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Coronavirus Pandemic

Umbilical cord blood-derived mesenchymal stem cells in treating a critically ill COVID-19 patient

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Abstract

Introduction: The coronavirus disease 2019 (COVID-19) pandemic is spreading rapidly. Critically ill cases of COVID-19 can rapidly progress to acute respiratory distress syndrome and multiple organ failures. However, no effective drugs have been available till now, leading to more than 300,000 deaths up to 29 April 2020. Here, we present a critically ill case utilizing umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs).

Case presentation: A 72-year-old man was admitted, with the diagnosis of COVID-19, ARDS, type-2 diabetes, diabetic nephropathy, renal insufficiency, and hypertension. His clinical condition continually developed to be life-threatening even receiving various treatment options including antiviral therapy and extracorporeal membrane oxygenation. Between 28 February and 8 March 2020, the patient was given 5-time intravenous infusions of UCB-MSCs. His hematological and biochemical indexes, including lymphocytes and renal function improved. Pulmonary static compliance increased significantly and PaO_2/FiO_2 ratio maintained stable. On March 10, he received lung transplantation.

Conclusions: Our current findings suggested that UCB-MSCs therapy may show some positive effect in treating critical COVID-19 to some extent, for its delaying deterioration of the disease and efficacy in respiratory and renal function, though limited.

Key words: UCB-MSCs; COVID-19; ARDS; respiratory failure.

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Introduction

In late December 2019, coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was first reported in Wuhan, Hubei Province, China [1]. Up to April 29, the rapidly spreading pandemic caused over 3,000,000 cases in more than 210 countries. Most patients with COVID-19 have mild flu-like symptoms and good prognosis, while quite a lot of patients who have comorbidities develop severe and critical pneumonia, acute respiratory distress syndrome (ARDS) and multiple organ failure. To date, an alarming number of critically ill COVID-19 cases have been reported, while effective therapies available for these patients are still limited, resulting in that most critically ill patients could not survive eventually.

The administration of mesenchymal stem cells (MSCs) has become attractive in recent years as one of the potential candidates for treating a wide range of diseases. A large literature has been demonstrated the efficacy of either systemic or direct intratracheal MSCs in experimental models of ARDS with either infectious or non-infectious causes [2,3]. Some clinical investigations also supported safety and possible efficacy of bone marrow mesenchymal stem cells (BM-MSCs) in treating patients with ARDS as well as brain injury and renal failure [4,5]. Compared to BM-MSCs, umbilical cord blood-derived mesenchymal stem cells (UCB-MSCs) possessed accessibility, lower immunogenicity, and higher proliferation capacity, while showing common effects of BM-MSCs [6]. The effectiveness of UCB-MSCs was proved in a wide range of diseases, including rheumatoid arthritis and other immune-related diseases [7,8]. However, few relevant studies have yet been published to report the UCB-MSCs therapy for critically ill cases with COVID-19. In this study, we reported one COVID-19 case of critical patient who was treated with UCB-MSCs and lung transplantation.

Case presentation

A 72-year-old man was admitted to Wuxi Fifth People's Hospital on 2 February 2020, after 1-day fever, chest discomfort, and dyspnea. The patient lived in

Xianning of Hubei Province and traveled to visit his relatives in Wuxi on January, 26, 2020, with his family. The patient had 10-year history of type-2 diabetes mellitus treated with oral hypoglycemics, and hypertension treated with metoprolol. On admission, his temperature was 37.3℃, and the blood pressure, pulse, and respiratory rate were 148/88 mmHg, 92 bpm, and 30 breaths /minute, respectively. Lung auscultation revealed rhonchi, and thoracic computed tomography (CT) exhibited a pneumonia-like properties in both sides of lung (Figure 1A). His throat swab, anal swab, and sputum sample were examined positive by Wuxi Center for Disease Control with reverse real-time PCR assay, and he was confirmed to be infected with SARS-CoV-2. Laboratory results exhibited significant lymphopenia, elevated C-reactive protein, renal insufficiency, and PaO_2/ FiO_2 < 200mmHg (Table 1). The diagnosis was COVID-19, ARDS, type-2 diabetes, diabetic nephropathy, renal insufficiency, and hypertension. For symptom management, the patient received non-invasive mechanical ventilation to improve oxygenation. Meanwhile, the patient received antiviral therapy consisting of recombinant human interferon and lopinavir/ritonavir as well as antibiotic therapy with piperacillin tazobactam. Other treatments included methylprednisolone, insulin for glycemic control, reductive glutathione for renal protection, and low molecular weight heparin for prophylactic anticoagulation.

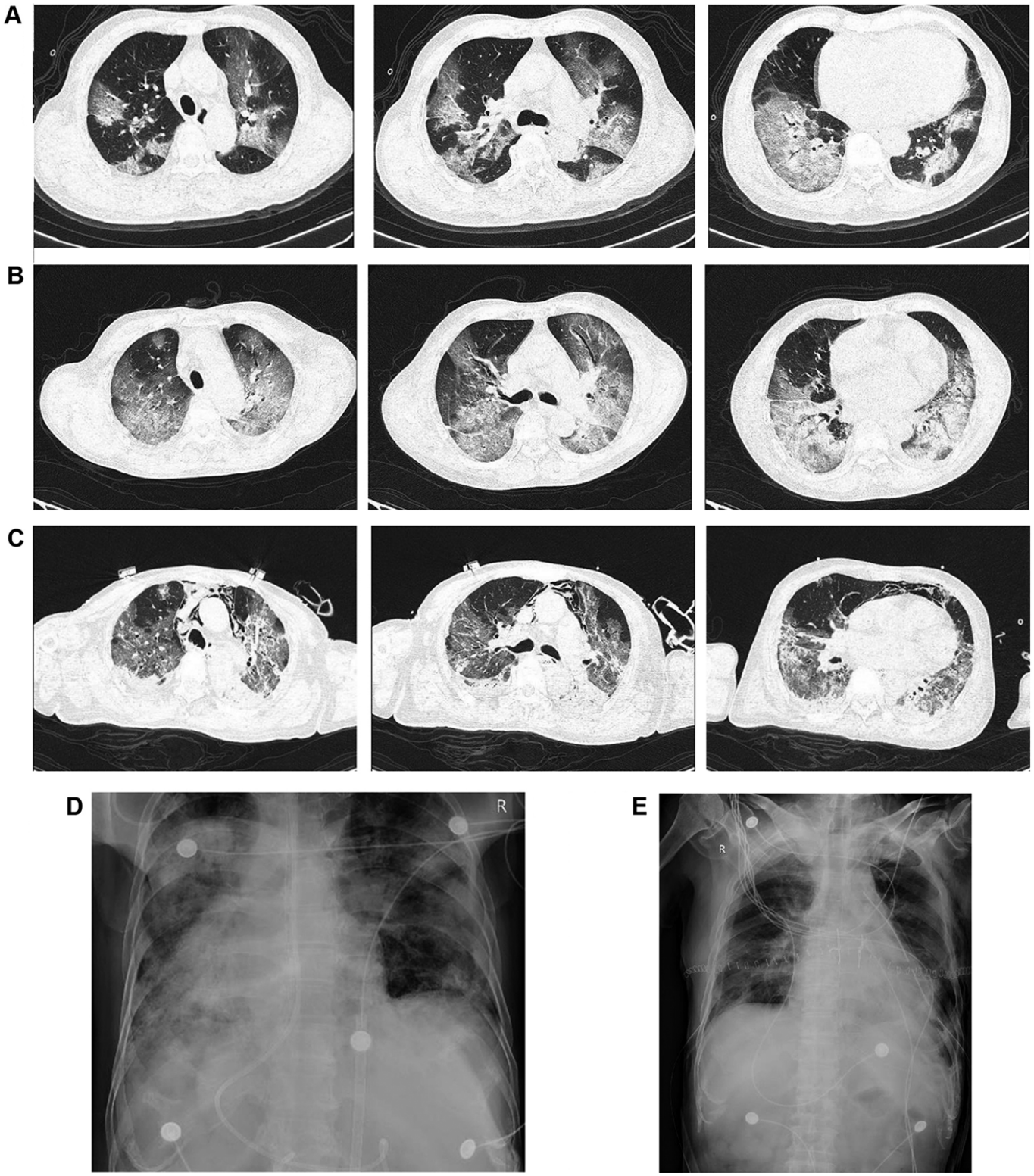
In spite of these therapy, his clinical condition continually deteriorated, CT scan on 10 February 2020 showed enlarged lesions with some consolidation on both sides of lung (Figure 1B). Ritonavir was stopped and changed to arbidol. Nasal feeding and continuous non-invasive ventilation were given in prone position (Figure 1D). Dexmedetomidine was given for continuous sedation to facilitate the coordination between human and ventilator. On February 20, the patient presented chest tightness and asthma, and his body temperature rose to 38.4℃. The blood gas analysis was as followed: pH 7.46, PaO_2 48.0mmHg, $PaCO_2$ 51.0mmHg, PaO_2/FiO_2 69mmHg, lactic acid 1.8mmol/L, suggesting exacerbation of ARDS (Table 1). He then was quickly given invasive mechanical ventilation. Midazolam was administered intravenously for 24 hours for sedation. The next day, pulmonary static compliance was 7.0 and ARDS continued to evolve to the critical stage.

Table 1. Pertinent laboratory values.

Laboratory Parameters	Feb. 2	Feb. 3	Feb. 10	Feb. 15	Feb. 20	Feb. 21	Feb. 24	Feb. 26	Mar. 10	Apr. 10
White-cell count ($\times10^9$/L)	8.06	--	11.58	10.26	7.88	6.82	6.36	5.36	8.77	10.87
Lymphocyte count ($\times10^9$/L)	0.19	--	0.12	0.17	0.18	0.26	0.38	0.28	0.67	0.53
Neutrophil count ($\times10^9$/L)	7.62	--	11.26	9.81	6.85	5.65	4.37	4.05	6.4	9.37
Hemoglobin (g/L)	125	--	92	91	91	92	96	96	99	84
Platelet count ($\times10^9$/L)	102	--	260	226	121	137	142	109	108	119
Procalcitonin (ng/ml)	--	14.31	--	3.45	0.56	0.79	0.72	2.6	1.62	6.59
C-reactive protein (mg/L)	149.42	--	81.9	196.3	72.9	58.6	42.8	20.9	47.1	8.8
D-dimer (μg/ml)	1.22	--	4.89	>20	8.93	7.48	13.24	12.49	8.35	2.56
Creatinine (μmol/L)	267	291	302	323	238	276	329	377	150	229
Blood urea nitrogen (mmol/L)	22.9	27.9	25.8	21.6	25.5	27.7	38.2	43.2	14.5	36.8
Alanine aminotransferase (U/L)	14	14	16	13	6	2	1	1	10	9
Aspartate aminotransferase (U/L)	28	30	32	31	15	16	13	12	19	22
Glucose (mmol/L)	12.5	33.1	11.2	5.2	8.1	7.8	16.2	11.6	7.8	8.3
pH	7.33	7.35	7.46	7.38	7.36	7.39	7.4	7.4	7.5	7.36
PaO_2 (mmHg)	69	81	57	69	48	90	92	89	231	86
$PaCO_2$ (mmHg)	42	32	34	37	51	52	60	46	32	37
SaO_2 (%)	90	100	91	93	86	97	97	98	100	100
FiO_2 (%)	60	60	60	60	70	90	60	60	60	60
PaO_2:FiO_2 (mmHg)	115	135	95	115	69	100	153	148	385	143
Lactic acid (mmol/L)	3.9	1.4	2.1	2.5	1.8	2	3	1.4	1.8	1.4
Pro-brain natriuretic peptide (pg/ml)	867	--	--	6892	4480	4401	1605	3934	964	789
Nucleic acid results	positve	--	positive	positive	positive	positive	negative	negative	--	negative

The normal ranges of these parameters are as following: white-cell count 3.5-9.5×10^9/L, lymphocyte count 1.1-3.2×10^9/L, neutrophil count 1.8-6.3×10^9/L, hemoglobin 130.0-175.0g/L, platelet count 125.0-350.0×10^9/L, procalcitonin 0.0-0.05ng/mL, C-reactive protein 0.0-10.0mg/L, D-dimer 0.0-10.0μg/mL, creatinine53.0-79.2 μmol/L, blood urea nitrogen 2.86-7.85mmol/L, alanine aminotransferase 10.0-49.0U/L, aspartate aminotransferase 0.0-34.0U/L, glucose 4.1-5.9mmol/L, pH 7.35-7.45, PaO_2 83.0-108.0mmHg, $PaCO_2$ 35.0-48.0mmHg, SaO_2 95.0-98.0%, PaO_2:FiO_2 400.0-500.0mmHg, lactic acid 0.5-2.2 mmol/L, pro-brain natriuretic peptide 0.0-125.0pg/mL.

Figure 1. Computer tomography scans and chest X-ray of the patient.



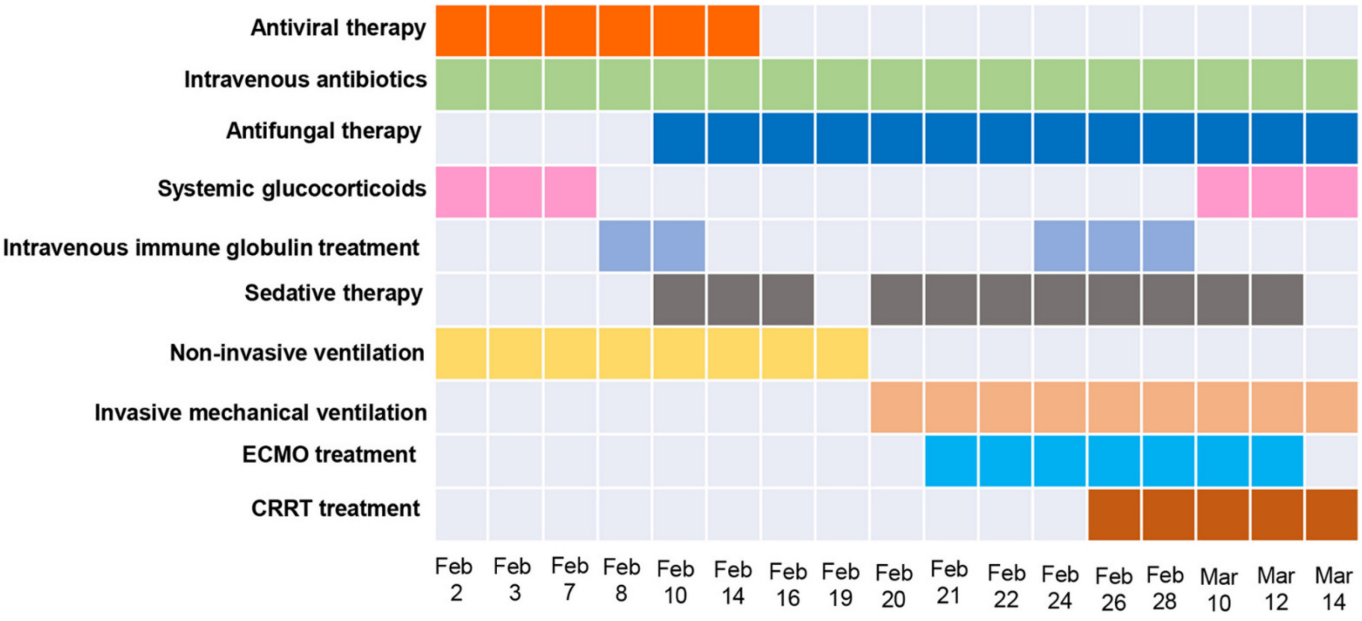
(A) Axial chest CT on February 3 showed pneumonia-like properties in both sides of lung; (B) Posteroanterior chest CT on February 10 showed enlarged lesions with patchy consolidation on both sides of lung; (C) Axial chest CT on March 8 showed more patchy shadows, enlarged heart, shadows of gas and effusion in mediastinum and thoraxes; (D) Prone ventilation chest X-Ray image was taken when the patient was ventilated in prone position on February 11; (E) Chest X-Ray after lung transplantation on March 12.

Table 2. Pertinent laboratory values during the period of UCB-MSCs therapy.

Laboratory Parameters	Feb. 27	Feb. 28	Feb. 29	Mar. 1	Mar. 2	Mar. 3	Mar. 4	Mar. 5	Mar. 6	Mar. 7	Mar. 8
White-cell count ($\times10^9$/L)	6.89	7.21	9.48	8.77	6.52	9.06	10.65	11.25	10.95	17.46	15.83
Lymphocyte count ($\times10^9$/L)	0.22	0.2	0.34	0.47	0.38	0.44	0.69	0.37	0.58	0.47	0.74
Neutrophil count ($\times10^9$/L)	4.95	5.91	7.08	6.4	4.79	6.81	8.02	9.71	7.87	14.32	12.78
Hemoglobin (g/L)	63	63	64	73	63	73	80	74	93	118	174
Platelet count ($\times10^9$/L)	114	114	99	108	85	78	77	63	106	142	125
Procalcitonin (ng/ml)	2.68	4.21	2.58	--	3.62	2.89	3.63	2.65	1.96	1.85	5.03
C-reactive protein (mg/L)	29.8	25.1	25.7	47.1	34.9	28	37.2	55	27.6	41.2	79.3
D-dimer (μg/ml)	12.62	15.71	12.08	8.35	7.41	17.81	15.29	20	13.34	>20	13.04
Creatinine (μmol/L)	306	328	201	150	139	131	122	125	126	126	121
Blood urea nitrogen (mmol/L)	33.9	32	20.9	14.5	13.5	12.6	12.3	13.8	13	13.9	13.7
Alanine aminotransferase (U/L)	5	6	10	12	9	12	11	14	15	17	14
Aspartate aminotransferase (U/L)	18	19	30	28	25	28	29	30	31	39	37
Glucose (mmol/L)	19.2	7.9	15.5	10.4	10.4	15.2	13.2	16.8	6.7	12.8	13.5
Ph	7.42	7.3	7.37	7.35	7.29	7.4	7.48	7.41	7.35	7.34	7.42
PaO_2 (mmHg)	159	133	136	113	120	118	109	125	116	104	114
$PaCO_2$ (mmHg)	43	53	41	43	53	39	50	34	41	48	38
SaO_2 (%)	99	99	99	98	98	99	99	98	98	99	99
FiO_2 (%)	60	60	60	60	60	60	60	60	50	50	50
PaO_2:FiO_2 (mmHg)	265	222	227	188	200	197	182	208	232	208	228
Lactic acid (mmol/L)	2.7	3.3	2	1.5	2	1.4	1.6	1	1.5	1.6	2.1
Pro-brain natriuretic peptide (pg/ml)	2485	2682	2353	--	2483	--	--	1726	--	1160	--
Pulmonary static compliance (ml/cmH_2O)	55	52	58	60	70	66	62	70	100	120	120
Nucleic acid results	negative	negative	--	negative	--	negative	--	negative	--	negative	--

The normal ranges of these indexes are as following: pulmonary static compliance 110.0-230.0mL/cmH_2O, the other normal ranges of indexes are same as those in description of Table 1.

Figure 2. Relative treatments of disease course according to days from hospital admission (February 2 - March 14).

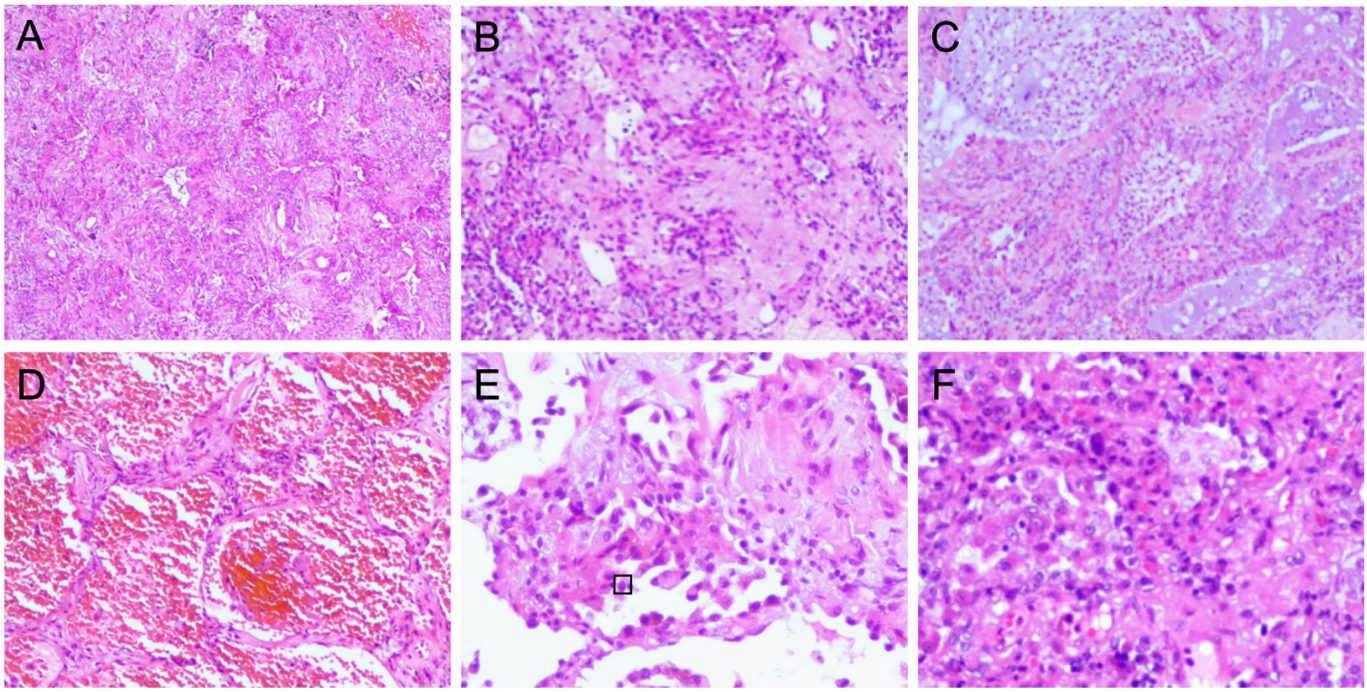


Thus, the patient received extracorporeal membrane oxygenation (ECMO) to prevent respiratory failure. On 26 February 2020, the patient's renal function worsened with significantly elevated creatinine and blood urea nitrogen and he received continuous renal replacement therapy (CRRT; Table 1, Figure 2). However, his respiratory sign and renal failure further developed to be life-threatening. Under the approval of the Chinese Food and Drug Administration (Clinical Trials Government Identifier: TS20190604404UE), an alternative treatment strategy with allogenic UCB-MSCs was planned.

The UCB-MSCs was prepared by a manufacturing company (Jiangsu EyeCure Biomedical Technology Co., Ltd) according to regulatory authority approved good manufacturing practice guidelines [9]. The standard procedure of extracting USB-MSCs was previously described [10]. Briefly, the Wharton's jelly was separated from umbilical cord by removing the blood vessels and then cut into 1-mm^3 pieces. The pieces were cultured in DMEM/F12 medium supplemented with 10% fetal bovine serum and 1% penicillin/streptomycin, and then incubated in 37℃ with 5% CO_2. USB-MSCs were then extracted and purified according to flow cytometry analysis.

Between 28 February and 8 March 2020, 1.5×10^6 USB-MSCs per kilogram of the patient's weight were infused intravenously every 48 hours, with a total of five-time infusion. Each infusion was operated for 60-80 minutes. After each infusion, vital signs were collected, and clinical parameters including ventilator and ECMO parameters were recorded. Blood was withdrawn for routine test, biomedical test and blood gas analysis. Adverse reactions and complications were also monitored. During these 10 days, the patient's body temperature was maintained at 36.4-37.3℃. No febrile, allergic or hemolytic reactions occurred. On the second day after UCB-MSCs infusion, his consciousness and mental status began to get better. The number of lymphocytes began to increase. Importantly, blood creatinine and urea nitrogen declined remarkably, suggesting renal function began to improve. Pulmonary static compliance increased significantly, and PaO_2/FiO_2 mostly maintained above 200mmHg, suggesting improvement of respiratory function (Table 2). However, the number of leukocytes and neutrophils still remained high. Follow-up chest CT

Figure 3. Histological analysis of the patient's lung tissue by H&E staining.



Histological examination of his lungs showed bilateral diffuse pulmonary fibrosis and interstitial infiltration of inflammatory cells, with fibrinous exudative necrosis in the alveolar cavity and hyaline membrane formation on alveolar wall. (A, B) Diffuse lamellar pulmonary fibrosis with focal hyaline degeneration (×100 magnification). (C) Fibrinous exudative necrosis in the alveolar cavity and exfoliative epithelial necrosis in bronchial mucosa (×100 magnification). (D) Hemorrhage in the alveolar cavity and fibrosis between alveoli (×100 magnification). (E) Alveolar epithelial hyperplasia and viral inclusion body in the cytoplasm (In the square; ×200 magnification). (F) Fibroblast proliferation, inflammatory cell infiltration, and type II pneumocytes hyperplasia (×200 magnification).

scan revealed more patchy shadows, grid-like changes, and enlarged heart, with shadows of gas and effusion in mediastinum and thoraxes, respectively (Figure 1C). ECMO and mechanical ventilation couldn't be removed due to no significant improvement of lung function. On 10 March 2020, a suitable lung donor was available for the patient, and he received lung transplantation. Postoperative chest X-ray was shown in Figure 1E. Histological examination of his lungs showed bilateral diffuse pulmonary fibrosis and interstitial infiltration of inflammatory cells, with fibrinous exudative necrosis in the alveolar cavity and hyaline membrane formation on alveolar wall (Figure 3). Viral inclusion bodies were shown in alveolar epithelial cells. On 15 March 2020, he was transferred from the ICU to lung transplantation department for pulmonary rehabilitation treatment. By April 10, he only needed to inhale O_2 through nose and could move on the ground. Unfortunately, the patient died eventually on 16 May 2020 because of transplant rejection.

Discussion

Here, we introduced UCB-MSCs infusion as an alternative therapy for the treatment of a critically ill patient with COVID-19. Critically ill patients usually presented ARDS, respiratory failure needing mechanical ventilation, shock, and/or other organ failure [11]. Previously, human MSC has been allowed for wide application in immune and inflammatory diseases. Moreover, plenty of preclinical studies have provided congruent and convincing evidence of MSC therapy effectiveness in treating many lung disorders, including ARDS, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis [12]. While lodged in lungs, MSCs exert anti-inflammatory, anti-apoptotic, and anti-microbial effects, protect the pulmonary endothelial and alveolar epithelial cells, enhance alveolar fluid clearance, and inhibit lung fibrosis via releasing soluble paracrine protein factors and extracellular vesicles [13].

In our case, after a series of treatments including invasive mechanical ventilation and ECMO, the clinical condition of the patient could not stop deterioration, evolving to critical stage with respiratory and renal failure. At this time, we chose MSC therapy with a total of 5 times. After USB-MSCs infusion, lymphocytes increased and renal function improved, as well as pulmonary static compliance increased significantly and PaO_2/FiO_2 ratio maintained stable. Although the final result was not good, all these improvements may delay serious deterioration of his condition to some extent, winning valuable time for waiting for the suitable lung donor and receiving lung transplantation.

COVID-19-induced ARDS and multiple-organ failure were reported to be associated with the cytokine storm. Some evidence shows that coronavirus can cause delayed release of antiviral factors interferon-α/β, and secrete high levels of pro-inflammatory cytokines, including tumor necrosis factor, interleukin-6, and interleukin-1β. These pro-inflammatory cytokines induce the apoptosis of T lymphocytes, which further hinders viral clearance [14]. Consistently, lymphopenia is one of the most common laboratory findings in COVID-19. In response to high levels of pro-inflammatory cytokines, MSCs can activate immune-suppressive pathways via upregulating inducible nitric oxide synthase and cyclooxygenase-2 expression levels, and stimulate the synthesis of regulatory T cells and anti-inflammatory macrophages, thereby reducing the occurrence of cytokine storms [15]. The effectiveness of MSCs for renal disease has also been identified. MSCs infusion exerts the protective role in activation of endogenous renal cells, promotion of angiogenesis, inhibition of apoptosis and inflammation, and using MSCs as a strategy to enhance survival in acute renal failure has also been proposed in some studies [16].

While his CT scan images and histological examination did not display improvement after UCB-MSCs infusion, but presented lung consolidation and evolved to diffuse pulmonary fibrosis. Several factors may contribute to this progression. Firstly, a large number of studies have identified that severe COVID-19 develops rapidly and lung consolidation including fibrosis may occur in severe and critical cases [17]. Secondly, pulmonary fibrosis is a representative subtype of progressive interstitial pneumonia, which is believed to be caused by exaggerated wound healing and chronic inflammation initiated by repetitive epithelial injury. The clinical course is usually chronic, while repetitive epithelial damage after SARS-CoV-2 infection leads to abundant release of cytokines and extremely severe respiratory dysfunction, which may contribute to acute exacerbation [18]. As an irreversible and fatal lung disease, in addition to lung transplantation, there are limited effective treatment strategies for pulmonary fibrosis. The rescue process enlightens us to further explore the possible effectiveness to prevent the development of pulmonary fibrosis by utilizing UCB-MSC treatment earlier in COVID-19 patients with ARDS.

Some limitations in this report may compromise the interpretation of the exact effects of UCB-MSCs in the

critical illness of SARS-CoV-2 infection. Firstly, elevated number of monocytes was detected in peripheral blood of our patient after UCB-MSCs therapy. Some studies have shown that MSCs are able to modulate the immune response via stimulating monocytes to secrete anti-inflammatory cytokines [19]. Furthermore, monocytes can differentiate into macrophages, which can be altered to the M2-like phenotype by MSCs induction, displaying the suppressive inflammatory activity [8,20]. Secondly, neutrophilia was another main risk for this patient [21]. We found an increased number of neutrophils after UCB-MSCs transplantation, which may result in some adverse effects on the prognosis. Complicatedly, extensive studies reported the converse views that MSCs displayed the function of inhibiting cell activation of immune system [22]. Thirdly, according to a recent clinical trial [23], the evaluation of efficacy outcome lacked several indexes, such as oxygenation index and Sequential Organ Failure Assessment score. Overall, with incomplete data in our case, including cytokines, immune cells and efficacy indexes, it is difficult to precisely evaluate the exact effect of the UCB-MSCs treatment.

It is difficult to clarify the relationship between UCB-MSCs therapy and COVID-19 from our case because of the unsuccessful rescue. However, our current findings suggested that UCB-MSCs therapy may be an adjuvant strategy to treat critically ill COVID-19 patients, for its delaying deterioration of the disease to some extent and efficacy in respiratory and renal function, though limited. Future studies are still required to investigate the safety and efficacy of UCB-MSCs therapy on critical COVID-19.

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Authors' contributions

XJ was the primary physicians and managed the patient. XJ and JT did the scientific literature searches, devised and wrote the report. YN, HW, LC, YQ, JF were involved in the diagnosis, management, and care of the patient. All authors have read and approved the final manuscript.

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