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人脐带间充质干细胞联合抗病毒等方法治疗新型冠状病毒肺炎

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［摘要］ 目的 探讨人脐带间充质干细胞 （hUCMSC） 联合抗病毒等方法对新型冠状病毒肺炎 （COVID-19） 重症患者的治疗作用。方法 在常规治疗的基础上，对 1 例 70 岁的女性 COVID-19 重症患者静脉输注三次异体 人脐带间充质干细胞，并对其抑制炎症反应和组织损伤的作用进行研究。结果 降低了主要炎症因子 IL-6 以及 C- 反应蛋白 （CRP） 等指标的水平，输注期间患者中性粒细胞与淋巴细胞的比值持续下降，T 细胞、NK 细胞和 B 细胞的绝对值持续回升，CT 影像结果显示肺部的炎症反应逐渐消退；未见不良反应。结论 异体人脐带间充 质干细胞联合抗病毒等方法对 COVID-19 重症患者安全有效，值得进行更多的临床探索。

［关键词］ 新型冠状病毒肺炎；人脐带间充质干细胞；IL-6；组织修复
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Human Umbilical Cord Mesenchymal Stem Cells Treatment Combined with Anti-Virus and other Treatments for COVID-19

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［Abstract］ Objective To explore the therapeutic effects of human umbilical cord mesenchymal stem cells （hUCMSCs） combined with anti-virus and other treatments on a critical patient with COVID-19. Methods A 70-year old female critical patient with COVID-19 was injected allogenic human umbilical cord mesenchymal

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stem cells for three times while the routine treatment was performed. The anti-inflammatory and tissue repair effects were investigated. Results No obvious side effect was observed in the treatment of hUCMSCs. Major inflammatory cytokine IL-6 and tissue injuring marker CRP were decreased after the injection. The ratio of neutrophil to lymphocyte, T cell count, NK cell count and B cell count were gradually increased during the hUCMSCs treatment. The CT images indicated that lung inflammation was also gradually decreased. Conclusion The combination of human umbilical cord mesenchymal stem cells and anti-virus and other treatments is safe and effective for critical patients with COVID-19, which is worthy of further clinical exploration.

[Key words] COVID-19; Human umbilical cord mesenchymal stem cells; IL-6; Tissue repair

The new coronavirus pneumonia (COVID-19, referred to as new coronary pneumonia) is an infectious disease caused by the infection of the new type of coronavirus 2019-nCoV (also known as SARS-CoV-2). As of February 29, 2020, more than 100,000 people worldwide have been infected with 2019-nCoV, of which the treatment of severe and critically ill patients is the main clinical problem. In addition to conventional antiviral treatment, how to safely and effectively control Inflammation and tissue damage are essential [1]. Human umbilical cord mesenchymal stem cells are rich in source and easy to prepare. They are considered to have the functions of inhibiting inflammation, homing and repairing damaged tissues, and have an important role in the treatment of autoimmune diseases [2-8]. The author has published a case report of umbilical cord mesenchymal stem cells in the treatment of critically ill patients with new coronary pneumonia, and found that mesenchymal stem cells can significantly inhibit inflammation and repair damaged tissues [9]. This article will discuss the treatment process and effect of a 70-year-old woman with severe new coronary pneumonia who was treated with human umbilical cord mesenchymal stem cells combined with antiviral methods.

1 Materials and methods

1.1 General information

A clinical study of MSC vein transplantation in a COVID-19-infected severe pneumonia hospitalized patient in the First People's Hospital of Yuxi City was conducted (Hospital Ethics Committee approval number: 2020 Lunshen L No. 1). The patient is a female, 70 years old, with a history of many years of hypertension. She had contacted relatives from Wuhan on January 19, 2010, and was sent to the hospital for treatment of paroxysmal cough with no obvious incentives on January 30, 2020. The test result of the pharyngeal swab sample the next day was positive for 2019-nCoV, CT examination showed signs of lung infection and was diagnosed as 2019-nCoV infection pneumonia. The main physical indications and treatment of the patient during hospitalization are shown in Figure 1 and Table 1. In addition to continuous cough symptoms, symptoms of fatigue, fever, diarrhea and chest tightness intermittently appear. Patient had symptoms of respiratory failure of varying degrees on the 6th to 14th days of admission. On the 6th to 9th days, proBNP, Lac and other markers reflecting tissue damage in the patient's blood were significantly increased. Inflammatory factors IL-6, CRP, neutrophil count number and neutrophil / lymphocyte ratio also increased significantly. The CT images on February 5th and 16th showed that the lamellar density of the upper and lower lungs increased, and the lesions of both lungs showed a progressive trend. On February 19, after consultation with an expert, she was diagnosed with new coronavirus pneumonia (critically ill). In addition to anti-viral and anti-infective treatments, supportive treatments such as high-flow nasal cannula oxygen therapy were also provided for these symptoms. Subsequently, according to the "New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Version 6)" recently released by the National Health and Safety Commission, Abidor and chloroquine phosphate were added for antiviral treatment.

1.2 Method

Cell preparation and transplantation: The clinical-grade hUC-MSC (certificate of conformity of China Food and Drug Certification Research Institute) is provided by Yunnan Yasheng Medical Technology Co., Ltd., Yunnan Technology Regenerative Medicine Research Institute Co., Ltd., and Shenzhen Beike Biotechnology Co., Ltd. Number: SH201401060). On the basis of the original treatment plan, cells were intravenously infused at a dose of 1×10^6 cells / kg body weight and a rate of about 40 drops / min on February 20, 23, and 26, respectively. Observation indicators: including the main safety indicators (infusion and allergies, secondary infections and life-threatening adverse events) and main efficacy indicators (cytokine variability levels, plasma C-reactive protein levels and blood oxygen saturation), secondary Efficacy indicators (patient symptoms and signs, absolute count analysis of lymphocyte subsets, chest CT).

2 Results

During the period of receiving cell therapy, the patient still maintained the conventional treatment plan, and there were no adverse reactions related to cell therapy, see Figure 1 and Table 1. During the stem cell treatment, the patient's lymphocyte count continued to rise, especially the T cell count (including CD4 + T cells and CD8 + T cells) significantly increased to normal levels, and the NK cell and B cell counts continued to rise; correspondingly the ratio of neutrophils / lymphocytes continued to decline, and the levels of major inflammatory factors IL-6 and CRP continued to decline, as shown in Figure 2. After stem cell treatment, the inflammation in the lungs of the patients was significantly reduced, see Figure 3.

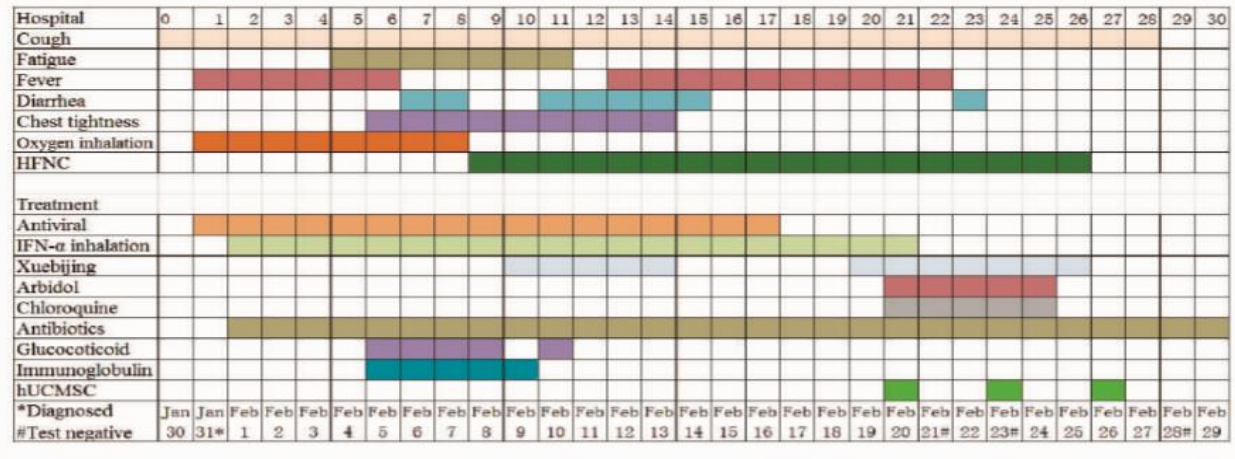

图 1　患者住院期间的基本症状和治疗情况

Fig. 1 The general vital sign and therapeutic of the COVID-19 patient

表 1　患者住院期间的主要血液生化指标

Tab. 1 The major blood clinical laboratory indexes of the patient

项目	正常值范围	发病后天数（d）										
		2	5	9	11	13	16	18	21	24	25	27
PCT (ng/mL)	0～0.05	0.05	0.15	0.13	0.14	0.15	0.14	0.13	0.07	0.12	0.14	0.13
proBNP (pg/mL)	0～325	88.8		870		328	74	89	122	616		
CK- MB (U/L)	0～24	0.88		1.32	0.76			0.63	0.67	0.83	0.82	0.8
CREA (μmol/L)	41～81	53				49	54		51	38	47	50
Lac (mg/L)	0.5～2.2	1.5	2	5.7	3.7	2.7	1.5	1.9	2.3	1.4		2.4
Tbil (μmol/L)	≤ 21	8.4			14.3	17.9	17.7		10.5	3.9	7.1	4.7
Dbil (μmol/L)	0～8	3.9			6.9	8.9	8.8		4.8	2.5	3.1	2.9
TP (g/L)	60～80	70.3			64	60.6	63.3		65.9	57.8	65.9	64.8
Alb (g/L)	40～55	43.2			25.4	31.8	32.7		35.8	25.4	37.5	35.3
ALT (U/L)	7～40	16			55	32	33		30	29	39	42
AST (U/L)	13～35	22			51	28	32		35	31	44	37
D- dimer (μ g/mL)	0～0.5	0.29	0.48	0.68			1.28		0.93	2.12	2.12	1.38

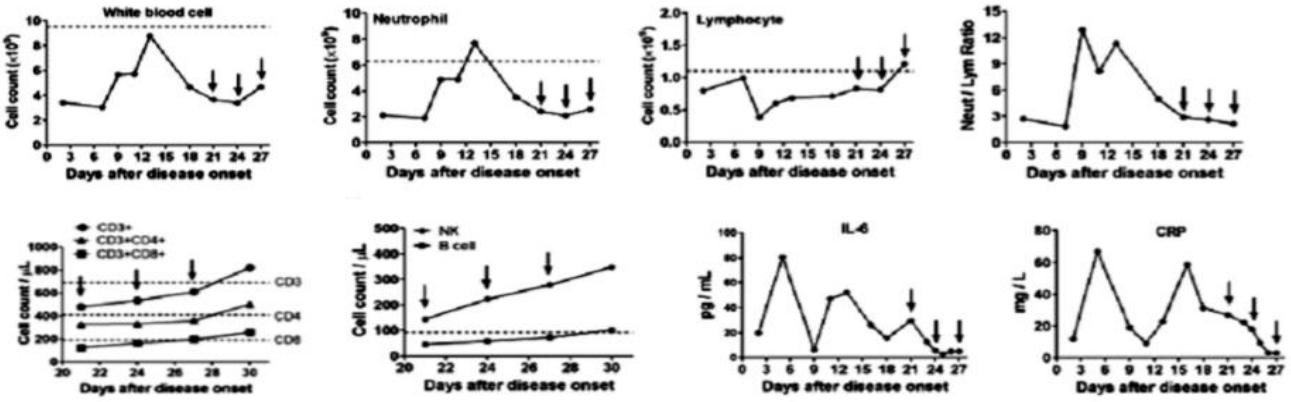

图 2　患者住院期间血液中的免疫细胞、IL-6 和 C 反应蛋白的变化情况

Fig. 2 The change of the immune cells, IL-6 and C-reaction protein levels of the patient peripheral blood

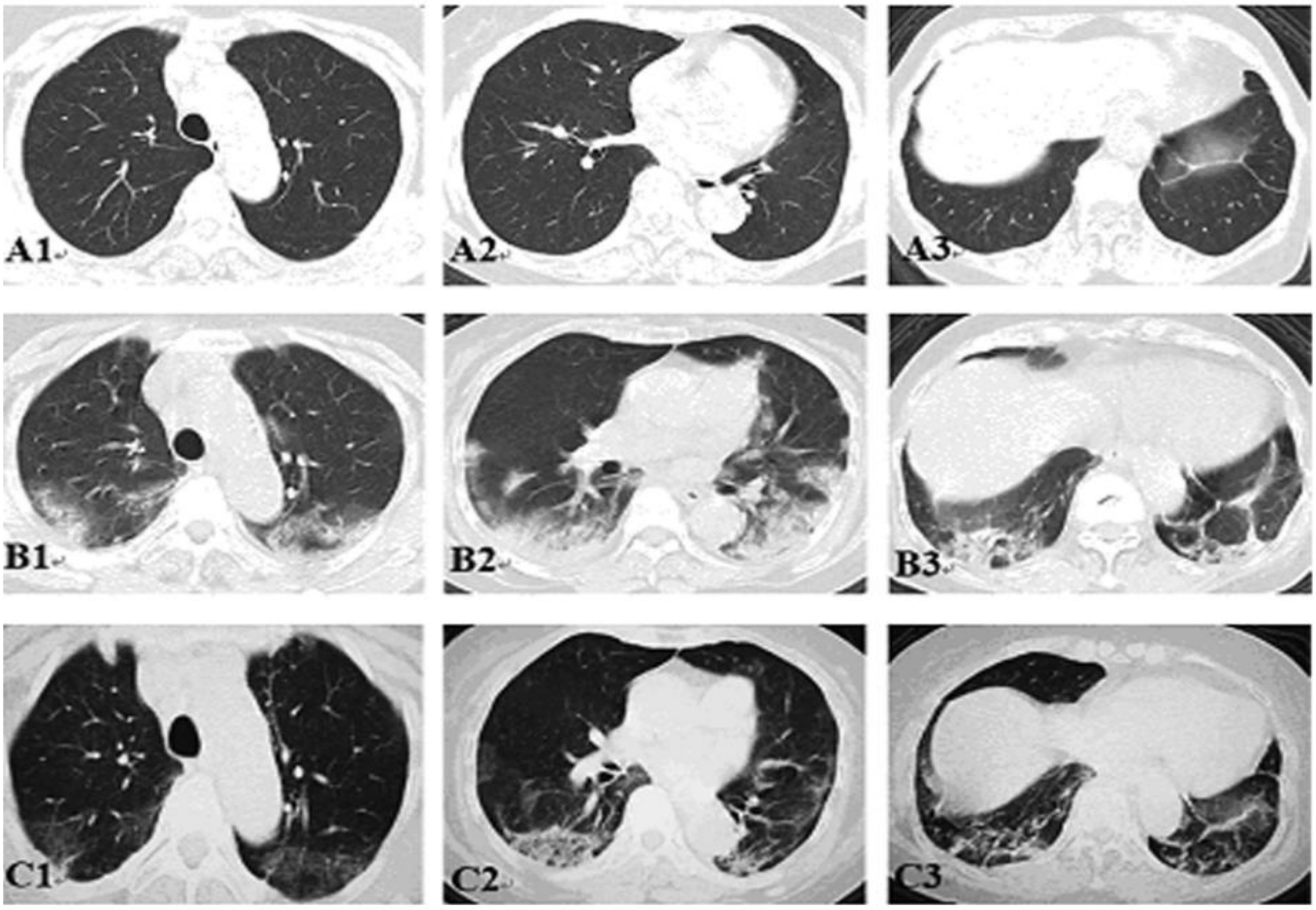

图 3　患者治疗前后肺部 CT

Fig. 3 The CT images of the lung before or after therapy

A1 ～ A3: Day 1 of diagnosis; B1 ～ B3: Day 17 of diagnosis; C1 ～ C3: Day 31 of diagnosis.

3 Discussion

The mortality rate of patients with mild coronary syndrome of new coronary pneumonia is relatively low, and the mortality rate of severe and critical illness is high, which is the focus of clinical treatment [10]. Currently, a variety of antiviral drugs are in clinical trials [11]. However, from the perspective of clinical practice, for severe and critically ill patients, in addition to anti-virus, rapid suppression of lung inflammation and improvement of patients' respiratory conditions may be the key to treatment [12]. Glucocorticoids and other immunosuppressive drugs have many side effects [13], and can damage the patient's antiviral immune response [14]. Therefore, it is very important to find therapies that can suppress inflammation without affecting the immune ability of patients. The results of this study showed that during stem cell infusion, the inflammatory response and inflammatory factors were significantly reduced, but the number of patients' lymphocytes, especially T cells and NK cells, continued to rise, suggesting that this is a promising treatment. Combined with the current understanding of new coronary pneumonia [15] and the author ’s previous reports [9], the author speculates that human allogeneic umbilical cord mesenchymal stem cell may benefit the new coronary pneumonia author through the following aspects: (1) Homing and repair of damaged tissue, mainly through secretion of factors that promote tissue regeneration; (2) Inhibition of inflammatory response, mainly through secretion of factors that inhibit inflammation and the neutralization of inflammatory factor receptors that express IL-6, G-CSF, etc. reduce inflammation; (3) The above effects provide a good environment for the decline of neutrophils and the proliferation of lymphocytes. These effects are combined with antiviral drugs or drugs that increase the number and function of lymphocytes to help eventually eliminate the virus.

In addition, besides IL-6, the author found that the blood IL-2, IL-4, IL-10, TNF-α and IFN-γ and other factors did not increase significantly. It can also be seen from the author's results that the ratio of neutrophils / lymphocytes may be a better indicator of the inflammatory status of patients with

new coronary pneumonia compared to a single type of cell count, which is basically consistent with the reports of other research groups [16]. It can also be seen from the results of CT imaging that the simple use of antiviral drugs is not particularly ideal for the rapid improvement of lung inflammation, and it needs to be combined with umbilical cord mesenchymal stem cell infusion and other repair therapies. In short, although this article is only a case study, combined with the previous research results of the author and other research groups, the author believes that umbilical cord mesenchymal stem cells have important application prospects in the treatment of severe and critically ill patients with new coronary pneumonia.

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