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

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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/mm³ (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

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

chestjournal.org e41
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 $14 \times 10^6$ 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 immunosassay 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.2-4 These studies
investigated influenza virus, respiratory syncytial virus,
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. 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. 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.

Among the 10 reported patients with HSV1P unaffected by transplantation, HIV, immunosuppressants, corticosteroids, burns, or malignancy, 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, and she had experienced a herpes virus lip infection several years earlier.

Acyclovir was generally selected for the treatment of HSV1P, except in two cases. The study patient improved spontaneously with no medications, 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,

Figure 2 – A-C, Cytologic evaluation 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).
whereas immunocompromised patients were treated with acyclovir for 17 ± 10 days. 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, 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, and in influenza-associated pneumonia in some clinical settings, but other reports have found them to be harmful. 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. 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.

### Table 1

| Year | Reference          | Age, y | Sex | Underlying Diseases                          | Skin, Oral, or Genital Lesion | Treatment                                    | Outcome   |
|------|--------------------|--------|-----|---------------------------------------------|-------------------------------|-----------------------------------------------|-----------|
| 1990 | Geradts et al⁹     | 30     | Female | Neurofibromatosis, severe scoliosis          | No                            | No antiviral treatment                        | Died      |
| 1994 | Martinez et al¹⁰   | 33     | Male | Psychological disease (depression)          | Erythematous oropharynx without exudates or vesicles | Acyclovir                                     | Recovered |
| 2001 | Miyazato et al⁶    | 49     | Male | None                                        | No                            | No antiviral treatment                        | Recovered |
| 2004 | Terzano et al¹⁴    | 46     | Female | None                                       | No                            | Acyclovir plus aerosolized ribavirin          | Recovered |
| 2009 | Reyes and Bolden¹² | 19     | Female | None                                       | No                            | Acyclovir, mechanical ventilation            | Recovered |
| 2012 | Bonacchi et al¹³   | 18     | Male | None                                       | No                            | Acyclovir, ECMO, mechanical ventilation       | Recovered |
| 2013 | Hunt et al¹¹       | 18     | Female | None                                       | No                            | Acyclovir, mechanical ventilation            | Recovered |
| 2014 | Mills et al⁸       | 39     | Male | None                                       | No                            | Acyclovir, mechanical ventilation, corticosteroid | Recovered |
| 2018 | Ishihara et al⁷    | 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.

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

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**Chest Imaging and Pathology for Clinicians**

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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. CT findings of HSV1P include multifocal segmental and subsegmental ground-glass opacities and consolidation, scattered distribution, and pleural effusion, 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 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 present 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.

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