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CASE REPORTS

Severe Acute Respiratory Syndrome in a Hemodialysis Patient

Bonnie Ching-Ha Kwan, MBBS, MRCP(UK), Chi-Bon Leung, MBChB, FRCP(EDIN), Cheuk-Chun Szeto, MD, MRCP(UK), Angela Yee-Moon Wang, MBBS, MRCP(UK), and Philip Kam-Tao Li, FACP, FRCP

• **Severe acute respiratory syndrome (SARS) is a highly infective disease caused by a newly identified coronavirus. We described the clinical course of the first long-term hemodialysis patient who developed SARS in the literature, and our experience in performing hemodialysis for this patient. Such patients may present with a less typical clinical picture, making diagnosis difficult. In this patient, the course of disease and duration of viral shedding was apparently prolonged, thus highlighting the need for increased infection control. Despite worsening the anemia in renal failure patients by causing hemolysis, ribavirin is well tolerated after dosage adjustment. Difficulties of diagnosis, infection control, and treatment of SARS in renal failure patients are discussed in this report. *Am J Kidney Dis* 42:1069-1074.**

INDEX WORDS: Severe acute respiratory syndrome (SARS); atypical pneumonia; coronavirus; renal failure.

SINCE MARCH 2003, there have been cases of severe acute respiratory syndrome (SARS) reported in over 30 countries around the world, including China, Vietnam, Singapore, Taiwan, Germany, France, Italy, Thailand, United Kingdom, the United States, and Canada.[1-5] In Hong Kong, over 1,500 cases have been reported to date, with more than 200 deaths. Since SARS is highly contagious by close contact,[1] infection control in dialysis units is a topic of utmost importance for practicing nephrologists in epidemic areas. We hereby describe our experience in the management of a long-term hemodialysis patient who developed SARS.

CASE REPORT

A 33-year-old man was diagnosed with systemic lupus erythematosus (SLE) in 1987. He progressed to end-stage renal disease and was started on maintenance hemodialysis via a left forearm arteriovenous fistula in 1997. His medications include labetalol, nifedipine retard, calcium carbonate, erythropoietin-β, ferrous sulphate, and folic acid supplements. His lupus has been quiescent since dialysis and he does not receive maintenance steroid or other immunosuppressive therapy. Apart from tertiary hyperparathyroidism awaiting parathyroidectomy (parathyroid hormone of 105 pmol/L) and anemia requiring 5,000 U erythropoietin weekly intravenously and occasional transfusion, he remained stable on dialysis.

On the day of his first presentation in March 2003, he was noted to have a fever of 38°C on arrival for a routine hemodialysis session. He also had chills and rigors, but there was no cough, sputum, dyspnea, or diarrhea. On examination, there were some crepitations in the right lung base. Because of his occupation, he made frequent travels to and stayed in southern China. There was no definite history of contact with SARS patients. He was admitted to the hospital after dialysis for the investigation of fever. Chest radiograph on admission showed right lower lobe consolidation (Fig 1A). His peripheral white cell count was $7 \times 10^3/\mu L$ ($7 \times 10^9/L$) (normal range [NR], 4.0 to $10.8 \times 10^3/\mu L$ [4.0 to $10.8 \times 10^9/L$]), and his absolute lymphocyte count was $0.5 \times 10^3/\mu L$ ($0.5 \times 10^9/L$) (NR, 1.3 to $3.6 \times 10^3/\mu L$ [1.3 to $3.6 \times 10^9/L$]). The platelet count was $113 \times 10^3/\mu L$ ($113 \times 10^9/L$) (NR, 140 to $380 \times 10^3/\mu L$ [140 to $380 \times 10^9/L$]). Serum creatinine kinase (CK) level was 144 IU/L (NR, 42 to 218 IU/L). He was initially suspected to have SARS because there was a cluster of cases in the territory and because of his contact in southern China. However, the rapid antigen test of his nasopharyngeal aspirate later revealed influenza A virus. Thus, the subsequent working diagnosis at that time was influenza, with possible superimposed bacterial pneumonia. He became afebrile with improving chest radiograph within 48 hours after treatment with cefotaxime, levofloxacin, and oseltamivir. He was discharged with a course of oral medication 4 days later.

Our patient noticed a dry cough and dyspnea subsequently after discharge. When he came back for his hemodialysis session 3 days after his discharge, he was again noticed to have a fever and was admitted. His peripheral white cell count was $8.0 \times 10^3/\mu L$ ($8.0 \times 10^9/L$), lymphocyte count $0.6 \times 10^3/\mu L$ ($0.6 \times 10^9/L$), and platelet count declined to $70 \times 10^3/\mu L$ ($70 \times 10^9/L$). His activated partial-thromboplastin time was prolonged at 59.7 seconds (NR, 24.8 to 38.0

From from Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong, China.

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Address reprint requests to Philip Kam-Tao Li, FACP, FRCP, Consultant and Chief of Nephrology, Department of Medicine and Therapeutics, Prince of Wales Hospital, The Chinese University of Hong Kong, Shatin, Hong Kong. E-mail: philipli@cuhk.edu.hk

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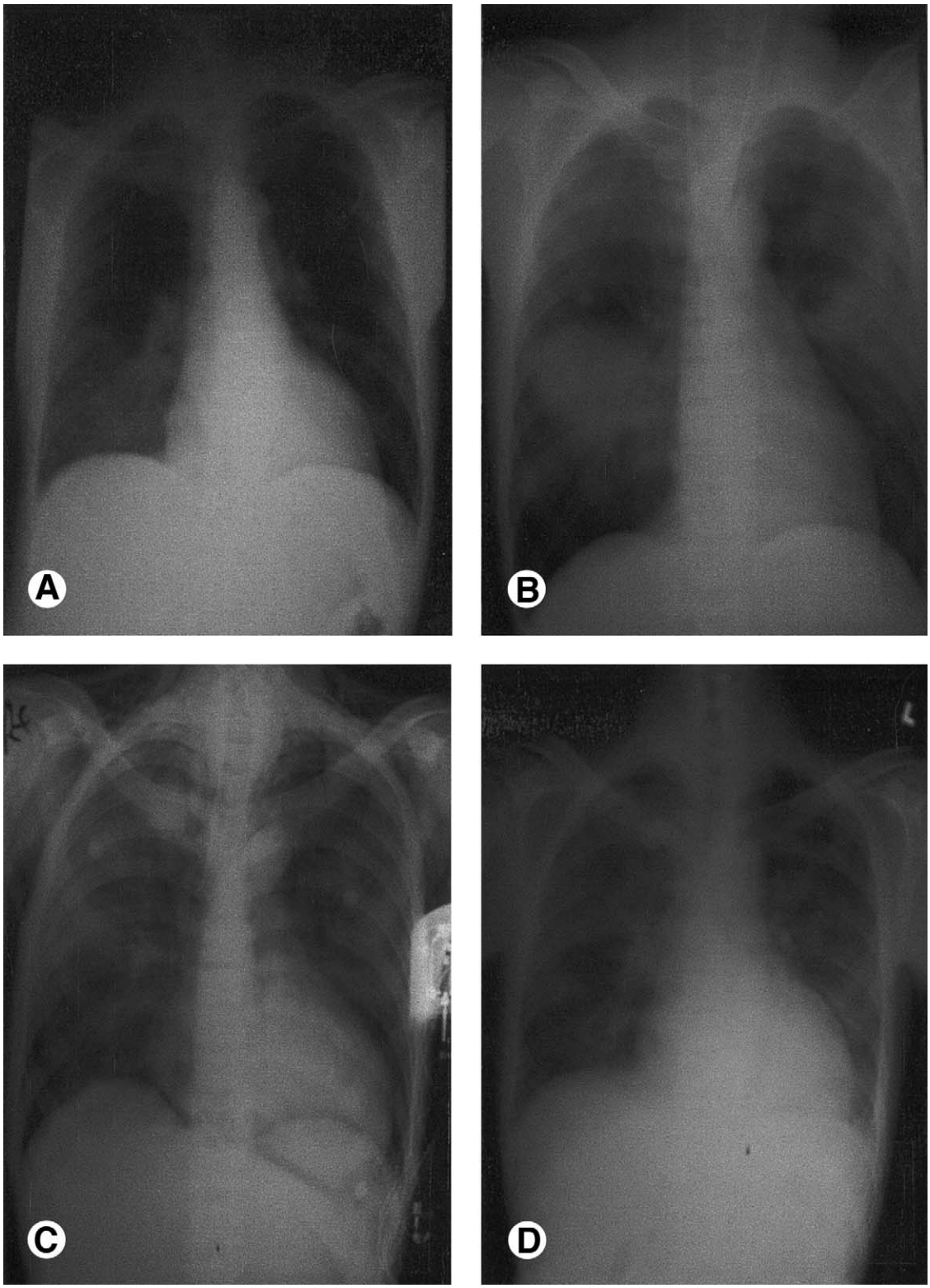

Fig 1. Serial chest radiograph: (A) on initial presentation; (B) 8 days after initial presentation, immediately before the first admission to intensive care unit; (C) 5 weeks after initial presentation, showing persistent bilateral pulmonary infiltrate despite ribavirin and corticosteroid; and (D) 8 weeks after initial presentation, showing slowly resolving pulmonary infiltrate.

seconds), and his D-dimer was elevated at 1,483 ng/mL (NR, <500 ng/mL). The serum CK level rose to 903 IU/L and the lactate dehydrogenase (LDH) level was 351 IU/L (NR, 87 to 213 IU/L). Alanine aminotransferase (ALT) was normal at 14 IU/L (NR, <58 IU/L). A repeated chest radiograph showed increasing right lower lobe consolidation. Based on his clinical features and history of travel, he was considered to fulfill the case definition of SARS given by the World Health Organization (WHO).[6]

Levofloxacin and cefotaxime were continued. He was put on 600 mg oral ribavirin thrice daily (30 mg/kg/day). However, his condition worsened rapidly and he was transferred to the intensive care unit the next day. He required endotracheal intubation and mechanical ventilation. A repeat chest radiograph showed bilateral pulmonary infiltrate (Fig 1B). Polymerase chain reaction (PCR) of a later stool sample identified the presence of SARS-associated coronavirus RNA. Paired serum subsequently also confirmed a 4-fold increase in the immunoglobulin G (IgG) titer of SARS-associated coronavirus. In view of the rapid deterioration and the possibility of a hyperactive immune system contributing to the disease process,[1,7] he was also treated with 500 mg intravenous methylprednisolone daily for 3 days, followed by 60 mg oral prednisolone daily (1 mg/kg/day). His condition improved and he became afebrile after methylprednisolone. He was extubated and discharged to a general ward designated for SARS patients 4 days later.

Hemodialysis Management

As soon as SARS was suspected during the second hospital admission, our patient received hemodialysis in a room with isolation facilities designated for SARS patients. Infection control measures of the dialysis unit staff followed the recommendation by the WHO,[8] with waterproof disposable gown, cap, gloves, face shield, and N95 facemask. A designated Gambro AK100 dialysis machine (Gambro, Lund, Sweden) was used with ordinary tap water supply passing through the Purtrex model PX10-9-7/8 filter (10-μm polypropylene; Osmonics Inc, Minnetonka, MN) without reverse osmosis or other water treatment. We used Fresenius F7 polysulfone dialyzer (Fresenius Medical Care, Bad Hamburg, Germany) without reuse. Spent dialysate was drained directly to the ward washbasin, which was connected to the main sewage drain by a U-trap. After a session of hemodialysis, the dialyzer and all blood tubings were discarded as infectious waste. Unspent dialysate concentrate and sodium bicarbonate cartridge were also discarded. The dialysis machine was disinfected by sodium hypochlorite solution according to the manufacturer's instruction. The dialysis machine was kept in a room in the SARS isolation ward between dialysis sessions and was only used for patients who had contracted SARS and required dialysis. Spent hypochlorite solution and rinse water were drained to the same washbasin, which did not receive additional disinfection.

Clinical Course

The subsequent clinical course and treatment are summarized in Fig 2. Despite some clinical improvement, our patient had intermittent fever, and the pulmonary infiltrate in his chest radiograph waxed and waned. The treatment was changed to 200 mg intravenous ribavirin every 8 hours for 1 week, followed by 600 mg oral ribavirin thrice daily. He received a further course of 500 mg intravenous methylprednisolone daily for 3 days on day 24 since fever onset. However, his oxygen requirement worsened, and there was a progression in the pulmonary infiltrate of his chest radiograph. Although he did not require endotracheal intubation, he was readmitted to the intensive care unit for close monitoring on day 28 (since fever onset).

In view of the protracted disease course and lack of radiographic improvement with ribavirin and corticosteroid (Fig 1C), he was further treated with 200 mL of convalescence plasma from a recovered SARS patient, and 5 mL/kg IgM-enriched human immunoglobulin (Pentaglobulin; Biotest, Dreieich, Germany) for 3 days on day 38 of his illness. He gradually improved, and his oxygen requirement was gradually reduced. Towards the end of the recovery phase, his oxygen saturation on room air remained above 96%. Since the patient became asymptomatic, a formal pulmonary function test was not performed to avoid inadvertent spreading of residual coronavirus during the forced expiration of spirometry. Chest radiograph improved slowly and continued to show bilateral basal infiltrate 8 weeks after the initial presentation (Fig 1D). A high-resolution computed tomography of thorax showed diffuse ground glass opacification, bilateral patchy consolidation, and fibrosis, features compatible with recovery phase of acute respiratory distress syndrome (ARDS) (Fig 3). He was given a total 4-week course of ribavirin and was put on 0.5 mg/kg/day oral prednisolone as maintenance to cover the ongoing pulmonary inflammation.

Despite adjustment in the dosage of ribavirin, he still experienced worsening of his anemia, requiring supportive transfusion. He received transfusions of a total of 20 U during his admission for about 3 months, compared to 10 U in the preceding 6 months (Fig 4).

PCR for RNA of SARS-associated coronavirus in the stool specimen performed on day 53 was still positive, and then 3 consecutive stool specimens were negative for viral culture starting from day 64 to day 75 (Fig 2). The patient recovered and was considered to be no longer infectious.

DISCUSSION

In this report, we described the clinical course of the first long-term hemodialysis patient reported in the literature who developed SARS and our experience in performing hemodialysis for him.

The initial clinical presentation of our patient was similar to that of other SARS patients. In the case series of our hospital ,[1] most patients present with fever, rigor, myalgia, dizziness, and diarrhea. The majority had lymphopenia, thrombocytopenia, prolonged activated partial-thromboplastin time, elevated D-dimer, CK, LDH, and ALT.[1] In general, our patient followed the typical 3-phase course of the illness: viral replicative phase, immune hyperactive phase, and then pulmonary destructive phase.[9] In the first phase, symptoms are similar to upper

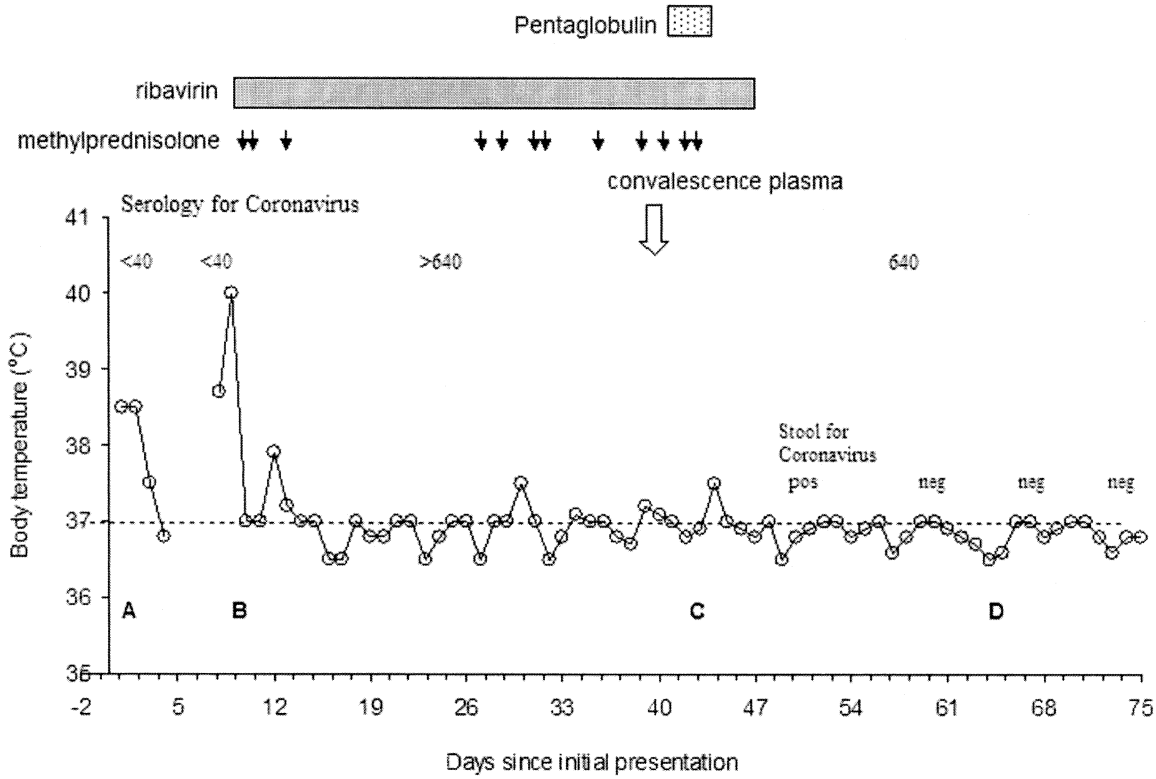

Fig 2. Fluctuation of body temperature. Bold letters along the X-axis indicate the time at which the corresponding chest radiograph in Fig 1 was performed. Note the temporal relationship between fever, radiographic change, and treatments given. Virology results including serology and stool specimen for coronavirus isolation are also shown.

respiratory infection with fever and myalgia. The second phase, due to immune response, causes febrile illness and rapidly increasing pulmonary inflammation with dyspnea. Postinflammatory fibrosis occurs in the third phase. However, our patient had an unexpectedly prolonged course of illness. He required hospitalization for more than 2 months, as compared to the average hospital stay of 14 to 25 days for other SARS patients.[1] The pulmonary infiltrate in his chest radiograph resolved only slowly and remained obvious almost 2 months after his initial presentation (see Fig 1D). Furthermore, PCR for SARS-associated coronavirus RNA was positive in his stool sample for almost 2 months. In other patients, the virus usually becomes undetectable in stool by week 5. It is postulated that renal failure patients cannot eliminate the SARS-associated coronavirus effectively because of their relatively depressed immunity. Similar observation has been described in other chronic viral infections of renal failure patients.[10]

We believe our patient probably contracted the SARS coronavirus during his travel to and stay in mainland China. Retrospectively, he fulfilled the WHO case definition of SARS[6] during his first presentation. The influenza A virus isolated from nasopharyngeal aspirate probably represented either a false-positive result or a genuine concomitant influenza A infection, which was endemic during that season in Hong Kong. It is important to note that neither serologic test nor PCR for SARS-associated coronavirus RNA was available when the patient was first admitted. Our patient highlights the difficulty in the diagnosis of SARS, as well as the need to consider double pathology when the circumstances are suspicious.

Our patient received dialysis in the renal unit along with the other patients during his hemodialysis on the day of his first admission, where patients were normally placed more than 3 feet from each other, and none of the other hemodialy-

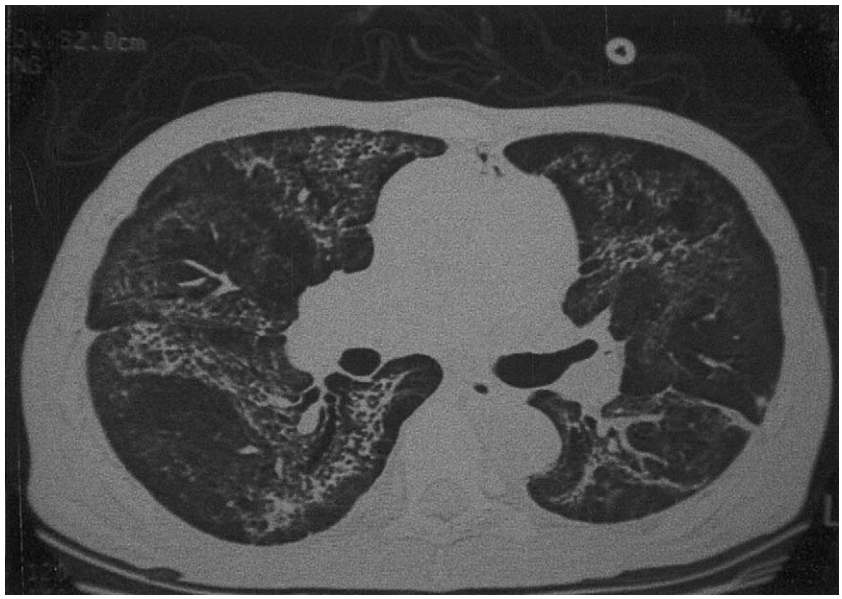

Fig 3. High resolution computed tomography of thorax 8 weeks after initial presentation. There is diffuse ground glass opacification, bilateral patchy consolidation, and fibrosis, features compatible with recovery phase of ARDS.

sis patients of the same session contracted the disease. Unfortunately, 2 dialysis nurses who took care of our patient during his early presentations developed SARS later. Fortunately, both of our nurses improved after treatment with ribavirin and corticosteroid. His subsequent hemodialysis was performed in isolation as described above.

Once the diagnosis of SARS was suspected in our patient, we worked closely with the hospital Infection Control Unit to enforce all the infection control measures (see above), and no more staff or other patients in the hemodialysis unit became infected. It is important to note that we allowed drainage of the spent dialysate through ordinary washbasin. We have not tested for the presence of SARS-associated coronavirus in spent dialysate of our patient. Since coronavirus is approximately 50 nm in diameter, it should not pass

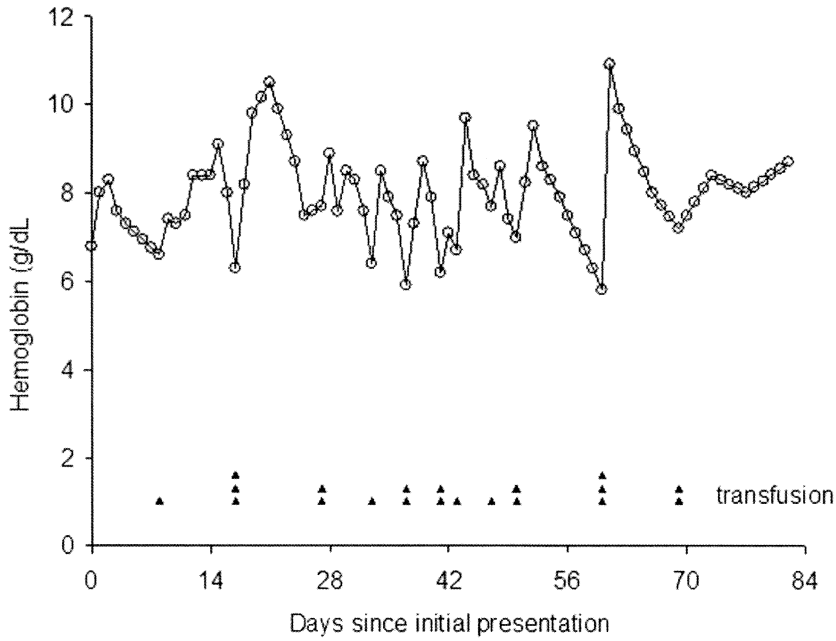

Fig 4. Time course of hemoglobin values and transfusions. Each triangle represents a unit of packed cell transfused. To convert hemoglobin in g/dL to g/L, multiply by 10.

through the conventional low-flux polysulfone membrane. However, the modern high-flux polysulfone dialyzer has a much larger pore size (for example, over 50% of the β2 microglobulin can be removed during a single session of dialysis[15]), and its use should be under great caution.

It is noted that the efficacy of the treatment regimen was not universally agreed.[11] Our patient was treated with ribavirin and steroid according to local experience.[1,7] Ribavirin is eliminated both by hepatic metabolism and renal excretion. There are few studies on the pharmacokinetics of ribavirin in patients with renal dysfunction. It is generally recommended that the dosage of ribavirin should be halved in patients with a glomerular filtration rate below 10 mL/min, and a supplemental dose should be administered after hemodialysis.[12] In fact, some studies found that it was necessary to reduce the dosage in order to maintain its plasma level[16] and to avoid significant hemolysis.[13,14] We followed the recommended dosage regimen adjustment in our patient.

In view of the resistant nature of the disease course in our patient, he was also given convalescence plasma and pentaglobulin. Both are being used as experimental treatments for SARS. Convalescence plasma contains neutralizing antibodies against coronavirus, and pentaglobulin has immunomodulating effects.[17] Both are used to halt the progression to pulmonary destructive phase.

In summary, we described a hemodialysis patient who contracted SARS with prolonged shedding of virus. With appropriate infection control measures, the staff with protective gear who were taking care of the patient were not infected. The use of ribavirin with appropriate dosage reduction was feasible in his treatment. Nephrologists need to be aware of the prolonged viral shedding and the possible infectivity of renal failure patients who have contracted SARS.

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