Case Report

Recovery of One ICU-Acquired COVID-19 Patient via Ozonated Autohemotherapy

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Abstract

The rapid spread of COVID-19 results in a pandemic throughout the world, however, there are currently no specific treatments available. We report the first case of ozonated autohemotherapy for a critically ill patient with COVID-19. The patient was diagnosed with severe acute respiratory distress syndrome (ARDS) and life-threatening refractory hypoxemia within 72 hours of the intensive-care unit (ICU) admission. To improve the oxygen delivery, the ozonated autohemotherapy was performed with 40 μg/ml of ozone in 100 ml of blood for 5 days on this patient, who then recovered from ARDS uneventfully and discharged from hospital after viral clearance. This case suggests ozonated autohemotherapy might be an alternative non-invasive medical treatment for critically ill COVID-19 patients.

Introduction

A coronavirus disease 2019, COVID-19, an enveloped RNA betacoronavirus,[1] is distributed globally since December 2019. As of March 22, 2020, more than 267,000 cases of COVID-19 had been reported to World Health Organization (WHO), from 184 countries and territories.[2] The WHO documented 81,416 confirmed cases in China, including 3,261 people have lost their lives; outside China, there were 185,597 infections and 7,940 deaths.[2] Patients with COVID-19, who might develop ARDS as short as 2 days after hospital admission,[1] have a high likelihood resulting in multiple organ failure and death. Urgent and efficient intervention for refractory hypoxemia and ARDS can improve both survival rate and outcomes after discharge from hospitals. However, at the moment, there is no anti-viral medicines, vaccines or specific clinical treatments for COVID-19. For

improving oxygen delivery, currently, there are two rescue strategies for COVID-19 patients with ARDS and severe refractory hypoxemia, either invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO), according to “Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment, the 7th version” by National Health Commission of the People's Republic of China.[3]

Ozone therapy has been reported to improve blood flow and tissue oxygenation to vital organs,[4-7] and also appears to stimulate the innate immune system by inducing the activation of nuclear factor activated T-cells.[7,8] Early studies on severe acute respirator syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) had shown that increased amounts of proinflammatory cytokines and extensive lung damage in both SARS-CoV and MERS-CoV patients;[9,10] these findings indicate that ozone therapy might be a new strategy to treat betacoronaviruses infected patients. Ozonated autohemotherapy is a recommended route of administration,[11] in which patient’s blood was withdrawn and then ozonated to return the patient. With this in mind, we present a case of critically ill ICU-acquired COVID-19 patient for whom an ozonated autohemotherapy was designed and implemented by a multidisciplinary team.

Case Report

A 56-year-old male was admitted to Tianjin University Haihe Hospital, Tianjin China, on February 11, with a 3-day history of subjective fever. The patient’s illness had begun on February 8, 2020, with a fever about 38 °C (measured by the patient using a fever thermometer at home), but without any other coexisting conditions, such as cough, sputum, headache, fatigue, chills, sore throat, stuffy nose, runny nose, wheezing, shortness of breath, nausea, vomiting, abdominal pain, or diarrhea. After taking Paracetamol for three days without any improvement, on February 10, 2020, the patient checked into the local fever clinic, where the patient was treated with Cefuroxime and

Acetaminophen and oropharyngeal swab specimens were collected. After the Tianjin CDC confirmed that the patient's oropharyngeal swabs tested positive for COVID-19 by RT-PCR assay, the patient was transferred to Tianjin University Haihe Hospital, the designated hospital for COVID-19 patients in Tianjin. On admission, the patient reported he had no medical or drinking history, but he had been smoking for 30 years, with 20-40 sticks per day.

On February 11, 2020, illness day 4, on admission at Tianjin University Haihe hospital, the patient had a body temperature of 37.7 ℃, pulse of 88 beats per minute, respiratory rate of 22 breaths per minute, blood pressure of 129/79 mmHg, and BMI of 22.4. Oxygen saturation was 94 percent while he was breathing ambient air. Besides body temperature, the remainder of physical examinations was remarkable. However, his laboratory results showed the P/F ratio of 340, and the elevated expressions of C-reactive protein and IL-6 were more one order of magnitude above normal physiological concentrations (Table 1). Patient's chest CT showed multiple bilateral ground-glass opacities, and the global CT lung severity score was 6 out of 20 (Figure 1). For symptom management, the patient received supportive treatments, consisting of lopinavir/ritonavir (400/100mg twice a day orally) and interferon-alpha (IFN-α) by inhalation twice a day (5000 kU in 2 ml of sterile water) as antiretroviral therapy.

On February 12, 2020, illness day 5, the patient's symptoms worsened, and his body temperature rose to 39.5℃ with dyspnea. His oxygen saturation value decreased to 80% during bed rest, while ABG analysis showed P/F ratio dropped to 194, indicating severe refractory hypoxemia. Given the changing clinical presentation, high-flow nasal cannula (HFNC) oxygen therapy was initiated, meanwhile the patient received intravenous

methylprednisolone (40 mg/day) and antibiotic agent cefperazone-sulbactam (3×3 g/day). On February 15, 2020, illness day 8, the chest CT showed that bilateral ground-glass opacities were increased and a small amount of bilateral pleural effusion in the peripheral lung, resulting in a 17/20 global CT lung severity score (Figure 1). Considering the patient's condition deteriorated progressively and the severity of COVID-19, the patient was admitted to ICU on February 16, 2020, while continued to be treated with allopathic medicine.

On February 19, 2020, illness day 12, the patient's chest CT showed that bilateral ground-glass opacities of lung fields were significantly increased with thickening of the bronchovascular bundles and pleural effusion, and the global CT lung severity score was 20/20 (Figure 1). The patient's condition deteriorated rapidly with development of ARDS and severe refractory hypoxemia, so in this case, the institutional review board approved the treatment of ozonated autohemotherapy on this patient. February 20, 2020, illness day 13, before the therapy, the patient's oxygen saturation value maintained between 93-96% with HFNC therapy (O_2: 60 liter/min, FiO_2: 85%); the lowest oxygen saturation was about 75% after the patient genteelly moved on the bed. While resting, the ABG analysis showed P/F ratio was 80 mmHg.

The ozonated autohemotherapy was initiated with an O_3 concentration equal to 40 µg/ml in 100 ml of blood. While 10 minutes after the ozonated autohemotherapy was initiated, the P/F ratio increased to 192 mmHg. In the next two hours after the infusion completed, the oxygen concentration of HFNC gradually decreased from 93% to 80% and the P/F ratio dropped to 118 mmHg, while the patient's oxygen saturation remained in the range of 98-100%. Nine hours after the ozonated autohemotherapy, the P/F ratio

was 106 mmHg, and the patient felt a significant improvement of respiratory function. The patient was treated with the ozonated autohemotherapy for another four consecutive days, twice a day. After the 5-day therapy, the patient's overall condition had stabilized, so on February 26, illness day 19, the patient was transferred from ICU to the COVID-19 general ward. The oxygen supplementation was gradually switched from HFNC to nasal catheter oxygen inhalation after 10 days, meanwhile the P/F ratio by ABG analysis improved incrementally. On March 1, 2020, illness day 23, the patient's oropharyngeal and sputum specimens turned negative for COVID-19. However, the patient's stool specimen was still positive until March 9, 2020, illness day 31 (Figure 2), when CT image also indicated the most exudation was absorbed and a global CT lung severity score was 6/20 (Figure 1). On March 11, 2020, after 32 days of illness, the patient was discharged from hospital. The summary of the patient's physical examinations, symptoms and results of RT-PCR testing for the COVID-19 are shown in Figure 2.

Methods

Specimen collection and diagnosis for COVID-19

Clinical specimens for COVID-19 diagnostic testing were obtained in accordance with WHO guidelines and the protocol established by Chinese Center for Disease Control and Prevention (China CDC).[12,13] Oropharyngeal swab specimens were collected with two synthetic fiber swabs; each swab was inserted into a separate sterile tube containing 2 to 3 ml of viral transport medium. Sputum was collected in a separate sterile 50 ml tube

containing 3 ml of viral transport medium. The stool specimens were each collected in a sterile 15 ml container with 3 to 5 ml of viral transport medium. Specimens were stored at 4°C until ready for shipment to the Tianjin CDC within 2 hours. Specimens for COVID-19 testing were collected on illness days 3, 11, 13, 18, 22, 23, 24, 25, 28, 30 and 31 included oropharyngeal swabs, sputum, and stool samples. The presence of COVID-19 in clinical specimen was tested by a real-time reverse-transcription-polymerase-chain-reaction (RT-PCR) assay at Tianjin CDC, and the primers and probes are available on the China CDC Laboratory Information website.[13]

Laboratory evaluations

Laboratory assessments consisted of a complete blood count, blood chemical analysis, and measures of absolute lymphocyte count, D-dimer, C-reactive protein, and interleukin-6 (IL-6). In this work, arterial blood gas (ABG) analysis measures a ratio of the partial pressure of arterial oxygen (PaO_2) to the fraction of inspired oxygen (FiO_2). A PaO_2/FiO_2 (P/F) ratio in the range of 200-300 indicates abnormal gas exchange, and a P/F ratio of 200 or less indicates severe hypoxemia and ARDS.[14]

Computed tomography (CT) was performed on illness days 4, 8, 12, and 31. Two board-certificated chest radiologists worked independently, between whom a consensus diagnosis was made. The extent of involvement of each abnormality was assessed independently for each lung lobe using a 5-scale (1: <25%; 2: 25-49%; 3: 50-74%; 4: 75-99%; 5: 100%). The sum of the detailed scores of the five lung lobes led to the determination of a global CT lung severity score (maximum, 20).

Ozonated autohemotherapy

This clinical protocol was approved as a complementary therapy by the institutional review board of Tianjin University Haihe Hospital on February 16, 2020, while the patient would continue to be treated with allopathic medicine. The patient was an adult recruited from COVID-19 specified ICU at Haihe hospital, and signed an informed consent about medical ozonated autohemotherapy on February 20, 2020.

The ozonated autohemotherapy was performed in form of intravenous infusion of ozonated blood. The protocol consisted of the drowning 100 ml of whole blood from patient's antecubital vein into a standard plastic disposable blood collection bag containing the anticoagulant solution (25ml). The blood was then mixed with 100 ml of O_2/O_3, with an O_3 concentration at 40 µg/ml by Kastner- Praxisbedarf Ozomed® Universal. The ozonized blood was then slowly re-infused into the same vein at 40 gtt/min or less during the first 5-minute infusion, and the infusion rate might increase up to 60~100 gtt/min depending on the patient response.

Results

Specimen testing for COVID-19

The initial oropharyngeal swabs obtained from this patient on day 3 of his illness were positive for COVID-19 (Figure 2). The oropharyngeal specimens obtained on illness days 11, 13, 18 and 22 were tested positive, which turned negative on illness day 23. Sputum specimens obtained on illness days 23, 24 and 25 were all negative. However, the stool specimens obtained on illness days 28 and 30 were tested positive. On illness day 31, March 9, 2020, the stool specimen was tested negative for COVID-19.

Discussion

An emerging outbreak of human infections with COVID-19 virus began in December

2019, and the full spectrum of this infectious disease is not yet fully understood. After admission, even though our case patient was administered with empirical antibiotic and antiviral treatments for 5 days, there was a progressive decline of lymphocytes, and significant increases in inflammatory biomarkers and D-dimer (Table 1). Our case patient's clinical features had suggested a high likelihood of occurrence of a cytokine storm and a risk of developing ARDS associated with poor prognosis, based on the reported clinical features of COVID-19 patients.[1] This patient did develop ARDS with severe refractory hypoxemia at day 9 of hospitalization, while the patient was treated with recommended antiretroviral therapy, antibiotic medicines and HFNC oxygen supplementation. Since the patient's chest CT ground-glass opacities and consolidation abnormalities achieved the worst global CT score 20/20, the priority treatment of this patient was to restore sufficient arterial oxygen content and to prevent multiple organ failure.

Typical lung protective ventilation strategies, invasive mechanical ventilation and ECMO, are highly invasive, special ventilator required, high risks for developing complications, and also extend the length of hospital stays. There is another option of improving oxygen delivery to correct hypoxemia, ozonated autohemotherapy, which is practiced in many countries in recent years. Noteworthy, there are multiple clinical trials described the effectiveness of ozonated autohemotherapy to promote the generation of anti-oxidative species as of a mild oxidative stress,[15] to decrease the production of the proinflammatory cytokine IL-6,[16] and to improve tissue oxygenation.[4] Combining ozonated autohemotherapy with antiretroviral therapy in a case of our severe ARDS patient with COVID-19 indeed provided essential oxygen content in blood as the P/F ratio

increased from 80 mmHg to 192 mmHg during the treatment. After five-day ozonated autohemotherapy (9 treatments in total), significant clinic improvement was achieved in our case severe COVID-19 patient, which might result from the ozone-stimulated innate immune system.

To our knowledge, this is the first successful use of ozonated autohemotherapy to treat a critically ill COVID-19 patient. Even though the exact mechanism of ozonated autohemotherapy for this case is less well characterized, ameliorating inflammation and tissue damage should play critical roles.[17,18] Without any clinical approved vaccine, medicine or treatment, ozonated autohemotherapy might be a worthy candidate as a clinical therapy for COVID-19 patients with refractory hypoxemia. Furthermore, ozonated autohemotherapy is not only a safe procedure without reperfusion damages, but also a much more economical and practical treatment, which might benefit the COVID-19 patients globally.

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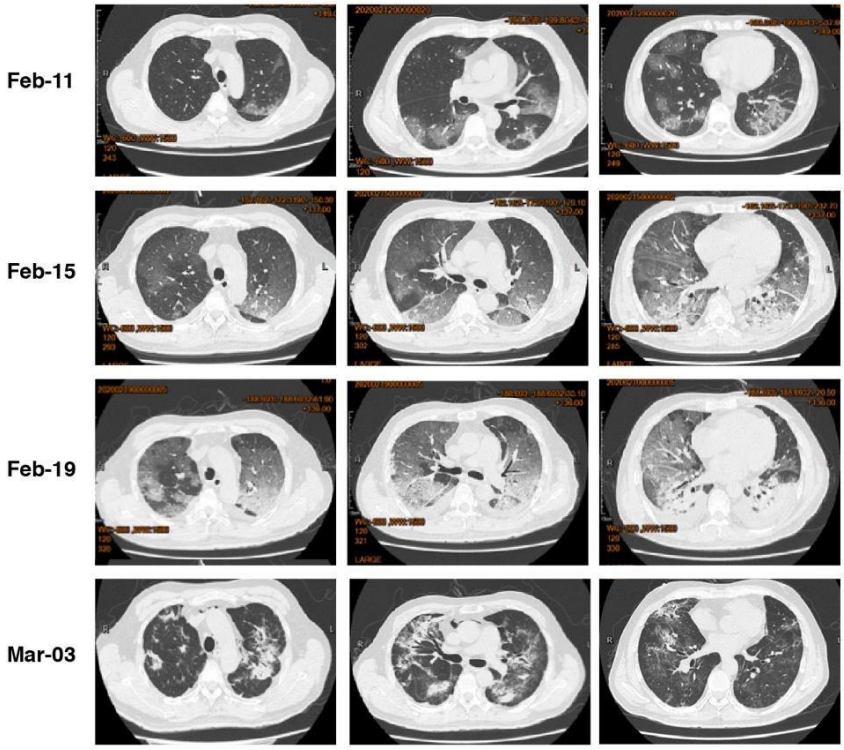

Figure 1. The computed tomography (CT) images for our case patient, which were performed on February 11 (illness day 4), February 15 (illness day 8), February 19 (illness day 12) and March 9 (illness day 31), respectively. On February 15, 2020, illness day 8, note the new foci of bilateral ground-glass opacities and the irregular patchy consolidation along the bronchovascular bundles, and also the appearance of a small amount of pleural effusion. On February 19, 2020, illness day 12, CT images show further enlarged and increased density of ground-glass opacities, consolidation, and pleural effusions. On March 9, 2020, illness day 31, the chest CT images demonstrate the extent and intensity of lesions are significantly reduced.

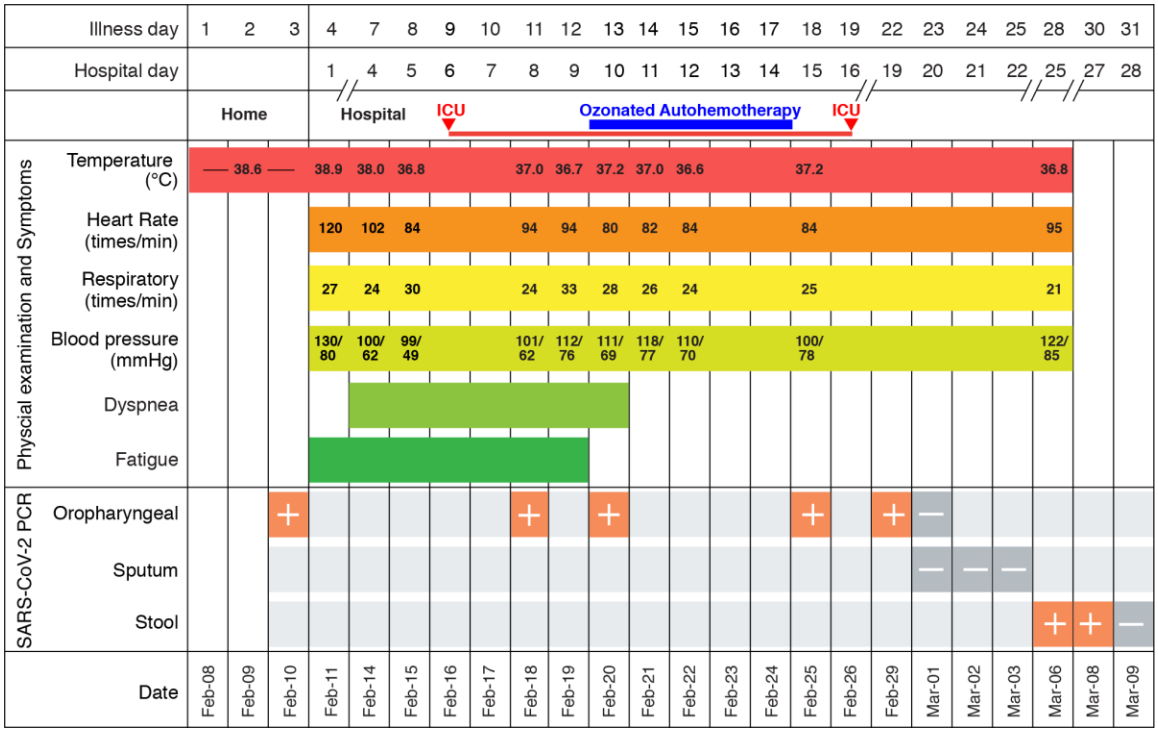

Figure 2. The summary of the patient's physical examination, symptoms and results of RT-PCR testing for COVID-19. Between February 8 and 10, 2020, the body temperature was measured by the patient using a fever thermometer at home, and the maximum was reported at 38.6 °C. The physical examinations were performed four times in the listed days, and the worst outcomes were shown. The red and blue lines represent the illness days, when the patient was in the ICU and treated with the ozonated autohemotherapy, respectively. According to Day of Illness and Day of Hospitalization, February 8 to March 11, 2020.

Table 1. Clinical Laboratory Results											
	Illness Day	4	5	7	12	13	14	15	17	20	25
	Hospital Day	1	2	6	9	10	11	12	14	17	22
Measure	Reference Range					Ozonated Autohemotherapy					
White-cell count (10^9/L)	**4.0-10.0**	**11.58$^{\delta}$**	**11.64$^{\delta}$**	**17.24$^{\delta}$**	**8.74**	**10.74$^{\delta}$**	**12.11$^{\delta}$**	**14.81$^{\delta}$**	**14.39$^{\delta}$**	**10.53$^{\delta}$**	**8.08**
Red-cell count (10^{12}/L)	4.0-5.5	3.85	3.73	3.94	3.45	3.4	3.52	3.31	3.59	3.86	3.73
Absolute lymphocyte count (10^9/L)	**0.8-4**	**0.78‡**	**0.78‡**	**0.44‡**	**0.96**	**0.89**	**0.38‡**	**0.57‡**	**0.99**	**1.08**	**1.78**
Hemoglobin (g/L)	120-160	134	131	134	118	114	119	112	122	132	128
Fibrinogen (g/L)	2.0-4.0	6.41	7.59	8.29	3.22	2.96	4.75	3.53	3.71	4.48	—
D-Dimer (mg/liter)	**0-0.55**	**0.27**	**0.14**	**0.46**	**5.7$^{\delta}$**	**4.67$^{\delta}$**	**2.35$^{\delta}$**	**1.79$^{\delta}$**	**3.31$^{\delta}$**	**1.53$^{\delta}$**	**0.75$^{\delta}$**
C-reactive protein (mg/L)	**0-10**	**213.5$^{\delta}$**	**268.5$^{\delta}$**	**300.0$^{\delta}$**	**21.1$^{\delta}$**	**31.8$^{\delta}$**	**60.4$^{\delta}$**	**19.0$^{\delta}$**	**10.8$^{\delta}$**	**24.2$^{\delta}$**	**1.8**
Procalcitonin (ng/ml)	0-0.5	0.175	0.164	—		0.04	—	—	0.066	—	0.004
Albumin (g/L)	35-50	35.9	33.6‡	29.4‡	25.9‡	—	29.7‡	29.7‡	34.2‡	35.9	38.5
Alanine aminotransferase (U/L)	21-72	20‡	18‡	23	39	—	38	30	33	46	38
Aspartate aminotransferase (U/L)	17-59	19	24	26	41	—	28	17	19	21	21
Alkaline phosphatase (U/L)	38-126	48	54	57	45	—	63	67	62	68	84
Creatine kinase (U/L)	55-170	101	133	81	131	—	137	64	72	—	20
Lactate dehydrogenase (U/L)	313-618	483	599	721$^{\delta}$	856$^{\delta}$	—	764$^{\delta}$	674$^{\delta}$	674$^{\delta}$	—	497
Blood urea nitrogen (mmol/L)	3.3-7.1	7	6	7	9$^{\delta}$	—	8$^{\delta}$	9$^{\delta}$	12$^{\delta}$	—	9$^{\delta}$
Creatinine (µmol/L)	58-110	100	102	101	65	—	94	73	86	—	77
Interleukin-6 (pg/ml)	**0-10**	**51.6$^{\delta}$**	**—**	**—**	**—**	**—**	**20.8$^{\delta}$**	**2.2**	**4.9**	**20.8$^{\delta}$**	**2**
P/F ratio (mmHg)	**400-500**	**340‡**	**194‡**	**—**	**—**	**80$^{‡↓}$**	**111$^{‡↓}$**	**112$^{‡↓}$**	**157$^{‡↓}$**	**385‡**	**362‡**

‡ The value in the patient was below the normal

$^{\delta}$ The value in the patient was above the normal

$^{↓}$ The value in the patient was before the therapy