Severe Acute Respiratory Syndrome in Dialysis Patients

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Abstract. Reviewed are the clinical features and outcome of 12 chronic dialysis patients (six men) who contracted severe acute respiratory syndrome (SARS) compared with 23 sex- and age-matched nonuremic SARS patients as controls. Eight were on peritoneal dialysis (PD) and four on hemodialysis. Mean age was 58 ± 12 yr for the dialysis patients, and 57 ± 12 yr for the controls. The presenting symptoms of dialysis patients were similar to the controls. With appropriate protection measures, hemodialysis was performed in a dedicated area of the SARS isolation ward, while PD was continued as intermittent PD. In all seven patients with PD effluent tested, SARS-related coronavirus (CoV) could not be identified by polymerase chain reaction (PCR) or viral culture. Three dialysis patients had persistent positive stool PCR after 5 wk, whereas all nondialysis patients had negative stool PCR after 1 wk. Despite dosage adjustment, ribavirin-induced hemolytic anemia was more severe in the dialysis patients. Dialysis patients required longer hospitalization than the controls, but the mortality was similar. With appropriate protective measures, dialysis could be safely performed. Dialysis patients with SARS often require prolonged hospitalization. Furthermore, these patients may have an extended period of viral shedding, which should be carefully monitored for the purpose of infection control.

From March to July 2003, there was a global outbreak of severe acute respiratory syndrome (SARS) (1). It affected more than 8000 people in over 30 countries (2), including China, Vietnam, Singapore, Taiwan, Germany, France, Italy, Thailand, the United Kingdom, the United States, and Canada (1,3–6). In Hong Kong, more than 1750 people contracted SARS, and nearly 300 people died (7).

There are additional difficulties in the management of chronic dialysis patients who contract SARS. For example, early diagnosis is difficult, dose of antiviral medications needs to be adjusted, and there are additional infection control issues in the disposal of spent dialysate (both hemodialysis and peritoneal dialysis [PD]) and in preventing cross-contamination within the dialysis unit. To date, there have only been isolated case reports on the management of SARS in chronic dialysis patients (8–10). Here we report the clinical features, treatment, and outcome of 12 dialysis patients with SARS from a hospital cluster in Hong Kong.

Materials and Methods

We reviewed all chronic dialysis patients from a hospital cluster in Hong Kong who were hospitalized for SARS during the epidemic period. SARS was defined according to the World Health Organization (WHO) criteria (11). The list was compiled after searching through the regional database for all of the patients who were diagnosed to have or who died of SARS. One of the patients has been described in a previous report (10).

We reviewed the case notes of the SARS group. The symptoms at presentation, presence of comorbidities, laboratory results, treatment regimens, need for admission to intensive care unit (ICU), length of hospital stay, and clinical outcome were reviewed. The results were further compared with a control group of 23 nondialysis SARS patients from the same hospital cluster that were matched for sex and age.

Virologic Studies

SARS-coronavirus (CoV) detection was done by real-time PCR (RT-PCR) (12). After the RNA was extracted with the QIAamp viral RNA Mini Kit (Qiagen, Hilden, Germany) from the appropriate specimens, reverse transcription of RNA was conducted on the basis of the primer set COR-1 and COR-2 (13). The lower detection limit was 50 virus copies per reaction. For viral isolation, specimens were inoculated onto African green monkey (Vero E6) cell monolayers (12). The cells showing cytopathic effects were then stained by indirect immunofluorescence technique with convalescent serum collected from a SARS patient.

Statistical Analyses

Statistical analysis was performed with SPSS for Windows version 11.0 (SPSS, Chicago, IL). Data are reported as mean ± SD unless otherwise specified. The groups are compared with Fisher’s exact test, t test, or Mann-Whitney U test as appropriate. A P value of less than 0.05 is considered significant. All probabilities are two-tailed.

Results

A total of six male and six female dialysis patients were included. Their mean age was 58 yr (range, 34 to 74 yr). Their mean duration of dialysis was 37.3 mo (range, 2.4 to 70.0 mo).

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Eight patients were on continuous ambulatory PD and four on hemodialysis. Five patients developed end-stage renal failure as a result of diabetic nephropathy, three from IgA nephropathy, two from lupus nephritis, one from hypertensive nephrosclerosis, and one from an unknown cause. The control group consisted of 12 men and 11 women with a mean age of 57 yr (range, 34 to 75 yr). Seventeen control subjects (74%) had other chronic diseases, including eight patients with cardiovascular diseases, four with diabetes, and one patient who required immunosuppressive agents.

Clinical Features

The presenting symptoms are summarized in Table 1. Among the 12 dialysis patients, most presented with fever. The presenting symptoms were similar between the dialysis and control groups, although myalgia, chills, and rigors were less common among dialysis patients. At presentation, all patients had changes in the chest radiograph, including two with bilateral radiographic changes.

The results of laboratory tests at presentation are summarized in Table 2. The dialysis group and the control group had similar prevalence of leukocytopenia and lymphopenia. Thrombocytopenia was marginally less frequent in the dialysis than the control group, and the dialysis group had a higher platelet count than the control group (249 ± 129 versus 157 ± 61 × 10^9/L, P = 0.07). At presentation, patients of the dialysis group had longer prothrombin time (13.2 ± 1.9 versus 10.3 ± 0.9 sec, P < 0.001) and activated partial thromboplastin time (43.8 ± 9.8 versus 36.1 ± 6.0 sec, P = 0.009). Most patients from both groups had elevated C-reactive protein, and the creatinine kinase levels were similar between the groups. The lactate dehydrogenase level was significantly higher in the dialysis than the control group (488 ± 170 versus 317 ± 123 IU/L, P = 0.002).

Antiviral Treatment

In our centers, treatment protocol of dialysis patients with SARS was similar to that of nondialysis patients, which has been described previously (1,14,15). The dose of ribavirin was half of that in patients with normal renal function (16). Four patients received erythropoietin. However, there was a high incidence of transfusion-dependent anemia in dialysis patients with SARS who were being treated with ribavirin. Eleven of 12 patients in the dialysis group and 7 of 23 patients in the control group required transfusion. The dialysis group required more units of blood than the control group (6.7 ± 9.8 versus 0.9 ± 1.6 units pack cell per person, Mann-Whitney U test, P < 0.001) (Figure 1). Most of the dialysis patients were kept on their usual dose of erythropoietin.

All patients received corticosteroids in the form of oral prednisolone, intravenous methylprednisolone, or hydrocortisone as antiinflammatory therapy. The average cumulative dose of hydrocortisone or equivalent in the dialysis group was 11.1 g (range, 2.5 to 41.1 g), which was similar to the control group (average, 17.8 g; range, 3.0 to 31.2 g). In the dialysis group, two patients received convalescence plasma, one received intravenous immunoglobulin, and one received pentaglobulin (Biotest, Dreieich, Germany), all because of a lack of clinical response to ribavirin and corticosteroid treatment. All of them recovered, although they required a period of observation in ICU.

Virologic Study

Eleven of the 12 dialysis patients had at least a fourfold increase in the serum IgG against SARS-related CoV. One patient died on day 7 of hospitalization, before any positive serologic response could be demonstrated. The diagnosis of SARS in this patient was established by a definite history of contact and clinical criteria; postmortem examination was not performed. RNA of CoV could be identified by PCR in the throat gargle of four patients (33%) in the dialysis group and seven (30%) in the control group (P = 0.9). CoV was identified in the stool of eight dialysis patients (67%), and three (25%) had persistent positive stool PCR 5 wk after the onset of symptoms. On the other hand, CoV could not be identified by PCR or viral culture in all patients of the control group 1 wk after the onset of symptoms. CoV was present in the urine of 1 patient in the dialysis group (on day 23 of her illness) and none in the control group. More importantly, CoV was not detected in the PD effluent by PCR or viral culture of all 7 patients tested.

Infection Control

The dialysis patients were kept in the SARS isolation ward along with the other nondialysis SARS patients. All PD patients were treated with intermittent PD during hospitalization. The dialysis exchange was done by the ward staff, who wore full protective gear as recommended by the WHO (19), including waterproof disposable gown, cap, gloves, face shield, and N95 face mask. Spent PD effluent was collected in 3-L glass bottles for volume measurement, then put into plastic drainage buckets and drained into the sluice of the ward or into the toilet. One liter of 2% hypochlorite solution (Hypo-6, Funchem, Hong Kong) was then used to rinse the sluice or the toilet. Used glass bottles and plastic drainage buckets were decontaminated with the same volume of 2% hypochlorite solution for 15 min and then rinsed before being used again.
Hemodialysis was performed in a room inside the isolation ward designated for SARS patients. The arrangement of hemodialysis has been described in our previous report (10). Briefly, the dialysis unit staff followed the infection control measures recommended by the WHO (19), and they wore full protective gear as mentioned above. Designated hemodialysis machines were used with ordinary tap water supply passing through the Purtrex model PX10-9-7/8 filter (10/H9262 m polypropylene, Osmonics, Minnetonka, MN) without reverse osmosis or other water treatment. Fresenius F7 polysulfone dialyzer was used, and spent dialysate was drained directly to the ward washbasin, which was connected to the main sewage drain by a U-trap. 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 after each hemodialysis session with sodium hypochlorite solution according to the manufacturer’s instructions. 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 Outcome

The clinical outcome of the two groups is summarized in Table 3. The proportion of patient that required ICU admission or endotracheal intubation was similar between the groups. However, patients in the dialysis group required longer hospitalization than the control group (62/37 versus 24/14 d, P = 0.005) (Figure 2). Three patients (25%) in the dialysis group died. The causes of death were cerebrovascular accident (two cases) and myocardial infarction (one case). None of the dialysis patients died of respiratory failure or other direct consequences of SARS. The mortality rate was similar to the control group. Of the dialysis group, three of the five patients with diabetes died, and one of the four patients with diabetes in the control group died.

Discussion

In this case series, we described the clinical course of 12 dialysis patients who contracted SARS. Dialysis patients have

### Table 2. Results of laboratory investigations on presentation

<table>
<thead>
<tr>
<th></th>
<th>Dialysis Group</th>
<th>Control Group</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of patients</strong></td>
<td>12</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td><strong>Hematology</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>total white cell count</td>
<td>7.9 ± 3.2</td>
<td>5.5 ± 1.8</td>
<td>0.009a</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>leucopenia, no. of cases (%)</td>
<td>1 (8%)</td>
<td>2 (9%)</td>
<td>0.9b</td>
</tr>
<tr>
<td>lymphocyte count</td>
<td>0.86 ± 0.37</td>
<td>0.84 ± 0.30</td>
<td>0.84a</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lymphopenia, no. of cases (%)</td>
<td>7 (58%)</td>
<td>15 (65%)</td>
<td>0.7b</td>
</tr>
<tr>
<td>platelet count</td>
<td>249 ± 129</td>
<td>157 ± 61</td>
<td>0.007a</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>thrombocytopenia, no. of cases (%)</td>
<td>2 (17%)</td>
<td>11 (47%)</td>
<td>0.14b</td>
</tr>
<tr>
<td>PT (sec, NR 8.8–10.8)</td>
<td>13.2 ± 1.9</td>
<td>10.3 ± 0.9</td>
<td>&lt;0.001a</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolonged PT, no. of cases (%)</td>
<td>12 (100%)</td>
<td>4 (18%)</td>
<td>&lt;0.001b</td>
</tr>
<tr>
<td>APTT (sec, NR 24.8–38.0)</td>
<td>43.8 ± 9.8</td>
<td>36.1 ± 6.0</td>
<td>0.009a</td>
</tr>
<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>prolonged APTT, no. of cases (%)</td>
<td>8 (78%)</td>
<td>7 (32%)</td>
<td>0.07b</td>
</tr>
<tr>
<td><strong>Biochemistry</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CK (IU/L, NR 42–218)</td>
<td>219 ± 237</td>
<td>179 ± 143</td>
<td>0.54a</td>
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<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elevated CK, no. of cases (%)</td>
<td>3 (25%)</td>
<td>6 (26%)</td>
<td>0.9b</td>
</tr>
<tr>
<td>LDH (IU/L, NR 87–213)</td>
<td>488 ± 170</td>
<td>317 ± 123</td>
<td>0.002a</td>
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<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elevated LDH, no. of cases (%)</td>
<td>12 (100%)</td>
<td>18 (78%)</td>
<td>0.14b</td>
</tr>
<tr>
<td>CRP (mg/L, NR &lt;9.9)</td>
<td>110.2 ± 63.3</td>
<td>57.4 ± 76.3</td>
<td>0.11a</td>
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<tr>
<td>mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>elevated CRP, no. of cases (%)</td>
<td>12 (100%)</td>
<td>22 (95%)</td>
<td>0.9b</td>
</tr>
</tbody>
</table>

PT, prothrombin time; APTT, activated partial thromboplastin time; CK, creatine kinase; LDH, lactate dehydrogenase; CRP, C-reactive protein.

Data are compared by a Student t test and b Fisher exact test.
a higher rate of contracting SARS compared with the general population. In our area, which serves 700 dialysis patients, 12 contracted SARS. The attack rate was 1 (1.72%) in 58 subjects, which was substantially higher than the general Hong Kong population (1 in 30,000, or 0.003%). This is probably related to the relative suppressed immunity of uremic patients and the frequent hospital admissions of patients on dialysis. Notably, 10 of the 12 dialysis patients contracted SARS during a previous hospital admission. In comparison, four patients in the control group were health care workers, and another five contracted SARS during a previous hospital stay.

At presentation, patients on dialysis exhibit similar symptoms (fever, myalgia, chills and rigors, gastrointestinal symptoms) as the nondialysis patients (1). However, it is our impression that dialysis patients tend to have less pronounced symptoms (8,9), which may be difficult to distinguish from uremic symptoms. In addition, dialysis patients tended to seek medical attention at a later stage, which might cause a delay in diagnosis and treatment. The dialysis patients might also have less marked changes in the chest radiograph. In our series, 17% of the dialysis group had bilateral radiologic changes. In comparison, a previous case series found that radiologic changes was present in 78% of patients, of whom 45% had multifocal or bilateral involvement (1).

Our dialysis patients were noticed to have the typical three-phase course of the illness: viral replicative phase, immune hyperactive phase, and then pulmonary destructive phase (22). To date, there is no established treatment regimen. In Hong Kong, the standard treatment at the time of the outbreak was ribavirin and corticosteroids (1). Notably, ribavirin is eliminated both by hepatic metabolism and renal excretion. Some studies found that it was necessary to reduce the dosage in patients with renal failure to avoid toxicity (18,24,25). Nevertheless, clinically apparent hemolysis is common in both uremic and nonuremic patients. Because of the preexisting anemia, dialysis patients were more likely to develop symptomatic anemia and required more blood transfusions. There were no reports of other significant adverse effects from ribavirin. There were no reports of major adverse effects of corticosteroids. The dialysis patients tolerated convalescence plasma and immunoglobulin well, although extra ultrafiltration was often required to avoid fluid overload.

Although dialysis patients often have impaired immune defense, they were able to mount a serologic response to the coronavirus. All of the 11 dialysis patients tested had at least a fourfold rise in antibody titer. However, there is currently no convenient means to measure the protective immunity against coronavirus. Dialysis patients apparently had a longer period of shedding of the virus. In nonuremic patients, tracheal aspirate and stool had a diagnostic yield of 66.7% and 56.5%, respectively, for the first 2 wk (11). The stool becomes negative 5 wk after the onset of symptoms. In our series, three dialysis patients had persistent positive PCR from stool after the fifth week. One patient had positive stool PCR for almost 8 wk. Interestingly, similar observations of prolonged viral shedding have been noted in other viral illnesses in chronic renal failure patients (25).

Although theoretically possible, we could not isolate coronavirus from the PD effluent. For hemodialysis, we did not test the spent dialysate for coronavirus. Notably, coronavirus is approximately 50 nm in diameter and should not pass through the conventional low-flux polysulfone membrane that we used. (A blood leak detector was routinely used to safeguard any occult leak.) For that reason, spent dialysate was drained through an ordinary washbasin without further disinfection procedures. In retrospect, an assay of the spent hemodialysate to confirm the absence of viral transfer across the dialyzer would have been helpful. Nevertheless, after the above infection control measures were enforced, none of the staff looking after the dialysis patients were infected.

Patients on dialysis were noted to have a much longer hospital stay compared with nonuremic patients. This prolonged length of stay is attributable to several factors. Dialysis patients tended to have concurrent medical problems and a prolonged course of disease. They were more likely debilitated and required additional hospital stay for rehabilitation. Finally, dialysis patients had an extended period of viral shedding, which often necessitated a prolonged hospital stay for the purpose of infection control.

The rates of ICU admission and intubation were similar between the groups, reflecting a similar degree of disease severity. The mortality rate of the dialysis group was 25%, which was similar to the control group (26%). This figure is much higher than the 4% quoted in a previous case series (1). Notably, our dialysis patients and the control group have a mean age of 58 and 57 yr, respectively, whereas the original case series reported by Lee et al. (1) consisted mainly of health care workers, mostly in their 20s and 30s. Advanced age and
the presence of comorbid conditions are understandably poor prognostic factors.

In summary, we described the clinical course of 12 dialysis patients who contracted SARS. Overall, dialysis patients had similar clinical features and mortality rates as the nondialysis SARS patients, after adjusting for age and coexisting medical condition. Ribavirin could be safely used at a reduced dosage, although blood transfusion is often required. With appropriate protective measures, both PD and hemodialysis could be safely performed. Dialysis patients often require prolonged hospitalization. Furthermore, they may have an extended period of viral shedding, which should be carefully monitored for the purpose of infection control.

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