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Clinical Presentation and Outcome of Severe Acute Respiratory Syndrome in Dialysis Patients

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● There was a major outbreak of severe acute respiratory syndrome (SARS) affecting more than 300 patients occurring in a private housing estate in Hong Kong, in which an infected renal patient was suspected to be the primary source. It is unknown whether renal patients would represent a distinct group of patients who share some characteristics that could predispose them to have higher infectivity. In this context, we have encountered 4 dialysis patients contracting SARS in a minor outbreak, which involved 11 patients and 4 health care workers, in a medical ward of a regional hospital. Of these 4 dialysis patients, 1 patient was receiving hemodialysis while the other 3 patients were on continuous ambulatory peritoneal dialysis. Fever and radiological changes were their dominant presenting features. All were having positive results for SARS-associated coronavirus ribonucleic acid by reverse transcriptase–polymerase chain reaction performed on their nasopharyngeal aspirates or stool samples. It appeared that treatment with high-dose intravenous ribavirin and corticosteroids could only resolve the fever, but it could not stop the disease progression. All 4 patients developed respiratory failure requiring mechanical ventilation on days 9 through 12. At the end, all of the patients died from sudden cardiac arrest, which was associated with acute myocardial infarction in 2 cases. From this small case series, it appeared that dialysis patients might have an aggressive clinical course and poor outcome after contracting SARS. However, a large-scale study is required to further examine this issue, and further investigation into the immunologic abnormalities associated with the uremic state in this group of patients is also warranted. Am J Kidney Dis 42:1075-1081.

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INDEX WORDS: Severe acute respiratory syndrome (SARS); dialysis; presentation; outcome.

M ANY COUNTRIES in the world have been seriously affected by the outbreaks of severe acute respiratory syndrome (SARS) since March 2003.1 It is a new emerging infectious disease with a novel coronavirus being identified as the causative agent.2,3 Hong Kong has been one of the most severely affected areas.4,5 Of the 1,755 cases reported in Hong Kong so far, 321 cases originated from a major outbreak in Amoy Gardens, a high-rise and densely populated private estate.6 An epidemiological investigation has linked the outbreak to a faulty sewage system. The system was probably contaminated by the excreta of an index case who was a patient with chronic renal disease on dialysis. While the exact spreading mechanism remains uncertain, it has been speculated that a patient having renal failure might carry an extraordinarily high viral load, which could lead to a large outbreak. It would also be interesting to know whether the clinical course and outcome of a renal patient having SARS would be different from that of other SARS patients. In this regard, we have encountered a minor SARS outbreak occurring in a ward of a regional hospital involving 11 patients and 4 health care workers. All of the cases fulfilled the modified World Health Organization (WHO) definition of SARS.2 Of these 11 patients, 4 were on dialysis. We have therefore taken the opportunity to examine the clinical courses and outcomes of these patients to see whether they represent a distinct patient group.

PATIENTS AND RESULTS

Setting

Kwong Wah Hospital is a major regional acute hospital in Hong Kong with over 1,200 beds. The SARS outbreak occurred in 1 of the general medical wards. The medical ward involved comprises 56 medical beds and a hemodialysis facility (Fig 1). The 56 medical beds spread over 9 rooms.
(6 for women and 3 for men). Each room could accommodate 4 to 10 patients. Common patient areas in the ward include the main corridor and toilet facilities (1 for men and 2 for women). All of the rooms share a common ventilation system with the ventilation duct outputs located at the ceiling (Fig 2). During the outbreak, the ventilation facility was providing 6 air changes per hour (ACH) with no high-efficiency particulate air (HEPA) filter in use.

Case Descriptions

The outbreak involved 11 female patients and 4 women health care workers. All of the SARS patients fulfilled the modified WHO definition of SARS. The mean age of the 11 patients was 66.3 ± 13.5 years (median, 68 years).

The First SARS Patient

The first SARS patient, a 57-year-old woman with no known contact with SARS patients, was admitted to room 8 of the ward on March 23, 2003, for some minor respiratory symptoms and fever. At that time, droplet precautions and contact precautionary measures were already implemented in the ward. The patient was subsequently transferred to the isolation ward on March 25, 2003, for suspected SARS infection. Her 6 roommates were then cohorted as suspected SARS contacts. The cohorting was intended to last for 10 days, during which time no new patients would be admitted to the same room or transferred out to another room and ward. During that period, anyone who developed suspicious symptoms of SARS was transferred to the isolation ward immediately. At the end, 4 of her 6 roommates and 2 health care workers having contact with the patient developed SARS (Fig 3). The 4 roommates who developed SARS were 46, 74, 81, and 87 years old, respectively. In addition, the first SARS patient probably also infected patient 1, who at that time was staying in room 6, through contact in the common patient areas.

Patient 1

Patient 1 was a 44-year-old diabetic woman who was newly diagnosed to have end-stage renal failure. She was admitted to room 6 of the ward because of uremic symptoms in February 2003. After staying in the hospital for about 1 month, she was stabilized with regular hemodialysis and was discharged on March 26, 2003. During the hospitalization, none of her roommates in room 6 suffered from SARS, but the first SARS patient was admitted to room 8 3 days.
before patient 1 was discharged from the hospital. Two days after her discharge from the hospital, she was readmitted to room 6 again because of fever, chills, and rigors. On admission, she was advised to put on a surgical mask, although she showed no symptom of upper respiratory tract infection other than fever. Her initial chest radiograph revealed an ill-defined right lower zone air-space opacity, which rapidly worsened after admission. She was then transferred to the isolation ward after staying in the original ward for 46 hours. Her 7 roommates were then cohorted for suspected SARS contacts. At the end, she (patient 1) was confirmed to have SARS, and 5 of her 7 roommates were also found to have SARS (Fig 4). The ages of these 5 patients varied from 60 to 74 years. Of these 5 cases, 3 were renal patients receiving chronic ambulatory peritoneal dialysis (CAPD) who had stayed in the same room with patient 1 for 12, 46, and 45 hours, respectively. Their times to first development of symptoms of SARS after the last exposure varied from 4 to 8 days. In addition, another 2 health care workers who had been exposed to patient 1 subsequently also developed SARS.

**Infection Control Measures**

After the outbreak, the movement of patients in the ward was stopped. All of the patients in the ward were closely monitored for clinical features of SARS. No visitors to the ward were allowed. A list of potential SARS contacts related to that ward was generated, and it was sent to the Department of Health of the Government for contact tracing and monitoring. All staff of the ward were required to monitor themselves for SARS, and all clinical staff were reminded to look out for suspected SARS cases to facilitate early identification and isolation. Infection control precautions were stepped up to the level of airborne precautions. Disposable gowns, caps, and gloves were used for direct patient care. Rooms 6 and 8 were thoroughly cleansed. Additional exhaust fans were installed for all patient rooms in the ward, after which the airflow rates of these patient rooms were increased to greater than 12 ACH.

After being diagnosed with SARS, patient 1 was hemodialyzed in an isolated area within the dialysis facility where the ventilation could provide 12 ACH. The hemodialyzers were not reused. Because the 3 CAPD patients were too weak to perform the CAPD exchanges themselves, they were switched to twice weekly intermittent peritoneal dialysis (IPD) using automated peritoneal dialysis machines (Home choice; Baxter Healthcare, McGraw Park, IL) to minimize staff exposure to the patients. Each IPD comprised 30 1-hour cycles of 2-L exchanges of 1.5%, 2.5%, or 4.25% dextrose solution, depending on the hydration status of the patients. Although we had not sent the spent dialysate for SARS-associated coronavirus study, all the body fluids of suspected or confirmed SARS-infected dialysis patients including the spent dialysate were regarded as potentially infectious and were handled with special precautions. The staff members who needed to handle or dispose the spent dialysate and those who conducted the CAPD exchanges or hemodialysis procedures for suspected or confirmed patient were protected with N95 respirators, eye shields, and disposable gowns, caps, and gloves. To minimize transport of potential infectious material, the drainage bags of spent peritoneal dialysate were emptied into the sink of the sluice room of the ward where the patients stayed. All the disconnected drainage bags were recapped to avoid leakage and were kept in a

**Fig 4. Diagram showing the bed locations of the SARS patients related to the readmission of patient 1 in room 6.**
covered container while pending disposal. For IPD, the pails used to receive and hold the spent dialysate were previously filled with 500 mL of hypochlorite solution. Extra precautions were also taken to avoid splashing during the emptying process, after which a large amount of hypochlorite solution was poured into the sink and left for 15 minutes before flushing. There were no more local transmission of SARS reported in the ward after the implementation of these measures.

Clinical Courses and Outcomes

Finally, 6 of the 11 patients (54.5%) involved in the outbreak died, while all 4 health care workers (27 to 55 years of age) survived and recovered. The 6 deceased patients included the 4 dialysis patients from room 6 and 2 patients from room 8. The 2 deceased patients from room 8 included the first SARS patient, who subsequently died of secondary sepsis and multiorgan failure following acute respiratory distress syndrome, and the 74-year-old woman, who died of superimposed severe bacterial pneumonia. With the exception of the first SARS patient who developed acute renal failure as a part of the manifestations of multiorgan failure, there had not been any significant change observed in the renal function of the SARS-affected individuals not on dialysis throughout their courses of illness.

The 4 SARS-affected dialysis patients all fulfilled the modified WHO definition of SARS. Fever was their dominant symptom (Table 1). They were all ethnic Chinese women ranging from 44 to 73 years of age. All were patients on CAPD, except for patient 1. Their durations of dialysis ranged from 1 to 104 months. Three were diabetic. None of them had a known history of ischemic heart disease, and they were all hepatitis B surface antigen negative. They were all nonsmokers. Patient 2 was originally admitted for vomiting after taking medications for the treatment of tuberculous lymphadenitis. Patient 3 was admitted for the treatment of CAPD peritonitis, which resolved during the cohorting period before she developed SARS. Patient 4 was admitted for mild hyperkalemia after an excessive ingestion of fruits. They all had fever \( >38^\circ C \) as the only initial presenting symptom of SARS, except for patient 4, who also complained of cough and sputum on presentation. None of them complained of myalgia or headache. Nevertheless, 3 patients

| Patient | Age (y) | Sex (M/F) | Mode of dialysis | Duration on dialysis (mo) | Significant comorbidity other than renal failure | Duration of exposure (h) | Time to the onset of symptom (d) | Clinical features | Laboratory findings before treatment with steroids and ribavirin |
|---------|---------|-----------|------------------|--------------------------|-----------------------------------------------|-------------------------|-------------------------------|-------------------|-------------------------------------------------------------|
| 1       | 44      | F         | HD               | 1                        | DM                                            | Index case of room 6     | 4                             | Fever             | Neutrophil count \( \times 10^9/L \) 2.6                    |
| 2       | 67      | F         | CAPD             | 12                       | DM, tuberculous lymphadenitis                  | 12                      | 5                             | Chills/rigors      | Lymphocyte count \( \times 10^9/L \) 0.7                       |
| 3       | 73      | F         | CAPD             | 104                      | DM                                            | 46                      | 8                             | Myalgia           | Platelet count \( \times 10^9/L \) 165                      |
| 4       | 71      | F         | CAPD             | 28                       | –                                              | 45                      | 8                             | Dyspnea           | Serum LDH (U/L)* 383                                      |

NOTE. To convert platelets in \( \times 10^9/\mu L \) to \( \times 10^9/L \), multiply by 1.
Abbreviations: DM, diabetic; LDH, lactic dehydrogenase; ALT, alanine aminotransferase; HD, hemodialysis.
*Normal range, 94 to 250 U/L.
†Normal range, 1 to 30 U/L.
(patients 1, 2, and 3) developed watery diarrhea up to 6 times per day 2 to 9 days after the onset of fever.

All of their initial chest radiographs showed localized air-space infiltrate or consolidation on presentation. There were 2 different patterns of radiological progression observed. While patient 1 showed progressive worsening and increasing in the air-space opacities, patients 2, 3, and 4 demonstrated another distinct pattern in their radiological changes. These 3 patients (patients 2, 3, and 4) also started with focal air-space consolidations on day 1 corresponding to the onset of fever (Fig 5A). Nevertheless, there was complete or partial resolution of the initial shadows on day 3, even before the commencement of specific antiviral and corticosteroid therapy (Fig 5B). The improvement, however, rapidly reversed afterwards, with worsening of the initial lesions, appearance of new opacities, and relentless progression to diffuse bilateral air-space opacification simulating acute respiratory distress syndrome (ARDS) (Fig 5C).

We treated all 4 patients with corticosteroids, ribavirin, and antibacterial agents, which was the prevalent standard treatment for SARS in Hong Kong at that time. They were treated initially with a combination of broad-spectrum antibiotics (intravenous meropenam or amoxycillin/clavulenate, plus levofloxacin or a second-generation macrolide), which was then followed by intravenous corticosteroids (hydrocortisone or methylprednisolone) and ribavirin therapy.

Prior to the commencement of corticosteroids and ribavirin, 3 patients had lymphopenia (0.6 to 0.7 × 10^9/L). No thrombocytopenia was observed. Their pretreatment serum lactate dehydrogenase ranged from 223 U/L (223 IU/L) to 503 U/L (503 IU/L), and only patient 2 had a slight increase in serum alanine aminotransferase level. No bacterial, fungi, mycoplasma, chlamidia, or common respiratory viruses were detected by the laboratory investigations. SARS-associated coronavirus ribonucleic acid (RNA) was detectable using reverse transcriptase–polymerase chain reaction (RT-PCR) in nasopharyngeal aspirate samples in all 4 patients on days 2 through 5 and in fecal samples in 3 patients (patients 1, 2, and 4) on days 2 through 9. All of the specimens were collected and sent fresh to a local government laboratory for analysis on the same day. The details of the methodology of the test had been described in a previous report, and the turnaround time was about 1 to 2 days. In addition, patient 1 also showed a more than 4-fold increase in the antibody titer for the SARS-associated coronavirus.

Regardless of the dosing and timing of administration, the clinical responses of the 4 renal patients to the combination therapy with ribavirin and corticosteroids had been consistently poor (Table 2). The treatment had been started between days 2 and 8. Two different dosing regimens of ribavirin were tried. Two patients (patients 1 and 2) received 4 mg/kg ribavirin thrice daily while the other 2 patients (patients 3 and 4) received 8 mg/kg ribavirin thrice daily. Patients 3 and 4 also received a higher daily dose of corticosteroids (4 mg/kg hydrocortisone every 4 hours or 15 mg/kg methylprednisolone daily) compared with patients 1 and 2 (4 mg/kg hydrocortisone every 6 hours). Although they all had their fever completely resolved within 48 hours, there had been no parallel response in the other clinical parameters, including radiological shadows and oxygen saturation. They all required endotracheal intubation for mechanical ventilation by days 9 through 12. There had been no obvious adverse event attributable to the treatment. Finally, all of the patients died with sudden cardiac arrest between days 11 and 33 of the onset of SARS. Death was preceded in 2 patients (patients 1 and 4) by acute myocardial infarction occurring within the same day.
DISCUSSION

Based on a 75-patient cohort study, the clinical progression of SARS has been observed to show a triphasic pattern. It was speculated that the tissue damage in patients having SARS was caused mainly by an unchecked cytokine storm occurring during the second phase. Because the uremic state is associated with a wide range of impairment in the lymphocyte and granulocyte functions, it is plausible that the abnormalities in their immune system could predispose them to a modified response to SARS-associated coronavirus infection.

All our dialysis patients had fever on presentation as the dominant symptom, whereas other systemic symptoms, such as myalgia and malaise, were inconspicuous. In addition, while the yield of the novel coronavirus RNA by RT-PCR in the early phase of the disease was reported to be modest in other nonselected series, it was readily detectable in the nasopharyngeal and stool samples of the 4 patients on days 2 through 8. In addition, there was interesting transient complete or partial resolution of the initial lung opacities on day 3 for the 3 CAPD patients. While the underlying pathogenetic mechanism remains unknown, the 3 CAPD patients (patients 2, 3, and 4) were apparently older in age and had undergone dialysis for much a longer time than had the hemodialysis patient (patient 1).

In addition, their responses to the combination treatment with ribavirin and corticosteroids were poor. Despite an apparent success in resolving the fever, the treatment had not been able to change the course of the disease and prevent the patients from developing respiratory failure. Because we had not serially monitored the viral load in the blood and the other body fluids of these patients, it is unknown whether the poor outcomes were related to uncontrolled viral infection, possibly predisposed by the underlying immunologic abnormalities and steroid treatment, or due to an overwhelming immune response.

In this report, the 4 dialysis patients showed extremely poor outcomes after contracting SARS. Nevertheless, with a small number of patients in this report, most of whom were old, were diabetic, and had significant comorbidities, it remains unclear whether dialysis patients actually belong to a specific clinical group carrying a particularly poor prognosis when contracted with SARS. A large-scale comparative study, therefore, would be helpful to further examine this issue.

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Table 2. Treatment Regimens and Outcomes of the 4 Dialysis Patients Having SARS

| Patient | Ribavirin | Hydrocortisone | Methylprednisolone | Outcome |
|---------|----------|----------------|--------------------|---------|
| 1       | 4 mg/kg every 8 h | 4 mg/kg every 6 h | — | Resolution of fever Day 9, Intubation Day 11, Death Day 33 |
| 2       | 4 mg/kg every 8 h | 4 mg/kg every 6 h | — | Resolution of fever Day 3, Intubation Day 11, Death Day 10 |
| 3       | 8 mg/kg every 8 h | 4 mg/kg every 6 h | 15 mg/kg daily | Resolution of fever Day 7, Intubation Day 9, Death Day 11 |
| 4       | 8 mg/kg every 8 h | 4 mg/kg every 4 h | — | Resolution of fever Day 7, Intubation Day 12, Death Day 13 |
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