Acute Respiratory Distress Syndrome Induced by COVID-19 successfully Treated by Multidisciplinary Treatment Including Steroid Pulse Therapy

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Abstract The patient was a 72-year-old woman who developed headache, fever, dyspnea, and taste disorder over a three-day period. A COVID-19 polymerase chain reaction (PCR) test was positive. As she was elderly and required oxygen supplementation, and was therefore admitted to our hospital on day 7 after the onset of headache. Her relevant past history included hypertension, which was treated by enalapril maleate. She was initially treated by dexamethasone (6 mg) per day, remdesivir and heparinization. However, her oxygenation deteriorated and she was transferred to the intensive care unit after tracheal intubation and mechanical ventilation on the 6th hospital day. Her initial PaO2/FiO2 (P/F) value was 150. She underwent additional treatment with glycyrrhizin and γ-globulin on the same day. Her P/F value fluctuated from <200 to the 260 within one day. She underwent tracheotomy on the 13th hospital day, and steroid pulse therapy (methylprednisolone [1 g per day for 3 days]) was administered on the 14th hospital day, following the administration of methylprednisolone (10 mg). Mechanical ventilation was withdrawn from the 19th hospital day. On the 27th hospital day, she was moved to a general ward with 2 L/min of oxygen. Consideration regarding the necessity of steroid pulse therapy is the key to the treatment of COVID-19 patients with ARDS. The indication of pulse steroid therapy, including the dosage duration, and subsequent steroid treatment is a further clinical question in relation to the treatment of COVID-19-induced ARDS.

Keywords: COVID-19, ARDS, steroid pulse

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1. Introduction

The World Health Organization has declared COVID-19 a worldwide pandemic, which represents a global threat to health and economic stability. Hypertension, diabetes mellitus and cardiovascular disease are comorbidities that increase susceptibility to SARS-CoV-2 infection, particularly in elderly individuals [1]. These comorbidities have been suggested to be risk factors for the development of severe outcomes in COVID-19 [1].

Angiotensin-converting enzyme 2 is expressed in the human vascular endothelial cells, respiratory endothelial cells, and other cell types, and is thought to be a primary mechanism of SARS-CoV-2 entry and infection. SARS-CoV-2 induces acute respiratory distress syndrome (ARDS), stimulates the immune response (i.e., cytokine storm) and causes vascular damage [2,3,4]. Steroids reduce inflammation by different mechanisms, depending of their concentration. Dexamethasone, a corticosteroid, has been found to improve survival in hospitalized patients who require supplemental oxygen, with the greatest effect observed in patients who require mechanical ventilation. Thus, the use of dexamethasone is strongly recommended in this setting [5]. We herein report the case of an elderly female patient with hypertension who developed COVID-19-induced ARDS and who was successfully treated by multidisciplinary treatments, including steroid pulse therapy.

2. Case Report

The patient was a 72-year-old woman who developed headache, fever, dyspnea, and taste disorder over a three-day period. Her son was positive for COVID-19. A COVID-19 polymerase chain reaction (PCR) test revealed that the patient was positive for COVID-19. As she was elderly and required oxygen supplementation, she was admitted to our hospital on the 7th day since the onset of headache. Her relevant past history included hypertension, which was treated by enalapril maleate. She was a non-smoker and did not consume alcohol. On arrival, her vital signs were as follows: Glasgow Coma Scale, E4V5M6; blood pressure, 150/86 mmHg; heart rate, 72
beats per minute; percutaneous saturation of oxygen under 3 L O₂/minute, 99%; body temperature, 36.6°C. Chest roentgenography showed bilateral, peripherally predominant opacity in the middle and lower lung fields. Electrocardiography showed an inverted T wave in V4-V6. Computed tomography (CT) showed right-dominant ground glass opacity in both lung fields (Figure 1). The main results of a biochemical analysis of the blood revealed lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, elevated inflammatory markers, and abnormalities in coagulation tests (Table 1). She was initially treated with dexamethasone (6 mg per day), remdesivir (200 mg, followed by 100 mg per day), heparinization, azithromycin (300 mg per day) for 3 days, and ceftriaxone (2 g per day) (Figure 2). However, her oxygenation deteriorated day by day and she was transferred to the intensive care unit after tracheal intubation and mechanical ventilation on the 6th hospital day. Her initial PaO₂/FiO₂ (P/F) value was 150. She underwent additional treatment with glycyrhizin (80 mg per day) and γ-globulin (5 g) on the same day. Her P/F value increased until the 9th hospital day, when it was over 300. However, from the 10th hospital day, her P/F value was fluctuated from under 200 to 260 within one day. She underwent tracheotomy on the 13th hospital day. Steroid pulse therapy (methylprednisolone [1 g per day for 3 days]) was initiated on the 14th hospital day. After ceasing sedation, she underwent training to sit and stand with mechanical ventilation. She also received intermittent spontaneous breathing training with oxygen. Mechanical ventilation was withdrawn on the 19th hospital day. On the 25th hospital day, her tracheal tube was removed. On the 27th hospital day, she was moved to a general ward but she still required 2 L oxygen per minute via nasal cannula. CT demonstrated pulmonary fibrosis due to COVID-19 after intensive care (Figure 1).

**Figure 1.** Chest computed tomography (CT) on arrival (upper) and on the 27th hospital day (lower) (On arrival, CT demonstrated ground glass opacities in the bilateral lung fields. After intensive care, her pneumonia became fibrosis)

| Table 1. Results of a biochemical analysis of a blood sample obtained on arrival |
|-----------------------------------------------|
| **Albumin** | 3.4 g/dL |
| **Aspartate aminotransferase** | 69 IU/L |
| **Alanine aminotransferase** | 32 IU/L |
| **Lactate dehydrogenase** | 456 IU/L |
| **Creatine kinase** | 590 IU/L |
| **Blood urea nitrogen** | 14.6 mg/dL |
| **Creatinine** | 0.69 mg/dL |
| **Sodium** | 138 mEq/L |
| **Potassium** | 3.7 mEq/L |
| **Calcium** | 8.2 mEq/L |
| **Brain natriuretic peptide** | 10.0 pg/mL |
| **C. reactive protein** | 4.81 mg/dL |
| **Krebs von den Lungen-6** | 198.5 U/mL |
| **Ferritin** | 889 ng/mL |
| **Procalcitonin** | 0.31 ng/mL |
| **White blood cell count** | 3400 μL |
| **Neutrophil** | 67 % |
| **Lymphocyte** | 25 % |
| **Hemoglobin** | 13.3 g/dL |
| **Platelets** | 71000 μL |
| **Prothrombin time-international normalized ratio** | 0.97 |
| **Activated partial thromboplastin time** | 36.7 second |
| **D-dimer** | 0.9 μg/mL |
On the 55th hospital day, she was moved to another hospital for rehabilitation requiring 1 L oxygen per minute via nasal cannula.

3. Discussion

There have been 4 English medical reports concerning the efficacy of steroid pulse treatment for COVID-19-induced severe pneumonia [6,7,8,9]. Low concentrations of glucocorticoid (≤7.5 mg/day) mediate effects via genomic events in the nucleus that regulate the transcription of pro-inflammatory molecules such as IL-1, IL-6, and TNF-α. Medium concentrations (7.5-30 mg/day) activate genomic and non-genomic events. Finally, very high concentrations (>100 mg/day) intercalate into cellular membranes, disturb cation transport through the plasma membrane and leak protons from the mitochondria [6]. As the glucocorticoid dose increases and the receptors become saturated, non-genomic effects come into play and, with the administration of pulses (500-1000 mg/day), a glucocorticoid-induced apoptotic effect occurs, which explains the very rapid immunosuppressive and anti-inflammatory effects [6]. In an inflammatory cytokine storm, steroid pulse therapy can change the outcome of COVID-19, enabling a complete recovery [6,7,8,9], as was observed in the present case. There is a clinical question regarding the timing, dosage, and duration of pulse steroid therapy and subsequent steroid treatment. The 4 published medical reports varied and showed no consistent approach. The timing ranged from 13 to 29 days from the onset of initial symptoms, the dose ranged from 125 mg to 1000 mg for 3 days, and the subsequent steroid treatments were not consistent. In survivors of severe COVID-19-induced ARDS, hypoxia induced by the complication of pulmonary fibrosis may remain as sequel [10,11]. Our case also showed pulmonary fibrosis necessitating oxygen supplementation after transfer to the general ward, even with almost constant steroid use. Long-term steroid use might reduce the fibrotic change after COVID-19-induced ARDS [12].

4. Conclusion

Consideration regarding the necessity of steroid pulse therapy is the key to the treatment of COVID-19 patients with ARDS.

The indication of pulse steroid therapy, including the dosage duration, and subsequent steroid treatment is a further clinical question in relation to the treatment of COVID-19-induced ARDS.

Conflict of Interest

The authors declare no conflicts of interest in association with the present study.

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List of Abbreviations

CT: computed tomography
ARDS: acute respiratory distress syndrome
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