

## A Case Report of Tracheobronchitis by Herpes Simplex Virus, Type I

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*Herpes simplex virus (HSV) infection of the lung and lower respiratory tract has been thought to be a rare and fatal disease, usually in patients with immunosuppression, severe burns, or prolonged intubation. However, recently, increasing numbers of patients have been reported to have a localized infection and some of them have recovered without specific therapy.*

*In Korea, there has been yet no proven case of HSV infection of the lower respiratory tract. Recently, we saw a case of localized HSV infection of the tracheobronchus. A 78-year-old male patient was admitted in acute respiratory failure, with COPD and old pulmonary tuberculosis. After the clinical condition improved, a bronchoscopy was done which revealed a localized area of swelling, hyperemia, and mucosal irregularity at the lower trachea and right upper lobar bronchus. Bronchial brushing and biopsy showed typical cytologic changes including intranuclear inclusion body. Viral culture of a bronchial washing revealed a growth of HSV, type I. The patient died of unrelated, acute myocardial infarction.*

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**Key Words :** *Herpes simplex virus, Tracheobronchitis, Old age, COPD, Cytology*

### INTRODUCTION

Herpes simplex virus (HSV) infection of the respiratory tract was first reported in 1949 by Morgan, who cultured HSV from the lung tissue of the patient with severe burns and atypical pneumonia.<sup>1)</sup> Since then, it has been well known that HSV can cause fatal respiratory infection in patients with burns,<sup>2-4)</sup> organ transplantation, malignancy, immunosuppressive therapy,<sup>5-9)</sup> prolonged intubation,<sup>3,4,10)</sup> and alcoholic liver disease.<sup>11)</sup>

Recently, several cases of localized infection in the respiratory tract of the patient with normal resistance have been reported, in some of them recovery occurred spontaneously.<sup>12,13)</sup>

We, also, have seen a localized HSV tracheobronchitis in a patient with chronic

obstructive lung disease, which was confirmed by the cytologic changes of the bronchoscopic biopsy and brushing, and a positive culture of the bronchial washing. In Korea, there has been no report of a case of proven HSV infection confined to the lower respiratory tract.

### CASE

A 78-year-old man was admitted with severe dyspnea and in a state of altered consciousness. He had suffered from cough, sputum, and exertional dyspnea for the previous 8 years. About 8 days before admission, respiratory symptoms had become worse with fever and chills, and treatment at a local clinic had failed to bring about any improvement. Two day before admission he had become drowsy.

Twenty-five years previously he had been treated with anti-tuberculous medication irregularly for 3 years and he had a history of smoking 60 pack year.

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On physical examination, the patient appeared to be severely emaciated, cyanotic, and dyspneic. He was drowsy. His blood pressure was 120/80mmHg, pulse rate 132/minute, respiration rate 35/minute, and temperature 36.5 C. The anteroposterior diameter of the thorax was markedly increased and rhonchi and crackles were heard on both lower lung fields. The other parts were normal and there was no evidence of herpetic lesion on either the lips or oropharynx.

Hemoglobin was 12.1gm%, and WBC count was 28,000/mm<sup>3</sup> with 90% neutrophils. An ECG revealed sinus tachycardia and left ventricular hypertrophy. Blood chemistry was normal except for mild hypoalbuminemia (2.7gm%). Arterial blood gas analysis on room air showed PO<sub>2</sub> of 30mmHg, and PCO<sub>2</sub> of 48mmHg. With 2L/min oxygen, PO<sub>2</sub> was 50mmHg and PCO<sub>2</sub> was 56 mmHg. Chest X-ray showed right upper lobe collapse and bilateral lower lung infiltration (Fig. 1).

Six sputum smears for AFB were all negative. The patient improved with 2L/minute O<sub>2</sub> inhalation, antibiotics (cephalosporin and gentamicin), bronchodilators, and chest physiotherapy. On the 6th hospital day, fiberoptic bronchoscopy was performed for the investigation of the lesion of the right upper lung. It revealed a localized area of swelling and hyperemia on the right lateral wall of the lower trachea, extending to the proximal part

of right upper bronchus. No definite blister or ulceration was found, but several discrete nodules were noticed (Fig. 2). At the cytologic study of broncheal brushing and washing, typical findings of HSV infection were observed : nuclei showed a ground-glass appearance with small, clear vacuoles, granular distribution of chromatin along the nuclear membrane, typical intra-nuclear eosinophilic inclusion bodies, and many, multinucleated giant cells (Fig. 3). Bronchoscopic biopsy revealed severe necrotic inflammation with squamous metaplasia, and the cytologic changes typical of HSV, which were mentioned earlier (Fig. 4). Three days later a repeated bronchoscopy was

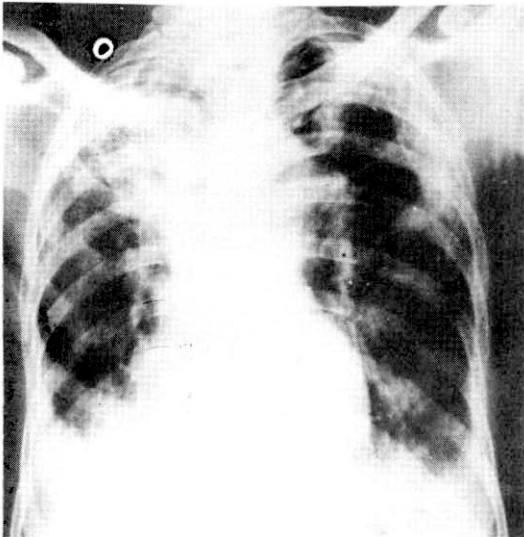


Fig. 1. Chest X-ray at the time of admission. Streaky and patchy densities with volume loss are seen on right upper lung with both lower lung infiltration.

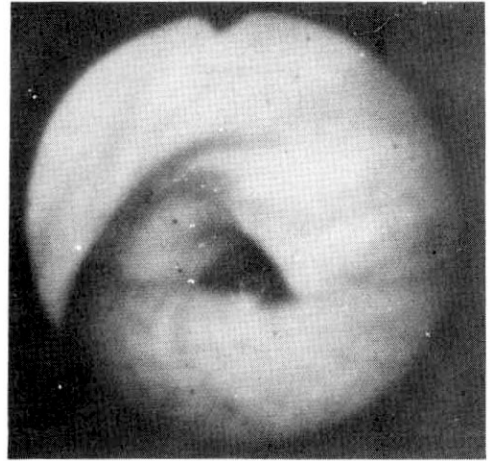


Fig. 2. The first bronchoscopic finding of the lower trachea. Note diffuse erythema, swelling and mucosal irregularity.

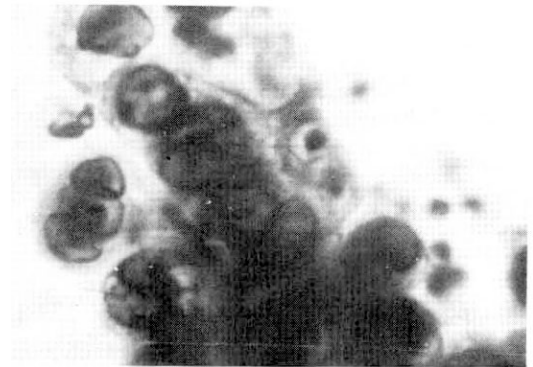


Fig. 3. Cytologic finding of the bronchial brushing. Nuclei of the cells show ground-glass appearance with peripheral condensation of chromatin. Note the typical eosinophilic intranuclear inclusion body and multinucleated giant cells (Papanicolau stain,  $\times 900$ ).

done to obtain material for culture, and this time, whitish pseudomembrane was found to cover the inflamed area (Fig. 5). Viral culture by the inoculation of the bronchial washing into Vero Cells (monkey kidney cells) with medium-199 at the Korean National Institute of Health resulted in the growth of HSV type 1.

Because on the 12th hospital day, the patient's condition began to get worse, with increasing sputum production and dyspnea, acyclovir was started. On the 3rd day of acyclovir therapy, the patient complained of a sudden onset of severe

chest pain, and collapsed. An ECG revealed extensive anterior wall myocardial infarction and he died several hours later.

Blood drawn before death revealed 480 units of S-GOT, 380 units of CPK, and 2,651 units of LDH.

## DISCUSSION

HSV is common pathogen invading the oropharyngeal mucosa, the skin, the genitalia, and the gastrointestinal tract, but respiratory tract involvement is relatively rare. After the first description in 1949 by Morgan,<sup>1)</sup> increasing numbers of cases have been reported.

Most of the respiratory infections were fatal in an immune-compromised host,<sup>5-9)</sup> in severe burns or in prolonged intubation with adult respiratory distress syndrome,<sup>16)</sup> and the diagnosis was made only by autopsy.<sup>1,3,4)</sup> However, recently, more cases with an antemortem diagnosis<sup>5,9,12,13,16-20)</sup> or localized infection which has healed spontaneously have been reported.

For the HSV infection, both humoral and cellular immunity are present, but like other viral infections, cellular immune response is thought to be much more important.<sup>21-23)</sup> Arvin reported a defect in lymphocyte transformation reaction on the challenge of HSV in the patient with lymphoma and recurrent HSV infection.<sup>20)</sup> Wilton observed the impaired release of the migration inhibition factor (MIF) from macrophage and lymphocyte cytotoxicity to HSV infection.<sup>22)</sup> Since O'Reilly also found a defective production of interferon and leucocytic release of MIF, an impaired cellular immune response has been suggested as a predisposition for recurrent HSV infection. In addition, Drew discovered the importance of alveolar macrophages in the defense against HSV.<sup>24)</sup> Therefore, a defect in the local immune response as well as impaired systemic immunity can be a predisposing factor for respiratory HSV infection.

Because HSV usually invades squamous epithelium, the respiratory tract is not a frequent site of infection. However, after the squamous metaplasia became induced by smoking, smoke inhalation during burns, or prolonged intubation, HSV infection became more frequent. In fact, most of the reported HSV infections have occurred in the areas of squamous metaplasia.<sup>19,25)</sup> Rarely, it can occur in the elderly patient without underlying disease,<sup>4,13,25,26)</sup> or even in the younger normal

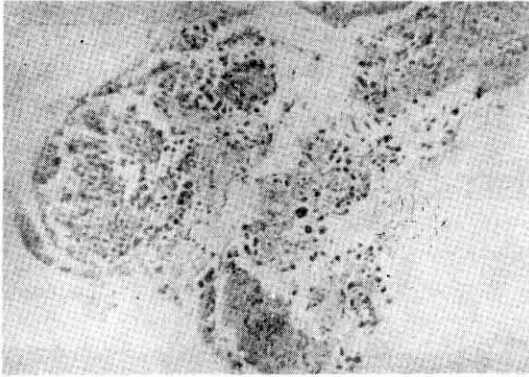


Fig. 4. Histopathologic finding of the bronchoscopic biopsy. Severe necrotic inflammation is found with squamous metaplasia. Many of the cells show typical cytologic change seen in Fig. 3 at the high power view. (Hematoxylin and eosin stain,  $\times 100$ )

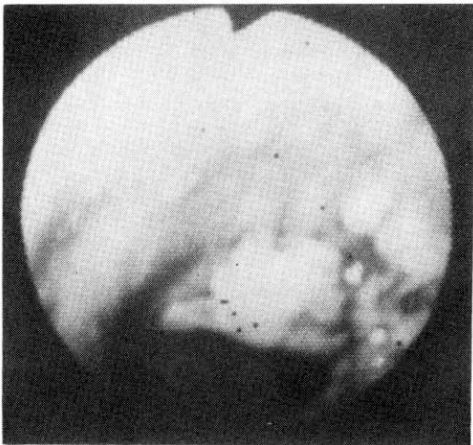


Fig. 5. The second bronchoscopic finding of the lower trachea (same area as Fig. 2). Multiple irregular patches of pseudomembranes are seen on top of the acute inflammation.

person.<sup>12,13)</sup> Our patient was a heavy smoking, elderly patient with chronic obstructive pulmonary disease, and squamous metaplasia was found on bronchoscopic biopsy.

HSV is relatively common inhabitant of the human salivary gland<sup>27)</sup> and in 2.7-11.5% of the patients with other respiratory disease, HSV has been cultured from the sputum or throat swab.<sup>28,29)</sup> Also, the fact that mucocutaneous HSV infection has been frequently found before, or at the same time of respiratory illness suggests the contagious spread or inhalation of contaminated material as a route of respiratory infection. However, hematogenous dissemination or spread via the nerve pathway have also been suggested.<sup>30,31)</sup>

The diagnosis of HSV infection can be made by viral culture, typical cytologic changes, histological findings, and the direct immunofluorescent study of infected tissue. Viral culture is a very sensitive and rapid test but in respiratory infection, active infection cannot be differentiated from colonization. In one study viral culture of the oropharyngeal secretions was positive for HSV in 1-5% of normal adults<sup>29)</sup> and 2.7-11.5% of patients with respiratory disease of other kinds.<sup>28,29)</sup> In the patient with pharyngitis, up to 22% of the pharyngeal swabs were positive.<sup>28)</sup> Therefore, a positive culture only is not sufficient for making a diagnosis. On the contrary, typical cytopathologic or histopathologic changes are the evidences of active infection. The ground-glass appearance of nucleus with multiple small vacuoles, the eosinophilic intranuclear inclusion bodies, and the multinucleated giant cells, which were seen in our case, are characteristic findings in HSV infections. Other viral infections can cause similar changes, but in cytomegalovirus infection, both intranuclear and intracytoplasmic inclusion bodies are present. The fact that inclusion bodies are usually basophilic and the huge size of an infected cell can make the diagnosis clear.<sup>32,33)</sup> Adenovirus can cause multiple inclusion bodies only in the nucleus, but multi-nucleated giant cells are usually absent.<sup>32,33)</sup> In respiratory syncytial viral infection, inclusion bodies are all intracytoplasmic.<sup>32,34)</sup>

In view of this, Ramsey proposed the following findings as criteria for the diagnosis of HSV pneumonia<sup>30)</sup>: parenchymal infiltration on the chest X-ray, positive viral culture from the lung tissue, and hemorrhagic or ulcerative inflammation with typical cytopathologic changes in the lung tissue from which the culture was taken.

Our case had definite HSV tracheobronchitis

on the basis of Ramsey's criteria. However, it is not likely that he had HSV pneumonia, too, because the right upper lung density on chest the X-ray was old atelectasis rather than infiltration, and the distal part of the bronchial mucosa of the right upper lobe was normal on the bronchoscopy.

The bronchoscopic appearance of HSV infection is not characteristic. Acute inflammatory change, with or without blisters, ulceration, or pseudomembrane has been described.<sup>13,16)</sup> In our case, pseudomembrane on top of acute inflammation was found on the second bronchoscopy.

The treatment of HSV is still unsatisfactory,<sup>5,13)</sup> but after the administration of adenosine arabinoside (Ara-A), the mortality and morbidity has been decreased.<sup>14)</sup> Ara-A has been reported to be effective for severe mucocutaneous HSV infection.<sup>35)</sup> Recently, acyclovir which is more potent and has fewer side effects, has been used with good results.<sup>15,20,36)</sup>

## REFERENCES

1. Morgan HR, Finland M: *Isolation of herpetic virus from a case of atypical pneumonia and erythema multiforme exudativum.* *Am J Med Sci* 217: 92, 1949
2. Foley FD, Greenawald KA, Nash G: *Herpes virus infection in burned patients.* *N Engl J Med* 182: 652, 1970
3. Nash G, Foley FD: *Herpetic infection of the middle and lower respiratory tract.* *Am J Clin Pathol* 54: 857, 1970
4. Nash G: *Necrotizing tracheobronchitis and bronchopneumonia consistent with herpetic infection.* *Human Pathol* 3: 283, 1972
5. Douglas RG Jr, Anderson MS, Weg JG: *Herpes simplex virus pneumonia: Occurrence in an allotransplanted lung.* *JAMA* 210: 902, 1969
6. Case records of the Massachusetts General Hospital (case 15-1973). *N Engl J Med* 188: 780, 1973
7. Cheever AW, Valsamis MP, Rabson AS: *Necrotizing toxoplasmic encephalitis and herpetic pneumonia complicating treated Hodgkin's disease.* *N Engl J Med* 272: 26, 1965
8. Case records of the Massachusetts General Hospital (case 28-1973). *N Engl J Med* 272: 26, 1965
9. Jordan SW, McLaren LC, Croshy JH: *Herpetic tracheobronchitis; cytologic and virologic detection.* *Arch intern Med* 135: 784, 1975
10. Frable WJ, Frable MA, Seney FD: *Virus infections of the respiratory tract; cytopathologic and*

- clinical analysis. *Acta Cytologic* 21 : 32, 1977
11. Caldwell JE, Porter DD : *Herpetic pneumonia in alcoholic hepatitis*. *J A M A* 217 : 1703, 1971
  12. Vernon SE : *Cytologic features of nonfatal herpesvirus tracheobronchitis*. *Acta Cytologica* 26 : 237, 1982
  13. Barney S, Graham, James D, Snell : *Herpes simplex virus infection of the adult lower respiratory tract*. *Medicine* 62 : 384, 1983
  14. Whitley RJ, Soong SJ, Dolin R, Galasso GJ, Ch'lien LT, Alfore CA : *Adenine arabinoside therapy of biopsy-proven herpes simplex encephalitis*. *N Engl J Med* 297 : 289, 1977
  15. Wade JC, Newton B, McLaren C, Flournoy N, Keeewney RE, Meyers JD : *Intravenous acyclovir to treat mucocutaneous herpes simplex infection after marrow transplantation : a double-blind trial*. *Ann Intern Med* 96 : 265, 1982
  16. Tuxen DV, Cade JF, McDonald MI, Buchanan MRC, Clark RJ, Pain MCF : *Herpes simplex virus from the lower respiratory tract in adult respiratory distress syndrome*. *Am Rev Respir Dis* 126 : 416, 1982
  17. Case records of the Massachusetts General Hospital. *N Engl J Med* 288 : 780, 1973
  18. Frable WJ, Kay S : *Herpesvirus infection of the respiratory tract ; electron microscopic observation of the virus in cells obtained from a sputum cytology*. *Acta Cytologica* 21 : 391, 1977
  19. Buss DH, Scharyj M : *Herpes virus infection of the esophagus and other visceral organs in adults ; incidence and clinical significance*. *Am J Med* 66 : 457, 1979
  20. Alford CA : *Acyclovir treatment of herpes virus infections in immunocompromised human*. *Am J MED* 73 (1A) : 225, 1982
  21. Arvin AM, Pollard RB, Rasmussen LF, Merigan TC : *Cellular and humoral immunity in the pathogenesis of recurrent herpes viral infections in patients with lymphoma*. *J Clin Invest* 65 : 869, 1980
  22. Wilton JMA, Ivanyi L, Lehner T : *Cell-mediated immunity in herpes-virus hominis infections*. *Br Med J* 1 : 723, 1972
  23. O'Reilly RJ, Chibbaro A, Anger E, Lopez C : *Cell-mediated immune response in patients with recurrent herpes simplex infections*. *J Immunol* 118 : 1095, 1977
  24. Herout V, Vortel V, Vondrackova A : *Herpes simplex involvement of the lower respiratory tract*. *Am J Clin Pathol* 46 : 411, 1969
  25. Case records of the Massachusetts General Hospital. *N Engl J Med* 288 : 1173, 1973
  26. Kaufman HE, Brown DC, Ellison EM : *Recurrent herpes in the rabbit and man*. *Science* 156 : 1628, 1967
  27. Glezen WP, Fernald GW, Lohr JA : *Acute respiratory disease of university students with special reference to the etiologic role of herpes virus hominis*. *Am J Epidemiol* 101 : 111, 1975
  28. Lindgren KM, Douglas RG, Couch RB : *Significance of herpes virus hominis in respiratory secretions of man*. *N Engl J Med* 278 : 517, 1968
  29. Ramsey PG, Fife KH, Hackman RC, Mehers JD, Corey L : *Herpes simplex virus pneumonia ; clinical, virologic and pathologic features in 20 patients*. *Ann Intern Med* 97 : 813, 1982
  30. Warren KG, Brown SM, Wroblewska Z, Gilden D, Koprowski H, Subak-sharpe J : *Isolation of latent herpes simplex virus from the superior cervical and vagus ganglions of human beings*. *N Engl J Med* 298 : 1068, 1978
  31. Koss LG : *Diagnostic cytology and its histopathologic bases*. 3rd ed. p.577, Philadelphia. JB Lippincott Co. 1979
  32. Becroft DMD : *Histopathology of fatal adenovirus infection of the respiratory tract in young children*. *J Clin Path* 20 : 561, 1967
  33. Adams JM, Imagawa DT, Zike K : *Relationship of pneumonitis in infants to respiratory syncytial virus*. *Lancet*, 81 : 502, 1961
  34. Ch'ien LT, Cannon NJ, Charamlla LJ, Dismukes WF, Whitley RJ, Buchanan RA, Alfore CA : *Effect of adenine arabinoside on severe herpes virus hominis infections in man*. *J Infect Dis* 128 : 658, 1973
  35. Mitchell CD, Gentry SR, Boen JR, Bean B, Groth KE, Balfour HH : *Acyclovir therapy for mucocutaneous herpes simplex infections in immunocompromised patients*. *Lancet* 1 : 1389, 1981
  36. Drew WL, Mintz L, Hoo R, Finley TN : *Growth of herpes simplex and cytomegalovirus in cultured human alveolar macrophages*. *Am Rev Respir Dis* 119 : 287, 1979