Case Report

Protracted course of coronavirus disease with severe acute respiratory distress syndrome: a case report

Kyohei Miyamoto, Takafumi Yonemitsu, Rikako Tanaka, Tsuyoshi Nakashima, Mami Shibata, Ryosuke Funahashi, Keiko Yamasaki, Mario Yamada, Kaori Tamoto, Keiichiro Akamatsu, Machiko Nishio, Hiroki Yamaue, and Seiya Kato

1Department of Emergency and Critical Care Medicine, 2Department of Infection Prevention and Control, 3Department of Thoracic and Cardiovascular Surgery, 4Department of Anesthesiology, 5Third Department of Internal Medicine, 6Department of Microbiology, and 7Second Department of Surgery, Wakayama Medical University, Wakayama, Japan

Background: Coronavirus disease (COVID-19) is a growing concern worldwide. Approximately 5% of COVID-19 cases require intensive care. However, the optimal treatment for respiratory failure in COVID-19 patients is yet to be determined.

Case presentation: A 79-year-old man with severe acute respiratory distress syndrome due to COVID-19 was admitted to our intensive care unit. Prone ventilation was effective in treating the patient’s hypoxemia. Furthermore, the patient received lung protective ventilation with a tidal volume of 6–8 mL/kg (predicted body weight). However, the patient’s respiratory failure did not improve and he died 16 days after admission because of multiple organ failure. Serial chest computed tomography revealed a change from ground-glass opacity to consolidation pattern in both lungs.

Conclusions: We report a protracted case of COVID-19 in a critically ill patient in Japan. Although prone ventilation could contribute to treating hypoxemia, its efficacy in preventing mortality from COVID-19 is unknown.

Key words: Acute respiratory distress syndrome, COVID-19, critically ill, prone ventilation, SARS-CoV-2

INTRODUCTION

CORONAVIRUS DISEASE (COVID-19) is a major growing concern worldwide. By 11 February 2020, 72,314 cases were reported in mainland China, and among 44,672 confirmed cases, 1,023 deaths were reported (case-fatality rate of 2.3%). In Japan, 1,160 confirmed cases, including 113 asymptomatic cases, were reported by the Ministry of Health, Labor and Welfare on 25 March 2020. Among the 1,047 symptomatic patients, 43 died (case-fatality rate of 4.1%).

The Chinese Center for Disease Control and Prevention reported that approximately 5% of COVID-19 cases progress to a critical stage and require intensive care, including mechanical ventilation. According to the Surviving Sepsis Campaign guideline for COVID-19, low tidal volume ventilation and prone ventilation are recommended for treating severe hypoxic respiratory failure. However, the optimal treatment for respiratory failure in COVID-19 patients is yet to be determined, likely because of the lack of specific information on the management and outcome of patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.

CASE REPORT

A 79-year-old man without relevant medical history presented to our hospital with progressive hypoxemia due to refractory pneumonia. Seven days before admission, he had presented to a different hospital with complaints of 5 days of fever, nausea, and loss of appetite. A chest computed tomography (CT) revealed small bilateral ground-glass opacities (GGOs) (Fig. 1C, D) in both lungs. He was diagnosed with pneumonia and admitted to the aforementioned hospital; he was treated with ceftazidime, followed...
by meropenem. At the day of admission to our hospital, he developed hypoxemia and was referred to the emergency department of our tertiary care hospital.

On arrival at the emergency department, the patient’s blood pressure was 120/74 mmHg; heart rate, 107 b.p.m.; Glasgow Coma Scale score, E4V5M6; body temperature, 38.6°C; respiratory rate, 40 breaths/min; and oxygen saturation, 92% while receiving 10 L/min oxygen through a face mask with reservoir. His Sequential Organ Failure Assessment (SOFA) scores were 10. He was immediately intubated and placed on mechanical ventilation. Chest CT and radiography revealed worsening of lesions, illustrated by a mix of GGO and consolidation patterns (Fig. 1A, E, F). The patient had lymphopenia, with slightly elevated creatinine level accompanied by markedly elevated C-reactive protein (Table 1). Even though the patient had no history of any epidemiological exposure to Wuhan or Hubei provinces, we undertook a nucleic acid amplification test (NAAT) of a throat swab sample for SARS-CoV-2 virus because of radiological findings and the refractory pneumonia despite treatment with antibiotics. Six hours after the admission, the NAAT was found to be positive, and the patient was diagnosed as having COVID-19 pneumonia. Blood culture was negative, and sputum culture revealed only normal flora.

After admission to our intensive care unit, the patient was treated with piperacillin/tazobactam, azithromycin, and norepinephrine. Although we initially administered methylprednisolone for severe pneumonia, we discontinued it after the cause was found to be a SARS-CoV-2 infection. On the first day of admission, the PaO2/FiO2 ratio was 91 during a positive end-expiratory pressure of 10 cmH2O. Low tidal volume pressure-controlled ventilation of 6–8 mL/kg (predicted body weight) with prone ventilation was started for severe acute respiratory distress syndrome (ARDS). The

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PaO2/FiO2 ratio rapidly improved to 282, 2 h after introducing prone ventilation. However, after going from prone to supine position, the oxygenation deteriorated and prone ventilation had to be restarted. Overall, we carried out six rounds of prone ventilation with a median duration of 18.5 h (range, 12–43 h). The tidal volumes and oxygenation values are shown in Figure 2.

On the 5th hospital day, we started the patient on lopinavir/ritonavir (400/100 mg twice daily) and vancomycin for the unresolved pneumonia. On the 11th hospital day, we discontinued piperacillin/tazobactam and vancomycin because of worsening renal functions and generalized fixed drug eruptions, coupled with lack of evidence regarding the ongoing bacterial infection. On the 10th and 12th hospital days, two NAATs of sputum specimens were negative, and we discontinued lopinavir/ritonavir. The chest CT on the 13th day revealed worsening of the consolidation pattern (Fig. 1B, G, H). The laboratory findings revealed coagulopathy and elevated serum creatinine and bilirubin levels (Table 1). On the 14th hospital day, we initiated continuous renal replacement therapy for worsening kidney functions and hyperkalemia. Furthermore, we increased the dose of norepinephrine and undertook a blood culture because of worsening hypotension. Therefore, the SOFA score increased to 16, suggesting multiple organ failure. On the 15th hospital day, we started the patient on linezolid because of the presence of gram-positive bacteria in the blood and sputum culture, which was later identified as methicillin-

| Variable                                      | Seven days before admission† | At the emergency department | Day 13 of hospitalization |
|-----------------------------------------------|-----------------------------|-----------------------------|--------------------------|
| White-cell count (per mm³)                    | 4,400                       | 8,670                       | 14,520                   |
| Lymphocyte count (per mm³)                    | 1,100                       | 1,040                       | 990                      |
| Hemoglobin (g/dL)                            | 16.8                        | 15.2                        | 9.5                      |
| Hematocrit (%)                               | 48.8                        | 42.9                        | 27.7                     |
| Platelet count (per mm³)                     | 129,000                     | 152,000                     | 149,000                  |
| Sodium (mmol/L)                              | 138                         | 138                         | 144                      |
| Potassium (mmol/L)                           | 4.2                         | 4.1                         | 4.1                      |
| Chloride (mmol/L)                            | 98                          | 107                         | 117                      |
| Urea nitrogen (mg/dL)                        | 24.3                        | 18.8                        | 28.1                     |
| Creatinine (mg/dL)                           | 1.1                         | 1.1                         | 1.7                      |
| Aspartate aminotransferase (IU/L)            | 36                          | 118                         | 60                       |
| Alanine aminotransferase (IU/L)              | 23                          | 61                          | 27                       |
| Lactate dehydrogenase (IU/L)                 | 215                         | 717                         | 453                      |
| Total bilirubin (mg/dL)                      | 0.9                         | 1.1                         | 6.3                      |
| International normalized ratio               | Not done                    | 1.14                        | 1.50                     |
| Fibrinogen (mg/dL)                           | Not done                    | 703                         | 498                      |
| C reactive protein (mg/dL)                   | 6.7                         | 23.5                        | 22.0                     |
| Procalcitonin (ng/mL)                        | Not done                    | 0.43                        | Not done                 |
| Arterial blood gas analysis                  |                            |                             |                          |
| pH                                           | Not done                    | 7.443†                      | 7.434‡                   |
| PaO2 (mmHg)                                  | Not done                    | 75.5†                       | 89.7§                    |
| PaCO2 (mmHg)                                 | Not done                    | 34.0†                       | 29.1§                    |
| HCO3⁻ (mmol/L)                               | Not done                    | 24.5†                       | 19.2§                    |
| Lactate (mmol/L)                             | Not done                    | 1.2†                        | 1.2§                     |
| Rapid antigen test                           |                            |                             |                          |
| Rapid antigen test for influenzae virus      | Negative                    | Negative                    | Not done                 |
| Rapid urinary antigen test                   | Not done                    | Negative                    | Not done                 |
| Pneumococcus                                 |                            |                             |                          |
| Rapid urinary antigen test for Legionella    | Not done                    | Negative                    | Not done                 |

† Laboratory tests carried out at the initial hospital.
‡ Analysis undertaken while patient was receiving 10 L/min oxygen through a face mask with reservoir.
§ Analysis undertaken while patient was under mechanical ventilation using pressure support mode with positive end-expiratory pressure 8 cmH₂O and FiO₂ 0.5.
resistant Staphylococcus aureus, indicating secondary bacterial pneumonia (Table S1). On the 16th hospital day, the patient died because of multiple organ failure.

**DISCUSSION**

**HERE WE REPORTED** a 79-year-old man with severe ARDS due to SARS-CoV-2 infection. According to our previous experience, we have applied prone ventilation for a longer duration than that stated in the abovementioned guideline, with a maximum duration of 43 h, which temporarily cured his hypoxemia.\(^4,5\) This allowed us to implement low tidal volume ventilation, bypassing the need for more invasive and resource-intensive procedures, such as extracorporeal membrane oxygenation (ECMO). Although prone ventilation is recommended for severe ARDS, published reports on the outcomes of prone ventilation used in COVID-19 patients are limited.\(^4\) A recent case series study from Wuhan, which included critically ill patients with COVID-19, reported that approximately 10% of patients were treated with prone ventilation.\(^6\) Although prone ventilation might mitigate hypoxemia, it is unclear whether it contributes to a decrease in mortality of patients experiencing ARDS.

In our case, the chest CT showed GGO predominantly in the dorsal lung area, which could explain the effectiveness of prone ventilation. The GGO did not improve; instead, it progressed to a consolidation pattern 3 days before the patient died, which could explain the dependence on prone ventilation and refractory clinical course. A recent observational study of COVID-19 patients showed that the prevalence of GGO decreases with time, and tends to be replaced by consolidation.\(^7\) Our reported radiological findings are in line with this.

The use of venovenous (VV)-ECMO for managing ARDS is controversial, and recent guidelines do not provide any specific recommendation regarding its use, due to the limited evidence on its efficacy.\(^8\) Accordingly, a recent

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**Fig. 2.** Course of ventilatory settings and PaO\(_2\)/FiO\(_2\) ratio in a critically ill 79-year-old Japanese man with COVID-19. Light gray shading indicates prone ventilation values over time. Dark gray shading indicates a tidal volume between 6 and 8 mL/kg. Although PaO\(_2\)/FiO\(_2\) improved during prone ventilation, it deteriorated following return to the supine position. Tidal volume was maintained between 6 and 8 mL/kg (predicted body weight). PEEP, positive end-expiratory pressure.
randomized controlled trial failed to determine a significant improvement in the mortality rate as a result of early VV-ECMO in patients with severe ARDS. In our hospital, we routinely use VV-ECMO for refractory hypoxemia (PaO2/FiO2 ratio < 100) under low tidal volume ventilation with prone positioning and/or a neuromuscular blocking agent. In this case, because the PaO2/FiO2 ratio rose to close to 300 after prone positioning, we did not use VV-ECMO or neuromuscular blocking agents, while successfully maintaining low tidal volume ventilation.

We introduced lopinavir/ritonavir and corticosteroids. Lopinavir/ritonavir was reported to be a promising antiviral agent for the treatment COVID-19, even though its efficacy has not yet been fully proven. By contrast, the use of corticosteroids has been discouraged because of the lack of evidence of their benefit in COVID-19 patients. Further studies will be required to fully understand the efficacy of these agents in the treatment of COVID-19.

CONCLUSION

We reported a case of a critically ill COVID-19 patient in Japan. Despite the effectiveness of prone ventilation in ameliorating hypoxemia, respiratory failure could not be improved and the patient finally died because of multiple organ failure accompanied by secondary bacterial infection. The lack of clinical or radiological improvement during hospitalization suggests refractory lung damage caused by severe ARDS from SARS-CoV-2 infections, which could require lung protective ventilation to be maintained for a long time, along with strict vigilance for secondary complications.

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DISCLOSURE

Approval of the research protocol: N/A.
Informed consent: Written informed consent was obtained from the patient’s family for publication. For privacy reasons, minimal epidemiological information is presented.
Registry and registration no. of the trial: N/A.
Animal studies: N/A.
Conflict of interest: None.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article at the publisher’s web-site:
Table S1. In vitro susceptibility of Staphylococcus aureus detected using blood culture on day 15 of hospitalization.