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## ARDS caused by herpes simplex virus pneumonia in a patient with Crohn's disease: a case report

Received: 14 June 1996  
Accepted: 30 October 1996

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**Abstract** Pneumonia caused by herpes simplex virus type 1 (HSV1) is rare and occurs in severely immunosuppressed patients. HSV1 can be detected in bronchoalveolar lavage (BAL) from patients presenting with respiratory failure, but its direct effect on disease is difficult to prove. We demonstrate the causative role of HSV1 in the case of a 44-year-old male with Crohn's disease who presented to the intensive care unit with the acute respiratory distress syndrome after surgery. BAL cells were cultured and immunofluorescence confirmed the presence of HSV1 during the first weeks

of illness. Increased IgG titers confirmed the diagnosis of a recurrent HSV1 infection. A lung biopsy specimen showed fibroproliferation without pathogens. Immunosuppressive therapy had been stopped and acyclovir was introduced at this time. The diagnostic difficulties in this patient underline the importance of early recognition of viral infection as a potential cause of severe pneumonia in severely ill, immunocompromised patients.

**Key words** Viral pneumonia · Immunosuppression · Complications

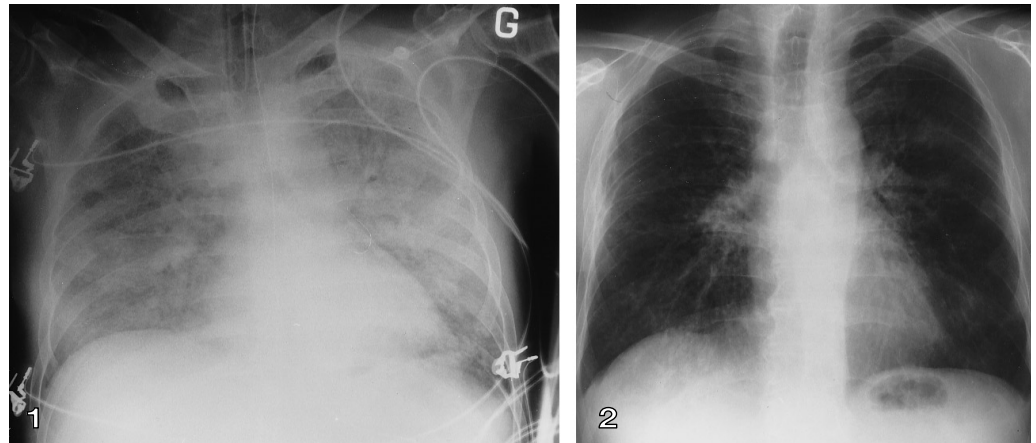
### Introduction

A large proportion of the adult population (> 85%) is serologically positive for herpes simplex virus type 1 (HSV1). As the virus remains in the latent form, infections can recur, but the incidence is low (33%) and the clinical manifestations are usually mild. However, severe disease can develop in immunosuppressed patients: herpetic tracheobronchitis and pneumonia have been described in patients severely immunosuppressed due to burns, malignancies, chemotherapy, transplantation, AIDS, and cell-mediated immunity deficiencies [1, 2]. Furthermore, HSV1 has been found (12%) in the lungs of patients presenting with severe respiratory distress [3–5].

In this report, we describe a patient with Crohn's disease who developed the acute respiratory distress syndrome (ARDS) due to pneumonia caused by HSV1.

### Case report

A 44-year-old Caucasian male, with a medical history of smoking, chronic bronchitis, spondyloarthritis, and Crohn's disease, had suffered numerous episodes of abdominal subocclusion and had undergone two intestinal resections. Despite an increase in immunosuppressive therapy during the previous 2 months (prednisone 50 mg/day and azathioprine 150 mg/day), the patient presented with a new acute episode of occlusion and needed ileocolic resection. Five days later, he developed dyspnea and fever without thoracic pain, and a left basal infiltrate was seen on chest X-ray, for which treatment with amoxicillin/clavulanate and netilmicin was started. Because of clinical deterioration, he was admitted to the intensive care unit (ICU) the next day (day 1). Clinical examination revealed malnutrition and rales in both lungs, a second chest X-ray showed diffuse bilateral alveolar infiltrates (Fig. 1). Arterial blood gas analysis showed severe hypoxemia at a fractional inspired oxygen (FIO<sub>2</sub>) of 0.3; pH 7.48; arterial carbon dioxide tension (PaCO<sub>2</sub>) 40 torr (5.3 kPa); arterial oxygen tension (PaO<sub>2</sub>) 50 torr (6.7 kPa); bicarbonate 28.5 mEq/l; base excess + 5 mEq/l; arterial O<sub>2</sub> saturation 85.5%. Other relevant laboratory data were a lymphopenia of 5%, with a total white blood cell count of  $9.8 \times 10^3/\text{mm}^3$ . Azathioprine was stopped and the patient was intubated.

**Fig. 1** Chest X-ray of the patient at admission to ICU**Fig. 2** Chest X-ray of the patient at discharge from the ICU**Table 1** Results of virological surveillance (*BAL* bronchoalveolar lavage, *ND* not done)

BAL (ICU days)	Herpes simplex detection by cell culture <sup>a</sup>	HSV1 detection by IF in BAL cells <sup>b</sup>	Antibody titers (CF) <sup>c</sup>	Antibody IgG titers (IF) <sup>d</sup>	Antibody IgM titers (IF) <sup>d</sup>
1	ND	Neg.	ND	ND	ND
2	Neg.	ND	ND	ND	ND
6	Pos.	100 %	< 1:10	1:20	Neg.
10	Pos.	75 %	ND	ND	ND
16	Neg.	25 %	1:20	1:160	Neg.
24	Neg.	ND	ND	ND	ND
26	ND	ND	1:320	1:2560	Neg.
33	Neg.	ND	ND	ND	ND
39	Neg.	ND	ND	ND	ND
45	ND	ND	> 1:320	ND	Neg.

<sup>a</sup> Isolation of herpesvirus was performed on human fibroblast and Vero cells. Typing was performed using monoclonal antibodies (Microtrak identification test from Syva, Thalwil, Switzerland)

<sup>b</sup> Direct detection of the virus in the cells from the BAL was done with the same reagents from Syva

<sup>c</sup> All sera tested by complement fixation (*CF*) were retested in parallel

<sup>d</sup> IgG and IgM titers against HSV1 were detected with the herpes immunofluorescence (*IF*) test kit from Gull Laboratories (Salt Lake City, Utah, USA)

Erythromycin was added to his treatment regimen for possible atypical pneumonia or legionella.

Because of the high suspicion of nosocomial infection and the lack of improvement under wide-spectrum antibiotic therapy, bronchoalveolar lavage (BAL) of the distal airways was regularly carried out to screen for pulmonary pathogens. Neither bacteria, mycobacteria, fungi nor *Pneumocystis carinii* were found, and the search for *Legionella* antigen in urine remained negative. Amoxicillin/clavulanate and netilmicin were stopped on day 7 and erythromycin on day 12. At this time, the culture of the BAL taken on day 6 was reported to be positive for HSV1. Despite the uncertainty of viral superinfection in our case, hydrocortisone was tapered off in order to restore natural host defense.

Subsequent analysis of BAL cells by immunofluorescence specifically confirmed the presence of HSV1 antigen on days 6, 10, and 16. The number of positive cells decreased until day 16. In addition, serological studies showed a sharp increase between days 16 and 45 by complement fixation and IgG increased between day 6 and day 26. The absence of IgM suggested that the patient was suffering from a recurrent virus (Table 1). The patient had no history of recurrent mucocutaneous infection.

On day 31, extension of pulmonary infiltrates, deterioration in gas exchange, and bleeding from esophageal erosions suggested a

recrudescence of HSV1 infection and treatment with acyclovir was started. Lung biopsy, performed by thoracotomy on day 51 because of lack of improvement, showed a nonspecific fibroproliferative pattern, with mild fibrosis and no pathogens. Sequential bacteriological analysis as well as serologies on days 6, 16, 26, and 45 for respiratory viruses (influenza A, B, parainfluenza types 1–3, adenovirus, respiratory syncytial virus), *Mycoplasma pneumoniae* and *Legionella* remained negative throughout the patient's clinical course. Tests for HIV antigen and antibody were negative.

Respiratory weaning was difficult and took 58 days until extubation was possible. The patient was discharged from the ICU on day 67, with pH 7.48, PaCO<sub>2</sub> 50 torr (6.7 kPa), PaO<sub>2</sub> 62 torr (8.3 kPa), bicarbonate 37.6 mEq/l, and arterial O<sub>2</sub> saturation 94 % at on FIO<sub>2</sub> of 0.25, and blood test results were in the normal range. Chest X-ray at this stage showed no infiltrates (Fig. 2), although the patient remained heavily dyspneic. His pulmonary function, tested 3 months later, revealed a severe restriction syndrome [vital capacity 1.5 l, total capacity 3.88 l (34 and 60 % of normal values, respectively), a ratio for vital capacity/forced expiratory volume in 1 s of 97 %, with a decreased diffusion capacity (DLCO of 27 % of normal value)].

## Discussion

In this patient, because of persistent ARDS and high fever, BAL of the distal airways was regularly carried out to screen for pulmonary pathogens. Virus cultures turned out to be positive for HSV1 only after day 12 on the BAL samples from days 6 and 10. Because herpesvirus pneumonia is rare, and the virus was detected late after the onset of ARDS, HSV1 was not at first considered to be the pathogen causing the pneumonia. Indeed, ARDS can be caused more commonly by nosocomial superinfections and the lack of sensitivity and specificity of BAL in patients taking antibiotics is well known.

Further analysis by immunofluorescence of the cells confirmed the presence of HSV1 antigen. The evolution of the serological results showed the actual immune response to HSV1 and confirmed this virus as the causative agent. The absence of IgM suggested a recurrence rather than a new infection. Furthermore, the virus disappeared when immunosuppressive treatment was stopped.

The clinical course was typical for ARDS with severe hypoxemia. An association between the detection of HSV1 and severe respiratory distress has been described by several authors [1, 4, 5]. Latent HSV1 can be reactivated by immunosuppression [4, 6–8] or surgery [5]. However, it can also occur in young immunocompetent men [9].

Our patient presented many known risk factors for HSV1 disease [10], i.e., immunosuppressive therapy,

malnutrition, mechanical ventilation, and a postoperative state with possible depressed cell-mediated immunity. The identification of these risk factors and the results of immunofluorescence and serology confirm the diagnosis of HSV1 pneumonia. The reestablishment of immunocompetency is usually sufficient to resolve herpes disease. However, recrudescence as esophageal ulceration needs to be treated. In these cases, acyclovir is the drug of choice, since it is effective and without known toxicity.

We don't know the reason why the lung biopsy in our patient was negative. However, among 20 patients with HSV1 pneumonia confirmed by autopsy, Ramsey et al. [4] reported that in six lung biopsy specimens the virus could not be found by either histologic examination or culture. They suggested that the tissue may have been obtained from an area free of herpesvirus infection or that the small amount of tissue obtained at biopsy did not contain a sufficient number of viral organisms to be detected by the techniques used.

In conclusion, this patient presented with an unusual type of pneumonia caused by herpes simplex virus. The immunosuppression, malnutrition, and previous surgery favored recurrence of the virus. The virus was isolated only after 2 weeks in sufficiently large amounts in early BAL samples. This case underlines the difficulties in diagnosing HSV1 pneumonia and emphasizes the importance of early investigation for viral infection as a potential cause of severe pneumonia in critically ill, immunocompromised patients.

## References

1. Tuxen DV, Cade JF, McDonald MI, Buchanan MRC, Clark RJ, Pain MCF (1982) Herpes simplex virus from the lower respiratory tract in adult respiratory distress syndrome. *Am J Respir Crit Care Med* 126: 416–419
2. Feldman S, Stokes DC (1987) Varicella zoster and herpes simplex virus pneumonia. *Semin Respir Infect* 2: 84–94
3. Prellner T, Flamholz L, Haidl S, Lindholm K, Widell A (1992) Herpes simplex virus – the most frequently isolated pathogen in the lungs of patients with severe respiratory distress. *Scand J Infect Dis* 24: 283–292
4. Ramsey PG, Fife KH, Hackman RC, Meyers JD, Corey L (1982) Herpes simplex virus pneumonia: clinical, virologic, and pathological features in 20 patients. *Ann Intern Med* 97: 813–820
5. Klainer AS, Oud L, Randazzo J, Freiteira J, Bisaccia E, Gerhard H (1994) Herpes simplex virus involvement of the lower respiratory tract following surgery. *Chest* 106: 8S–15S
6. Charasse C, Liégaux JM, Le Tulzo Y, Camus C, Thomas R, Cartier F, Ramée MP, André P (1992) Fatal co-infection with pulmonary tuberculosis and herpes simplex virus 1 pneumonia under steroid treatment. *Eur Respir J* 5: 108–111
7. Smyth RL, Higenbottam TW, Scott JP, Wreghitt TG, Stewart S, Clelland CA, McGoldrick JP, Walwork J (1990) Herpes simplex virus infection in heart-lung transplant recipients. *Transplantation* 49: 735–739
8. Caldwell JE, Porter DD (1971) Herpetic pneumonia in alcoholic hepatitis. *JAMA* 217: 1703
9. Martinez E, de Diego A, Paradis A, Perpina M, Hernandez M (1994) Herpes simplex pneumonia in a young immunocompetent man. *Eur Respir J* 7: 1185–1188
10. Camazine B, Antkowiak JG, Nava ME, Lipman BJ, Takita H (1995) Herpes simplex viral pneumonia in the postthoracotomy patient. *Chest* 108: 876–879