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Case Report

Integrated therapeutic plasma exchange and traditional Chinese medicine treatment in a patient with severe COVID-19: A case report

Chia-Wei Lin^a, Wei-Chen Hsu^a, Chien-Lu Lu^b, Su-Hsing Cheng^{c,d}, Cheng-Pin Chen^{c,*}, Yu-Chang Hou^{a,e,f,g,*}^a Department of Chinese Medicine, Taoyuan General Hospital, Taoyuan City 330, Taiwan, China^b Department of Nephrology, Taoyuan General Hospital, Taoyuan City 330, Taiwan, China^c Department of Infectious Disease, Taoyuan General Hospital, Taoyuan City 330, Taiwan, China^d School of Public Health, Taipei Medical University, Taipei City 110, Taiwan, China^e Department of Bioscience Technology, Chung Yuan Christian University, Taoyuan City 320, Taiwan, China^f School of Chinese Medicine, College of Chinese Medicine, China Medical University, Taichung City 404, Taiwan, China^g School of Traditional Chinese Medicine, College of Medicine, Chang Gung University, Taoyuan City 333, Taiwan, China

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ABSTRACT

This report presents the case of a 59-year-old man with severe COVID-19 that gradually progressed to cytokine release syndrome and then acute respiratory distress syndrome; he was successfully treated via integration of therapeutic plasma exchange and traditional Chinese medicine. The patient initially presented with a sore throat, severe muscle aches, productive cough and fever. On the worsening of symptoms, remdesivir was administered. However, as the symptoms continued to worsen and a cytokine release syndrome was suspected, oxygen was provided through a high-flow nasal cannula (50 L/min) and therapeutic plasma exchange was performed to prevent worsening of the acute respiratory distress syndrome. On the same day, a course of traditional Chinese medicine was introduced in consultation with the infectious house staff. The patient's symptoms gradually improved; the levels of C-reactive protein and D-dimers reduced, and the patient was weaned to a simple oxygen mask and eventually to room air. This is the first reported case of the integration of these treatments. Together, they prevented the patient from requiring intubation, played a role in cytokine management, and also improved the clinical symptoms, including productive purulent sputum, cough, frequent stool passage and intermittent fever, with no adverse effects. As a result, the patient was discharged within two weeks of the integration of these treatments. Therefore, the integration of therapeutic plasma exchange and traditional Chinese medicine is an effective therapy for patients with severe COVID-19.

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected a large proportion of the global population. There have been 245,373,039 confirmed cases of coronavirus disease 2019 (COVID-19), including 4,979,421 deaths, as of 29 October 2021 [1]. According to the World Health Organization (WHO) Clinical

Management Living Guidance announcement of January 25, 2021, most patients infected with the SARS-CoV-2 developed mild (40%) or moderate (40%) disease, while approximately 15% and 5% developed severe and critical disease, respectively [2]. The WHO recommends systemic corticosteroids and remdesivir for patients with COVID-19. A 2021 summary of 19 articles about plasma exchange included data from 76 patients with COVID-19 who had been treated with therapeutic plasma exchange (TPE) [3]. Several studies have reported the use of traditional Chinese medicine (TCM), including Lianhua Qingwen capsules combined with Western medicine (WM) [4] and Taiwan Chingguan Yihau [5] in patients with COVID-19. However, there have been no

* Corresponding authors at: Department of Chinese Medicine, Taoyuan General Hospital, Taoyuan City 330, Taiwan, China (Y.C. Hou).

E-mail addresses: jangbin@gmail.com (C.P. Chen), houyc0115@gmail.com (Y.C. Hou).

reports on the integration of TPE and TCM for patients with severe COVID-19.

2. Case presentation

The patient provided written informed consent for the publication of this case report. The study complied with the guidelines of the *Helsinki Declaration* and was approved by the instructional review board of our institution (protocol No: TYGH110-3). CARE guidelines were followed in the preparation of this case report.

A 59-year-old man with medication-controlled hypertension (amlodipine and valsartan 5 mg + 80 mg/tablet (Exforge) 1 dose per day; average blood pressure: 118/77 mmHg) presented with a sore throat, severe muscle aches, a productive cough and fever. He was referred to the emergency department for a COVID-19 test. His test result was positive 4 days later, and he was instructed to quarantine at a designated facility. Due to persistent chest tightness and pain, the patient was transported to our hospital 2 days later. The patient was administered oxygen, via a nasal cannula, antibiotics and steroids. On hospital day 3, a chest X-ray revealed cardiomegaly with increased infiltration in both lungs (Fig. 1A). On hospital day 6, the patient was administered 200 mg of remdesivir followed by 100 mg daily for 5 days. The patient continued to experience progressive shortness of breath, chest tightness, chest pain, and oxygen desaturation, reaching 75%. The patient's oxygen support was changed from a nasal cannula to a non-rebreathing mask at a flow rate of 15 L/min, and he was transferred to the negative pressure isolation ward for intensive care.

A chest X-ray obtained on hospital day 6 revealed diffuse infiltration in both lungs with left costophrenic angle blunting, suggesting a large pleural effusion with normal mediastinum and

heart size (Fig. 1B). The patient had elevated C-reactive protein (CRP) and D-dimer levels (Table 1), suggesting cytokine release syndrome (CRS). An oxygen supply with a high-flow nasal cannula (HFNC; FiO₂: 100%, 50 L/min) was administered. TPE was considered to prevent progression to acute respiratory distress syndrome (ARDS). The patient was initially treated with 1.5 times the whole-body plasma volume on hospital day 8, followed by 1.0 times the whole-body plasma volume daily until hospital day 10, for a total of three sessions of TPE.

Based on a consultation with the infection house staff, TCM was prescribed on hospital day 8 as an integrative treatment to reduce the patient's clinical symptoms of productive purulent sputum, cough, frequent stool passage and intermittent fever (Table 2). All TCMs were purchased from Kaiser Pharmaceutical Co., Ltd. and had Good Manufacturing Practice (GMP) certification. The batch numbers are shown in Table 2. TCMs were decocted in water for approximately 60 minutes to form a final volume of 1800 mL for 6 days; 300 mL were taken daily in two doses of 150 mL each. WM and TCM were administered one hour apart.

After the treatment changes made on hospital day 8, the patient's hypoxia symptoms gradually improved, and he was weaned off the HFNC oxygen therapy over the next nine days (Fig. 2). The patient's CRP and D-dimer levels decreased (Table 1), and his clinical symptoms improved. However, the patient continued to present with leukocytosis (Table 1), representing the increase of heat-toxins; therefore, the TCM was adjusted to include more components that clear heat-toxins, which is correlated with improved infection control (Table 2).

On hospital day 14, the patient was switched from HFNC to a simple oxygen mask (Fig. 2) and was weaned to room air by hospital day 17. A chest X-ray obtained on hospital day 15 revealed diffuse ground-glass opacities and infiltration in both lung fields,

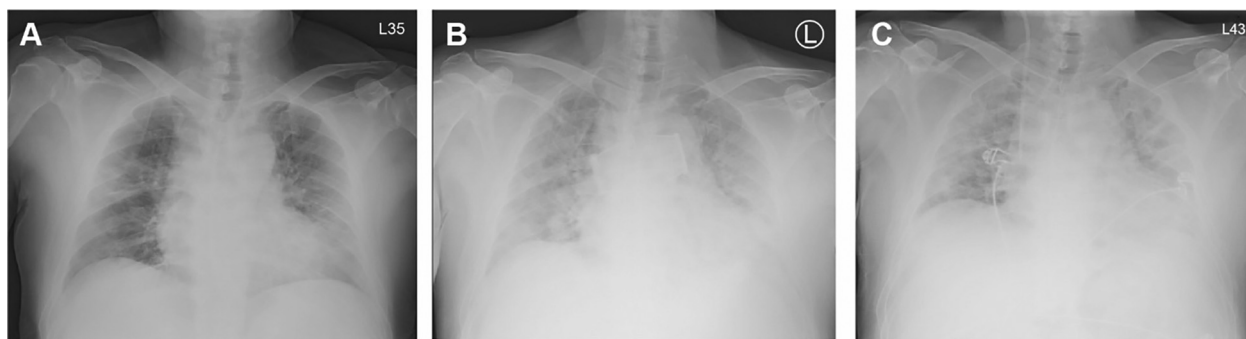


Fig. 1. Chest X-rays obtained during the hospital stay. A: hospital day 3; B: hospital day 6; C: hospital day 15.

Table 1

Laboratory data.

Index	Day 6	Day 8	Day 9	Day 10	Day 11	Day 12	Day 14	Day 18	Day 22
D-dimer (µg/mL)	0.9	–	8.1	–	–	3.9	5.4	3.4	2.6
LDH (U/L)	–	–	–	–	–	644	–	366	–
CPK (U/L)	–	–	–	–	–	19	–	112	–
Ferritin (ng/mL)	–	–	–	220.5	374.1	378.47	–	–	–
CRP (mg/dL)	14.6	–	5.5	–	–	0.6	0.4	0.1	–
WBC (×10 ³ /µL)	–	–	15.93	–	–	20.59	–	16.56	13.95
Seg (%)	–	–	86.5	–	–	92.5	–	86.5	72.1
BUN (mg/dL)	–	30.4	30.4	–	–	29.7	–	24.1	24.4
CRE (mg/dL)	–	0.98	0.94	–	–	0.97	–	0.91	1.00
GOT (U/L)	–	19	23	–	–	33	–	20	21
GPT (U/L)	–	19	19	–	–	31	–	30	29

LDH: lactate dehydrogenase; CPK: creatine phosphor kinase; CRP: C-reactive protein; WBC: white blood cell; Seg: segment; BUN: blood urea nitrogen; CRE: creatinine; GOT: glutamic oxaloacetic transaminase; GPT: glutamic pyruvic transaminase.

Table 2
Composition of traditional Chinese medicine prepared for the patient from hospital day 8 to hospital day 19.

Medication (Batch number)	First period of TCM (hospital days 8–13) (g)	Second period of TCM (hospital days 13–19) (g)
<i>Ephedra</i> (200728)	11.25	11.25
<i>Semen pruni armeniaca</i> (200131)	11.25	11.25
<i>Licorice</i> (A14430)	11.25	11.25
<i>Gypsum</i> (20020601)	18.75	18.75
<i>Fritillaria thunbergia</i> (20221218)	11.25	11.25
<i>Radix platycodonis</i> (N31428)	11.25	11.25
<i>Mori cortex</i> (200602)	15	15
<i>Pinellia ternate</i> (N21036)	11.25	11.25
<i>Trichosanthes kirilowii</i> (QAA02216)	15	15
<i>Scutellaria baicalensis</i> (QA09027)	11.25	11.25
<i>Moutan cortex</i> (A20927)	11.25	–
<i>Houttuynia cordata</i> Thunb (CHA14027)	18.75	–
<i>Atractylodes lancea</i> (A06436)	11.25	11.25
<i>Citri reticulatae pericarpium</i> (QA11028)	11.25	11.25
<i>Jujubae fructus</i> (N24533)	7.5	7.5
<i>Radix Isatidis</i> (QA08941)	–	15
<i>Herba Taraxaci</i> (190930)	–	37.5

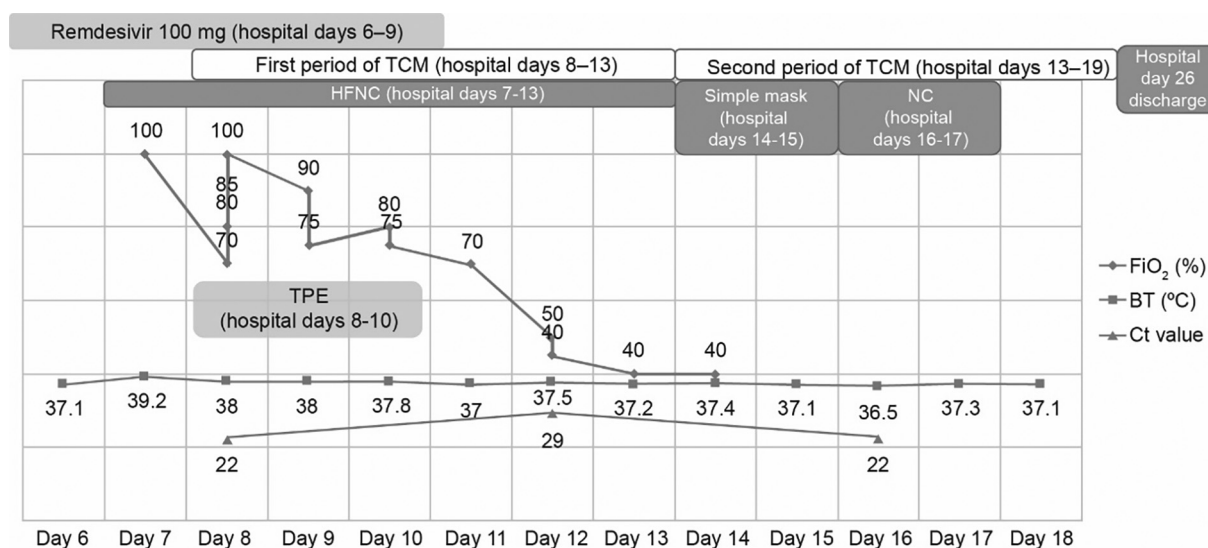


Fig. 2. The patient's oxygen requirements during integrative treatment. TPE: therapeutic plasma exchange; TCM: traditional Chinese medicine; HFNC: high-flow nasal cannula; NC: nasal cannula; BT: body temperature; Ct: cycle threshold; FiO₂: fraction of inspiration O₂.

despite improved clinical symptoms, suggesting COVID-induced lung injuries (Fig. 1C).

The patient's follow-up cycle threshold of real-time reverse transcription polymerase chain reaction for SARS-CoV-2 increased from 22 on hospital day 8 to 37 and 35.5 on hospital days 20 and 23, respectively, which were within the acceptable range for hospital discharge. The patient was successfully discharged on hospital day 26 and continued regular follow-up at an outpatient clinic. The timeline of this case is shown in Fig. 3.

3. Discussion

To our knowledge, this is the first case report of a patient with severe COVID-19 who was successfully treated with the integration of TPE and TCM. Infection with COVID-19 can result in severe respiratory symptoms, including ARDS, which is induced by CRS. Elevated serum interleukin-6 (IL-6) levels correlate with respiratory failure and poor clinical outcomes in patients with CRS [6], which is a major cause of morbidity and mortality in patients with

COVID-19. Therefore, suppressing CRS may be the key to reducing mortality. Although it is not yet recommended as regular therapy for patients with COVID-19, its use has been reported for patients with severe COVID-19 in several countries. TPE is defined as the replacement of a patient's plasma with allogeneic or autologous plasma to decrease or remove certain pathological substances and prevent further damage. It has been suggested that TPE may be beneficial for patients with sepsis, if administered within 12 hours, as it would remove pathogenic cytokines [7]. TPE may be an effective treatment for CRS and sepsis, which can develop in patients with severe COVID-19. As of June 2021, there are over 200 studies concerning COVID-19 and TPE on the PubMed database.

Gucyetmez et al. [8] reported that lactate dehydrogenase, D-dimer, ferritin, IL-6, CRP and procalcitonin levels decreased significantly in patients who underwent TPE; therefore, it can improve CRS and reduce the risk of thrombosis in patients with COVID-19. A retrospective propensity-matched controlled study, conducted by Kamran et al. [9] found that TPE is significantly associated with decreased hospitalization time, improved survival rate,

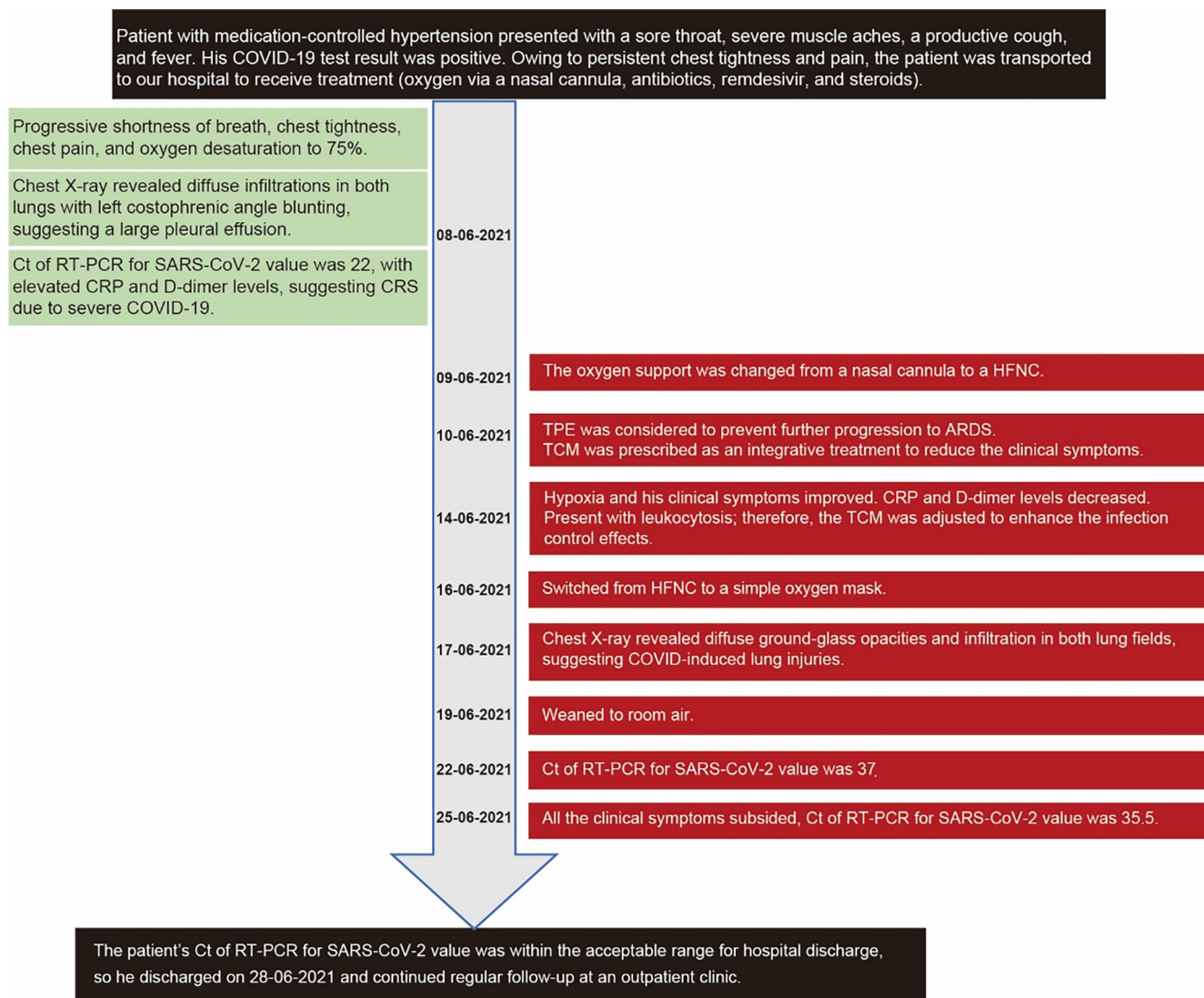


Fig. 3. The timeline of this case. ARDS: acute respiratory distress syndrome; COVID-19: coronavirus disease 2019; Ct: cycle threshold; CRP: C-reactive protein; CRS: cytokine release syndrome; HFNC: high-flow nasal cannula; RT-PCR: real-time polymerase chain reaction; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TCM: traditional Chinese medicine; TPE: therapeutic plasma exchange.

and shortened time to resolve CRS in patients with COVID-19, though the timing of polymerase chain reaction negativity remained unchanged with the addition of TPE. In a randomized controlled trial, TPE reduced the duration of mechanical ventilation and length of stay in the intensive care unit [10].

COVID-19 symptoms are similar to TCM's understanding of heat and/or damp disease, including fever, cough, productive sputum and diarrhea. Based on the current case report, TCM improves clinical symptoms and the chest X-ray image, prevents severe outcomes, and reduces the length of the hospital stay, which is consistent with previous studies [4,11–13]. Since the patient in this case report presented with symptoms of damp-heat disease, especially in the lungs, according to TCM theory, the treatment required clearing lung heat and resolving phlegm. The TCM was prescribed based on the combination of TCM basic theory, clinical experience and modern pharmacology, and was adjusted according to the patient's clinical presentation.

The patient received a TCM based on Ma-Xing-Shi-Gan-Tang with added components that had expectorant, antipyretic, anti-inflammatory and anti-diarrheal effects. The Ma-Xing-Shi-Gan-Tang, consisting of *Ephedra*, *semen Pruni armeniaca*, *licorice* and

gypsum, is generally used to treat lung heat. Previous studies on Ma-Xing-Shi-Gan-Tang focus on treating chronic obstructive pulmonary disease, allergic rhinitis and tuberculosis [14–16]. Ma-Xing-Shi-Gan-Tang has been reported to have antitussive and antipyretic effects, which may be due to the inhibition of histaminergic and acetylcholinergic receptors that activate both sympathomimetic α - and β -adrenergic receptors [17]. The most recent study focusing on the mechanism underlying the effects of Ma-Xing-Shi-Gan-Tang on COVID-19 revealed that Ma-Xing-Shi-Gan-Tang may block viral entry by inhibiting its adsorption and replication. In addition, the results showed that Ma-Xing-Shi-Gan-Tang could regulate immune and inflammatory function, which may confer added advantages when managing COVID-19 and its sequelae [18]. To enhance the antitussive and expectorant effects, *Fritillaria Thunbergia*, *Radix Platycodonis*, *Mori cortex*, *Pinellia Ternate* and *Trichosanthes Kirilowii* were added to the formula for their individual properties. *Fritillaria Thunbergia* reduces the frequency of cough [19]. *Radix Platycodonis* has been reported to have apophlegmatic and antitussive effects, as it clears mucin in the airways [20]. *Mori cortex* has antiasthmatic and antitussive effects via an increase in nitric oxide in the bronchi, leading to dilation of the bronchial

smooth muscles [21]. *Pinellia ternate* can decrease coughing and sputum production [22]. *Trichosanthes kirilowii* contains several amino acids that act as expectorants, including aspartic acid that increases cell-mediated immunity to suppress secretions in the respiratory tract and cysteine that reduces the viscosity of sputum [23]. *Scutellaria baicalensis*, *Moutan cortex* and *Houttuynia cordata* Thunb have antipyretic effects. Baicalin, a characteristic constituent of *Scutellaria baicalensis*, may decrease the levels of tumor necrosis factor- α (TNF- α), IL-1 β , IL-6 and other cytokines in the hypothalamus, serum and cerebral spinal fluid [24]. *Moutan cortex* can inhibit inflammatory chemokines [25], and paeonol, a constituent of *Moutan cortex*, decreases the secretion of TNF- α , IL-1 β , IL-6 and IL-10 [26]. The mechanism of *H. cordata* Thunb is similar to that of *Moutan cortex*, as it downregulates IL-6 to achieve anti-inflammatory effects [27]. When integrated with TPE, these TCM herbs play a role in cytokine management, which is important when treating CRS. In addition, the patient in this report received *Atractylodes lancea*, *Citri reticulatae pericarpium* and *Jujubae fructus* to prevent diarrhea. β -Eudesmol, present in *Atractylodes lancea*, has a two-way regulation of enterogastric peristalsis [28], while *Citri reticulatae pericarpium* has similar functions in the gastrointestinal tract [29]. Jujube polysaccharide is a useful constituent of *Jujubae fructus* and can enhance mucus and protect the intestinal tract from contacting the hazardous substance, improving intestinal health [30].

Since the patient's clinical symptoms improved, the TCM regimen was adjusted to treat the patient's persistent leukocytosis; in other words, the TCM syndrome type changed from heat disease to heat disease with heat-toxins. *Moutan cortex* and *H. cordata* Thunb were replaced with *Radix Isatidis* and *Herba Taraxaci* to enhance the effects of infection control. *Radix Isatidis* and *Herba Taraxaci* are considered in TCM to clear heat-toxins, which is comparable to the concept of viruses, bacteria and other infectious sources. When leukocytosis is present, inflammation and infection cannot be ruled out. Although the mechanism is unclear, *Radix Isatidis* has antiviral effects [31], and is frequently used to treat viral infections [32]. Further, *Herba Taraxaci* has antibacterial and antiviral effects [33].

The guidelines for integrating TCM and WM for COVID-19 have been published recently and recommend prescription granules, decoctions, patent medicines and Chinese herbal injections for treating COVID-19 [34]. The guidelines also emphasize the principle of syndrome differentiation to address different stages of the disease and conditions of individual patients [35]. Additionally, similar case reports published on PubMed have also been reviewed by us, and most of them follow the guidelines mentioned above. Our case report also followed this recommendation, by using the TCM recommended in the guidelines and following the principle of syndrome differentiation [36–39].

Furthermore, a previous study has shown that the use of TCM and basic treatments can reduce all-cause mortality in severe and critical COVID-19 patients [40]. In the case published here, we provide a new combination by integrating TCM with TPE to prevent intubation by downregulating cytokines to stop the CRS. In addition to helping to suppress cytokines, similar to TPE, TCM was able to improve the patient's clinical symptoms that were unrelated to CRS.

4. Conclusion

The patient's clinical symptoms improved, permitting his oxygen requirements to be reduced from HFNC to a nasal cannula and finally, to room air, following the addition of TCM and TPE to remdesivir and steroids. This prevented the patient from requiring

intubation. The integration of TCM and TPE did not result in damage to the liver or kidneys. This case report indicates that integrating TPE and TCM is a therapeutic option for patients with severe COVID-19.

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Authors' contributions

YCH contributed to the conception of this research; CWL collected the data and wrote the original paper; YCH, WCH, CPC and SHC reviewed and edited the manuscript; CPC and CLL were responsible for contacting the patient. All authors read and approved the final version of the manuscript accepted for publication.

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Declaration of competing interest

There are no conflicts to declare.

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