Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.4586-20
Intern Med 60: 435-439, 2021
http://internmed.jp

【 CASE REPORT 】

Two Cases of Primary Rhinovirus Pneumonia with Multiple Pulmonary Nodules

Yasuhiro Morimoto[1], Takashi Ishiguro[1], Keisuke Kasuga[1], Kenji Takano[1], Ryota Ozawa[1], Taisuke Isono[1], Yuto Akiyama[1], Yasuhito Kobayashi[2], Yoichi Kobayashi[1], Yoshihiko Shimizu[2] and Noboru Takayanagi[1]

Abstract:
Two patients, a 60-year-old man and 43-year-old woman, presented to our hospital with symptoms of respiratory tract infection. These patients showed imaging findings of multiple small nodules, ground-glass opacities, and consolidations. In case 1, although antibiotics were started, bilateral shadows spread widely, which made us suspect interstitial pneumonia. The condition improved after steroid administration, and there has been no recurrence since completing this treatment. In case 2, the patient recovered rapidly with antibiotics only. In both cases, we performed bronchoalveolar lavage, in which only human rhinovirus infection was detected by multiplex polymerase chain reaction testing, and primary rhinovirus pneumonia was diagnosed.

Key words: human rhinovirus, viral pneumonia, nodules, multiplex PCR, corticosteroid

(Intern Med 60: 435-439, 2021)
(DOI: 10.2169/internalmedicine.4586-20)

Introduction

Human rhinovirus (HRV), which is the most common pathogen of the common cold, is a member of the enterovirus genus, family *Picornaviridae*. In recent years, HRV has been reported to cause not only upper but also lower respiratory tract infection including primary viral pneumonia (1). Some studies of community-acquired pneumonia have reported that HRV is the most common virus in viral pneumonia (2, 3).

We herein report two cases of HRV pneumonia diagnosed by multiplex polymerase chain reaction (PCR) from bronchoalveolar lavage (BAL) fluid. Our two cases showed computed tomography (CT) findings of multiple nodules, which are rare in HRV. Some nodules were randomly distributed, as in case 1, while others showed a centrilobular distribution, as in case 2. We describe these cases and review the clinical and radiological features of HRV pneumonia.

Case Reports

Case 1

A 60-year-old man who worked as a dentist presented to our hospital with a 1-week history of general fatigue, a fever, and a cough in mid-January 2019. He did not have rhinorrhea or a sore throat. His history included bronchial asthma for 30 years, and he had received corticosteroid administration (prednisolone 20 mg daily for 2 weeks) for treatment of an asthma attack until 10 days before admission to our hospital. Arthralgia, myalgia, and a fever of 38.7°C also developed one day before his presentation, and he was admitted for a further evaluation. Although he had had no evident contact with sick people, he treated about 30 patients a day at his dental clinic. He had never smoked or drank, had never been exposed to dust, and had no relevant family medical history.

His vital signs included a blood pressure of 100/68 mmHg, heart rate of 78 beats/min, and respiratory rate of

[1]Department of Respiratory Medicine, Saitama Cardiovascular and Respiratory Center, Japan and [2]Department of Pathology, Saitama Cardiovascular and Respiratory Center, Japan
Received: February 1, 2020; Accepted: June 21, 2020; Advance Publication by J-STAGE: August 29, 2020
Correspondence to Dr. Yasuhiro Morimoto, morimoto0130@jikei.ac.jp

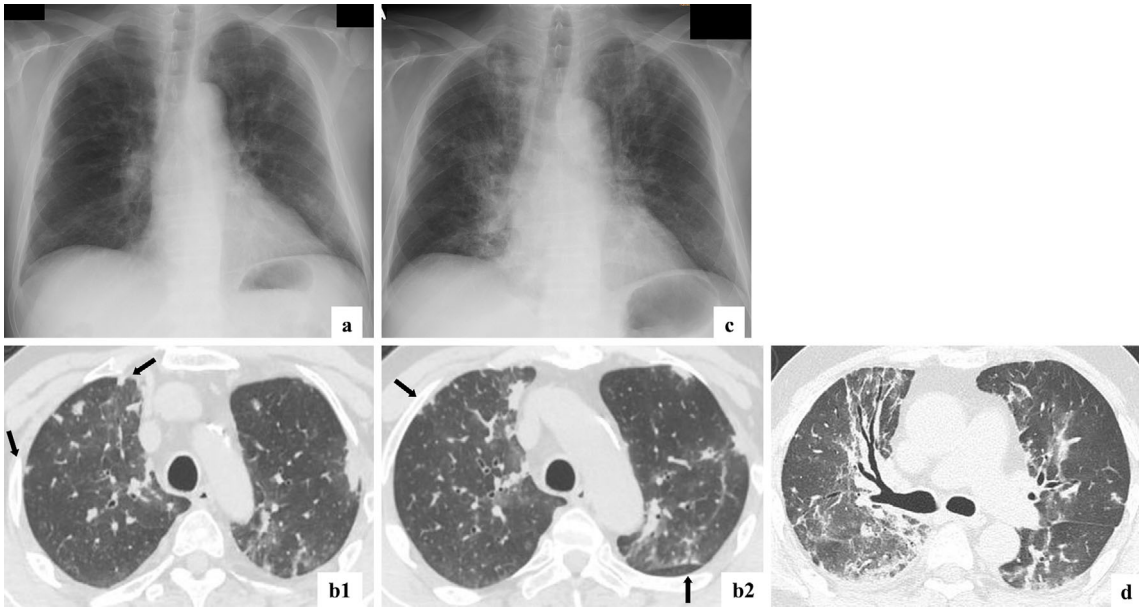

Figure 1. **Chest imaging findings of case 1. Chest X-ray on admission showed nodules in the bilateral lung fields (a). Computed tomography showed diffuse bronchial wall thickening and bilateral small nodules that existed along the airways, but some nodules were randomly distributed (arrows) (b1, 2). Chest X-ray performed on hospital day 10 showed increased bilateral shadows (c). Computed tomography on hospital day 10 showed bilateral consolidations and shrinkage change with bronchodilation and distortion (d).**

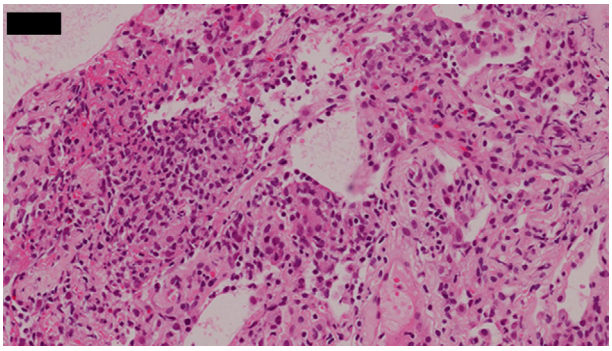

Figure 2. **Histological findings of case 1. A transbronchial lung biopsy showed the accumulation of macrophages with few eosinophils and neutrophils. Exudates of fibrins and mild alveolitis were also found.**

20/min. His body mass index was 24.2 kg/m^2. Arterial blood gasses under ambient air showed a pH of 7.49, $PaCO_2$ of 37.2 Torr, PaO_2 of 72.1 Torr, and HCO_3^- of 27.4 mmol/L. Laboratory tests showed a white blood cell (WBC) count of 9,800/mm^3 (neutrophils, 5,500/mm^3; lymphocytes, 3,400/mm^3; eosinophils, 200/mm^3; and monocytes, 700/mm^3), hemoglobin, 16.0 g/dL; platelet count, 13.1×10^4/mm^3; aspartate aminotransferase (AST), 31 IU/L; lactate dehydrogenase (LDH), 253 IU/L; blood urea nitrogen, 7 mg/dL; creatinine, 0.7 mg/dL; C-reactive protein, 3.2 mg/dL; and procalcitonin, 0.069 ng/mL. Autoantibodies were negative. Rapid nasopharyngeal or oropharyngeal diagnostic test and urinary antigen testing for influenza virus, *Streptococcus pneumoniae*, *Legionella* spp., and *M. pneumoniae* were all negative, as was cytomegalovirus antigenemia determined by the C7-horseradish peroxidase (HRP) method.

Chest X-ray showed nodules in the bilateral lung fields (Fig. 1a). CT showed diffuse bronchial wall thickening and bilateral small nodules existing along the airways, but some nodules were randomly distributed (Fig. 1b). We suspected pulmonary septic emboli, but a repeat blood culture was negative, and no focus of infection outside the lung was found by systemic surveys.

We started piperacillin/tazobactam, but his respiratory condition worsened, and bilateral shadows had increased on hospital day 10 (Fig. 1c). CT showed bilateral ground-glass opacities (GGOs), consolidations, and shrinkage change with bronchodilation and distortion (Fig. 1d). We performed BAL from the anterior segment of the right upper lobe (49 of 150 mL recovered), which showed 10.0×10^5 cells/mL (neutrophils, 23.5%; lymphocytes, 74.1%; eosinophils, 2.0%; and basophils, 0.4%). A transbronchial lung biopsy from the anterior basal segment of the right upper lobe revealed the accumulation of macrophages with few eosinophils and neutrophils, and exudates of fibrins and mild alveolitis were also found (Fig. 2).

We initially suspected interstitial pneumonia and started methylprednisolone 1 g daily for 3 days, followed by 60 mg daily, which improved his condition. BAL fluid showed positive results for HRV on multiplex PCR [FTD Resp 21 Kit (Fast Track Diagnostics, Silema, Malta), which detects the following respiratory pathogens: influenza A and B viruses; coronaviruses NL63, 229E, OC43, and HKU1; human parainfluenza viruses 1-4; human metapneumovirus A/B;

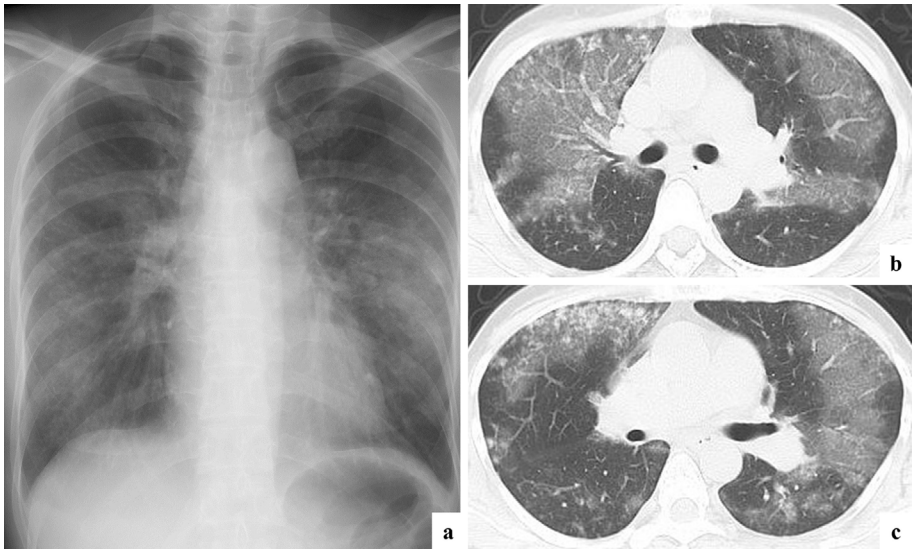

Figure 3. Chest imaging findings of case 2. Chest X-ray showed bilateral consolidation (a). Computed tomography showed bilateral ground-glass opacities and centrilobular nodules (b, c).

respiratory syncytial virus A/B; adenovirus; enterovirus; human parechovirus; bocavirus; and *Mycoplasma pneumoniae*] but negative results for other viruses and *M. pneumoniae*. Cultures of BAL fluid, blood, and bronchial aspirates were also negative for bacteria including *M. pneumoniae*.

The methylprednisolone was then decreased. His fever abated on hospital day 13, and his respiratory condition improved. Specific antibody titers against *M. pneumoniae*, *Chlamydophila pneumoniae*, *C. psittaci*, *Legionella* spp., influenza virus, adenovirus, respiratory syncytial virus, and parainfluenza virus (serotypes 1-4) in paired sera did not increase. Bilateral GGOs, consolidations, and shrinkage change with bronchodilation and distortion improved on CT at 40 days after discharge. The methylprednisolone was gradually tapered and discontinued six months after discharge, and there has been no recurrence in the five months since discontinuing steroids.

Case 2

A 43-year-old housewife presented to our hospital with rhinorrhea, sore throat, chills, a fever of 39-40°C, and dyspnea for 10 days at the end of November 2018. She had visited a local physician who started her on levofloxacin, but her body temperature did not decrease, and she developed a dyspneic cough for which she was referred to our hospital. She had never smoked or drank, had no apparent personal or family medical history, and had no evident contact with sick people.

Her body mass index was 18.7 kg/m^2. A physical examination revealed bilateral fine crackles, and arterial blood gases under O_2 of 1 L/min by nasal cannula showed a pH of 7.49, $PaCO_2$ of 34.2 Torr, PaO_2 of 144.0 Torr, and HCO_3^- of 25.3 mmol/L. Laboratory tests showed a WBC of 5,400/mm^3 (neutrophils, 3,900/mm^3; lymphocytes, 700/mm^3; eosinophils, 500/mm^3; and monocytes, 300/mm^3), hemoglobin, 12.9 g/dL; platelets, 22.1×10^4/mm^3; AST, 22 IU/L; LDH, 220 IU/L; blood urea nitrogen, 5 mg/dL; creatinine, 0.6 mg/dL; C-reactive protein; 7.1 mg/dL; and procalcitonin, 0.266 ng/mL. Autoantibodies were negative. A rapid influenza diagnostic test and urinary antigen testing for *S. pneumoniae*, *Legionella* spp., and *M. pneumoniae* were negative.

Chest X-ray showed bilateral consolidations (Fig. 3a), and CT showed bilateral GGOs and bilateral small centrilobular nodules (Fig. 3b, c). We performed BAL (84 of 150 mL recovered) from the lateral segment of the right middle lobe, which showed 11.8×10^5 cells/mL (macrophages, 37.2%; neutrophils, 3.6%; lymphocytes, 40.0%, and eosinophils, 19.2%). BAL fluid did not yield significant pathogens. Multiplex PCR (FTD21 Resp Kit) of the BAL fluid showed positive results only for HRV.

Once ceftriaxone was administered, her fever abated by hospital day 3, and she was discharged on hospital day 10. Specific antibody titers against *M. pneumoniae*, *C. pneumoniae*, *C. psittaci*, *Legionella* spp., influenza virus, adenovirus, respiratory syncytial virus, and parainfluenza virus (serotypes 1-4) in paired sera did not increase. Her chest imaging findings improved quickly, and the bilateral GGOs had disappeared by two weeks after discharge.

Discussion

As the one of the most common pathogens to infect humans and the most important cause of the common cold (4), HRV has been implicated in 30% to 50% of all cases of acute respiratory disease. In recent years, HRV has been reported to be a major cause of exacerbations of asthma and other chronic pulmonary diseases (5, 6) and has also been found to cause lower respiratory tract infections, including pneumonia (1).

Our patient in case 2 showed symptoms of upper respiratory tract infection, such as rhinorrhea and sore throat, whereas the patient in case 1 had no such symptoms, which

indicates that HRV pneumonia should not be ruled out when patients do not have symptoms of upper respiratory tract infection. A previous study reported that, in patients with primary viral pneumonia, only 20.8% had sore throat and 3.8% had rhinorrhea (7).

In the study of the pathogens of community-acquired pneumonia requiring hospitalization conducted by the Centers for Disease Control and Prevention in 2015, respiratory viruses were detected more frequently than bacteria. The most common pathogen was HRV, which accounted for 9% of the total patients (8). Neither of our two cases was associated with severe respiratory failure, but some severe cases have been reported. Of 49 mechanically ventilated patients with severe community-acquired pneumonia, 24 had viral infection (49%), and HRV was the most common virus, accounting for 58% of the infections (3). In another report of 20 patients with HRV-associated community-acquired pneumonia, 14 developed respiratory failure, and 13 required mechanical ventilation (9).

The CT findings of HRV pneumonia include bilateral multifocal patchy consolidations, multiple GGOs, interlobular septal thickening, and pleural effusion, but nodules are rare (9-11). Our two cases showed bilateral nodules, with case 1 showing randomly distributed nodules and case 2 showing centrilobular nodules. In case 1, although viral culture of blood was not performed and viremia was not proven, the imaging findings suggested hematological spread. In a previous report on 356 children and 146 adults with HRV pneumonia, 57 patients showed HRV viremia, all children (12). In another study, HRV viremia was found in 10 (11.4%) of 88 HRV-infected children: 7 of 28 children with an asthma attack, 2 of 26 with a common cold, and 1 of 25 with bronchiolitis (13). Factors associated with HRV viremia were sampling within 24 hours from the onset of symptoms and asthma. The increased susceptibility of individuals with asthma to viral, particularly HRV, infections has been considered (14). Although why the present case 1 showed viremia is unclear, we suspect that the immunocompromised state caused by systemic steroids for the asthma attack experienced before developing pneumonia might have been involved. To our knowledge, there have been no reports of HRV viremia in adults, but our experience showed that HRV viremia in adults can develop under such conditions. In contrast, Case 2 suggested transbronchial spread.

Various histologic patterns of lung injury have been described in viral pneumonia. Some viruses produce specific nuclear changes or characteristic cytoplasmic inclusions (15). However, the histologic characteristics of HRV pneumonia are not well known. Case 1 in the present study showed an accumulation of macrophages with few eosinophils and neutrophils, exudates of fibrins, and mild alveolitis, which reflect the GGOs and consolidations on CT. However, pulmonary nodules were also found on CT in this patient. Minute necrotic nodules can be found in some cases with *Varicella* pneumonia (16). Multiple necrotic and hemorrhagic lesions with interstitial edema and mononuclear cell infiltration in chickenpox pneumonia have also been reported (17). However, we were unable to detect such histologic lesions in our patient with HRV viremia.

Treatment of HRV infection generally consists of supportive care. Some studies have reported the efficacy of interferon-α, blockade of the intercellular adhesion molecule (ICAM)-1 receptor, capsid-binding agents, and 3C protease inhibitors for HRV infection (4), but these therapies have not been approved for use in Japan. In case 1, we initially suspected hematogenous infection, such as septic pulmonary embolism, and started antibiotics, but they were not effective, and no significant pathogens were isolated, including from blood cultures. We subsequently administered systemic corticosteroid because this patient's condition deteriorated rapidly, and CT findings showed expanding GGOs in the lung fields, which suggested acute progressive interstitial pneumonia. About half of cases of suspected acute progressive interstitial pneumonia are reportedly viral pneumonia (7). The effectiveness of steroids in viral pneumonia has been suggested only in limited viruses (18, 19), and the efficacy of steroids for HRV pneumonia has been reported only in a limited number of cases (20). However, our patient's respiratory condition improved after the administration of steroids. Proinflammatory cytokines and chemokines have been shown to play a role in the disease course (4). It is worth keeping track of whether or not blocking these proteins affects the clinical outcome. Corticosteroids may have alleviated the excessive inflammatory response in case 1. In contrast, the patient in case 2 did not receive corticosteroids but instead antibiotics, and her condition also improved. Significant pathogens were not detected by culture and paired sera, indicating that her recovery was primarily due to supportive care. A treatment strategy for HRV pneumonia has not been established yet, and further studies are needed.

In conclusion, we presented two cases of HRV pneumonia with prominent multiple nodules. Each pattern of progression was suggested to be hematogenous and by transbronchial spreading, although such an image pattern seems to be rare in HRV pneumonia. Multiplex PCR was useful for diagnosing these cases. Further cases are needed to establish effective treatment strategies for HRV pneumonia.

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

Financial Support

A part of this study was supported by a Research Fund from Saitama Cardiovascular and Respiratory Center under Grant Nos. 16ES, 17ES, and 18ES.

References

1. Falsey AR, Walsh EE. Viral pneumonia in older adults. Clin Infect Dis **42**: 518-524, 2006.

2. Lieberman D, Shimoni A, Shemer-Avni Y, Keren-Naos A, Shtainberg R, Lieberman D. Respiratory viruses in adults with community-acquired pneumonia. Chest **138**: 811-816, 2010.

3. Karhu J, Ala-Kokko TI, Vuorinen T, Ohtonen P, Syrjälä H. Lower respiratory tract virus findings in mechanically ventilated patients with severe community-acquired pneumonia. Clin Infect Dis **59**: 62-70, 2014.
4. Bennett JE, Dolin R, Blaser MJ. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. **2**: 2113-2121, 2015.
5. Khetsuriani N, Lu X, Teague WG, Kazerouni N, Anderson LJ, Erdman DD. Novel human rhinoviruses and exacerbation of asthma in children. Emerg Infect Dis **14**: 1793-1796, 2008.
6. Miller EK, Edwards KM, Weinberg GA, et al. New Vaccine Surveillance Network. A novel group of rhinoviruses is associated with asthma hospitalizations. J Allergy Clin Immunol **123**: 98-104, 2009.
7. Ishiguro T, Kobayashi Y, Uozumi R, et al. Viral pneumonia requiring differentiation from acute and progressive diffuse interstitial lung diseases. Intern Med **58**: 3509-3519, 2019.
8. Jain S, Self WH, Wunderink RG, et al.; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. N Engl J Med **373**: 415-427, 2015.
9. Wang K, Xi W, Yang D, et al. Rhinovirus associated with severe adult community-acquired pneumonia in China. J Thorac Dis **9**: 4502-4511, 2017.
10. Choi SH, Huh JW, Hong SB, et al. Clinical characteristics and outcomes of severe rhinovirus-associated pneumonia identified by bronchoscopic bronchoalveolar lavage in adults: comparison with severe influenza virus-associated pneumonia. J Clin Virol **62**: 41-47, 2015.
11. Koo HJ, Lim S, Choe J, Choi SH, Sung H, Do KH. Radiographic and CT features of viral pneumonia. Radiographics **38**: 719-739, 2018.
12. Lu X, Schneider E, Jain S, et al. Rhinovirus viremia in patients hospitalized with community-acquired pneumonia. J Infect Dis **216**: 1104-1111, 2017.
13. Xatzipsalti M, Kyrana S, Tsolia M, et al. Rhinovrusviremia in children with respiratory infections. Am J Respir Crit Care Med **172**: 1037-1040, 2005.
14. Wark PA, Johnston SL, Bucchieri F, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. J Exp Med **201**: 937-947, 2005.
15. Torres HA, Aguilera E, Safdar A, et al. Fatal cytomegalovirus pneumonia in patients with haematological malignancies; an autopsy-based case-control study. Clin Microbiol Infect **14**: 1160-1166, 2008.
16. Meyer B, Stalder H, Wegmann W. Persistent pulmonary granulomas after recovery from varicella pneumonia. Chest **89**: 457, 1986.
17. Triebwasser JH, Harris RE, Rhoades ER. Varicella pneumonia in adults. Medicine **46**: 409-423, 1967.
18. Li H, Yang SG, Gu L, et al.; National Influenza A (H1N1) pdm09 Clinical Investigation Group of China. Effect of low-to-moderate dose corticosteroids on mortality of hospitalized adolescents and adults with influenza A (H1N1) pdm09 viral pneumonia. Influenza Other Respir Viruses **11**: 345-354, 2017.
19. Cheng VC, Tang BS, Wu AK, Chu CM, Yuen KY. Medical treatment of viral pneumonia including SARS in immunocompetent adult. J Infect **49**: 262-273, 2004.
20. Ishiguro T, Yoshida Y, Kobayashi Y, Shimizu Y, Takayanagi N. Primary rhinovirus pneumonia in which bronchoalveolar lavage fluid yielded human rhinovirus. Respir Med Case Rep **28**: 100910, 2019.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (https://creativecommons.org/licenses/by-nc-nd/4.0/).

Ⓒ 2021 The Japanese Society of Internal Medicine