JAMER 2022;7(1):26-30

Mesenchymal Stem Cell Therapy in Severe COVID-19 in a Young Male Healthcare Worker with Tetralogy of Fallot

Fallot Tetralojisi Olan Genç Erkek Sağlık Çalışanının Şiddetli COVID-19'unda Mezenkimal Kök Hücre Tedavisi

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ÖZ

Şiddetli akut solunum yolu sendromuna neden olan yeni bir tip koronavirüs ilk olarak 2019 Aralık ayının sonunda Çin'in Wuhan kentinde tanımlanmış ve hastalık hızla dünya çapında yayılmıştır. COVID-19 hafif hastalıktan şiddetli pnömoniye kadar bir dizi semptomla karakterize edilebilir. Kardiyovasküler hastalıklar COVID-19'un şiddetini ve mortaliteyi artırıyor. Fallot Tetralojisi en sık görülen siyanotik doğuştan kalp hastalığıdır.
Bu vaka, bir sağlık çalışanı ve Fallot Tetralojisi öyküsü olan yetişkin bir COVID-19 hastasıdır. Hastaya solunum sıkıntısı nedeniyle Yüksek Akışlı Nazal Oksijen tedavisi uygulandı. Ayrıca hastalık kritik süreçteyken Mezenkimal Kök Hücre uygulandı. Mezenkimal Kök Hücre tedavisinin ikinci gününden itibaren hastada klinik ve laboratuvar iyileşme gözlendi. Fallot Tetralojisi geçmişi olan genç sağlık çalışanı, COVID-19 nedeniyle yoğun bakıma ihtiyaç duydu. Hastaya verilen antiviral tedavilere yanıt alınamadı. Hastanın tedavisinde Yüksek Akışlı Nazal Oksijen ve Mezenkimal Kök Hücre kullanıldı.

Anahtar Kelimeler: COVID-19, mezenkimal kök hücre, fallot tetralojisi

ABSTRACT

A novel type of coronavirus (SARS-CoV-2), which causesevere acute respiratory syndrome, wasfirst identified in Wuhan, China at the end of December 2019 and the disease rapidly spread worldwide. COVID-19 may be characterized by a range of symptoms, mild illness to severe pneumoniae. Cardiovascular diseases increase severity and mortality in COVID-19 patients. Tetralogy of Fallot is the most common cyanotic congenital heart disease. The present case is an adult COVID-19 patient with a history of Tetralogy of Fallot, who is a healthcare worker. High Flow Nasal Oxygen therapy was used due to respiratory distress. In addition, Mesenchymal Stem Cells were applied while the disease was in critical process. The clinical and laboratory improvement were observed in the patient from the second day of treatment of Mesenchymal Stem Cells. The young healthcare worker with a history of Tetralogy of Fallot needed critical care due to COVID-19. Response to the antiviral treatments given to the patient could not be obtained. High Flow Nasal Oxygen and Mesenchymal Stem Cells were used in the treatment of the patient.

Keywords: COVID-19, mesenchymal stem cells, tetralogy of fallot

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Geliş tarihi/Received: 16.10.2021
Kabul tarihi/Accepted: 10.03.2022

JAMER 2022;7(1):26-30

INTRODUCTION

At the end of 2019, severe acute respiratory syndrome due to a novel coronavirus (SARS-CoV-2) infection appeared in China and caused a major global outbreak (1). The disease named 2019 novel coronavirus disease (COVID-19) is characterized by a range of symptoms, mild illness presenting with symptoms of an upper respiratory tract infection (dry cough, mild fever, sore throat) to severe pneumoniae.

Tetralogy of Fallot (ToF) is the most common type of cyanotic congenital heart disease (2). COVID-19 may be more severe in patients with a history of cardiovascular disease and the risk of death is increased. COVID-19 disease may itself cause direct and indirect cardiovascular complications including acute myocardial damage, myocarditis, arrhythmias, and venous thromboembolism. Also, treatments for COVID-19 may have cardiovascular side effects (3). That's because the management of cardiovascular disease (CVD) patients with COVID-19 is challenging. Stem cell therapy is recently have promising results for very difficult-to-treat disease. In particular, Mesenchymal Stem Cell (MSCs) has come to the fore in stem cell treatments. High resource potential, high proliferation ability, low risk of serious side effects and easy application are advantages of MSCs. MSCs may prevent cytokine storm with its immunomodulating feature and regeneration ability. Due to its contribution to the regeneration of respiratory epithelium MSCs prevent fibrosis in COVID-19 patients. Although it is not yet a standard recommendation in the treatment of COVID-19 with these thoughts, it is promising among the treatments that can be used (4).

Surviving Sepsis Campaign Guideline on the management of critically ill adults with COVID-19 has recommended the use of High Flow Nasal Oxygen (HFNO) instead of standard oxygen. Non-Invasive Mechanical Ventilation (NIMV) is a weak recommendation and supported by low-quality evidence in these guidelines and may reduce the rate of intubation compared to the conventional oxygen. HFNO is also reported to be more comfortable for the patient than NIMV (5).

CASE REPORT

A 43-year-old male patient working as a medical secretary, with a history of his last operation while he is six years old due to ToF. The patient's symptoms related to ToF improved after six years of operation. He applied to the pandemic outpatient clinic of Kayseri City Hospital in April 2020 with symptoms of fever and fatigue. His vital signs were stable, except that his body temperature which was 38.5^{0}C. Widespread bilateral interstitial infiltrations were noteworthy on the lung X-ray (Figure 1).

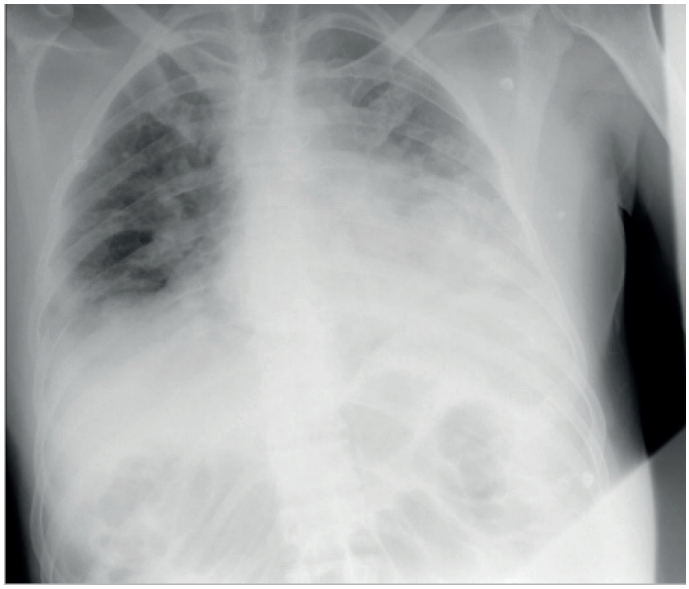

Figure 1. Widespread bilateral interstitial infiltrations are noteworthy on the lung x-ray.

Computed Tomography (CT) findings showed ground-glass opacities in the lower lobe and posterobasal segment of the left lung compatible with viral pneumonia (Figure 2) .

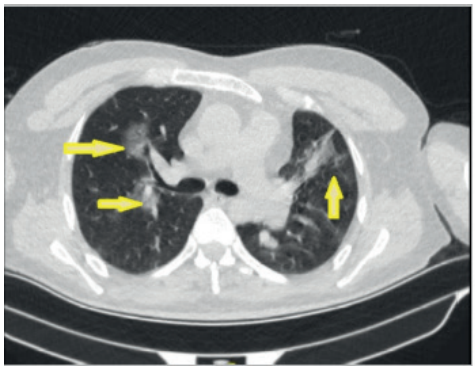

Figure 2A. In the CT section of the patient, infiltrations and interstitial involvement and ground glass areas are observed.

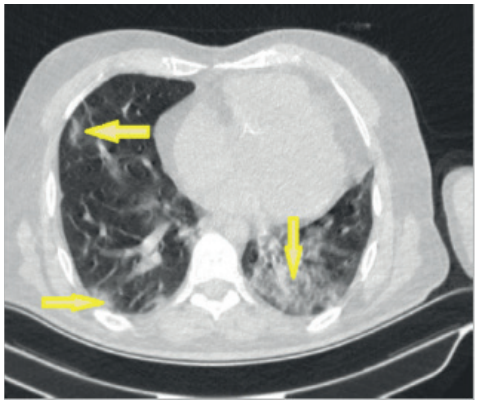

Figure 2B. In the CT section of the patient, peripheral ground-glass areas attract attention.

Hydroxychloroquine 400 mg/day maintenance after loading 800 mg/day, clarithromycin 1gr/day, ceftriaxone 2gr/day and oseltamivir 150mg/day treatments were initiated. On the first day of his hospitalization, the SARS-Cov-2 Polymerase Chain Reaction (PCR) test from the nasopharyngeal swab was negative. Clarithromycin and hydroxychloroquine were discontinued when the corrected QT Distance (QTc) was 530 milliseconds (ms) on Electrocardiography (ECG) performed on the second day of treatment. Levofloxacin 500mg/day treatment for atypical pneumonia was initiated. QTc times were between 480-520 ms in daily ECG follow-ups . The symptoms of patient did not improve, while bacterial cultures of blood, urine and sputum remained negative. On the fourth day of his hospitalization, the SARS-Cov-2 PCR swab sample was tested again and it was negative. Oseltamivir treatment that the patient was receiving was completed and discontinued after five days. On the eighth day of hospitalization second control CT was performed and revealed a progression with consolidated areas accompanied by multilobar peripheral and centrally located ground glass density areas in both lungs. Ceftriaxone 2g/day was changed by piperacillin-tazobactam 13.5 g/day. The patient had respiratory distress with respirator a rate of 35/minute and an oxygen saturation (SpO2) of 86% while receiving 6lt/minute nasal oxygen, he transferred to intensive care unit (ICU). In admission to the ICU, the respiratory rate was 34 / min, body temperature was 37.6^{0}C, heart rate was 112/min, and the measured systolic blood pressure was 132 mmHg . There was a significant increase in the C-reactive protein (CRP) (Table 1). Favipiravir 600 mg/day maintenance after loading 1600 mg/day was added to the patient's treatment. Piperacillin-Tazobactam 13.5 gr/day was continued and levoflaxacin was stopped. Elongation continued in QTc in ECG and was calculated as 504 ms. Due to the low oxygen saturation and tachypnea HFNO therapy was initiated. The HFNO treatment was started with current 60lt / min and fraction of inspired oxygen (FiO2) value 60% and titration was performed with oxygen saturation >90%. The rapid antibody test performed on the 11th day of symptoms began was positive, and the patient was treated with 1x10^6/kg MSCs. MSCs used were products produced in the Erciyes University Genome and Stem Cell Center in the unit of good manufacturing process, originating from an allogeneic umbilical cord. These products were intravenously infused in saline and administered to the patient. The respiratory distress of patient improved after two days after the treatment with MSCs, and the flow in HFNO treatment was reduced to 40 lt/min and FiO2 to 40%. CRP, D-Dimer, Ferritin values gradually decreased (Table 1). Favipiravir treatment was completed after five days.

Table 1. Trends in laboratory test of patient with COVID-19 during his hospitalization and receiving MSCs therapy

Laboratory measures	Normal ranges	At admission to hospital	At admission to ICU	1st day of MSCs	3th day of MSCs	7th day of MSCs
White blood cell count	4.5-10×109/l	6.8	7.3	9.8	6.4	7.3
Neutrophil count, ×109/l	1.8-7.5	4.04	6.2	8.5	4.3	4.9
Lymphocyte count, ×109/l	0.8-3.2	1.2	0.8	0.6	1.2	1.4
Aspartate aminotransferase, u/l	0-40	23	41	54	105	38
Alanine aminotransferase, u/l	0-41	35	32	40	143	109
Procalcitonin, ng/ml	< 0.5	0.07	0.26	0.35	0.22	0.05
C-reactive protein, mg/dl	0-5	7.5	95	183	34	13
Lactate dehydrogenase, u/l	135-225	204	370	663	305	250
Ferritin, ng/ml	30-400	303	871	2123	1750	776
D-dimer, ng/ml	0-500	310	400	6940	560	300
Fibrinogen mg/L	2000-4000	510	4480	6430	5190	5180

Trends in laboratory test of patient with COVID-19 during treatment.
*MSC: Mesenchymal Stem Cells

On the eighth day of his admission to the ICU, the patient was separated from HFNO and started with conventional 4lt/min nasal oxygen treatment, since there was no respiratory distress and normal oxygen saturations despite decreased HFNO support. The patient was transferred to the inpatient clinics on the 10th day of ICU hospitalization and was discharged two days after.

DISCUSSION

This current case was an adult COVID-19 patient with a history of ToF , who was also a healthcare worker . The Surviving Sepsis Campaign guideline recommends HFNO as a poor recommendation and poor-quality evidence for oxygenation of COVID-19 patients (5). However, this presented patient was received HFNO and there was no need for intubation during his ICU stay.

Although the SARS-CoV-2 PCR test from the nasopharyngeal swab was negative twice, the treatment for COVID-19 was initiated as the patient's CT had findings compatible with COVID-19, later the antibody test was also found positive. In the diagnosis of COVID-19, the sensitivity of PCR is not high and repeated samples are recommended. In order to avoid delay in diagnosis, considering CT findings as well as PCR testing is recommended (6).

Both a history of a congenital cyanotic CVD and working as a healthcare worker may have caused the disease to be more severe in this presented patient. Driggin et al previously reported that in patients with a history of CVD, the disease severity and mortality is higher, and health professionals with CVD face this risk with increased contact (3). Both clinical and laboratory responses were observed after the MSCs applied to our patient. Although there are no large randomized controlled trials about the use of MSCs in the treatment of COVID-19, the results of seven COVID-19 patients undergoing MSCs in China have been reported (7). These patients showed a marked decrease in proinflammatory cytokines, especially on the second day after MSCs . This data was also compatible with our patient's laboratory results. In order for the effect of our patient to be generalized, randomized controlled studies are needed regarding the use of MSCs in the treatment of COVID19.

Favipiravir is an antiviral agent that selectively and potently inhibits the RNA-dependent RNA polymerase of RNA viruses. Evidence for favipiravir is limited. Currently, available information is not sufficient to recommend favipiravir for COVID-19 treatment, and additional studies are needed (8). In this presented patient, MSCs were applied on the third day of favipiravir treatment. Even though favipiravir may have an effect on the patient's response, we thought that MSCs may have an effect here. Because, on the third day after favipiravir treatment was initiated, the patient continued clinical and laboratory deterioration. At the same time, the evidence showing the efficacy of favipiravir is insufficient. Randomized controlled studies are needed to demonstrate the efficacy of favipiravir.

CONCLUSION

It should be kept in mind that also in younger adults with COVID 19, comorbidities may be observed. We can conclude from this study that stem cell may be an alternative in patients who worsen despite standard antiviral treatments. HFNO can be effective by delaying patients with respiratory distress to go to intubation. Patients should be followed closely in terms of side effects and changing drugs should be considered if necessary. Large randomized controlled studies are needed regarding the efficacy of both HFNO and MSCs in treatment.

Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study has received no financial support.
Ethics Committee Approval: While writing this case report, the data of a patient were taken from the system with the knowledge and permission of the patient and the hospital administration. In addition, written consent was obtained from the patient.
Authors' contributions: Conseption/Design of Study- RCY, AUK; Data Acquisition- RCY, EEE; Critical Revision of Manuscript- RCY, AUK, EEE; Final Approval and Accountability- RCY, EEE, AUK, -İÇ; Supervision- RCY, EEE, AUK, İÇ.

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