Successful treatment of a critically ill patient with COVID-19 using tocilizumab and human umbilical cord mesenchymal stem cells: a case report

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Case Report

Keywords: COVID-19, tocilizumab, human umbilical cord mesenchymal stem cells, critically ill, case report

Posted Date: July 6th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-39985/v1

Abstract

Background A worldwide outbreak of coronavirus disease 2019 (COVID-19) has drawn global attention. However, up to now, no standard and effective therapy are available. Case presentation A 62-year-old man with a history of hypertension and diabetes was diagnosed with COVID-19 pneumonia. He suffered from obvious shortness of breath and severe hyoxemia. Normal treatments like supportive therapy and antiviral drugs didn't seem to improve his conditions. Then, he was given tocilizumab and human umbilical cord mesenchymal stem cells. After that, his respiratory symptoms and lung infectious lesions gradually subsided, and he was successfully discharged eventually. Conclusions For critically ill COVID-19 patients, immunological treatment like tocilizumab human umbilical cord mesenchymal stem cells should be considered.

Background

Just around December 12,2019, an outbreak of a novel coronavirus pneumonia occurred in Wuhan, China, which caused an unprecedented panic and anxiety. Soon the unknown coronavirus was found to be a relative of the coronaviruses responsible for the deadly severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS) [1–2]. So, the new virus was named as SARS-CoV-2. To date, the World Health Organization (WHO) declared that the new coronavirus pneumonia (COVID-19) constituted a global epidemic.

Like SARS and MERS infection, the SARS-CoV-2 causes flu-like symptoms including fever, cough, fatigue and anhelation, and radiographic imaging shows evidence of pneumonia [3]. However, since SARS-CoV-2 is a new virus, no effective medicines are available. Clinical trials are currently underway to evaluate the safety and efficacy of these antiviral drugs for COVID-19.

Although the pathophysiology for SARS-CoV-2 has not been well understood, it was very likely to resembles that of SARS-CoV. Based on research on SARS-CoV, acute lung injury may result from aggressive inflammation initiated by virus infection [4]. Thus, controlling the inflammatory cytokine storm may be a key therapy strategy. Tocilizumab (TCZ) is a humanized IgG1 monoclonal antibody (mAb) that binds to IL-6 receptors to block the proinflammatory signaling pathway triggered by the IL-6/IL-6R complex [5]. Clinical trials about TCZ on COVID-19 are being conducted in Wuhan. Besides, mesenchymal stem cells (MSCs) have been demonstrated to possess immunomodulatory functions and have been investigated in various immune disorders [6]. A case report of a critically ill patient with COVID-19, whose conditions improved after the therapy of MSCs has been reported in China [7]. Here, we report a case of combining TCZ with MSCs to treat a critically ill patient infected with SARS-CoV-2.

Case Presentation

A 62-year-old man living in Wuhan suffered from cough, productive purulent yellow sputum, shortness of breath and chest distress, accompanied by a running nose on January 25, 2020. Neither fever, fatigue,

sore throat nor myalgia was reported. He had a history of hypertension and diabetes. Oropharyngeal swab tests of SARS-CoV-2 by qualitative real-time reverse-transcriptase-polymerase-chain-reaction (RT-PCR) assay were positive and he was confirmed as a COVID-19 patient on February 3. Chest CT scan showed multiple patchy consolidation and ground-glass opacities. He was given oxygen support and antiviral therapy (No details available). But his conditions were getting worse, then he was referred to our hospital on February 19.

On admission, physical examination revealed unstable vital signs with oxygen saturation of 66% when breathing ambient air. His respiratory rate was 30 breaths per minute, with pulse of 127 beats per minute and blood pressure of 143/89 mmHg. He had no fever. Symptoms like cough, expectoration, shortness of breath and chest distress were obvious. Arterial blood gas analysis indicated hyoxemia with arterial oxygen tension (PaO2) of 63 mmHg and carbon dioxide tension (PaCO2) of 33 mmHg. Data from laboratory tests showed that the patient had a high level of inflammation with increased white blood cells(WBC, 13.1*10^9/L, normal range: 3.5–9.5*10^9/L) and C-reactive protein(CRP,75.68 mg/L, normal range:0–4 mg/L) and procalcitonin(PCT,0.22 ng/mL, normal range: 0-0.05 ng/mL).

Considering serious respiratory symptoms, the patient received high-flow oxygen therapy (the fraction of inspired oxygen (FiO_2): 100%, oxygen flow rate: 50L/min). Other supportive treatments were started in accordance with Chinese guidelines. Noticeably, Ulinastatin (3 million IU, administered intravenously once a day) was injected to block inflammatory cascade reactions.

A week later, however, the patient presented a worsening in respiratory symptoms. His oxygen saturation was around 90% under therapy of high-flow oxygen. The patient was admitted to intensive care unit (ICU) on February 27. Chest X-ray showed right lung was almost white and large haziness shadow was observed in left lung (Fig. 1A). Thus, the parameters of the high-flow oxygen were adjusted to oxygen concentration of 100% and oxygen flow rate of 50L/min. Then oxygen saturation reached up to 100%. Arterial blood gas analysis showed a ratio of PaO_2 to FiO_2 was 281 mmHg. Laboratory tests showed that the concentration of PCT was higher than before. Figure 2 showed the dynamics of inflammatory markers. However, one day later, on February 28, his oxygen saturation suddenly decreased to 85% and respiratory rate rose up to 44 breaths per minute. Therefore, high-flow oxygen was switched to ventilatory supportive care using positive end-expiratory pressure of 8cmH_2O. Then oxygen saturation gradually reached 93%. Nevertheless, the patient became dysphoric and oxygen saturation dropped to 91% five hours later. So, oxygen support was changed back to high-flux nasal oxygen delivery. The concentration of interleukin 6(IL-6) was measured on February 29, and as expected, it was significantly higher than its upper limit (Seen in Fig. 2), which meant there existed systemic inflammatory storm caused by virus infection. To control inflammation related with IL-6, TCZ (400 mg, administered intravenously once) was initiated on the next day. There were no adverse reactions.

Since March 2, his conditions were getting better and the set parameters of oxygen support were gradually down-regulated with oxygen saturation around 98%. Oropharyngeal swab tests of SARS-CoV-2 on March 3 and March 10 were both negative. On March 4, high-flow oxygen therapy was ceased and

oxygen support through nasal cannula with oxygen flow rate of 5L/min was taken instead. Chest X-ray on March 12 indicated that pulmonary edema and inflammation has been greatly ameliorated (Fig. 1B). Thus, the patient was transferred to general ward. On March 17, the patient had neither fever, chest distress or expectoration. His appetite became normal and enteral nutrition was stopped. But he still felt shortness of breath and couldn't be capable of walking around on room air. Dry cough was prominent especially at night. His chest CT on March 17 indicated multiple patchy ground-glass shadows in both lobes, predominantly confined to the peripheral and middle zones of the lung (Fig. 3A, 3C, 3E and 3G). On March 23, after negotiating with his family members and himself, the patient received stem cell therapy in the following hospital stay. The protocol of stem cell therapy was that 40 million human umbilical cord mesenchymal stem cells (hUC-MSCs, purchased from Vcanbio Cell & Gene Engineering Corp. LTD, Tianjin, China) injected through peripheral vein 3 times every three days. The last transfusion was finished on March 29. No side effects were observed. Other supportive care remained as before. Now, as of today, March 31, he is able to breathe free without nasal cannula when engaging in daily activities. It was noticeable that he could walk 50 meters far away when breathing ambient air. His oxygen saturation was around 96% on room air. Meanwhile, he reported no dry cough and mild shortness of breath after activity. CT examination on March 30 also showed multiple absorption of infectious lesions in both lungs compared with CT on March 17 (Fig. 3B, 3D, 3F and 3H). The results of nucleic acid detection of COVID-19 on March 17,18,24 and 29 were all negative. Finally, he was successfully discharged. The oxygen support mode from the admission day to March 31 was shown in Fig. 4.

Discussion

Studies have indicated that inflammatory cytokine storm is one of important mechanisms underlying the deterioration of COVID-19[8]. SARS-CoV-2 infects the respiratory tract and causes release of pro-inflammatory cytokines including IL-1b and IL-6[9]. Wan et al explored the cellular immunity and cytokines status of patients with COVID-19 and found that CD4 + T, CD8 + T, IL-6 and IL-10 were significantly different between mild and severe patients, which suggested that T cell and cytokines could be used to predict severity [10]. The Chongqing Three Gorges Central Hospital summarized their clinical experience and proposed to monitor the changes of cytokines during the treatment process to optimize the treatment plan and predict the prognosis [10]. As a lack of specific drugs for SARS-CoV-2, drugs targeting cytokine storm and reducing immunopathology should be considered [11]. Glucocorticoid could block the over-activated inflammation, but it has more side-effect and has been found to be unsatisfactory towards COVID-19[12]. In contrast, monoclonal antibody or stem cell therapy may be plausible therapeutic strategies to curb immunopathology caused by the viral infection.

TCZ is the first IL-6 inhibitor, has been approved for RA and giant cell arteritis and other immune-mediated diseases [13]. Sheng et al reported that TCZ could suppress cytokine production, inflammation activation and phagocytosis in sepsis due to its effects on controlling "cytokine storm" [14]. The study revealed that TCZ might also be efficacious in other types of acute severe systemic inflammatory diseases including virus infection.

MSCs are multi-potent cells that originate from various adult tissues including bone marrow, umbilical cord and adipose [15]. Except for their multi-lineage differentiation, MSCs have been learnt to exert immunoregulatory properties. They are capable of interacting with various types of immune cells like T cells, B cells and macrophages. These interactions result in various growth factors and immunomodulatory factors [16–17]. Therefore, MSCs may have beneficial effects for preventing or attenuating the cytokine storm owing to the coronavirus infection. It has been reported that MSCs accumulate in the lung and improve pulmonary microenvironment and further improve lung function after entering the human body [18–19]. Multiple clinical trials using stem cell therapy to treat COVID-19 from China have been registered at www.clinicaltrials.gov.

We report a case of TCZ and hUC-MSCs used in a critically ill COVID-19 patient with classic respiratory symptoms as onset presentations. He developed severe pneumonia and could not maintain a normal oxygen saturation without high-flow oxygen. Although he received standard supportive care including antivirus drugs, nutrition support, immune enhancement and antibiotic treatment for more than one month, his respiratory symptoms didn't seem to get much improvement. Blood workup revealed high expressions of inflammatory factors that indicated the possibility of cytokine storm. Therefore, he was under treatment with TCZ once on March 1. TCZ blocked the system inflammation cascade and accelerated the improvement of lung function. Since then, both his clinical manifestations and blood indexes were getting better. Repeated oropharyngeal swab tests for COVID-19 nuclei acid were negative. But his respiratory function and pulmonary images didn't recover completely. He still felt anhelous and need oxygen support all the time. After finishing 3 intravenous transfusions of hUC-MSCs, shortness of breath and dry cough have been enormously alleviated. He was capable to breathe free without nasal cannula when engaging in daily activities. After approximate two-month hospitalization, he was finally discharged.

In the case, we also used Ulinastatin to alleviate inflammation injury. Ulinastatin, a urinary trypsin inhibitor, is commonly applied in acute inflammatory diseases such as acute pancreatitis in clinical practice. No study has reported its application in COVID-19. Nevertheless, Ulinastatin has been proved to exert an anti-inflammatory effect on lipopolysaccharide-induced acute lung injury, decreasing the lung wet/dry weight ratio, neutrophils, macrophages activity [20]. The underlying mechanism of Ulinastatin caters to the pathologic change of lung in COVID-19 infection. Therefore, there was synergetic anti-inflammation in drug combination of Ulinastatin and TCZ in our case.

Conclusions

So far, symptom-alleviating treatment and supportive care are the mainstay therapies for COVID-19. Various clinical trials are being conducting to discover effective drugs. However, up to now, clinical data on COVID-19 therapy is limited. We successfully treated a critically ill patient through combing TCZ with hUC-MSCs. Our case revealed that immunological treatment was a promising option in COVID-19 patients.

Abbreviations

COVID-19, coronavirus disease 2019; SARS, severe acute respiratory syndrome;

MERS, Middle East respiratory syndrome; WHO, World Health Organization;

TCZ, Tocilizumab; MSCs, mesenchymal stem cells; RT-PCR, real-time reverse-transcriptase-polymerase-chain-reaction; hUC-MSCs, human umbilical cord mesenchymal stem cells; PaO2, arterial oxygen tension; PaCO2arterial carbon dioxide tension; WBC, white blood cells; CRP, C-reactive protein; PCT, procalcitonin; ICU, intensive care unit

Declarations

Ethics approval and consent to participate: The ethics committee of Huoshenshan Hospital approved the study.

Consent for publication: Written informed consent for publication of the patient's clinical details and clinical images was obtained from the patient. A copy of the consent form is available for review by the Editor of the journal.

Availability of data and materials: The datasets used and /or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests: The authors declare that they have no competing interests.

Funding: Not applicable.

Authors' contributions: Conception and design: LY, JL; Administrative support: JQW, SQH, YCX, YCH; Provision of study materials or patients: JQW, SQH, JL; Collection and assembly of data: LY, JQW, SQH, YCH; Data analysis and interpretation: LY, FYW, JL; Manuscript writing: All authors; Guarantor of the article: JL; Final approval of manuscript: All authors.

Acknowledgements: Not applicable.

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Figures

Figure 1

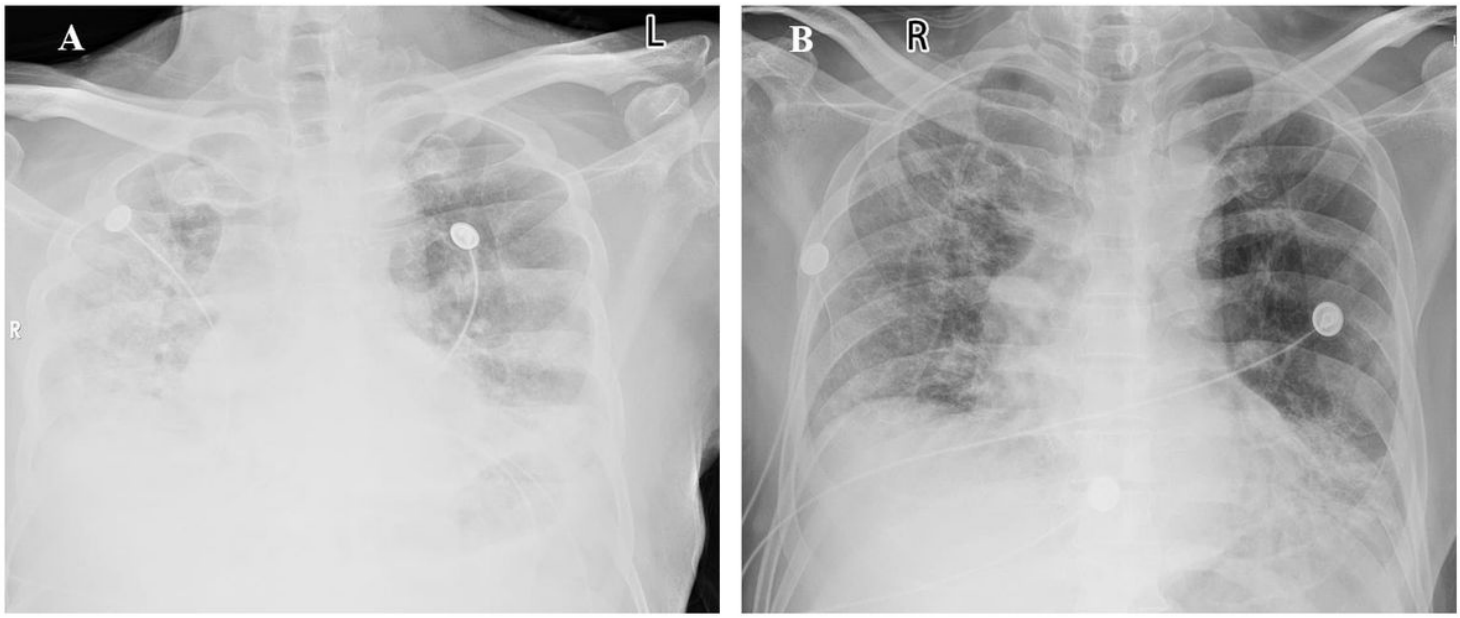

Figure 1

Chest X-ray of the patient. A: Chest X-ray on February 27, hospital day 8. B: Chest X-ray on March 12, hospital day 22.

Figure 2

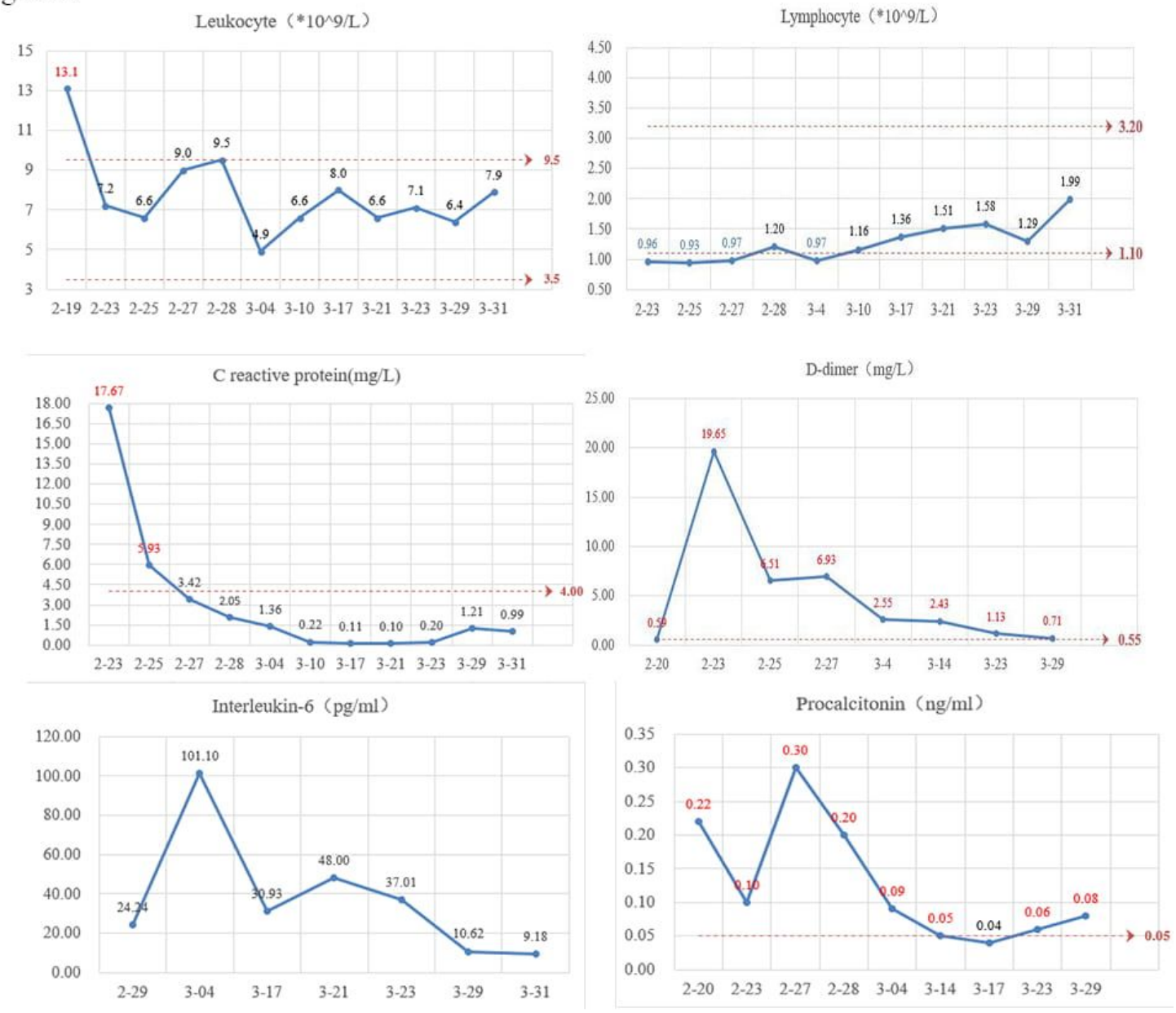

Figure 2

Serial laboratory results of inflammatory markers.

Figure 3

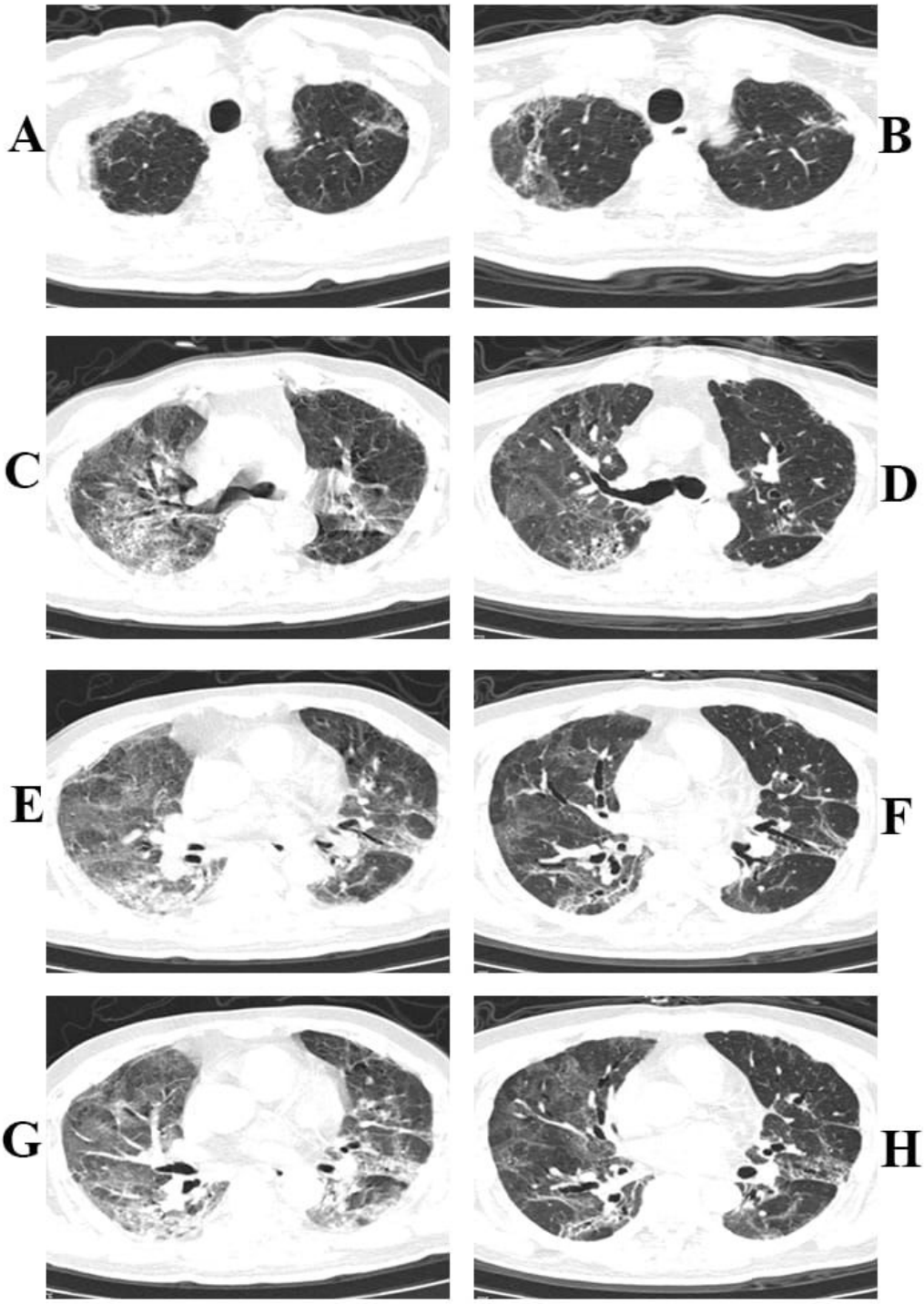

Figure 3

Chest CT scans of the patient. A, C, E and G: CT images on March 17, indicting multiple patchy and ground glass shadows with uneven density and fuzz edge in both lungs. B, D, F and H: CT images on March 30 after 3 times of mesenchymal stem cells therapy, indicating multiple absorption of lesions in both lungs.

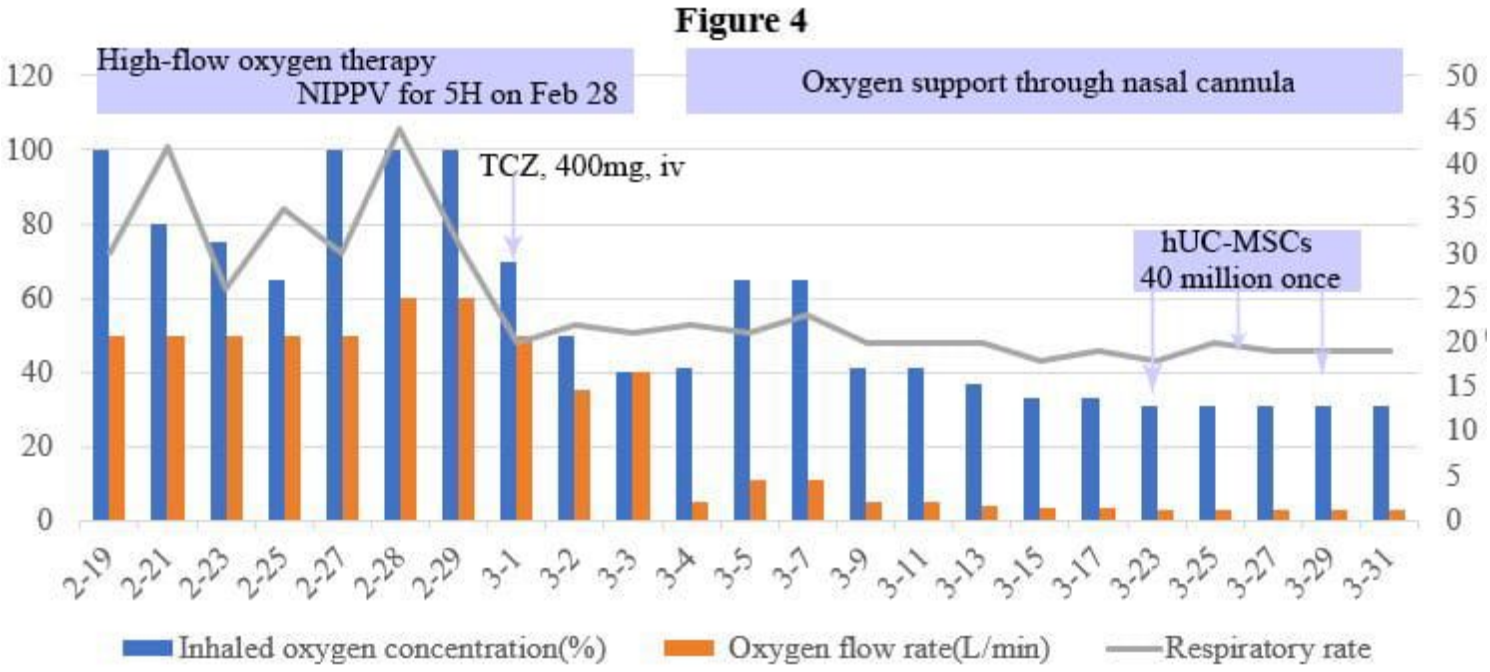

Figure 4

The oxygen support mode and respiratory rate of the patient from February 19 to March 31. NIPPV: Non-invasive positive pressure ventilation; H: Hour; Feb: February; TCZ: Tocilizumab; hUC-MSCs: Human umbilical cord mesenchymal stem cells.