CASE REPORT

Severe herpes simplex virus pneumonia in an elderly, immunocompetent patient

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SUMMARY

Although not common, herpes simplex virus (HSV) pneumonia can occur in immunocompromised patients. However, HSV pneumonia in immunocompetent hosts is very rare. The authors encountered a very rare case of severe HSV pneumonia in an immunocompetent host. The patient was an 85-year-old Japanese woman who presented with severe intractable pneumonia refractory to empirical antimicrobial therapy. Furthermore, the causative microorganisms remained unknown. Therefore, cytological examination of bronchoalveolar lavage fluid and protected brush biopsy of the lower respiratory tract were performed, which indicated herpes virus-infected cells with nuclear inclusions; PCR assay was positive for HSV DNA. Accordingly, the patient was diagnosed with HSV pneumonia. Her respiratory condition improved immediately after initiation of acyclovir monotherapy. In selected cases of intractable pneumonia refractory to standard antimicrobial therapy, the possibility of HSV pneumonia should be pursued.

BACKGROUND

Many cases of community-onset pneumonia are treated with empirical antimicrobial therapy, but when physicians come across patients with intractable pneumonia refractory to antimicrobial therapy, they need to consider the possibility of viral pneumonia.¹ Herpes simplex virus (HSV) pneumonia in immunocompromised hosts has been reported.^{2–7} However, HSV pneumonia in immunocompetent hosts is very rare. Furthermore, the pathogenicity of HSV pneumonia and diagnostic methods for it remain unknown.⁸ We encountered a case of severe intractable HSV pneumonia in an immunocompetent patient who was successfully treated. Since HSV pneumonia is a treatable condition, it is important to include it in the differential diagnosis of difficult-to-treat pneumonia cases.

CASE PRESENTATION

An 85-year-old Japanese woman was emergently transferred to our hospital due to worsening respiratory failure. Fever and cough had begun 5 days before the transfer. The patient had visited a nearby doctor and was diagnosed with common cold before arriving at our hospital. Symptomatic treatment was performed and the patient was not admitted at this time. However, the symptoms exacerbated. The patient was diagnosed with pneumonia when she visited the same doctor again and was, in turn, emergently transferred to us. She had no significant

history of hospitalisation or residence in a nursing home. She had no sick contacts, history of overseas travel, use of a spa or public bath or exposure to animal pets. She was a housekeeper, with no history of smoking or alcohol consumption. Her medical history was significant only for hypertension and dyslipidaemia. Physical examination findings at the time of admission included the following: alert; blood pressure 136/70 mm Hg; heart rate 120 beats/min; respiratory rate 26 breaths/min; body temperature 38.6°C and oxygen saturation 90% (on 10 L oxygen via a non-rebreather mask). Diffuse coarse crackles were present in both lung fields. No other findings were noted.

INVESTIGATIONS

Laboratory investigations revealed the following: PaO₂ of arterial oxygen 57 mm Hg (breathing 10 L oxygen via non-rebreather mask); white blood cell count 17 600/μL; C reactive protein level 38.58 mg/dL (normal <10 mg/dL). There were no other remarkable findings noted in blood tests. Rapid screening test findings were negative for influenza A antigen/B antigen, urinary pneumococcal capsular antigen and urinary Legionella antigen. Sputum gram staining findings before antibiotic treatment included many neutrophils and the bacteria were not recognised. Radiographic chest examination revealed infiltration in both lung fields (figure 1). A chest CT examination revealed bilateral consolidations accompanied by air bronchogram (figure 2).

DIFFERENTIAL DIAGNOSIS

The patient was diagnosed with severe community-onset pneumonia with acute respiratory distress syndrome. Significant hypoxaemia was present; consequently, emergency tracheal intubation and ventilator management were applied. For the treatment of community-onset pneumonia, sulbactam/ampicillin 3 g four times a day and azithromycin 500 mg per day were administered for a total of 13 days. However, no treatment effect was observed and the respiratory condition worsened. Furthermore, test results were negative for blood culture, sputum bacterial culture (including Legionella and fungal culture) and mycobacterial cultures (negative results persisted after 2 months) from the lower respiratory tract aspirates, mycobacterial PCR, and influenza PCR. Paired sera for *Mycoplasma pneumoniae* and *Chlamydia pneumoniae* were sent, with no increases observed in the antibody titres after 2 weeks. Serum cytomegalovirus pp65

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Figure 1 Chest radiography. X-ray on day of admission. Radiographic chest examination revealed infiltration in both lung fields.

antigenaemia was negative. Sputum eosinophil results were negative. Markers for interstitial pneumonia, including Krebs von den Lungen-6 were 410 U/mL (normal <500 U/mL). Results of autoimmune antibody detection related to lung disorders were all negative. The patient was diagnosed with refractory pneumonia of an unknown cause. Therefore, on day 12, bronchoalveolar lavage and brushing were performed. As a result, findings suggesting HSV-infected cells with intranuclear inclusions were observed in bronchoalveolar lavage cytology and bronchial brush cytology (figure 3). Qualitative HSV-DNA PCR (amplified using AmpliTaq DNA Polymerase (Thermo Fisher Scientific, USA)), performed on a bronchoalveolar lavage fluid sample, was positive, indicating HSV pneumonia. The results for simultaneous bacterial and mycobacterial cultures were negative.

Figure 2 Plain chest CT on day of admission. A chest CT examination revealed bilateral consolidations accompanied by air bronchogram.

Figure 3 Cytopathological findings. Bronchoalveolar-lavage fluid specimen (Panel A, arrows; Papanicolaou stain, 400×) and bronchial brush (Panel B, arrows; Papanicolaou stain, 400×) smears reveal cytopathic cellular changes of multinucleation, nuclear ground-glass opacities and intranuclear inclusion (Cowdry A type), collectively diagnostic of herpes simplex infection.

TREATMENT

After antimicrobials were discontinued, monotherapy using acyclovir 500mg three times a day was started, resulting in substantial improvement in respiratory condition, and continued for a total of 14 days.

OUTCOME AND FOLLOW-UP

The patient was extubated on day 24. She was discharged from the hospital. She is currently living well, 5 years after discharge. The patient underwent detailed examination for the possibility of immunodeficiency. Chest, abdominal and pelvis CT scans with contrast were normal. Immunoglobulin level was normal, the HIVI/II antigen/antibody test was negative, real-time HIV-1 PCR was negative and no abnormal findings were confirmed in a bone marrow biopsy.

DISCUSSION

This case suggested two important clinical implications. HSV pneumonia needs to be considered even in an immunocompetent host. In addition to the exclusion of other causes, cytopathological examination and HSV-DNA PCR of lower respiratory tract specimens are important for diagnosis.

In patients with community-onset pneumonia refractory to standard antimicrobial therapy, we should consider the possibility of HSV pneumonia even for an immunocompetent host. Although HSV pneumonia is rare, there have been some reports in immunocompromised hosts. It has been reported in patients with AIDS,² burns,³ pregnancy⁴ and malignant tumours⁵ and haematopoietic stem cell transplant⁶ and solid organ transplant recipients.⁷ All patients in these reports had some immunodeficiency and underlying disease(s) affecting immunity. When we searched PubMed using the keywords 'herpes simplex virus pneumonia and immunocompetent, healthy person, non-immunocompromised', only seven articles were found (table 1).⁹⁻¹⁵ Furthermore, although the cases in these reports involved young to middle-age individuals, our case was the oldest. In these cases, fever, myalgia, shortness of breath, cough, pleuritic chest pain, dyspnoea, nausea, vomiting, diarrhoea and abdominal pain are reported as initial symptoms. In addition, no symptoms of skin or oral mucosa have been reported.⁹⁻¹⁵ These symptoms cannot be distinguished from common cold or common pneumonia or gastroenteritis. Clinical symptoms and findings were non-specific, and diagnosis was difficult in all cases.

In the present case as well, we first considered common pneumonia. However, no therapeutic effect was noted after

Table 1 Literature reports of HSV pneumonia in immunocompetent adults

Reference no.	Age/sex	Prehospital symptoms	Bronchoscopy date	Cytopathology	PCR	Outcome
9	30 years/female	Fever and RS	Not reported (autopsy)	Cowdry type A inclusions	Positive for HSV	Intubation death
10	33 years/male	Fever, myalgia and RS	Bronchial biopsy on day 15	Cowdry type A inclusions	Not reported	Intubation improved with ACV
11	49 years/male	Fever and RS	Bronchial brush No date reported	Intranuclear inclusions	Not reported	Improved
12	28 years/male	Fever and RS	Tracheal biopsy No date reported	Cowdry type A inclusions	Positive for HSV-1	Improved with ACV
13	19 years/female	Fever and RS	Bronchial brush No date reported	Cowdry type A inclusions	Not reported	Intubation improved with ACV
14	18 years/female	Fever, RS and GIS	Bronchial alveolar lavage on day 11	Cowdry type B inclusions, Tzanck cells	Positive for HSV-1	Intubation improved with ACV
15	39 years/male	RS and GIS	Bronchial alveolar lavage on day 5	Not reported	Not reported	Intubation improved with ACV

ACV, acyclovir; GIS, gastrointestinal symptoms; HSV, herpes simplex virus; RS, respiratory symptoms.

standard antimicrobial therapy and the aetiology of pneumonia was unknown. Therefore, bronchoalveolar lavage and bronchial brushing were performed. Accordingly, HSV pneumonia was suspected based on cytopathological examination and HSV-DNA PCR positivity. Clear improvement was achieved after acyclovir monotherapy was started, which also indicated that this patient, in fact, had HSV pneumonia. Furthermore, the case was considered to be of community-onset HSV pneumonia because other microorganisms related to the occurrence of pneumonia were not detected in other investigations. However, as the bronchoscopic examination was performed at a latter date, the possibility of a reactivation effect during intensive care unit assisted ventilation cannot be completely excluded. The patient did not have any comorbidities that could cause immunodeficiency. Thus, this may be an extremely rare case of community-onset HSV pneumonia in an immunocompetent host.

Second, in addition to the exclusion of other causes, cytopathological examination and HSV-DNA PCR of lower respiratory tract specimens are important for diagnosis of HSV pneumonia. The aspirates of the lower respiratory tract and bronchoalveolar lavage fluid may be HSV-DNA PCR positive in patients undergoing long-term ventilator management.^{16–19} However, pathogenicity and necessity of treatment remain unknown. This may be due to differences in study methods, control groups and diagnostic methods.⁸ Improvement and standardisation of diagnostic methods is required to identify the pathogenicity of HSV in the lower respiratory tract in future studies. As a diagnostic method for HSV pneumonia, we recommend excluding other common causes, seeking both cytopathological confirmation and HSV-DNA PCR positivity of lower respiratory tract specimens and confirming the increase of paired serum HSV antibody titres.

The clinical symptoms and findings of HSV pneumonia are non-specific and may have been diagnosed as unknown cause. In selected cases of community-onset pneumonia refractory to standard antimicrobial therapy, the possibility of HSV pneumonia should be considered even for immunocompetent hosts. This report described a case of HSV pneumonia in an elderly immunocompetent host with cytopathic effect and clinical evidence. It is expected that the discussion regarding indications for treatment when HSV is detected in the lower respiratory tract of an immunocompetent host with refractory pneumonia will continue. While we do not recommend routine treatment with acyclovir, this treatment option should

be kept in mind when the severity is high and other causes of pneumonia are ruled out, and when typical cytopathological findings are detected in addition to HSV-DNA PCR positivity in the affected lower respiratory tract, as described in the present report.

Learning points

- ▶ Herpes simplex virus (HSV) pneumonia needs to be included in the differential diagnosis of intractable community-onset pneumonia even in an immunocompetent host.
- ▶ The clinical symptoms and findings of HSV pneumonia are non-specific and can be mistaken for common cold or common pneumonia.
- ▶ In addition to the exclusion of other causes, cytopathological examination and HSV-DNA PCR of lower respiratory tract specimens are important for diagnosis.

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