



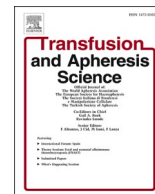
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## Human placenta-derived mesenchymal stromal cells transfusion in a critically ill infant diagnosed with Coronavirus Disease 2019 (COVID-19): A case report

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## ABSTRACT

Coronavirus disease 2019 (COVID-19) is still an emergency in many countries. Herein, we report treatment with human placental-derived mesenchymal stromal cells transfusion (hPD-MSCT) in a critically ill infant diagnosed with COVID-19. A 28-day-old male infant with a history of pneumonia was referred to our center with decreased SpO<sub>2</sub> (92%) and fever (38.5 °C). Real-time reverse transcription polymerase chain reaction (RT-PCR) and chest computed tomography (CT) confirmed COVID-19 infection. Considering the deteriorating clinical status of the patient despite the routine treatments (SpO<sub>2</sub> 82%), human placental derived mesenchymal stromal cells (hPD-MSCs) was transfused to him on day 9 and 11 ( $7 \times 10^6$  cells/session). The patient's general condition started to change 3 days after hPD-MSCT and poor feeding and low SpO<sub>2</sub> improved day by day. On day 20, the patient was discharged (SpO<sub>2</sub> 97%) and our one-year follow-up showed a successful response to the treatment with no reported complications. hPD-MSCT may be considered as a possible treatment option in infants/children diagnosed with COVID-19 who fail to respond to conventional therapies. However, required dose, safety, and mechanistic studies are still warranted to further investigate this treatment.

### 1. Background

Coronavirus disease 2019 (COVID-19) which causes by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been spread all over the world and has led to a pandemic emergency [1]. The most prominent sign of this disease has been mentioned as pneumonia [2], however, other organ(s) dysfunction/failure has been reported especially in critically ill patients [3]. One of the most important pathways in the pathogenesis of COVID-19 in critically ill patients is cytokine storm which is the result of excess pro-inflammatory cytokines release [2]. Acute respiratory distress syndrome (ARDS) is among the most

important concerns in COVID-19. Different pathways have been suggested for ARDS which among them is inflammation, especially cytokine storm has been known to has a solid role [4]. Thus, suppression of inflammation and related pathways have been suggested as one of the most important treatment options in critically ill patients diagnosed with COVID-19 [5].

This report highlights the successful treatment with allogeneic human placental-derived mesenchymal stromal cells transfusion (hPD-MSCT) in a 1-month-old male patient with a history of previous pneumonia and a current diagnosis of severe COVID-19 accompanied with a long follow-up period.

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## 2. Case report

### 2.1. Ethics approval and consent to participate

This study was confirmed by the Medical Ethics Committee of Kermanshah University of Medical Sciences, Kermanshah, Iran (IR.KUMS.REC.1399.065). Also, this case belongs to a pilot clinical trial registered in the Iranian Registry of Clinical Trials (IRCT20200418047121N2). The aims and methods of this trial were clearly explained to the patient's legal guardians according to their knowledge of the issue. Finally, they were asked to sign a consent form freely to start the intervention.

### 2.2. Cell isolation

Mesenchymal stromal cells (MSCs) derived from human placenta tissue (single donor) were isolated and identified as previously has been fully described by our team [6]. The donor was checked for different infections such as hepatitis B virus (HBV), hepatitis C virus (HCV), human immunodeficiency virus (HIV), mycoplasma, and cytomegalovirus (CMV) by polymerase chain reaction (PCR). Only the cells exhibited surface expression of mesenchymal markers (CD 73, CD 105, and CD 44) and were negative for hematopoietic markers (CD 45, CD 34, and HLA-DR) identified as placental MSCs. Also, the cells were assessed for adipogenic, chondrogenic, and osteogenic differentiation potentials at passages 2–3. Finally, passage 4 was used for transfusion.

### 2.3. Case presentation

Our hospital received the transfer of a 28-day-old infant who was born from a singleton term pregnancy by cesarean delivery from a healthy mother with no underlying condition, other than well-controlled pregnancy hypothyroidism. The neonate was referred given the complicated course he underwent after birth with admission to the neonatal intensive care unit (NICU) with the diagnosis of severe neonatal asphyxia which progressed to fever and a productive cough. On arrival, the infant was moderately dehydrated with a respiratory rate of 55 breaths per minute and SpO<sub>2</sub> of 92% (details in Table 1). Given these findings, he was admitted to the intensive care unit where noninvasive O<sub>2</sub> therapy was started (FiO<sub>2</sub>: 21–40%, 6–8 liters O<sub>2</sub> per minute). Considering the COVID-19 pandemic, nasopharyngeal sample collection was performed for the infant with real-time reverse transcription-polymerase chain reaction (rRT-PCR) confirming COVID-19 infection. Moreover, chest computed tomography (CT) showed bilateral alveolar consolidations (mostly in central aspects of the lungs) with no pleural and pericardial effusions (Fig. 1A); findings in keeping with acute respiratory distress syndrome (ARDS). Laboratory investigations demonstrated leukocytosis and elevated C-reactive protein (details in Table 2), while urine, cerebrospinal fluid (CSF), and blood cultures were all negative.

Broad-spectrum antibiotics were started based on our center's guideline (ampicillin: day 1–3; cefotaxime: day 1–9; Clindamycin: day 7–22; meropenem: day 10–22) and the patient was observed regarding each of his clinical and para-clinical statuses. Also, salmeterol and budesonide were administered for days 0–22 and 0–19 respectively. After more than a week and on hospital day (HD) 8, despite the non-

invasive oxygenation support, the SpO<sub>2</sub> of the patient decreased to 82% (without oxygen supply). Considering the lack of clinical response to the routine medications and deterioration of the vital signs, the patient was a candidate for the hPD-MSCT. The hPD-MSCT started with  $7 \times 10^6$  cells on HD 9 and 11 through the cubital vein (injection duration: 60 min) as well as 30 mg of intravenous hydrocortisone which no side effect was observed and he was observed for any possible side-effect (s) every day. A new chest CT scan has been performed on HD 15 which revealed beginning of resolution of consolidation with gradually growing patchy ground glass opacification (Fig. 1B). Considering the significant improvement in clinical status (Table 1) as well as laboratory variables (Table 2) of the patient he was discharged on HD 20. Also, a new chest X-ray was performed a week after the discharge day which showed resolution of the central opacification (Fig. 1C). In this case, we have performed a 250-day follow-up which showed no adverse effect related to hPD-MSCT or any sign/symptom in favor of respiratory issues. This follow-up is still ongoing for at least one year for any side effects regarding the treatment.

## 3. Discussion

In this report, a 30-day male infant that had an unknown history of pneumonia (to us at admission) with further confirmed SARS-CoV-2 infection was successfully treated with hPD-MSCs. The patient's clinical status has been improved following the intervention. Not only the clinical manifestations (Table 1) but also laboratory variables have been improved following the intervention (Table 2).

Recently, few studies have evaluated the outcome of allogeneic MSCs infusion for patients with COVID-19. Liang et al. [7], have reported a successful intervention in a critically ill 65-year-old woman who did not respond to the regular treatments in 12 days. Three sessions of human umbilical cord mesenchymal stromal cell transplantation (hUCMSCT) with  $5 \times 10^7$  cells/session were administered for her with an interval of 3 days. On the HD 30, the patient was discharged. Unfortunately, no further follow-up was reported by the authors [7]. Another study by Shu et al., on 12 patients diagnosed with COVID-19 was performed with an endpoint of 14 days. They have shown that the hUCMSCT reduced IL-6 and CRP levels as well as improved lung inflammation compared to the control group. Also, significant clinical improvement was observed on HD 7 and all of the patients of the intervention group were discharged [8]. One of the main important differences between the mentioned study and the current report is the previous pneumonia of the patient. However, other bolded differences such as the age of the patient and the source of MSCs are among the important differences with other reports.

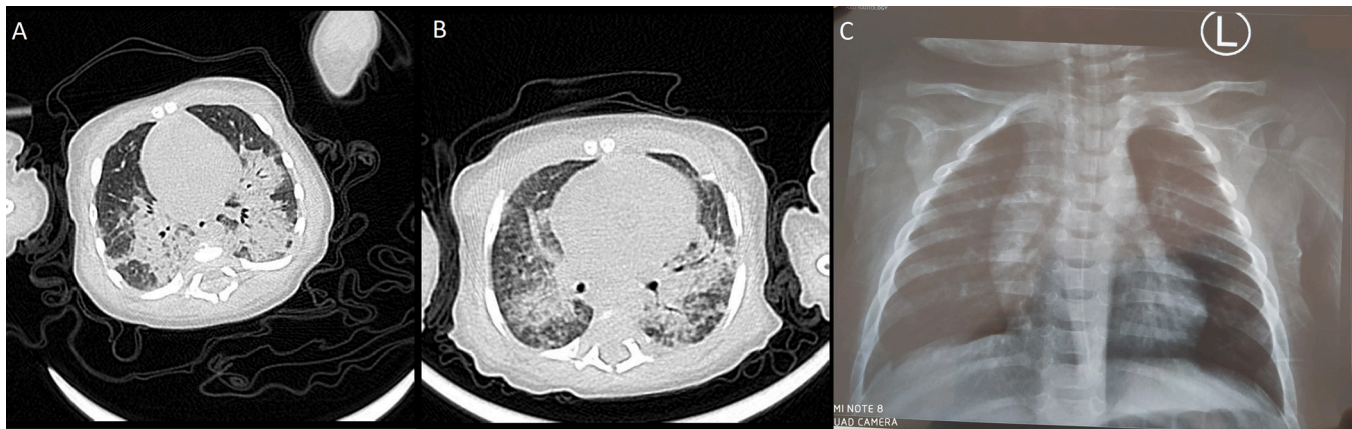
MSCs have been used in the clinic for many years to treat different inflammatory diseases such as systemic lupus erythematosus (SLE) [9] and graft-versus-host disease [10]. In a recent (2020) systematic review and meta-analysis, the authors have shown that both autologous and allogeneic MSCs with different sources are safe to be used in the clinic [11]. The immunomodulation effect of the MSCs has been reported to be from the regulation of different immune system cells responsible for inflammation. MSCs promote the survival of monocytes and induce differentiation toward macrophage M2 anti-inflammatory phenotype that expresses CD 206 and CD 163. Also, activated MSCs secrete prostaglandin E2 that drives resident macrophages with an M1 pro-inflammatory phenotype toward an M2 anti-inflammatory phenotype. Also, MSCs exert their immune suppressive potential through cell-cell contact and by secretion of immune regulatory molecules [12–14]. MSCs display broad immunomodulatory properties including affecting the proliferation and function of T cells, Natural killer T cells, T regulatory cells B cells, and dendritic cells. However, several soluble factors have been shown to play a major role in the immunosuppressive effects of MSCs, including prostaglandin E2, transforming growth factor  $\beta$ 1, indoleamine 2,3-dioxygenase, nitric oxide, hepatocyte growth factor, and IL-10 [12,13]. Also, the antimicrobial role of MSCs has been reported [15] which could be effective for those COVID-19 patients with

**Table 1**

Clinical findings of the patient in the time lapse of hospitalization.

Variable	Admission	A Day before hMSCT	Discharge day
Respiratory (breath/minute)	55	39	37
Pulse rate (beat/minute)	115	137	130
SpO <sub>2</sub> (%)	92	82	97
Body temperature (°C)	38.5	38.2	37.3

hMSCT: Human mesenchymal stromal cells transfusion.



**Fig. 1.** Radiological findings during hospitalization and follow-up. **A:** Computed tomography (CT) scan in the hospital day (HD) 1 showing bilateral alveolar consolidations mostly in central parts with no pleural and pericardial effusions. **B:** Chest CT scan on the HD 15 showing beginning of resolution of consolidation with gradually growing patchy ground glass opacification. **C:** Chest X-ray a week after discharge showing resolution of the central opacification.

**Table 2**

Laboratory finds of the patient in the time lapse of hospitalization.

Variable	Admission	A Day before hMST	Discharge
White-cell count (per mL)	18,200	16,700	10,200
Absolute lymphocyte count (per mL)	6734 (37%)	7348 (44%)	4896 (48%)
Absolute neutrophil count, (per mL)	9646 (53%)	8851(53%)	4998 (49%)
Platelet count $\times 10^3$ (per mL)	671	705	258
Hemoglobin (gr/dL)	12.1	11.1	10
Hematocrit (%)	36.3	33.5	31
C-reactive protein (mg/L)	2 +	NA	Negative
Creatinine (mg/dL)	0.81	0.54	0.5
Urea (mg/dL)	18	11	9
Aspartate aminotransferase (U/L)	NA	46	8
Alanine aminotransferase (U/L)	NA	16	26

hMST: Human mesenchymal stromal cells transfusion; NA: Not available. During the hospitalization, other laboratory parameters such as levels of total bilirubin, prothrombin time (PT), partial thromboplastin time (PTT), Na, and K were in the normal range.

secondary bacterial infections such as hospital-acquired infections, especially in intubated patients.

#### 4. Conclusion

According to our knowledge, this is the first report on an infant who received hPD-MSCs for COVID-19. The patient was in the critically ill stage of the disease and didn't respond to the conventional treatments. As we know so far, hPD-MSCs just have been used in the trials/case series/case reports but further dosage investigation for each disease/disorder, its safety, and mechanistic studies are still warranted to further clinical administration.

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#### CRediT authorship contribution statement

**Kamran Mansouri, Mehrdad Payandeh, Reza Yarani:** Study design and concept. **Mehrdad Payandeh, Reza Habibi:** Clinical interventions. **Kamran Mansouri, Mehrdad Payandeh, Reza Habibi, Amir Hossein Norooznezhad, Avnesh S. Thakor, Feizollah**

**Mansouri:** Clinical team. **Kamran Mansouri, Zohreh Hoseinkhani, Mitra Bakhtiari, Farzaneh Esmaili:** Stem cell-related laboratory investigation/preparation. **Amir Hossein Norooznezhad:** Drafting the first version of the manuscript. All authors have participated in the revising the manuscript and have approved the final form.

#### Conflict of interests

Authors declare no conflict of interests.

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