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Case Report

MSC Treatment of a Critically Ill COVID-19 Patient with Neurological Symptoms: A Case Report

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ABSTRACT

Background: COVID-19 is a new respiratory tract infectious disease caused by SARS-CoV-2. Some patients presented neurological symptoms, such as mental distress, confusion, and coma besides respiratory symptoms, which brings new challenge to cure these symptoms.

Case: Here we describe a case of COVID-19 patient with initial symptoms of feeble, somnolence, and further developed to light coma, very poor spirit but no distinct fever, cough, and dyspnea. Since the regular treatment was ineffective, this patient was enrolled and received MSC infusion. The outcome suggested that MSC was able to enhance immune function and improve the conscious disorder of the patient. This patient's consciousness turned light coma to clear gradually since 5th day after MSC infusion without other symptoms arose. Meanwhile, her lymphocyte subgroup counts and liver function indexes had recovered close to normal. During the observation, no adverse events were detected by doctors.

Conclusion: We imply that MSC can be a safe and potential effective adjuvant therapy for COVID-19 with neurological symptoms.

Keywords: COVID-19; Human umbilical cords mesenchymal stem cells; Neurological symptoms; SARS-CoV-2

ABBREVIATIONS

COVID-19: Coronavirus Disease 2019; MSCs: Mesenchymal Stem Cells; NEU: Neutrophil; AST: Aspartate Aminotransferase; ALT: Alanine Transaminase; SPO2: Blood Oxygen Saturation; CT: Chest Computerized Tomography; LYM: Lymphocyte; WBC: White Blood Cell; MONO: Monocytes; PLT: Blood Platelet

Recently, some clinical researches suggested that massive inflammatory cell infiltration and inflammatory cytokines secretion were found in COVID-19 patients' lungs, alveolar epithelial cells and capillary endothelial cells were damaged, causing acute lung injury [1,6]. Many studies have shown that SARS-CoV-2 induces disease through its spike protein specifically recognizes the angiotensin I converting enzyme 2 receptor (ACE 2) [6,7]. The main organ injured by SARS-CoV-2 is the lung. Actually, ACE 2 is widely present in many organ and tissues [8]. COVID-19 can also affect the nervous, digestive, urinary, blood and other systems [2,9].

Therefore, when early symptoms are other systemic disorders, it is often easy to misdiagnose and delay treatment, and eventually developing into a serious disease which hard to cure. Therefore, understanding the detailed clinical symptoms and characteristics of COVID-19 is important for the prevention and treatment of the disease. Therefore, we collated the electronic medical records of 82 COVID-19 cases from our hospital to describe the epidemiological, clinical, laboratory, and radiological characteristics, treatment, and outcomes of these patients. We hope to contribute to the research on COVID-19, and hope that the world can work together to defeat SARS-CoV-2 as soon as possible.

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INTRODUCTION

It has been confirmed that COVID-19 can not only cause damage to lung function, but also cause liver, kidney and coagulation function damage and show corresponding symptoms, which might cause mortality of the COVID-19 patients [1]. Recent studies have shown that some COVID-19 patients had some neurological symptoms, suggesting possible evidence that the virus had attacked the nervous system [2,3].

It has been reported that COVID-19 patients were characterized with hyper inflammation and immune function disorder [1,4]. Mesenchymal Stem Cell (MSC) is one kind of human adult stem cell which has been widely used in hundreds of clinical trials, including lung diseases [5,6]. Previous clinical studies suggested that MSC can promote the recovery of immune function, improve symptoms and promote recovery in COVID-19 patients [7].

In this study, we reported a case of critically ill COVID-19 patient who presented with somnolence and poor spirit and later developed a shallow coma. And we described the improvement of the patient's condition after receiving MSC treatment as well as the effect of MSC on improving the immune function of the patient.

CASE STUDY

Study design

This pilot study was approved by the ethics committee of Puren Hospital Affiliated to Wuhan University of Science and Technology (No. 2020-001), and was issued in Chinese Clinical Trial Registry (ChiCTR2000029990) and ClinicalTrials.gov (NCT04339660). The clinical grade MSCs were supplied, for free, by Shanghai University, Qingdao Co-orient Watson Biotechnology group co. LTD and the Institute of Basic Medical Sciences, Chinese Academy of Medical Sciences.

Case presentation

A 70-year-old woman with obvious fatigue, somnolence and in appetence without Respiratory symptoms for 3 days was admitted to hospital on Jan 24, 2020. She had fatigue, dizziness, intermittent pain on waist and lower limbs for a half year and was diagnosed with lacunar infarction 3 year ago (Figure 1A). Furthermore, this patient also had a history of sicca syndrome, type 2 diabetes, thrombocytopenia, and hypothyroidism after thyroid nodule surgery. Acarbose, leucogen and L-thyroxine were being taken as her underlying diseases treatment.

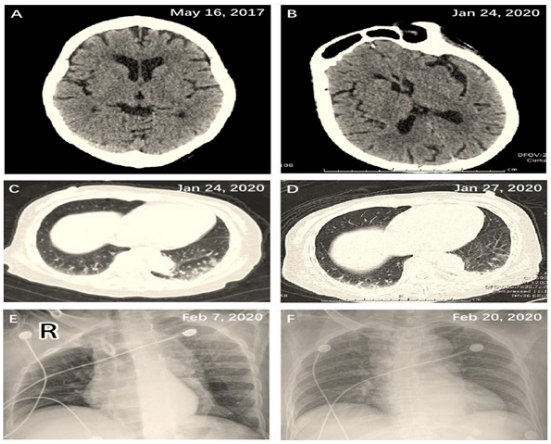


Figure 1: Cerebral and chest computerized tomography (CT) and X-ray images of the critically COVID-19 patient.

On Jan 24 when she admitted, she was somnolence, poor mental response, with sparse eyebrows and low breath sounds but no dry or wet rales in both lungs. She had a limb muscle strength grade III, positive suspicious of Babinski's sign. CT imaging of chest showed a slight infection in the left lower lung with no obvious changes in the brain CT (Figures 1B-1C). Then anti-inflammatory and symptomatic supportive treatments were implemented to her (Figure 2).

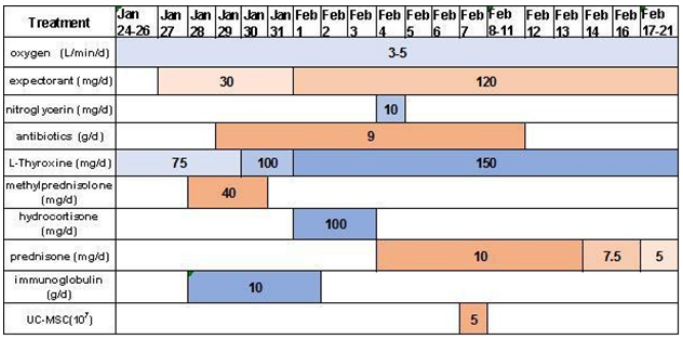
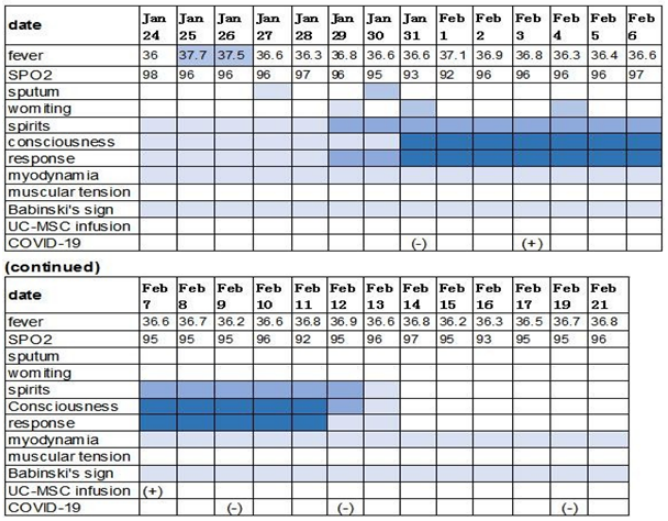


Figure 2: The major treatment of this critically severe COVID-19 patient. The depth of color indicates the doses of drugs.

After a slight fever on Jan 25 and 26, the CT of chest reviewed showed infections on the two lower lungs with bilateral pleural thickening and was diagnosed as viral pneumonia (Figure 1D). From Jan 28 to Jan 30, the patient presented much worse spirit, somnolence, nausea, and vomiting one time and was considered as critically ill. From Jan 31 to Feb 6, her neurological symptoms were even worsened and developed symptoms of light coma, very poor spirit, and non-response, with no respiratory symptoms. On examination, lymphocyte count and its ratio in whole white blood cells kept lower levels. And her liver function test showed obvious increase indexes (Table 1). Moreover, the second SARS-CoV-2 test showed positive and she was diagnosed as pneumonia with COVID-19 on Feb 3.

Since the existing treatments were ineffective to improve her symptoms, her family members agreed to participate in our clinical trial. And she was drawn into the MSC-treatment group. On Feb 7, as shown in Figure 2, this patient was transfused with MSCs intravenously at 1 × 106 cells per kilogram of weight. Her vital signs kept steady during and after the infusion. No infusion related and allergic reactions was found, nor the related adverse events. Chest X-ray photograph showed the infection improved significantly (Figure 1E).

The patient's neurological symptoms hadn't changed until on Feb 11 and 12 (Figure 3), she could open the eyes, response to painful stimulation and response to questions though not to the point. On Feb 13, she can answer the doctor's question correctly. Since Feb 14, the 7th day after MSC infusion, this patient recovered her spirit and response, presenting clear conscious and stable vital signs. The SARS-CoV-2 test of this patient turned negative on Feb 9, and was further confirmed on Feb 12 and Feb 19 (Table 1). From the monitoring data of peripheral blood, the lymphocyte count ratio rose to normal level (23.9%) on Feb 19 with AST, ALT and DBIL, etc declined gradually. Moreover, the thyroid function was detected improvement on Feb 12.



date	Jan 24	Jan 25	Jan 26	Jan 27	Jan 28	Jan 29	Jan 30	Jan 31	Feb 1	Feb 2	Feb 3	Feb 4	Feb 5	Feb 6
fever	36	37.7	37.5	36.6	36.3	36.8	36.6	36.6	37.1	36.9	36.8	36.3	36.4	36.6
SPO2	98	96	96	96	97	96	95	93	92	96	96	96	96	97
sputum														
womiting														
spirits														
consciousness														
response														
myodynamia														
muscular tension														
Babinski's sign														
UC-MSC infusion														
COVID-19								(-)			(+)			

(continued)

date	Feb 7	Feb 8	Feb 9	Feb 10	Feb 11	Feb 12	Feb 13	Feb 14	Feb 15	Feb 16	Feb 17	Feb 19	Feb 21
fever	36.6	36.7	36.2	36.6	36.8	36.9	36.6	36.8	36.2	36.3	36.5	36.7	36.8
SPO2	95	95	95	96	92	95	96	97	95	93	95	95	96
sputum													
womiting													
spirits													
Consciousness													
response													
myodynamia													
muscular tension													
Babinski's sign													
UC-MSC infusion	(+)												
COVID-19			(-)			(-)						(-)	

Figure 3: The major symptoms, signs of this critically severe COVID-19 patient. The depth of color indicates the severity of symptoms

RESULTS

The inflammatory cytokines and lymphocyte subgroups were analyzed in this study. The inflammatory factors IL-1β and TNF-α remarkably decreased on Feb 9 along with an increase to normal level of complement C3. And similar data obtained on Feb 12 (Table 2). Moreover, after MSC infusion (on Feb 7), the number of these T cell subgroups including CD45+T, CD3+T, CD3+CD4+T and CD3+CD8+T increased obviously on both Feb 9 and Feb 15. The B cell group of CD19+ ratio recovered to normal level on Feb 9. And NK cell (CD16+CD56+) counts increased by nearly 5 times (190/μL) 2 days after MSC infusion (Table 3). X-ray imaging of chest showed no obvious abnormality was observed (Figure 1F). This patient finally discharged on Mar 10 and was able to walk around the bed.

DISCUSSION

In a recent study, 78 (36.4%) patients of 214 patients with COVID-19 had neurological manifestations; some of them had impaired consciousness [8,9]. Recently, in some COVID-19 individuals, the virus may invade the brain through multiple routes [10]. These atypical presentations might lead to miss or erroneous diagnoses then increase the chance of transmitting the infection. Since this patient was diagnosed as COVID-19 on Feb 3, we considered her disorder of consciousness might be caused by the attack of SARS-CoV-2 virus to her brain.

It was also reported that intravenous infusion of autologous MSCs appears to be a feasible and safe therapy that may improve functional recovery after stroke in patients [11]. Following MSC infusion, this patient's consciousness turned light coma to a clear state gradually without other symptoms arose. Meanwhile, her lymphocyte ratio in peripheral blood and liver function indexes had recovered close to normal. And her lymphocyte subgroup counts by FCM demonstrated that both the functions of innate immunity and adaptive immunity were significantly increased after MSC treatment. During the observation, no adverse events were detected by the doctors. We suggested that MSC could be a potential adjunctive therapy for COVID-19 with neurological symptoms.

Table 1: The major clinical laboratory characteristics of this COVID-19 patient.

Items	Jan-25	Jan-27	Jan-28	Jan-30	Jan-31	Feb-03	Feb-05	Feb-07	Feb-09	Feb-12	Feb-15	Feb-19	Reference range
WBC	5.4	_	6.3	9.3	10.1	9.2	9.5	8.6	11.6	9.9	7.9	5.4	3.5-9.5 × 109/L
NEU	3.6	_	3.8	6	7	6.8	6.9	6.1	7.9	7.6	5.2	3.5	1.8-6.3 × 109/L
LYM	1.4	_	1.6	2.3	1.5	1.7	1.7	1.6	2	1.2	1.4	1.3	1.1-3.2 × 109/L
LYM	25.6	_	25.8	24.4	15.3	17	17.9	19	17.2	12.2	17.3	23.9	20-50 %
MONO	0.4	_	0.8	0.9	1.5	0.7	0.9	0.8	1.6	1	1	0.5	0.1-0.6 × 109/L
MONO	7.7	_	13.2	10.1	14.5	7.8	9.1	9.3	13.5	9.8	12.7	9.6	3.0-10.0 × 109/L
PLT	58	_	50	80	62	82	69	78	89	72	57	61	125-350 × 109/L
AST	64.5	56	52.1	_	56.6	_	90.3	97.6	85.5	74.7	62.2	56.5	13-35 U/L
ALT	37.9	32.3	27	_	33.2	_	53.6	68.2	72.4	67.2	59.8	53.9	7-40 U/L
TBIL	17	24.1	22.2	_	20.9	_	37.5	35.6	38.5	32.6	28.5	28	0-21 μmol/L
DBIL	7.7	13.4	12.4	_	10.9	_	19.2	20.5	21.4	19.3	15.3	16.1	0-8 μmol/L
TBA	_	32.6	30	_	61.7	_	34.5	19	69.1	38.1	37.2	26.8	0-12 μmol/L
CG	_	16.5	14.5	_	31.1	_	16.1	6.5	40.4	18.7	18.4	12.2	0-2.7 μmol/L
T3	_	_	_	_	_	_	_	_	_	0.3	0.4	_	0.89-2.49 nmol/L
T4	_	_	_	_	_	_	_	_	_	67.6	73.7	_	64.4- 186.6 nmol/L
FT3	_	_	_	<1.35	_	<1.35	_	_	_	1.5	2	_	2.76-6.45 pmol/L
FT4	_	_	_	5.4	_	11.1	_	_	_	10.8	11.4	_	6.44-18.02 pmol/L
TSH	_	_	_	45.3	_	9.3	_	_	_	5	17.5	_	0.35-5.1 ulU/ml

Table 2: The major clinical laboratory characteristics of this COVID-19 patient.

Factors	Jan-25	Feb-09	Feb-12	Reference range	45.3
IL-1	42.3	<5	<5	<5.00 pg/ml	45.3
TNF-	15.6	8.53	10.7	<8.10 pg/ml	45.3
IL-10	<5	<5	<5	<9.10 pg/ml	45.3
C3	0.53	0.71	0.63	0.7-1.4 g/L	45.3

Table 2: The major clinical laboratory characteristics of this COVID-19 patient.

Item	Feb-07	Abnormal prompt	Feb-09	Feb-15	Reference range	Unit
CD3+%	55.22		58.58	43.22	50-87	%
CD3+CD4+%	34.24		24.99	24.34	21-51	%
CD3+CD8+%	20.24		29.81	17.29	12-47	%
CD19+%	32.62	H	19.51		3-19	%
CD16+CD56+%	7.16		16.29		3-37	%
CD3+CD4+CD8+%	0.08		0.49	0.26	0-1.5	%
4/8 Ratio	1.71		0.84	1.41	0.71-2.78	/
CD45+Lym#	518	L	1177	838	1530-3700	/ul
CD3+#	289	L	691	365	955-2860	/ul
CD3+CD4+#	182	L	288	205	550-1440	/ul
CD3+CD8+#	107	L	350	146	320-1250	/ul
CD19+#	162		237		90-560	/ul
CD16+CD56+#	35.6	L	190		150-1100	/ul
CD3+CD4+CD8+#	0.42		4.98	2.29	0-24	/ul

CONCLUSION

It was suggested that this critically ill COVID-19 patient was admitted with initial symptoms of feeble and somnolence, possibly due to the attack of SARS-CoV-2 to her brain, with symptoms aggravated after regular treatment. The outcome of MSCs infusion revealed that MSC was able to enhance immune function and improve the conscious disorder of the patient. We imply that MSC can be a safe and potential effective adjuvant therapy for COVID-19 with neurological symptoms.

ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The study was conducted in Puren Hospital Affiliated to Wuhan University of Science and Technology, and approved by the ethics committee of the hospital (Number: 2020-001), and issued in ClinicalTrials.gov (NCT04339660, and informed consent was confirmed by the participant.

CONSENT FOR PUBLICATION

Written informed consent was obtained from the patient for publication of this case report and any accompanying images.

AVAILABILITY OF DATA AND MATERIAL

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable requests.

COMPETING INTERESTS

All authors declare no Conflicts of interest.

FUNDING

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AUTHOR CONTRIBUTIONS

RJZ: Statistical analysis and writing articles modify the articles; YZ: Screening cases, sample collection, Lymphocyte subgroup analysis and Related testing, data statistics; KL: transport MSCs; XL: Screening cases and Follow up patients; DZC: Informed consent and enrolled patients; YXL and Robert CHZ: Technical guidance; YL and DYX: Project manager and Overall planning.

All authors read and approved the final manuscript.

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