VWS Wong 黃煒燊
D Dai 戴樂群
AKL Wu 胡家倫
JJY Sung 沈祖堯

Treatment of severe acute respiratory syndrome with convalescent plasma

用康復者血漿治療嚴重急性呼吸系統綜合症

In March 2003, an outbreak of severe acute respiratory syndrome started in Hong Kong. A 57-year-old woman had a typical presentation, including fever, non-productive cough, malaise, lymphopenia, and raised liver aminotransferases. The clinical course and successful treatment with convalescent plasma, ribavirin, and corticosteroids are discussed.

2003 年 3 月嚴重急性呼吸系統綜合症在香港爆發。一名 57 歲女性出現此病的典型症狀，包括發燒、乾咳、全身乏力、淋巴細胞減少和肝轉氨酶上升。本文討論了患者的臨床治療過程，以及使用康復者血漿、利巴韋林和皮質類固醇的成功治療病例。

Case report

A 57-year-old woman was admitted to the Prince of Wales Hospital in March 2003 because of fever. She had good past health, and had been visiting her husband who was a patient in the Prince of Wales Hospital from mid-February to mid-March, 2003. Her husband was being treated in a bed next to a man with pneumonia, who was later confirmed to be the index case causing the outbreak of severe acute respiratory syndrome (SARS). The woman developed fever and chills in mid-March 2003. She also complained of myalgia and headache involving the whole head. She only had an occasional non-productive cough and no shortness of breath. She could walk more than 500 m on level ground without difficulty. There were no urinary or bowel symptoms. She had not recently travelled outside Hong Kong. She denied direct contact with the SARS index case. Her husband subsequently died of congestive heart failure, but had no features of SARS.

At admission to hospital, her temperature was 39.5°C. She was haemodynamically stable. The chest was clear on auscultation. No bronchial breath sound or percussion dullness was noted.

Chest X-ray was performed on the day of admission, which demonstrated infiltrative shadows in the periphery of bilateral lower zones (Fig 1). Her urea and electrolytes were normal. Alanine aminotransferase level was elevated at 216 U/L (reference level, <58 U/L). Creatine kinase level was 418 U/L (reference range, 32-180 U/L). Her haemoglobin level was 117 g/L (reference range, 120-150 g/L), the platelet count was within the reference range at 344 $x10^9$/L, as was her white blood cell count at 6.5 $x10^9$/L, with lymphopenia of 0.4 x 10^9/L. Routine sputum culture was negative. Nasopharyngeal aspirate did not isolate influenza A, influenza B, or respiratory syncytial virus. Serological tests for *Mycoplasma pneumoniae*, *Chlamydia psittaci*, Legionella, *Coxiella burnetii*, adenovirus, and respiratory syncytial virus were negative. Thus, the patient fulfilled the case definition of SARS by the World Health Organization.

She was treated with intravenous cefotaxime 3000 mg per day, oral levofloxacin 500 mg per day, and oseltamivir 150 mg per day. She remained febrile, however, and there was no improvement in chest X-ray. On day 3, oral ribavirin 3600 mg per day and prednisolone 1 mg/kg/day were substituted for the previous medications. The fever subsided during the next 3 days

Key words:
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關鍵詞：
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Department of Medicine and Therapeutics, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, Hong Kong
VWS Wong, MB, ChB, MRCP
D Dai, MB, BS, FRCP
AKL Wu, MB, ChB, MRCP
JJY Sung, MD, PhD

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Correspondence to: Dr VWS Wong

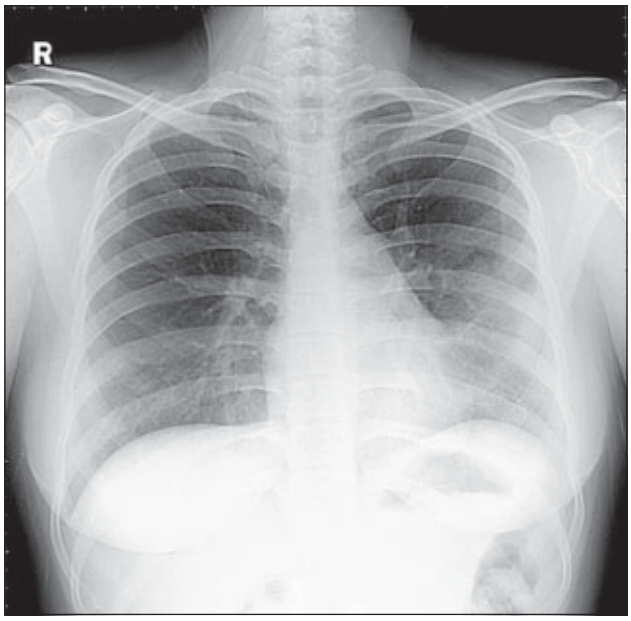

Fig 1. Chest X-ray at admission to hospital in March 2003

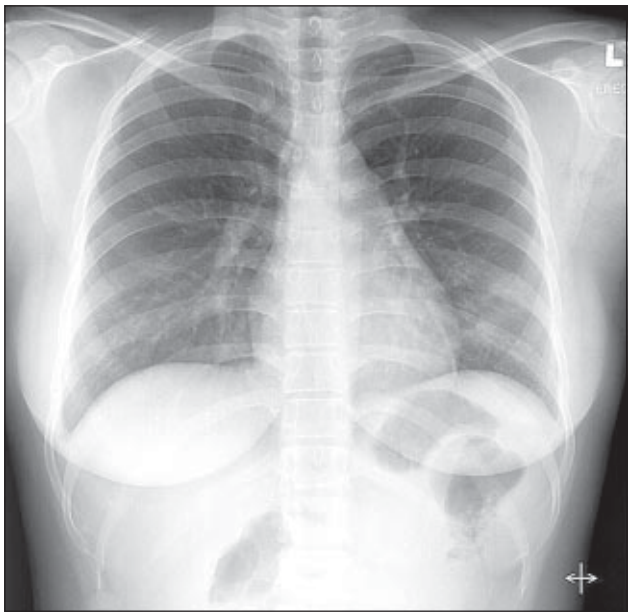

Fig 3. Chest X-ray 2 weeks later

(Fig 2). Chest X-ray also showed resolution of consolidation, but lymphopenia persisted (range, 0.2-0.5 x 10^9/L).

On day 14, the patient had a relapse of low-grade fever to 37.9°C. She was otherwise asymptomatic. She did not have shortness of breath, chills, or rigors. The respiratory rate was 18 breaths per minute. Sepsis work-up was negative. C-reactive protein was 3.7 mg/L (reference level, <9.9 mg/L), a low value not suggestive of bacterial infection. Chest X-ray showed increased alveolar shadows at the right lower zone and she was considered to have residual disease from SARS. She was given two doses of intravenous methylprednisolone 500 mg 1 day apart, followed by 200 mL of plasma donated by SARS patients in their convalescent phase. No adverse reaction occurred after administration of convalescent plasma. The fever subsided, chest X-ray showed further resolution of basal lung infiltrates (Fig 3), and she made an uneventful recovery.

Discussion

From November 2002 to April 2003, more than 1800 people are reported to have contracted SARS, resulting in 62 deaths. This patient fulfilled the case definition for SARS by the World Health Organization and had a typical presentation. Most patients have had fever and chills.[1-3] Non-productive cough, dyspnoea, and malaise are also common symptoms. Respiratory symptoms can be surprisingly minor, while severe respiratory failure requiring mechanical ventilation can occur. Common laboratory findings including lymphopenia, and raised liver aminotransferases were also found in this patient.

Interestingly, despite initial improvement with oral antiviral and steroid agents, this patient had an exacerbation of disease in the second week of treatment. After aggressive immunomodulatory therapy, the patient improved and made

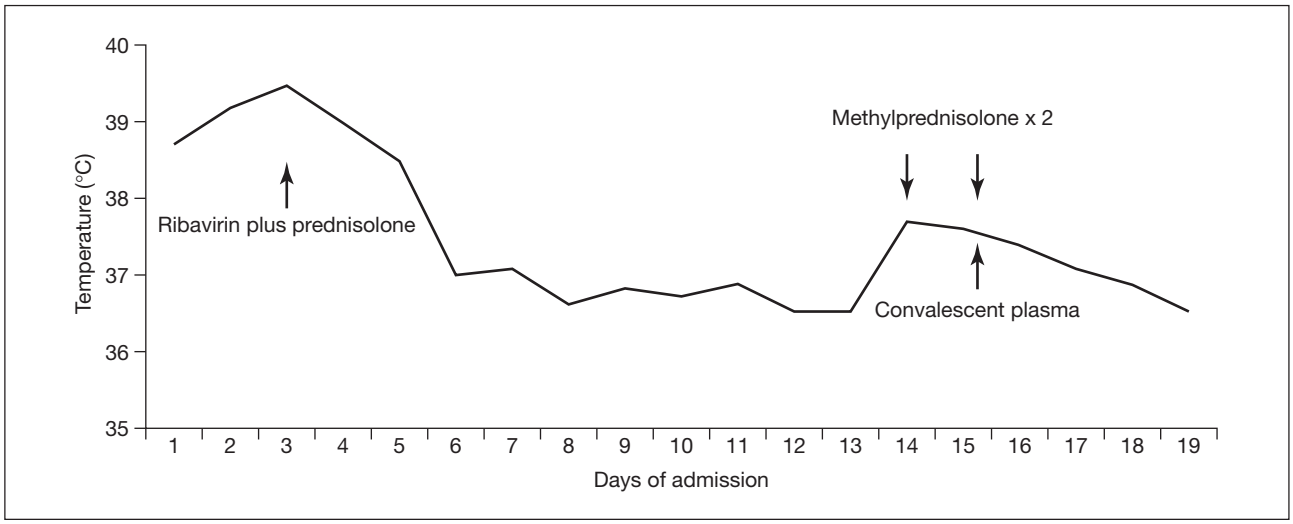

Fig 2. The fever profile of the patient during admission
Arrows indicate the time when specific treatments were administered

an uneventful recovery. Of particular note is the persistent lymphopenia, which may be an indication of persistent disease activity. Careful monitoring of clinical, radiological, and haematological parameters is essential to detect early relapse.

This patient demonstrated probable therapeutic benefits of ribavirin, convalescent plasma, and corticosteroids. The aetiological agent of SARS is still under investigation. So far, a novel coronavirus and human metapneumovirus have been identified in the respiratory specimens of some patients.[2] The significance of either virus needs further clarification. Ribavirin, a broad-spectrum antiviral agent for a variety of DNA and RNA viruses, may be useful in reducing viral load.[4] Another way to reduce viral load is to administer immunoglobulins against the virus. Plasma obtained from patients recovering from SARS potentially contains immunoglobulins against the virus. For this patient, the fever decreased after administration of convalescent plasma. Specific immunoglobulins are often administered for the prevention rather than treatment of viral infections, however. For example, respiratory syncytial virus immunoglobulins have reduced the necessity for admission to hospital due to respiratory syncytial virus infection by 41% for infants who are at high risk for the disease.[5] The timing and mechanism of action of convalescent plasma in SARS warrants further studies.

Autopsy of patients dying from SARS shows extensive alveolar damage and inflammation. Features mimicking bronchiolitis obliterans organising pneumonia have also been noted on computed tomography in some patients. From initial clinical experience, SARS can develop in stages, including acute constitutional symptoms, acute viral pneumonitis, acute lung injury, and even acute respiratory distress syndrome, evolving over 1 to 2 weeks. Initial infection followed by a hyperactive immune response appears to underlie the severe manifestations of SARS. Therefore, corticosteroids are used to dampen excessive lung damage due to an inflammatory response. Anecdotal experience shows improvement for a number of patients after high-dose corticosteroids.

In conclusion, this report is of a woman with typical features of SARS who demonstrated a favourable response to ribavirin, convalescent plasma, and corticosteroids.

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