pressure of arterial oxygen (PaO<sub>2</sub>) of 70.9 Torr, and HCO<sub>3</sub><sup>-</sup> of 25.3 mmol/L. Laboratory data showed a white blood cell count of 8,100/mm<sup>3</sup> (neutrophils, 78.3%; lymphocytes, 10.7%; eosinophils, 2.4%; basophils, 0.4%; and monocytes, 8.2%), hemoglobin of 12.8 g/dL, platelets of 23.0×10<sup>4</sup>/mm<sup>3</sup>, aspartate aminotransferase (AST) of 56 IU/L, lactate dehydrogenase (LDH) of 253 IU/L, creatinine of 0.6 mg/dL, C-reactive protein (CRP) of 1.7 mg/dL, and procalcitonin of 0.090 ng/mL. Her Krebs von den Lungen-6 (KL-6) level was 1,096 U/mL. Autoantibodies were all negative, and anti-human immunodeficiency virus (HIV) antibody was also negative. Rapid nasopharyngeal or oropharyngeal diagnostic tests for influenza virus and *Mycoplasma pneumoniae* and urinary antigen tests for *Streptococcus pneumoniae* and *Legionella* spp. were all negative. Chest X-ray showed bilateral ground-glass opacities (GGOs) and

consolidations (Fig. 1a). Chest computed tomography showed GGOs and consolidations in both lung fields (Fig. 1b and c). Pleural effusion or lymphadenopathy were not found. We performed bronchoscopy and the BAL procedure from the internal segment of the right middle lobe. BAL fluid (85 of 150 mL recovered) showed 3.5×10<sup>5</sup> cells/mL (neutrophils, 1.6%; lymphocytes, 62.0%; macrophages, 32.0%; and eosinophils, 4.4%) but did not show any microorganisms by Gram staining or yield significant pathogens including *M. pneumoniae* or *Legionella* spp. Cytology of the BAL fluid showed no significant findings. A transbronchial lung biopsy specimen showed alveolitis, fibrin exudation, and intraluminal organization (Fig. 2). Blood culture was negative. We suspected her of having influenza-associated pneumonia and started ampicillin/sulbactam and peramivir. Her chest shadows gradually improved, and her fever abated on hospital day (HD) 6. Oxygen by nasal canula was stopped on HD 10, and she was discharged on HD 16. Specific antibody titers against *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, *Legionella* spp., influenza virus, adenovirus, and respiratory syncytial virus in paired sera did not increase, but antibodies against HPIV were not measured. We analyzed the BAL fluid with multiplex PCR, which showed positive results only for HPIV-1. Two years after discharge, she has not relapsed.

### Case 2

A 66-year-old woman presented to our hospital with cough, sputum, and sore throat of 3 weeks duration in May. She initially visited a local physician who detected abnormal shadows on her chest X-ray and then referred her to our hospital. She had not received any antibiotics before presenting to our hospital. She had a history of gastric carcinoma when she was 61 years old and had undergone gastrectomy. Her cancer had not recurred. She was an ex-smoker with

Brinkman index of 880, but she had never been exposed to dust. On admission, her vital signs included a body temperature of 36.4°C, respiratory rate of 22/min, systolic blood pressure of 116 mmHg, and heart rate of 65 beats per min. Chest auscultation showed bilateral coarse crackles. An arterial blood gas analysis under ambient air showed a pH of 7.48, PaCO<sub>2</sub> of 34.9 Torr, PaO<sub>2</sub> of 99.3 Torr, and HCO<sub>3</sub><sup>-</sup> of 25.2 mmol/L. Laboratory data showed a white blood cell count of 5,700/mm<sup>3</sup> (neutrophils, 59.9%; lymphocytes, 31.9%; eosinophils, 3.4%; basophils, 0.4%; and monocytes, 4.4%), hemoglobin of 12.2 g/dL, platelets of 24.6×10<sup>4</sup>/mm<sup>3</sup>, AST of 23 IU/L, LDH of 215 IU/L, creatinine of 0.53 mg/dL, CRP of 0.3 mg/dL, and KL-6 of 328 U/mL. Autoantibodies were negative, as was an anti-HIV antibody test. Rapid nasopharyngeal or oropharyngeal diagnostic tests for influenza virus and *Mycoplasma pneumoniae* and urinary antigen tests for *S. pneumoniae* and *Legionella* spp. were all negative. Chest X-ray showed bilateral consolidation (Fig. 3a), and chest computed tomography showed non-segmental and subpleural consolidation bilaterally in the lower lobes (Fig. 3b). No centrilobular pulmonary nodules, pleural effusion, or lymphadenopathy was detected. We performed bronchoscopy and BAL from the lateral segment of the right lower lobe. BAL fluid (70 of 150 mL recovered) showed 1.6×10<sup>5</sup> cells/mL (neutrophils, 3.3%; lymphocytes, 35.9%; macrophages, 54.5%; and eosinophils, 6.3%) but did not show any microorganisms by Gram staining or yield significant pathogens including *M. pneumoniae*. Cytology of the BAL fluid also showed no significant findings. We could not obtain adequate specimens for evaluation via transbronchial lung biopsy. We initially suspected her of having cryptogenic organizing pneumonia (COP) and administered prednisolone 20 mg daily. Her chest shadows gradually improved, and she was discharged on HD 9. We analyzed the BAL fluid with multiplex PCR, which showed positive results only for HPIV-1. Specific antibody titers against *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, *Legionella* spp., influenza virus, adenovirus, and respiratory syncytial virus in paired sera did not increase, but antibodies against HPIV were not measured. We then gradually tapered the prednisolone and stopped it two months after hospital discharge. At four years since her treatment, she has not developed a relapse.

## Discussion

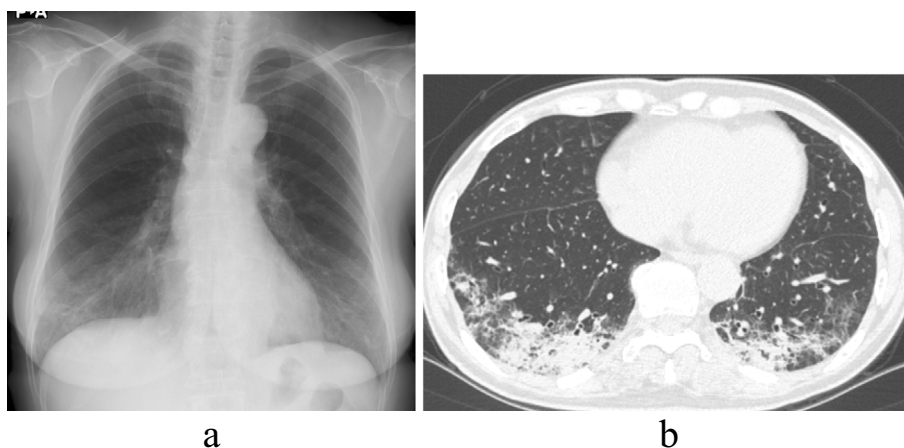
We herein report two immunocompetent patients with primary HPIV-1 pneumonia. One patient required oxygen supplementation on admission, and both patients recovered without the administration of antiviral agents.

Most HPIV infections in adults cause mild upper respiratory tract symptoms, but the elderly or those with a compromised immune system are associated with progressive disease (3-5). HPIV is responsible for 1 to 15% of acute respiratory illnesses in adults. In other studies, 0.2 to 11.5% of hospitalized patients with pneumonia were found to have

HPIV infection (1, 2). Furthermore, HPIV is present in 7.6% of severe pneumonias, which indicates that HPIV is a frequent pathogen of both non-severe and severe pneumonia (6). However, previous reports that investigated virus infections in patients with pneumonia used nasopharyngeal or oropharyngeal swabs to detect viruses, which raises the possibility of upper respiratory tract infection by HPIV. Furthermore, these studies include mixed viral and bacterial infections, and the clinical characteristics of the immunocompetent patients with primary HPIV pneumonia are not fully known. In our two cases, HPIV was detected in BAL fluid, which indicated the HPIV in our cases to be a pathogen of not the upper airways but the lower respiratory tract and of pneumonia. In addition, BAL fluid did not yield other significant pathogens, nor did specific antibody titers against other pathogens of pneumonia in paired sera increase, which support the diagnosis of primary HPIV infection in our patients.

Four subtypes of HPIV (HPIV-1, 2, 3, and 4) have been identified, and HPIV-3 is the most prevalent serotype of infections. Among adults hospitalized with pneumonia, HPIV-3 was found in 3.1% of patients (7, 8). The causative virus in our patients was HPIV-1, a subtype found in 2.5% of adult pneumonias (5, 9). Although our patients recovered successfully, Tamaki et al. reported a fatal case of viremia due to HPIV-1 in a patient with adult T-cell leukemia-lymphoma treated with mogamulizumab (10), which indicates that HPIV-1 can also be a fatal pathogen in immunocompromised patients.

Diseases mainly suspected in our patients before identification of HPIV-1 via multiplex PCR testing were primary influenza virus pneumonia and COP, respectively. A previous study reported that viral pneumonia is frequently misdiagnosed as COP (11). In the differentiation of these diseases, sore throat is a more frequent symptom of viral pneumonia than of acute interstitial lung diseases including COP (11), and our patients both had sore throats. However, typical symptoms in adult patients with HPIV infection include fever, rhinorrhea, cough, and a sore throat, which do not clinically distinguish it from other respiratory viruses (7). Cunha et al. reported that the clinical presentation of HPIV pneumonia closely mimics H1N1 pneumonia (12). Chest CT findings in our patients included bronchial wall thickening, bilateral consolidations, and GGOs, which were compatible with typical CT findings of HPIV pneumonia, e.g., multifocal patchy consolidation with GGOs, and centrilobular nodules with bronchial wall thickening (13); however, these findings seem nonspecific for HPIV pneumonia. Pokharel et al. reported multinucleated giant cells with organizing pneumonia as findings suggestive of HPIV infection (14), but the sensitivity and specificity of the pathologic findings were not known and these findings were not present in our patients. Thus, it is important to include viral infections in the differential diagnosis and investigate respiratory specimens with viral PCR tests. HPIV causes epidemics during the spring season or a small secondary period of in-



**Figure 3.** Chest imaging of Case 2. Chest X-ray on admission showed nodules in the bilateral lung fields (a). Computed tomography showed diffuse bronchial wall thickening and bilateral ground-glass opacities (b).

creased activity in the fall, and thus seasonality and local epidemiology may be clues suggestive of HPIV pneumonia.

Currently, no treatments with proven efficacy are approved for the treatment of HPIV infections. Corticosteroids, generally dexamethasone and budesonide, are associated with fewer clinic visits and admissions for croup and the reduced use of nebulized epinephrine (15). We initially misdiagnosed our patient in Case 2 as having COP and administered corticosteroids. The efficacy of corticosteroid administration in immunocompetent adult patients with HPIV pneumonia is not known. Some data suggest favorable effects on varicella-zoster virus (in combination with acyclovir) and hantavirus (16) and in influenza-associated pneumonia in some clinical settings (17, 18). Among 13 previously reported patients with influenza-associated pneumonia, corticosteroids were administered without neuraminidase inhibitors in 6 and were effective (11). Among the patients with viral pneumonia due to non-influenza viruses, corticosteroids were administered to 21, 1 of whom did not survive, but were effective in the other 20 patients (95.2%) (11). However, the mainstay of therapy in patients with HPIV infection is considered to be the reduction of immune suppression, which includes corticosteroids use (9). Further studies are needed to clarify the significance of corticosteroids as a treatment option for primary HPIV pneumonia in immunocompetent patients. However, much of the available data for the use of antiviral agents in the treatment of HPIV comes from immunocompromised patients. The efficacy of antiviral drugs in immunocompetent adults with HPIV pneumonia has not been fully evaluated, and thus further studies are needed.

One limitation of this report is that the possibility of detecting viruses from the upper respiratory tracts when using the BAL technique cannot be denied. To avoid this concern and ensure that samples are obtained only from the lower respiratory tract, intubation or use of a protected specimen brush is required.

In conclusion, we experienced two immunocompetent pa-

tients with primary HPIV-1 pneumonia. Primary HPIV pneumonia can resemble influenza-associated pneumonia and COP, and HPIV pneumonia should be included in the differential diagnosis of such cases.

**The authors state that they have no Conflict of Interest (COI).**

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