High dose intravenous methylprednisolone in the treatment of severe acute respiratory syndrome

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The case of a 72-year-old woman with probable severe acute respiratory syndrome is reported. While on treatment with ribavirin and antibiotics (for community-acquired pneumonia), the patient continued to have progressive clinical deterioration and chest radiographic evidence of respiratory deterioration. Pulse dose intravenous corticosteroids were used in an unsuccessful attempt to treat the inflammatory component of this respiratory illness.

Key Words: *Acute respiratory distress syndrome; Atypical pneumonia; Corticosteroids*

Severe acute respiratory syndrome (SARS) is becoming a worldwide infectious disease. This is a report of a tertiary case of probable SARS with treatment using pulse methylprednisolone.

CASE PRESENTATION

A 72-year-old woman was assessed at the Toronto General Hospital (Toronto, Ontario) for fever. Her past medical history included hypertension and hypercholesterolemia. She had a remote 30-pack year history of smoking. Three weeks before presentation, her husband presented to the emergency department with rapid atrial fibrillation. He was discharged from the emergency department after treatment, but returned nine days later with a febrile illness and respiratory symptoms consistent with SARS. Subsequently, it was determined that the person adjacent to his journey during his initial visit was a member of the SARS index family in Toronto (1). Seven days after his admission, he died of respiratory failure.

Our patient was treated prophylactically with oseltamivir phosphate and doxycycline hyclate. While in home isolation, she developed fever and was followed closely by the Public Health Department. The fever continued for two weeks before admission. Five days before admission, she developed nausea, watery diarrhea, anorexia and significant malaise. When she presented to hospital, her complaints were intractable fever and malaise.

On admission, her heart rate was 80 beats/min and regular, blood pressure was 130/80 mmHg, respiratory rate was 16 breaths/min, oxygen saturation was 91% on room air and temperature was 38.9°C. Bibasilar crackles were present on auscultation of the chest. The remainder of the physical examination was normal.

La méthylprenisolone intraveineuse à forte dose dans le traitement du syndrome respiratoire aigu sévère

On fait état ici du cas d'une femme de 72 ans atteinte d'un syndrome respiratoire aigu sévère probable. Alors qu'elle était traitée par ribavirine et antibiotiques pour une pneumonie extra-hospitalière, l'état de la patiente a continué de se détériorer, radiographies à l'appui. Des corticostéroïdes intraveineux en doses pulsées ont été utilisés sans succès pour tenter de traiter la composante inflammatoire de cette maladie.

Laboratory studies revealed: white blood cell count $5.96 \times 10^9/L$, absolute neutrophil count $4.18 \times 10^9/L$, absolute lymphocyte count $1.54 \times 10^9/L$, hemoglobin 134 g/L, platelet count $191 \times 10^9/L$, sodium 124 mM, potassium 2.7 mM, creatinine 98 µM, creatine kinase 429 U/L and lactate dehydrogenase 490 U/L. The rest of the laboratory studies were unremarkable. Her arterial blood gas measurements were: pH 7.55, partial pressure of arterial oxygen 66 mmHg and partial pressure of arterial carbon dioxide 28 mmHg. The electrocardiogram and chest radiograph (Figure 1) were normal on admission.

Initial therapy consisted of intravenous (IV) ribavirin – 2 g as a loading dose, followed by 1 g every 6 h for four days, followed by 0.5 g every 8 h for three days. She was also treated with a 14-day course of gatifloxacin. She became afebrile on day 3. However, disease progression was evident on serial chest radiographs. A right mid-upper lung infiltrate occurred on day 2 of admission.

By day 6, she developed a dry cough and was becoming increasingly dyspneic. She asked that neither invasive ventilation nor cardiopulmonary resuscitation be undertaken. By day 10, she required 100% oxygen by face mask, and her chest radiograph revealed extension of the disease to her left lung. Therapy with IV methylprednisolone (60 mg daily) and meropenem (empirically, for extended broad-spectrum antibiotic coverage) was initiated.

After there was no clinical improvement by day 14 and progression of the disease on the chest radiograph (Figure 2), pulsed 250 mg IV methylprednisolone daily for three days followed by 60 mg IV methylprednisolone daily was given. In addition, oral ribavirin was reinitiated at 800 mg three times daily. Her clinical course stabilized until day 19, but she

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Figure 1) Normal chest x-ray (day 1)

remained on 100% fractional inspired oxygen. On day 21, she died from a respiratory arrest. The autopsy findings were consistent with acute respiratory distress syndrome.

DISCUSSION

SARS has become a global health issue. A novel coronavirus has been implicated as the etiological agent (1-4). To date, there is no known effective treatment. Ribavirin IV, corticosteroids and broad-spectrum antibiotics have been tried (1,4). It has been recognized that advanced age, specific laboratory indexes and pre-existing comorbidities predispose patients to worse outcomes. To our knowledge, this is the first report of high dose IV corticosteroid treatment of SARS outside of Hong Kong.

The most important risk factor for the development of SARS is close contact with a patient that has active disease (febrile illness) (1-4). We were not able to isolate coronavirus from our patient. However, she had had extensive exposure to her husband who had died of SARS before the implementation of isolation for patients with suspected or probable disease. In addition, she had visited the index hospital multiple times before the implementation of isolation and screening. Finally, she developed a febrile illness at a time after exposure that was consistent with SARS. There are several possible reasons for the lack of coronavirus isolation in our patient. First, there was no invasive procedure (ie, bronchoscopy) done early in the course of her illness. Second, at the time of autopsy, a significant period of time had passed since her febrile illness. Third, with current techniques, coronavirus is not isolated from every patient with SARS. Throughout her illness, multiple cultures of different sites did not show any other infection that could explain her symptoms.

Her course was characterized by an early febrile phase, followed by respiratory deterioration in the second to third week. SARS has been characterized by an early febrile illness followed by remission and subsequent development of respiratory illness in the second week in a few patients (1,4).

Corticosteroids decrease inflammation, which is one of the major obstacles to healing from acute lung injury.

Figure 2) Progressive diffuse bilateral disease (day 14)

Corticosteroids have been used in the treatment of other acute severe respiratory illnesses with acceptable results. These include bronchiolitis obliterans organizing pneumonia (5) and acute respiratory distress syndrome (6), caused by unresolving bacterial pneumonia, septic shock and aspiration. Some patients with SARS develop diffuse lung infiltrates late in the course of their illnesses, which may be consistent with an inflammatory response to the original infection. The present study indicates that this may not be responsive to steroids.

Our patient was at high risk of developing severe disease because of her age and biochemical abnormalities. She developed diffuse lung infiltrates and hypoxemia late after admission, while having no symptoms or signs of infection. High dose IV corticosteroids were used in an attempt to reverse the inflammatory process. This approach has been used successfully in treating some SARS patients in Hong Kong (4). Further investigations are needed to determine the role of pulse dose corticosteroids in patients with SARS.

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