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Umbilical Cord-Mesenchymal Stromal Cells (UC-MSCs) Therapy in COVID-19 Patients with Severe Inflammatory Immune Response: A Case Report

Pompini Agustina Sitompul[1], Nina Mariana[1], Surya Oto Wijaya[1], Rumaisha Satyawati[1], Adria Rusli[1], Titi Sundari[1], Rosamarlina Rosamarlina[1], Faisal Rizal Matondang[1], Haruyuki Dewi Faisal[1], Vivi Setiawaty[1*], Mohammad Syahril[1]

Prof. Dr. Sulianti Saroso National Infectious Disease Hospital, Jakarta, Indonesia[1]

Correspondence author: 1*

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ABSTRACT

A 71-year-old woman was admitted to the hospital on 7 July 2020 diagnosed with critically ill COVID-19 disease on a ventilator. The symptoms started three days before; fever, fatigue, and shortness of breath. She had a history of hypertension and diabetes mellitus. Blood test showed signs of severe inflammatory immune response and critical of clinical course. An intervention of Umbilical Cord Mesenchymal stem cells (UC-MSCs) therapy was planned as an add-on therapy. Evaluation was conducted by clinical presentation, blood drawing and radiography examination. We highlight that the patient showed promising clinical, laboratory, and radiological improvement after therapy. However, we cannot conclude whether the improvement is caused by UC-MSCs therapy itself since it is only a single case report and an old case report that the Covid-19 vaccinations are not already available at that time. Therefore, further studies were needed to investigate this result.

1. Introduction

COVID-19 can lead to lung fibrosis, acute respiratory distress syndrome (ARDS), and multiorgan failure resulting in death [1]. The mortality rate in COVID-19 patients with ARDS is 52.4%. Severe COVID-19 might is caused by the prothrombotic state, hyperinflammation, immunothrombosis, and overactive immune response, which can trigger cytokine storm. Therefore, therapies that can reduce the excessive inflammatory response to prevent cytokine storm and immunothrombosis could be the critical steps for the patient's treatment [2].

Mesenchymal stem cell (MSC) is a new potential treatment for COVID-19 with ARDS, among other potential medication options. MSC were multipotent cells that have been the treatment for the inflammatory disorder, systemic lupus erythematosus, and autoimmune disease. MSC has been reported to modulate hyperinflammatory processes, overactive immune, secrete antimicrobial molecules, generate tissue repair, restrict lung fibrosis, and ARDS [2], [3]. Here, we describe a case of severe inflammatory immune response

of COVID-19 patients with Umbilical Cord Mesenchymal Stromal Cells (UC-MSCs) therapy.

2. Case Report

A 71-year-old woman was admitted to the hospital on 7 July 2020 diagnosed with critically ill COVID-19 disease on a ventilator. The symptoms started on 4 July 2020 with fever, fatigue, and shortness of breath. She had a history of hypertension and diabetes mellitus. Laboratory test showed normal leucocyte and procalcitonin levels; lymphocytopenia (absolute lymphocyte count: 71 cell/mm^2); thrombocytopenia (thrombocyte: 126 10^3/µL), and D-dimer 1.3 mg/L. On day 6, there was no clinical improvement and a comprehensive laboratory test showed high levels of D-dimer (2.1 mg/L), CRP (64.58 mg/dL), lactate acid (2.7 mmol/L), pro-BNP (35.32 pg/mL), normal liver and renal function, and low levels of albumin (2.8 g/dL). Laboratory tests of cytokine levels and lymphocyte subpopulation (CXCR3+CD4+; CXCR3+CD8+; CXCR3+CD56) showed in table 1. Chest radiograph showed bilateral pneumonia and borderline cardiomegaly (figure 1 a).

Table 1. Cytokines and lymphocyte subpopulation levels before and after UC-MSCs therapy

Cytokines	Results on day 6 (before UC-MSCs therapy)	Results on day 12 (5 days after UC-MSCS[a] therapy)
VEGF[b] (pg/mL)	41.33	49.38
Ferritin (ng/mL)	337	421
IL-6[c] (pg/mL)	18.8	6.54
LIF [d]	3.64	6.57
CXCR3+CD4+	2.69	1.1
CXCR3+CD8+	0.6	0.5
CXCR3+CD56	1.9	1.9

[a]Umbilical Cord Mesenchymal stem cells; [b]Vascular endothelial growth factor; [c.] Interleukin 6; [d.] Leukemia Inhibiting Factor

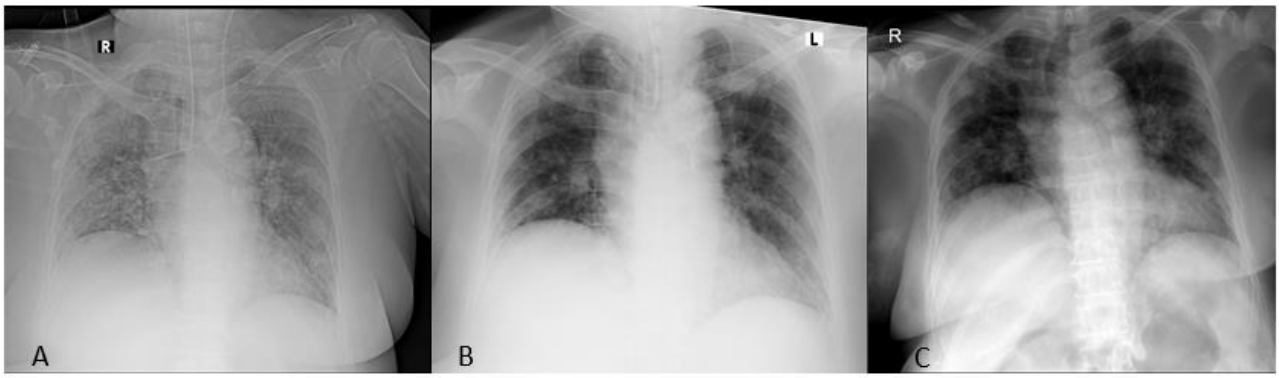

Figure 1. Chest radiograph on day 6/before UC-MSCs therapy (a), on day 15 (b), and on day 24 when the patient was discharged

Considering these signs of severe inflammatory immune response and critical of clinical course, an intervention of Umbilical Cord Mesenchymal stem cells (UC-MSCs) therapy was planned as an add-on therapy. On day 7, a single dose of UC-MSCs therapy via intravenous routes (80 x 10^6 cells with 100 cc saline solution 0.9%). Premedication before transplantation was diphenhydramine, dexamethasone, and heparin. No acute or delayed reactions or adverse effects were detected following the administration of the treatment. Besides UC-MSCs therapy, empiric antibacterial treatment, such as ceftazidime, was also given intravenously to the patient. The empiric antibacterial treatment was replaced with tigecycline and amikacin

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based on blood culture results. Micafungin was also given to the patient after the blood culture test was confirmed of fungal infection. In addition, she was treated with N-acetylcysteine, enoxaparin, comorbidities treatment, and others of supportive treatment.

On day 12, the clinical condition was similar, but laboratory tests of cytokine levels and lymphocyte subpopulation after UC-MSCs therapy showed in table 1. On day 15, the blood test showed levels of D-dimer (1.5 mg/L), CRP (123.21 mg/L), and chest radiograph improvement (figure 1b). On day 19, the patient showed clinical improvement, and the laboratory test showed D-dimer reduction to 1 mg/L and CRP reduction to 59.17 mg/L. The patient then was extubated. On day 24, the patient was discharged with a chest radiograph was shown in figure 1c.

3. Discussion

Earlier in the COVID-19 pandemic, there was no specific medication for COVID-19. Patients with the severe clinical condition require hospitalization and need medications [4], [5]. Severe clinical conditions are caused by cytokine storm leading to ARDS. Therefore, cytokine storm inhibition is the key factor in treating COVID-19 patients [6]. Mesenchymal stem cells therapy has the potential to control cytokine storm [7]. Stem cells can be obtained from the umbilical cord, adipose tissue, Wharton jelly, placenta, dental pulp. Among all stem cell sources, the umbilical cord is the most reliable, safe, common source, and has no sign of tumorigenicity [1].

We presented 71-year-old women with critically ill COVID-19 and severe inflammatory immune response. Elderly patients with the underlying disease were more vulnerable to COVID-19 infection leading to respiratory distress, based on epidemiological data [8]. In this patient, the high level of IL-6 and other clinical signs showed a severe inflammatory immune response. Thus, we considered giving UC-MSCs therapy as an add-on therapy. IL-6 decrease after UC-MSCs therapy compares to before therapy showed the role of UC-MSC therapy in suppressing the inflammatory process. MSC therapy suppresses the inflammatory process thru IL-10 that activates Janus tyrosine kinase 1 (JAK1) and tyrosine kinase-2 that reduce pro-inflammatory cytokines expressions, such as IL-6, IL-1, IL-17A, and TNF-α. [9], [10]. However, other cytokines levels, such as VEGF, ferritin, Leukemia Inhibiting Factor (LIF) increase after UC-MSCs therapy, while there was a suppression of CXCR3+CD4+ and CXCR3+CD8+. Other than that, this patient showed D-dimer and CRP reduction following UC-MSCs therapy. MSC therapy can modulate the overactive immune system that leads to control cytokines storm, decrease D-dimer and CRP level [9], [10]. We also observed the improvement in the pulmonary radiological result after UC-MSCs therapy, such as the improvement of patchy GGOs. MSC therapy can stimulate lung injury improvement by stimulating leaky pulmonary blood vessel repair by VEGF and PDGF leading to angiogenesis, pulmonary infiltrates, and bilateral GGOs reduction [11- 13]. There was no serious side effect following UC-MSCs therapy.

4. Conclusions

In conclusion, a mesenchymal stem cell has anti-inflammatory, immunomodulatory, and regenerative properties. UC-MSCs therapy showed a promising therapeutic result in this case, as seen in the clinical, laboratory, and radiological improvement. However, we can not conclude whether the improvement is caused by UC-MSCs therapy itself since it is only a single case report and an old case report that the Covid-19 vaccinations are not already available at that time. Therefore, further studies were needed to investigate this result.

Ethics approval and consent to participate

This case is a part of the clinical trial study that was ethically approved by the ethics board of the Faculty of

Medicine Universitas Indonesia (KET-A36/UN2.F1/ETIK/PPM.00.02/2020).

Declaration of interest
The authors declare that they have no conflict of interest

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