Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

CHEST

A 72-Year-Old Woman With Respiratory Failure and Bilateral Ground-Glass Opacities

Yuri Baba, MD; Takashi Ishiguro, MD, PhD; Mina Gochi, MD, PhD; Yoshihiko Shimizu, MD, PhD; and Noboru Takayanagi, MD, PhD

A 72-year-old woman with diabetes mellitus was admitted to our hospital because of dyspnea on exertion. Sputum cytologic evaluation revealed intranuclear inclusion bodies in the cells; we therefore considered viral pneumonia and performed a bronchoscopy. The bronchial washing fluid was positive for immunoperoxidase staining of herpes simplex virus type 1 (HSV1) and HSV1 polymerase chain reaction. The patient was diagnosed as having pneumonia due to HSV1 and was successfully treated with acyclovir. CHEST 2020; 158(1):e41-e45

KEY WORDS: bronchoscopy; herpes simplex virus pneumonia; immunoperoxidase staining

A 72-year-old Japanese housewife was admitted to our hospital due to anorexia and dyspnea on exertion. She had been diagnosed several years earlier with type 2 diabetes mellitus and hypertension. She had also developed lip herpes several years ago. She had no history of smoking or drinking. She had been anorexic for 5 days before and developed dyspnea on exertion from 3 days prior to referral and admission to our hospital. She had had no contact with any people showing infectious symptoms prior to her presentation, and she had not been started on any new medications for the past few years.

Physical Examination Findings

On admission, the patient's body temperature was 37.6°C, and oxygen saturation measured by pulse oximetry under inhalation of oxygen at 3 L/min by nasal cannula was 93%. Her lips and pubic region showed no exanthema. Auscultation revealed diffuse fine crackles. Her peripheral limbs were not edematous.

Diagnostic Studies

A chest radiograph showed bilateral patchy opacities distributed predominantly in the upper lung fields (Fig 1A). No pleural effusion or obvious lymphadenopathy was observed. Chest CT images obtained during inspiration revealed multifocal patchy ground-glass opacities (Fig 1B), bronchial wall thickening, and interlobular septal thickening but no pleural effusion or lymphadenopathy. Laboratory data on admission showed a WBC count of 8,800/mm^3 (neutrophils 72.5%, lymphocytes 17.9%, monocytes 4.9%, and eosinophils 4%), lactate dehydrogenase level of 577 IU/L, C-reactive protein value of 6.8 mg/dL, Krebs von den Lungen-6 value of 4,338 U/mL, and glycosylated hemoglobin of 7.1%. Her immunoglobulin level was within normal range, and anti-HIV antibodies were negative, as were results of a rapid influenza diagnostic test.

Because the patient had no symptoms of upper respiratory tract infection, contact with other people

ABBREVIATIONS: HD = hospital day; HSV1 = herpes simplex virus type 1; HSV1P = herpes simplex virus type 1 pneumonia; PCR = polymerase chain reaction

AFFILIATIONS: From the Department of Respiratory Medicine (Drs Baba, Ishiguro, Gochi, and Takayanagi) and Department of Pathology (Dr Shimizu), Saitama Cardiovascular and Respiratory Center, Saitama, Japan; and the Department of Respiratory Medicine (Drs Baba and Gochi), Jikei University Kashiwa Hospital, Kashiwa City, Japan.

CORRESPONDENCE TO: Takashi Ishiguro, MD, PhD, 1696 Itai, Kumagaya, Saitama 360-0105, Japan; e-mail: ishiguro.takashi@pref.saitama.lg.jp

DOI: https://doi.org/10.1016/j.chest.2019.11.054

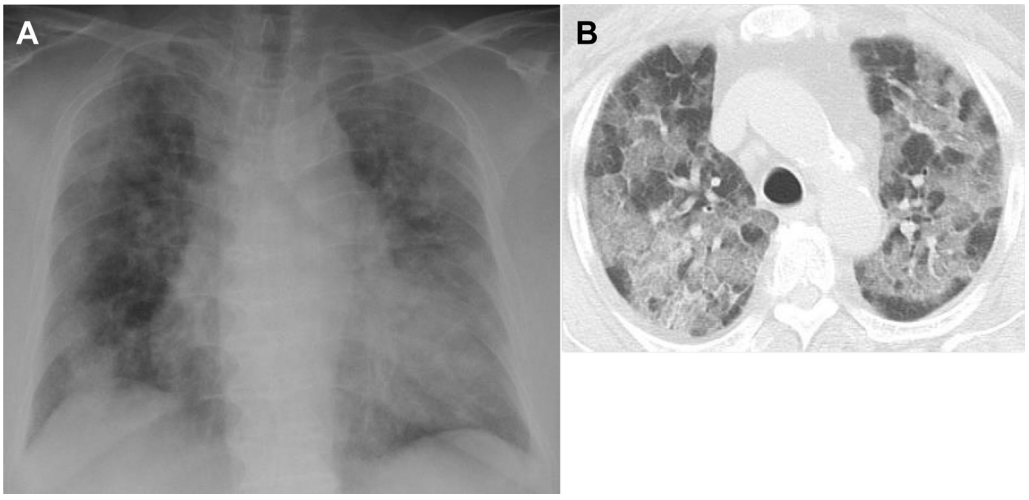

Figure 1 – *A, Chest radiograph on admission showed bilateral patchy opacities distributed predominantly in the upper lung fields. Pleural effusion and lymphadenopathy were not observed. B, Chest CT image on admission showed multifocal segmental and subsegmental ground-glass opacities, bronchial wall thickening, and interlobular septal thickening but no pleural effusion or lymphadenopathy.*

with infectious symptoms, or a history suggestive of drug-induced lung diseases but did have fine crackles and diffuse, bilateral patchy ground-glass opacities in her chest,[1] we initially suspected acute interstitial pneumonia and administered prednisolone (50 mg/d), which is often used in the treatment of acute interstitial pneumonia. Because we could not completely rule out community-acquired pneumonia due to atypical pathogens, we administered azithromycin 2 g on hospital day (HD) 1. On HD 3, the shadows on the patient's chest radiograph increased. We therefore changed the steroid therapy to pulse therapy (methylprednisolone 1 g daily for 3 days). Her respiratory condition continued to worsen, however.

What Study Should Be Conducted Next?

On HD 7, we began to suspect viral pneumonia because of a sputum cytology finding of intranuclear inclusion bodies in the cells (Fig 2A). Because of the patient's worsening respiratory condition, she was intubated, and a bronchoscopy was then performed to obtain a definitive diagnosis. Cytologic evaluation of the bronchial washing fluid obtained from the right upper lobe revealed intranuclear inclusion bodies (Fig 2B). Results of culture of the bronchial washing fluid were negative for bacteria, fungus, and mycobacteria. Immunoperoxidase staining for herpes simplex virus type 1 (HSV1) of lymphocytes using bronchial washing fluid was positive (Fig 2C), and the fluid was also positive for HSV1 by polymerase chain reaction (PCR) testing. PCR for HSV type 2, varicella zoster virus, influenza virus A and B, respiratory syncytial virus, parainfluenza virus type 1 through 4, human coronavirus, human adenovirus, human metapneumovirus, enterovirus, human rhinovirus, and human bocavirus was negative. The quantity of HSV1 by PCR was high at 14×10^6 copies/mL. Specific IgG antibodies against *Legionella* species, *Mycoplasma pneumoniae*, *Chlamydia pneumoniae*, *Chlamydia psittaci*, and influenza virus were not significantly increased in the paired sera.

Diagnosis: Viral Pneumonia due to HSV1

The patient was diagnosed as having HSV1 pneumonia (HSV1P) based on these results. On HD 11, she was started on acyclovir 15 mg/kg/d for 16 days. The bilateral shadows on the patient's chest radiograph then improved. Serum anti-HSV1 IgG measured by using an enzyme-linked immunoassay method and complement fixation method was $>$ 128 times normal and 32 titers on admission, respectively, and her HSV1 IgG titers had remained high. HSV1 IgM was negative at all measurements. After discharge on HD 62, the patient has continued to be followed up as an outpatient and has not developed relapse of HSV1P.

Discussion

Clinical Discussion

The bacterial pathogens of pneumonia have mainly been identified on the basis of culture, paired sera, and rapid diagnostic test results. PCR testing directed at respiratory viruses has been reported to find viruses more frequently than had been previously thought.[2-5] These studies investigated influenza virus, respiratory syncytial virus,

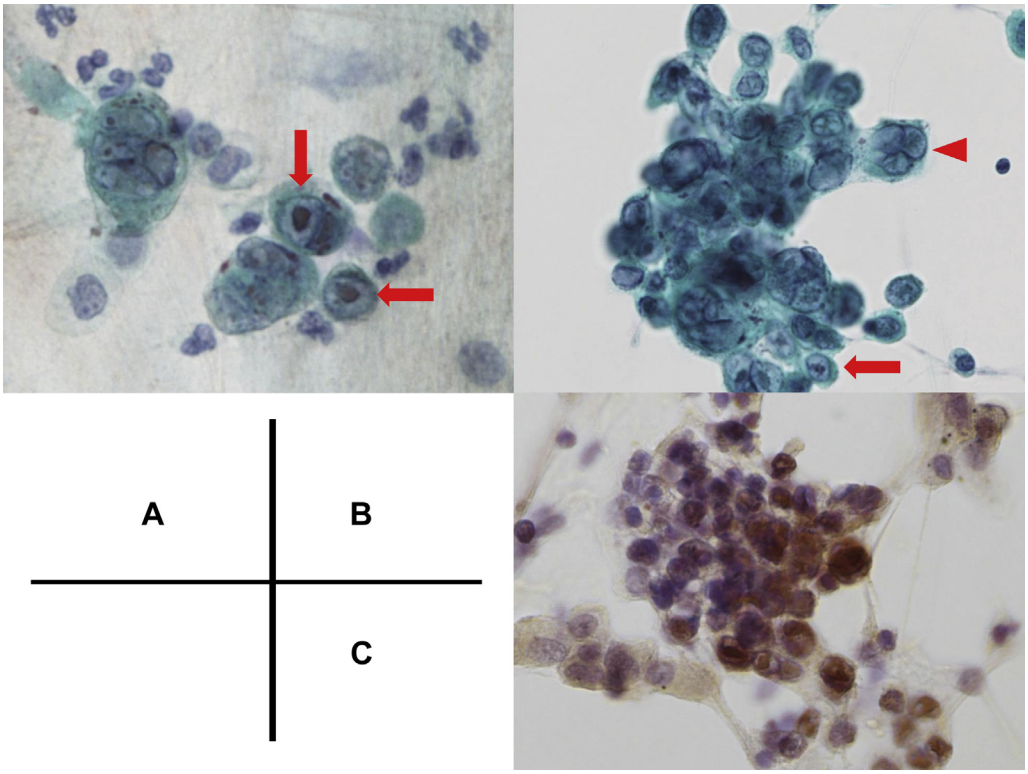

Figure 2 – *A-C, Cytologic evalaution of respiratory samples. A, Sputum cytologic evaluation revealed intranuclear inclusion bodies (arrow) (Papanicolaou stain, ×400). B, The bronchial washing fluid showed intranuclear inclusion bodies (arrow) separated from the surrounding nuclear chromatin and multinucleated cells with ground-glass changes in the involved nuclei (arrowhead) (Papanicolaou stain, ×400). C, The bronchial washing fluid was positive for immunoperoxidase staining of herpes simplex virus type 1 (×400).*

coronavirus, human metapneumovirus, and adenovirus, but HSV was not included in previous reports investigating the frequency of viral infection in community-acquired pneumonia. HSV1P is rare and mostly observed in transplant recipients and those receiving immunosuppressants or steroids. As far as we know, the number of reports of HSV1P is limited to 10 cases of patients unaffected by transplantation, HIV, immunosuppressants, corticosteroids, burns, or malignancy[6-14] (Table 1). Unfortunately, although we did not initially suspect HSV1P in the current patient, cytologic findings of sputum provided a diagnostic clue, and we subsequently investigated HSV infection. The findings obtained following bronchoscopy were very helpful in diagnosing HSV1P. HSV can be cultured from the oral cavity of 1% to 5% of asymptomatic adults, and it is difficult to identify HSV as a pathogen of pneumonia when the virus is cultured from the sputum.[15] To confirm the diagnosis of HSV1P, it is important to prove that HSV is positive by using PCR and according to typical cytologic and histologic findings from the lower respiratory tract and alveoli.[15-17]

Among the 10 reported patients with HSV1P unaffected by transplantation, HIV, immunosuppressants, corticosteroids, burns, or malignancy (Table 1), eight of the 10 were aged < 50 years, and seven had no underlying diseases. Only the current patient had diabetes mellitus with mild elevation of her glycosylated hemoglobin value, which made it difficult for us to suspect HSV1P. Therefore, although HSV1P is rare, physicians should consider it in the differential diagnosis of patients with no underlying diseases or a fragile immunologic state. A noteworthy fact is that no skin, oral, or genital lesions suggestive of HSV infection were found in any of the patients with HSV pneumonia.

HSV has two patterns of acute infection: primary infection and reactivation. The infection pattern in the current patient was considered to be reactivation because her anti-HSV1 IgG level was high,[18] and she had experienced a herpes virus lip infection several years earlier.

Acyclovir was generally selected for the treatment of HSV1P,[6-14,19] except in two cases (Table 1). The study patient improved spontaneously with no medications,[6] and a postmortem diagnosis of HSV1P was made in the other patient. One study reported a mean treatment duration of 9 ± 3 days in immunocompetent patients,

TABLE 1] Reported Cases of Primary HSV Pneumonia Unaffected by Transplantation, HIV, Immunosuppressants, Corticosteroids, or Malignancy

Year	Reference	Age, y	Sex	Underlying Diseases	Skin, Oral, or Genital Lesion	Treatment	Outcome
1990	Geradts et al[9]	30	Female	Neurofibromatosis, severe scoliosis	No	No antiviral treatment	Died
1994	Martinez et al[10]	33	Male	Psychological disease (depression)	Erythematous oropharynx without exudates or vesicles	Acyclovir	Recovered
2001	Miyazato et al[6]	49	Male	None	No	No antiviral treatment	Recovered
2004	Terzano et al[14]	46	Female	None	No	Acyclovir plus aerosolized ribavirin	Recovered
2009	Reyes and Bolden[12]	19	Female	None	No	Acyclovir, mechanical ventilation	Recovered
2012	Bonacchi et al[13]	18	Male	None	No	Acyclovir, ECMO, mechanical ventilation	Recovered
2013	Hunt et al[11]	18	Female	None	No	Acyclovir, mechanical ventilation	Recovered
2014	Mills et al[8]	39	Male	None	No	Acyclovir, mechanical ventilation, corticosteroid	Recovered
2018	Ishihara et al[7]	85	Female	Hypertension, dyslipidemia	No	Acyclovir	Recovered
2019	Study patient	72	Female	Diabetes mellitus	No	Acyclovir, corticosteroid	Recovered

ECMO = extracorporeal membrane oxygenation; HSV = herpes simplex virus.

whereas immunocompromised patients were treated with acyclovir for 17 ± 10 days.[20] Acyclovir was administered to the study patient for 16 days, and there has been no relapse of HSV1P. Few comments are available regarding events following recovery from HSV1P; however, one patient developed acute inflammatory demyelinating polyneuropathy (a variant of Guillain-Barré syndrome) following improvement with acyclovir,[10] which should alert physicians to potentially serious outcomes.

Another concern is corticosteroids, which we initially administered for a suspected diagnosis of acute interstitial pneumonia. Limited data suggest favorable effects of corticosteroids on varicella zoster virus (in combination with acyclovir), hantavirus,[21] and in influenza-associated pneumonia in some clinical settings,[22,23] but other reports have found them to be harmful.[24] The study patient's condition clearly worsened following corticosteroid therapy. Patients with acute interstitial pneumonia report progressive dyspnea, cough, fever, and, occasionally, flu-like symptoms, which overlap with the symptoms of viral pneumonia. Careful attention should be paid in the differentiation of viral pneumonia prior to administering corticosteroids.

Pathologic Discussion

Cytologic features characteristic of HSV infection can be found at the margins of ulcers or in the alveolar cells, and they include small eosinophilic intranuclear inclusion bodies separated from the surrounding nuclear chromatin by a clear halo (Cowdry type A inclusions) and a single or multinucleated cells with ground-glass changes in the involved nuclei.[15,25] The study patient exhibited these findings, which were compatible with HSV infection. We initially did not suspect HSV1P, but screening of sputum cytology samples provided a clue for correcting our strategies for diagnosis and treatment.

Radiologic Discussion

The chest radiograph findings of HSV1P have been described in a few reports. Most described bilateral consolidation, but nodules with irregular margins and ground-glass opacities have also been reported.[15] CT findings of HSV1P include multifocal segmental and subsegmental ground-glass opacities and consolidation, scattered distribution, and pleural effusion,[25] which, except for pleural effusion, were also found in the study patient. Furthermore, interlobular septal thickening and bronchial thickening have been reported in viral pneumonia[26] and were also found in the current patient.

Teaching Points

1. *HSV1 virus is a cause of community-acquired pneumonia.*
2. *Although HSV1P is considered to be rare, it can develop in patients with diabetes mellitus with a mild increase in glycosylated hemoglobin levels and without any complications of diabetes mellitus itself.*
3. *When HSV1P is suspected, investigation of samples obtained from the lower respiratory tract is recommended.*
4. *No skin, oral, or genital lesions suggestive of HSV infection were found in any of the patients with reported HSV1P unaffected by transplantation, HIV, immunosuppressants, corticosteroids, burns, or malignancy.*
5. *Hasty administration of corticosteroids may be harmful to patients with viral pneumonia, and thus it is important to rule out viral pneumonia prior to the administration of corticosteroids.*

Acknowledgments

Financial/nonfinancial disclosures: The authors have reported to *CHEST* the following: T. I. was supported by a Research Fund from Saitama Cardiovascular and Respiratory Center [Grant Nos. 16ES, 17ES, and 18ES]. None declared (Y. B., M. G., Y. S., N. T.).

Other contributions: The ethical committee of Saitama Cardiovascular and Respiratory Center approved the report of the present case. *CHEST* worked with the authors to ensure that the Journal policies on patient consent to report information were met.

References

1. Johkoh T, Muller NL, Taniguchi H, et al. Acute interstitial pneumonia: thin-section CT findings in 36 patients. *Radiology*. 1999;211(3):859-863.
2. Jain S, Self WH, Wunderink RG, Fakhran S, Balk R, Bramley AM; CDC EPIC Study Team. Community-acquired pneumonia requiring hospitalization among U.S. adults. *N Engl J Med*. 2015;373(5):415-427.
3. Marcos MA, Esperatti M, Torres A. Viral pneumonia. *Curr Opin infect Dis*. 2009;22(2):143-147.
4. Ruiz M, Ewing S, Marcos MA, et al. Etiology of community-acquired pneumonia: impact of age, comorbidity, and severity. *Am J Respir Crit Care Med*. 1999;160(2):397-405.
5. Templeton KE, Scheltinga SA, van den Eeden WC, Graffelman AW, van den Broek PJ, Claas EC. Improved diagnosis of the etiology of community-acquired pneumonia with real-time polymerase chain reaction. *Clin Infect Dis*. 2005;41(3):345-351.
6. Miyazato A, Kishimoto H, Tamaki K, Nakama K, Saito A. Herpes simplex virus bronchopneumonia in a non-immunocompromized individual. *Intern Med*. 2001;40(8):836-840.
7. Ishihara T, Yanagi H, Ozawa H, Takagi A. Severe herpes simplex virus pneumonia in an elderly, immunocompetent patient. *BMJ Case Rep*. 2018;2018. pii: bcr-2017-224022.
8. Mills B, Ratra A, El-Bakush A, Kambali S, Nugent K. Herpes simplex pneumonia in an immunocompetent patient with progression to organizing pneumonia. *J Investig Med High Impact Case Rep*. 2014;2(2):2324709614530560.
9. Geradts J, Warnock M, Yen TS. Use of the polymerase chain reaction in the diagnosis of unsuspected herpes simplex viral pneumonia: report of a case. *Hum Pathol*. 1990;21(1):118-121.
10. Martinez E, de Diego A, Paradis A, Perpiñá M, Hernandez M. Herpes simplex pneumonia in a young immunocompetent man. *Eur Respir J*. 1994;7(6):1185-1188.
11. Hunt DP, Muse VV, Pitman MB; Case records of the Massachusetts General Hospital. Case 12-2013. An 18-year-old woman with pulmonary infiltrates and respiratory failure. *N Engl J Med*. 2013;368(16):1537-1545.
12. Reyes CV, Bolden JR. Herpes simplex virus type-1 pneumonitis in immunocompetent young woman. *Heart Lung*. 2009;38(6):526-529.
13. Bonacchi M, Di Lascio G, Harmelin G, Pasquini A, Peris A, Sani G. Extracorporeal membrane oxygenation for refractory, life-threatening, and herpes simplex virus 1-induced acute respiratory distress syndrome. Our experience and literature review. *Am J Emerg Med*. 2012;30(6). 1014.e3-1014.e10.
14. Terzano C, Petroianni A, Ricci A. Herpes simplex pneumonia: combination therapy with oral acyclovir and aerosolized ribavirin in an immunocompetent patient. *Curr Ther Res Clin Exp*. 2004;65(1):90-96.
15. Graham BS, Snell JD Jr. Herpes simplex virus infection of the adult lower respiratory tract. *Medicine (Baltimore)*. 1983;62(6):384-393.
16. Nash G, Foley FD. Herpetic infection of the middle and lower respiratory tract. *Am J Clin Pathol*. 1970;54(6):857-863.
17. Ikeda K, Nakashima A, Tsukino M, Fujita H, Ikeda A. A case of herpes simplex virus pneumonia with adult respiratory distress syndrome [in Japanese]. *J Jpn Soc Respir Endoscopy*. 1990;12(5):530-535.
18. Chandrasekar PH. Case 12-2013: a woman with pulmonary infiltrates and respiratory failure. *N Engl J Med*. 2013;369(6):583-584.
19. Straus SE, Rooney JF, Sever JL, Seidlin M, Nusinoff-Lehrman S, Cremer K. NIH Conference. Herpes simplex virus infection: biology, treatment and prevention. *Ann Intern Med*. 1985;103(3):404-419.
20. Schuller D; Lower respiratory tract reactivation of herpes simplex virus. Comparison of immunocompromised and immunocompetent hosts. *Chest*. 1994;106(suppl 1):3S-7S; discussion 34S-35S.
21. Cheng VC, Tang BS, Wu AK, Chu CM, Yuen KY. Medical treatment of viral pneumonia including SARS in immunocompetent adult. *J Infect*. 2004;49(4):262-273.
22. Salluh JI, Póvoa P, Soares M, Castro-Faria-Neto HC, Bozza FA, Bozza PT. The role of corticosteroids in severe community-acquired pneumonia: a systematic review. *Crit Care*. 2008;12(3):R76.
23. 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*. 2017;11(4):345-354.
24. Jatti T, Vanto T, Heikkinen T, Ruuskanen O. Systemic glucocorticoids in childhood expiratory wheezing: relation between age and viral etiology with efficacy. *Pediatr Infect Dis J*. 2002;21(9):873-878.
25. Aquino SL, Dunagan DP, Chiles C, Haponik EF. Herpes simplex virus 1 pneumonia: patterns on CT scans and conventional chest radiographs. *J Comput Assist Tomogr*. 1998;22(5):795-800.
26. Franquet T. Imaging of pulmonary viral pneumonia. *Radiology*. 2011;260(1):18-39.