Herpes simplex pneumonia in a young immunocompetent man

E. Martinez*, A. de Diego*, A. Paradis**, M. Perpiñá*, M. Hernandez**

Herpes simplex virus (HSV) is a wide spread pathogen that has been isolated from nearly all visceral and mucocutaneous sites [1]. HSV infection of the lower respiratory tract may occur through extension of tracheobronchitis or from haematogenous dissemination of oral or genital mucocutaneous disease [2, 3]. Most cases have been reported in immunocompromised patients (HIV infection, recipients of bone marrow transplantation, malnutrition, malignancy, burns and the elderly), or in subjects with severe respiratory distress [4, 5]. However, recent studies [6] have shown that HSV can also be isolated from respiratory tract secretions in non-immunocompromised patients with prolonged requirement for mechanical ventilation. Documented cases are few, and are frequently based on autopsy data due to high mortality rates before acyclovir treatment was available.

We present the case of a young normal man with bilateral pneumonitis and severe hypoxaemia, caused by extension of primary herpetic bronchitis, which responded successfully to acyclovir treatment.

Case report

A 33 year old man was admitted to hospital because of progressive dyspnoea and fever. He had been well until two weeks previously when he began to have dry cough, headache, myalgia and malaise. Five days before admission, he experienced the onset of fever, that rose as high as 40°C, and increasing dyspnoea. He had no history of smoking, exposure to animals, recent travel, use of intravenously administered drugs, homosexual practices or blood transfusions. He had performed clerical work and his past clinical history was unrevealing, except for a depression that he had suffered in the last year, which was treated with benzodiazepines and tricyclic antidepressants.

On examination, the patient was sweaty, cyanotic and tachypnoeic at rest. The oropharynx was erythematous without exudates or vesicles. There was no rash or lymphadenopathy. Diffuse inspiratory crackles were heard in the lower lobes of both lungs. Heart, abdomen and genitalia were normal.

Temperature was 38.5°C, pulse rate was 110 beats·min⁻¹ and respiration rate was 40 breaths·min⁻¹. White cell count was 9.7 × 10⁹·l⁻¹, with 83% neutrophils, 9.3% lymphocytes (CD4: 1,110 × 10⁶ cells·l⁻¹ and CD4/CD8 ratio 1.09), and 0.2% eosinophils. The arterial blood gases whilst breathing room air showed: pH 7.48; arterial oxygen tension (PaO₂) 5.1 kPa and arterial carbon dioxide tension (PaCO₂) 5.3 kPa. Routine blood chemistry,
serum immunoelectrophoresis and urinalysis were normal. Bedside chest X-ray obtained on admission showed interstitial and alveolar infiltrates in the left lower lobe, and the left diaphragm was elevated (fig. 1). Parenteral erythromycin and cefotaxime were initially prescribed.

On the second hospital day, the dyspnoea worsened, the patient was admitted to the intensive care unit and an endotracheal tube was inserted. During assessed ventilation with 100% oxygen, PaO₂ was 8.2 kPa and PaCO₂ was 4.7 kPa. Fibreoptic bronchoscopy, 24 h after initiation of mechanical ventilation, showed hyperaemic mucosa in the main left bronchus. Microscopic examination of specimens obtained at bronchoalveolar lavage and bronchial brush showed no acid-fast bacilli, fungi, Legionella or Pneumocystis carinii; virus cultures for cytomegalovirus were negative. A sputum culture yielded a few colonies of Pseudomonas spp. that were sensitive to cefotaxime. Blood cultures were also negative. Tests for HIV antigen and antibody were negative. A tuberculin skin test (purified protein derivative (PPD) 2 IU) was negative, whilst a test with mumps antigen was positive at 48 h.

The patient did not improve on the following days, hypoxaemia persisted, and temperature rose to 39.5°C. On the fifth hospital day, a chest X-ray showed interstitial and alveolar bilateral infiltrates (fig. 2). Five days later, the patient remained febrile. Vancomycin and ciprofloxacin were added and cefotaxime was discontinued.

On the 15th hospital day, a second fibreoptic bronchoscopic examination revealed a narrowed and diffusely erythematous mucosa, with some ulcerated vesicles on the main left bronchus. Microscopic examination of a bronchial biopsy showed replacement of the epithelium by a fibrinopurulent exudate with necrotic cells (fig. 3a), as well as typical herpetic intranuclear changes, including ground-glass and Cowdry A type inclusions (fig. 3b). Immunoperoxidase staining using antibodies to herpes virus was positive.

On the 20th hospital day, treatment with acyclovir was initiated (10 mg·kg⁻¹ t.i.d. for one week) whilst erythromycin and vancomycin were discontinued. The patient did not receive steroids. Two days later, his temperature was normal and the symptoms improved, being successfully weaned from ventilatory assistance, 20 days after he was admitted to the intensive care unit. On the 22nd hospital day, ciprofloxacin was discontinued. On the following week, a chest X-ray showed clearing of the infiltrates (fig. 4) and acyclovir was discontinued. On the 30th hospital day, a repeated bronchoscopy was normal and biopsy specimens from the left bronchus failed to show intranuclear inclusions.

Seroconversion to herpes virus (titre increases from 1:1000 to 1:1,800) but not to other virus (cytomegalovirus, respiratory syncytial, influenza, adenovirus, Varicella or Epstein-Barr), Chlamydia, Mycoplasma, Legionella or Rickettsias helped to confirm the diagnosis. A complete study of cellular and humoral immunity was performed, which was normal.

Three months after discharge, the patient was asymptomatic and a repeated HIV test was also negative.
Herpes simplex pneumonitis was first described in 1949 [7]. It has been considered as a rare entity and has been reported only in immunosuppressed patients. Pulmonary HSV infection has frequently been associated with intubation or mechanical ventilation in subjects with chronic disorders [5]. The cause may be that HSV usually infects squamous epithelium; therefore, only those factors that produce squamous metaplasia of the tracheobronchial tree, as occurs in endotracheal intubation, would lead to lower respiratory tract infection.

To our knowledge, there are few studies of immunocompetent patients with herpetic pneumonitis [3, 6, 8]; most of which were reported in elderly subjects or in patients with chronic underlying disorders. Recently, Schuller et al. [6] have published a retrospective review of HSV infection in immunocompromised and nonimmunocompromised hosts; they found that nonimmuno-compromised subjects were 20 yrs older and had more severe underlying disease than immunocompromised patients; in addition, HSV infection was associated with higher morbidity and mortality, as well as longer stays on mechanical ventilation when it occurred in the nonimmunocompromised host.

HSV lower respiratory tract infection can present either as focal necrotizing pneumonitis through extension of herpetic tracheobronchitis, or as disseminated pneumonia due to haematogenous dissemination from oral or genital mucocutaneous disease. Clinically, the patients have fever above 38.5°C, cough, dyspnoea and mucocutaneous lesions, which appear after or at the same time [3].

In the present case, both herpetic tracheobronchitis and pneumonia co-existed without mucocutaneous lesions. It could be argued, as has been previously reported [5, 6, 9], that tracheal intubation could predispose to dissemination of infection, but in our case, radiological and clinical findings were previous to the intubation procedure.

The diagnosis of HSV pneumonia is usually based on cytological and histological findings and confirmed by viral culture or serological methods. Tissue culture is the most sensitive and specific diagnostic test [10]. Pathologically, HSV infection is located mainly in the trachea and large bronchi, and manifested by focal or diffuse ulcers and deposits of fibrinous exudate. Parenchymal involvement is characterized by nodular or confluent necrotic foci in the lung, with ghost of alveolar septa and eosinophilic, proteinaceous exudate containing necrotic neutrophils and cellular debris [3, 9].

Cytological features characteristic of HSV infection can be located at the margins of ulcers or in the alveolar cells. They include small eosinophilic intranuclear inclusions separated from the surrounding nuclear chromatin by a clear halo (Cowdry type A inclusions), and single or multinucleated cells with ground-glass changes in the nuclei involved [2, 10]. In our case, diagnosis was based on cytological and histological findings of bronchial mucosa and confirmed by a significant rise in HSV antibody titres.

Acyclovir or vidarabine treatment, as well as other supportive measures such as oxygen or ventilatory support, have been recommended. Today, acyclovir (800 mg oral 5 times a day for one week, or 10–15 mg·kg⁻¹ t.i.d for one week) is considered to be the treatment of choice [10]. When given early, it alters the course of infection, improving the survival and shortening the evolution. In the present case, acyclovir reversed clinical and pathological findings in a few days.

We conclude that HSV infection has to be considered in nonimmunosuppressed patients with pneumonitis and severe hypoxaemia who do not respond to conventional treatment. Prompt recognition and institution of acyclovir treatment may improve the course of infection.

References

4. 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 1982; 126: 416–419.
7. Morgan HR, Finland M. Isolation of herpes virus from...
a case of atypical pneumonia and erythema multiforme
exudativum: with studies of four additional cases. *Am

8. Russler SK, Tapper MA, Knox KK, Liepins A, Carrigan
DR. Pneumonitis associated with co-infection by human
herpes virus 6 and Legionella in an immunocompetent

9. Nash G, Foley FD. Herpetic infection of the middle and
lower respiratory tract. *Am J Clin Pathol* 1970; 54:
857–863.

10. Strauss SE, Rooney JF, Sever JL, Seidlin M, Nusinoff-
Lehrman S, Cremer K. Herpes simplex virus infection:
103: 404–419.