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# Two cases of primary human parechovirus pneumonia in adults

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ABSTRACT

Human parechoviruses (HPeV) are mainly isolated from upper respiratory tract infection and gastroenteritis in children. HPeV has not been screened for in the past studies of community-acquired pneumonia (CAP) in adults, and its association with CAP is unknown. We present two cases that HPeV was detected by multiplex polymerase chain reaction for respiratory viruses using bronchoalveolar lavage fluid and diagnosed as pneumonia caused by HPeV.

## 1. Background

Human parechoviruses (HPeV) belong to genus *Parechovirus* of the large and growing family of *Picornaviridae* with a single-stranded positive-sense RNA whose genome is packed into a nonenveloped icosahedral capsid [1]. Two HPeV types isolated and identified in 1961 as echovirus 22 and 23 of the genus *Enterovirus* [2] were then re-named HPeV1 and HPeV2, respectively, in the 1990s [3,4]. HPeV are ubiquitous viruses found throughout the world that frequently cause upper respiratory tract infection and gastroenteritis, and sometimes meningitis and sepsis-like syndrome, in children. Recently, HPeV was reported to cause epidemic myositis in adults in Japan [5]. Although various viruses have been reported to cause adult community-acquired pneumonia (CAP), multiplex polymerase chain reaction (PCR) analysis for respiratory viruses in past representative studies of adult CAP did not include HPeV, and their involvement in adult lower respiratory tract infection is unknown.

## 2. Case report

### 2.1. Case 1

A 74-year-old man presented to our hospital with dyspnea and cough in May. He had developed productive cough, sore throat, and nasal discharge three weeks before, muscle pain two weeks before, and fever and dyspnea three days before his admission. He had no medical, family, or social history of note, and no close contact with infected people. He was an ex-smoker (10 pack-years). His vital signs included a body temperature of 37.6 °C, heart rate of 116 beats/min with a regular rhythm, and blood pressure of 137/84 mmHg. On physical examination, fine crackles were audible on the dorsal side of the bilateral lower lung regions, but no other remarkable findings were seen. Chest X-ray showed consolidation and reduced volume of the right lung (Fig. 1-A). Computed tomography (CT) (Fig. 2) on admission showed bilateral consolidation (right dominant), ground-glass opacities (GGOs) around the consolidations, and air-bronchogram accompanying traction bronchiectasis within the consolidations. The GGOs in part had non-segmental distribution. His arterial blood gases under ambient air showed a pH of 7.45, $PaO_2$ of 70.2 Torr, $PaCO_2$ of 35.7 Torr, and bicarbonate of 24.3 mmol/L, and biochemical examination of his blood and urine showed elevation of the erythrocyte sedimentation rate and C-reactive protein and aspartate aminotransferase levels. Pneumococcal and *Legionella* urinary antigen test, *Mycoplasma* antigen from throat swab specimens, and influenza antigen from nasal swab specimens were all negative. Autoantibodies were negative. No bacteria other than oral flora were cultured in the sputum cultures. We performed bronchoscopy and bronchoalveolar lavage (BAL) in the right middle lobe (with 20 of 150 mL recovered). The total cell count of the BAL fluid was $5.3 \times 10^5$ cells/mL, including 44.7% lymphocytes (cluster designation [CD]4/CD8 ratio, 3.16), 7.1% eosinophils, and 23.9% neutrophils. BAL fluid yielded no bacteria, and adequate specimens for evaluation could not be collected from transbronchial lung biopsy.

We diagnosed him as having CAP and started antibiotics (ampicillin/sulbactam + clarithromycin). Consolidation and volume reduction of

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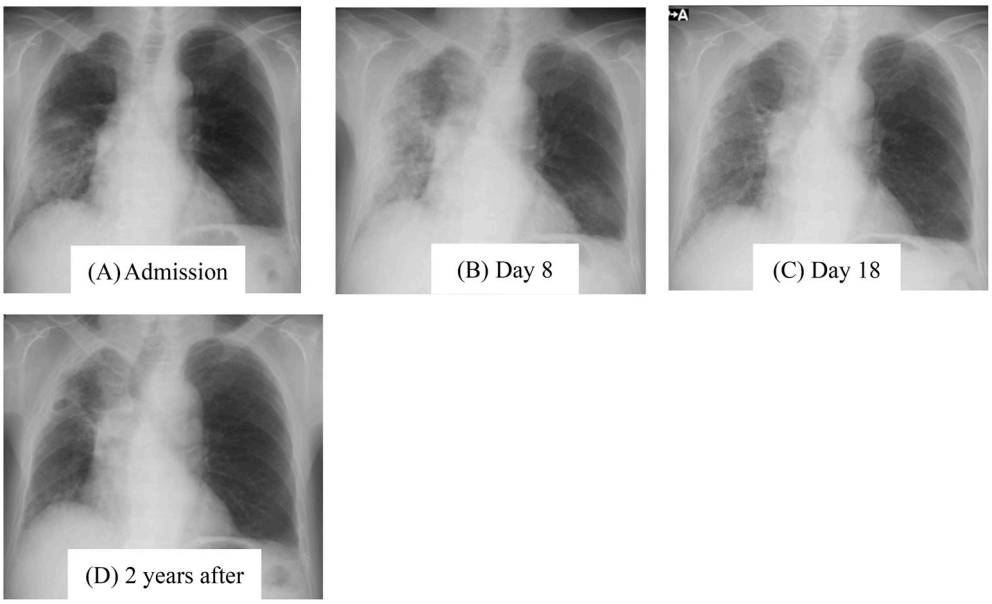


**Fig. 1. Chest X-rays in case 1.** Chest X-ray on admission (A) showed consolidation and reduced volume of the right lung. The greatest deterioration had occurred on day 8 (B), and by the time of discharge on day 18, they had improved but were still somewhat present (C). The reduced volume of the right lung has remained after two years (D).

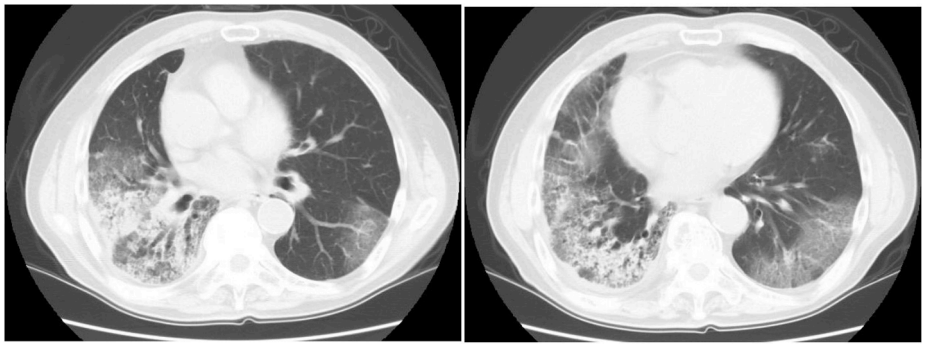

**Fig. 2. Chest computed tomography (CT) in case 1.** Chest CT on admission showed bilateral consolidation (right dominant), ground-glass opacities (GGOs) around the consolidation, and air-bronchogram accompanying traction bronchiectasis within the consolidation. The GGOs in part showed non-segmental distribution.

the right lung continued to deteriorate, reaching a peak on the 8th day of hospitalization, but they gradually improved (Fig. 1-B, C). Serum antibody titers against *Mycoplasma pneumoniae*, *Legionella* sp., *Chlamydophila pneumoniae*, *Chlamydia psittaci*, adenovirus, human parainfluenza virus, RS virus, and influenza virus in the convalescent phase did not significantly increase compared with those measured in the acute phase. Pneumonia has not recurred as of 2 years after discharge, but the reduced volume of the right lung has remained (Fig. 1-D). Multiplex real-time reverse transcriptase PCR (RT-PCR) with a commercially available kit (FTD Resp 21 Kit; Fast Track Diagnostics, Silema, Malta) for respiratory viruses using frozen-stored BAL fluid was performed later and was positive only for HPeV. We ultimately diagnosed him as having

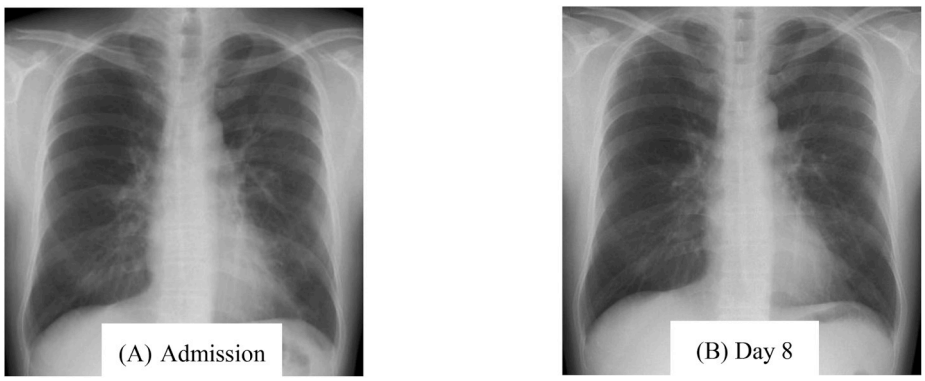


**Fig. 3. Chest X-rays in case 2.** Chest X-ray on admission (A) showed nodular consolidation on both sides of the lung that had almost resolved at day 8 (B).

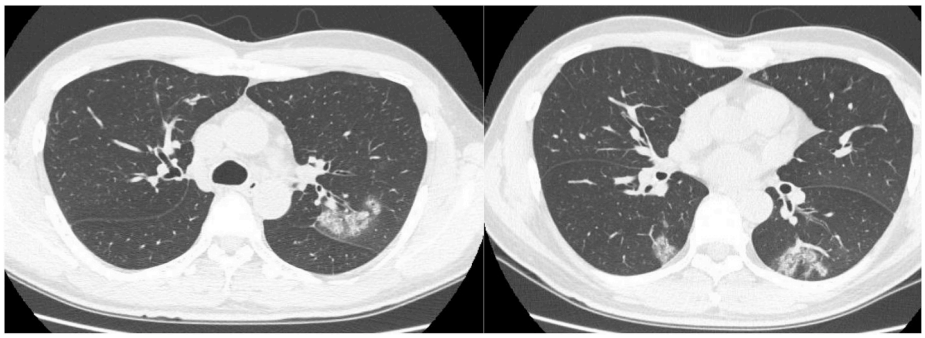

**Fig. 4. Chest computed tomography (CT) in case 2.** Chest CT on admission showed patchy consolidation and GGOs along the bronchial vascular bundle in the upper and lower lobes of the left lung and upper segment of the right lower lobe. Traction bronchiectasis and volume reduction of the lungs were not observed.

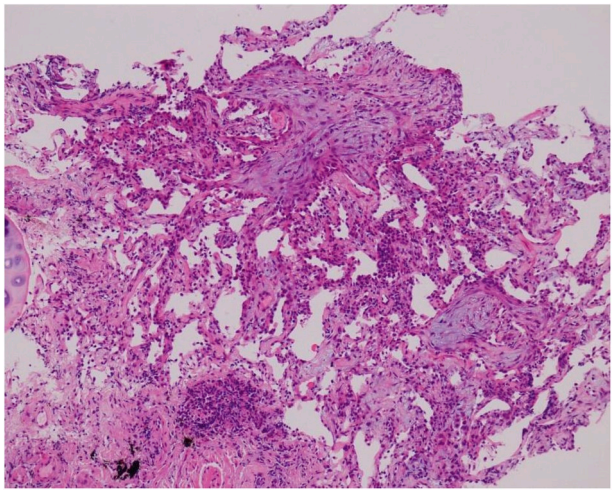

**Fig. 5. Histologic findings.** Histologic findings from transbronchial lung biopsy in case 2 showed organization, swollen pneumocytes, and alveolar septal thickening with inflammatory cells (hematoxylin and eosin staining; magnification, × 50).

primary HPeV pneumonia.

### 2.2. Case 2

A 46-year-old man had a fever and sore throat 10 days before hospital admission, and shortness of breath developed 6 days before admission in May. A local physician diagnosed him as having CAP and administered levofloxacin, but the symptoms did not improve and he presented to our hospital. He had no medical, family, or social history of note, and no close contact with infected people. He was an ex-smoker (15 pack-years). His vital signs included a body temperature of 37.4 °C, heart rate of 81 beats/min with a regular rhythm, and blood pressure of 99/66 mmHg. On physical examination, fine crackles were audible on the dorsal side of the left middle lung regions, but no other remarkable findings were seen. Chest X-ray (Fig. 3-A) showed nodular consolidation on both sides of the lungs. Chest CT (Fig. 4) on admission showed patchy consolidation and GGOs along the bronchial vascular bundle in the upper and lower lobes of left lung and S6 of the right lung. Neither traction bronchiectasis nor volume reduction of the lungs were observed. His arterial blood gases under ambient air showed a pH of 7.46, $PaO_2$ of 85.9 Torr, $PaCO_2$ of 36.9 Torr, and bicarbonate of 25.4 mmol/L, and biochemical examination of his blood and urine showed an elevated C-reactive protein level of 7.62 mg/dL but no other remarkable findings. Pneumococcal and *Legionella* antigen test in urine, *Mycoplasma* antigen from throat swab specimens, and influenza antigen from nasal swab specimens were negative. Autoantibodies were negative. Sputum cultures showed no bacteria cultured other than oral flora.

We performed BAL in the right middle lobe (with 69 of 150 mL recovered). The total cell count of the BAL fluid was $2.1 \times 10^5$ cells/mL, including 80.8% macrophages, 12.7% lymphocytes (CD4/CD8 ratio, 10.6), 4.9% eosinophils, and 1.6% neutrophils. BAL fluid yielded no bacteria, but transbronchial lung biopsy revealed organization, swollen pneumocytes, and alveolar septal thickening with inflammatory cells (Fig. 5).

We administered antibiotics (ampicillin/sulbactam + clarithromycin), and his clinical symptoms and chest infiltrates improved promptly after admission. A follow-up chest X-ray (Fig. 3-B) was clear, and he was discharged on the 10th hospital day with no complications. Serum antibody titer against *M. pneumoniae*, *Legionella* sp., *Chlamydophila pneumoniae*, *Chlamydia psittaci*, adenovirus, human parainfluenza virus, RS virus, and influenza virus measured in the convalescent phase did not significantly increase compared with those in the acute phase. Multiplex real-time RT-PCR for respiratory viruses using BAL fluid was positive only for HPeV. We finally diagnosed him as having primary HPeV pneumonia.

## 3. Discussion

HPeV, which are common viruses in upper respiratory tract infection and gastroenteritis in children, are transmitted from person to person chiefly through fecal-oral contact. Harvala et al. reported that 1.2% of upper respiratory tract specimens from children were positive for HPeV by PCR screening [6]. Serological data indicates that the antibody levels of HPeV increase rapidly with age, and over 90% of children have been infected with HPeV type 1 by two years of age [6,7]. However, there are also reports that antibody titers gradually decrease with age [8], and nearly 20% of adults do not have antibodies of HPeV type 3 [9]. Although many adults have neutralizing antibodies of HPeV, some adults without infection in childhood suffer a primary infection, whereas some adults with infection in childhood are re-infected as the antibody titers decrease with age.

To our knowledge, there is no large population study of the prevalence of HPeV infection in adults, and the characteristics of HPeV infection in adults remain unknown. It has been sporadically reported in Japan that HPeV3 causes viral myositis in adults [4]. Although HPeV infection is diagnosed by isolation from respiratory specimens, serologies, and nucleic acid amplification testing with PCR, most facilities cannot do these examinations in general practice. Thus, HPeV infection in adults may be underrecognized.

According to recent studies of CAP in adults, viruses account for 27–39% of all CAP etiologies [10–12]. Multiplex RT-PCR used in these studies has detected coronaviruses 229E, HKU1, NL63, and OC43; human metapneumovirus (HMPV); human rhinovirus; influenza viruses A and B; human parainfluenza virus types 1, 2, and 3; and respiratory syncytial virus, and HPeVs were not included among them. Therefore, the frequency of HPeV infection in adult CAP is unknown. In our two

cases, we used a commercially available kit for detection of respiratory pathogens on a Rotor-Gene Q instrument (Quiagen, Hilden, Germany) with a multiplex RT-PCR, which can detect HPeV. In addition, HPeVs were detected from BAL fluid, which increases the possibility of our two cases being pneumonia.

We reported that among 53 patients who were diagnosed as having viral pneumonia with one or more viruses identified by PCR of BAL fluid, 18 (34.0%) were positive for HPeV, 3 were positive for HPeV alone, and the remaining 15 patients were coinfected with other viruses [13]. Harvala et al. reported that HPeVs were more likely to cause coinfection with other respiratory viruses than others in upper respiratory tract infection in children, and they suggested that HPeV plays an exacerbating role in other respiratory virus infections [6]. However, our two patients did not show mixed infection with HPeV by multiplex PCR, paired serum, and culture.

In most patients with viral pneumonia, treatment is mainly supportive care, and no treatment specific to HPeV has been reported. Our two patients improved with supportive care.

There are two limitations. First, we cannot completely rule out just upper airway tract infection by HPeV in our two patients. Our two patients were not intubated, and BAL fluid taken from non-intubated patients may be contaminated by the upper respiratory tract. Second, we could not identify the genotypes of HPeV in our two cases. To date, HPeVs have been classified into 19 genotypes [14]. HPeV1 and HPeV3 are the most often detected [6], and each presents a different symptom set and pathology. Although we could not identify the genotypes of HPeV in our two patients due to lack of resources, genotypes prone to pneumonia need to be clarified in future research.

We herein report two cases of HPeV pneumonia in adults, which has not been reported so far to our knowledge. HPeV has not been searched for in previous large-population studies of CAP. We think that HPeV pneumonia in adults is not infrequent and may be underrecognized. It will thus be necessary to accumulate knowledge on the relationship between HPeV infection and CAP in the future.

## Declaration of competing interest

None.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.rmcr.2019.100949.

## References

[1] G. Stanway, P. Joki-Korpela, T. Hyypiä, Human parechoviruses-biology and clinical significance, Rev. Med. Virol. 10 (1) (2000) 57–69.
[2] R. Wigand, A.B. Sabin, Properties of ECHO types 22, 23 and 24, Arch. Gesamte Virusforsch. 11 (1961) 224–247.
[3] H. Harvala, P. Simmonds, Human parechoviruses: biology, epidemiology and clinical significance, J. Clin. Virol. 45 (2009) 1–9.
[4] T. Hyypiä, C. Horsnell, M. Maaronen, M. Khan, N. Kalkkinen, P. Auvinen, L. Kinnunen, G. Stanway, A distinct picornavirus group identified by sequence analysis, Proc. Natl. Acad. Sci. U.S.A. 89 (1992) 8847–8851.
[5] K. Mizuta, M. Kuroda, M. Kurimura, Y. Yahata, T. Sekizuka, Y. Aoki, T. Ikeda, C. Abiko, M. Noda, H. Kimura, T. Mizutani, T. Kato, T. Kawanami, T. Ahiko, Epidemic myalgia in adults associated with human parechovirus type 3 infection, Yamagata, Japan, Emerg. Infect. Dis. 18 (2008) 1787–1793, 2012.
[6] H. Harvala, I. Robertson, E.C. McWilliam Leitch, K. Benschop, K.C. Wolthers, K. Templeton, P. Simmonds, Epidemiology and clinical associations of human parechovirus respiratory infections, J. Clin. Microbiol. 46 (2008) 3446–3453.
[7] P. Joki-Korpela, T. Hyypiä, Diagnosis and epidemiology of echovirus 22 infections, Clin. Infect. Dis. 27 (1998) 129–136.
[8] S. Tanaka, Y. Aoki, Y. Matoba, K. Yahagi, T. Itagaki, Y. Matsuzaki, K. Mizuta, Seroepidemiology of human parechovirus types 1, 3, and 6 in Yamagata, Japan, Microbiol. Immunol. 60 (2014) 854–858, 2016.
[9] M. Ito, T. Yamashita, H. Tsuzuki, N. Takeda, K. Sakae, Isolation and identification of a novel human parechovirus, J. Gen. Virol. 85 (2004) 391–398.
[10] S. Jain, W.H. Self, R.G. Wunderink, S. Fakhran, R. Balk, A.M. Bramley, C. Reed, C. G. Grijalva, E.J. Anderson, D.M. Courtney, J.D. Chappell, C. Qi, E.M. Hart, F. Carroll, C. Trabue, H.K. Donnelly, D.J. Williams, Y. Zhu, S.R. Arnold, K. Ampofo, G.W. Waterer, M. Levine, S. Lindstrom, J.M. Winchell, J.M. Katz, D. Erdman, E. Schneider, L.A. Hicks, J.A. McCullers, A.T. Pavia, K.M. Edwards, L. Finelli, CDC EPIC Study Team, Community-acquired pneumonia requiring hospitalization among U.S. adults, N. Engl. J. Med. 373 (2015) 415–427.
[11] L.C. Jennings, T.P. Anderson, K.A. Beynon, A. Chua, R.T. Laing, A.M. Werno, S. A. Young, S.T. Chambers, D.R. Murdoch, Incidence and characteristics of viral community-acquired pneumonia in adults, Thorax 63 (2008) 42–48.
[12] J. Johnstone, S.R. Majumdar, J.D. Fox, T.J. Marrie, Viral infection in adults hospitalized with community-acquired pneumonia: prevalence, pathogens, and presentation, Chest 134 (2008) 1141–1148.
[13] Ishiguro T, Kobayashi Y, Uozumi R, Takata N, Takaku Y, Kagiyama N, Kanauchi T, Yoshihiko S, Takayanagi N. Viral pneumonia requiring differentiation from acute and progressive diffuse interstitial lung disease. Intern. Med. (In press).
[14] E. Karelehto, C. Cristella, X. Yu, A. Sridhar, R. Hulsdouw, K. de Haan, H. van Eijk, S. Koekkoek, D. Pajkrt, M.D. de Jong, K.C. Wolthers, Polarized entry of human parechoviruses in the airway epithelium, Front. Cell. Infect. Microbiol. 8 (2018) 294.