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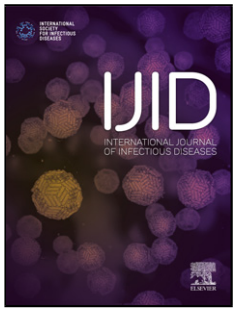

Successful recovery of severe COVID-19 with cytokine storm treating with extracorporeal blood purification

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Highlights

- The prognosis of critical cases of COVID-19 might be changed if the intervention of EBP was performed timely.
- EBP may help to attenuate the progression of ARDS.
- Evaluating FDPs as sensitive marker of injury and prognosis of COVID-19 is warranted.

Abstract

COVID-19 associated cytokine storm could induce ARDS rapidly and the patients would require the support of mechanic ventilation. However, the prognosis was not that optimistic. The outcome might be changed if the intervention of EBP was performed timely. We present a case of severe SARS-CoV-2 infection who recovered from cytokine storm.

Key words: COVID-19; cytokine storm; ARDS; extracorporeal blood purification

Background

The coronavirus disease 2019 (COVID-19) broke out throughout the world now. The total number of deaths has been Over 88900 up to now. The patients with confirmed COVID-19 progressed to acute respiratory distress syndrome (ARDS) rapidly in an incident rate as high as 41.8%[1], and many of them require mechanic ventilation. In a cohort of an intensive care unit (ICU) from Italy, 1287 cases need respiratory support, and among them, 88% of patients (1150 cases) had to be supported with mechanical ventilation[2]. Apart from the desperate lacking of ventilator all over the world, mechanical ventilation could also cause barotrauma and ventilator-associated lung injury.

Cytokine storm has been disclosed as the main pathological characteristic of COVID-19[3], and it is also the direct pathogenic contributor to induce ARDS. Cytokines could be eliminated effectively by extracorporeal blood purification (EBP)[4], which thus could interrupt the initiation and progression of inflammation cascade in the scenario of COVID-19. Accordingly, there may be a chance of avoiding incubation and mechanical ventilation. Herein, we report a case of severe SARS-CoV-2 infection with cytokine storm, who was completely recovered from cytokine storm using extracorporeal blood purification.

Case presentation

A 62- year- old male presented to the hospital with 8-day history of fever and 6-day history of cough and chest distress. The patient had a history of gallstone. He got fever on day 1 (February 14, 2020) and had chill, headache, muscle soreness, fatigue, nausea, cough, and chest distress and shortness of breath on day 3. Then, he was quarantined in a hotel. Being tested positive

for SARS-CoV-2 on day 5, he received oseltamivir, moxifloxacin and Lianhua Qingwen capsule (Chinese medicine) in the outpatient.

He was admitted to the hospital with fever, cough and mild chest distress on day 9. Arbidol, hydroxychloroquine, oseltamivir, and Lianhua Qingwen capsule were administered. Supplemental oxygen was delivered by nasal cannula at 2 L/min. Alterations in hepatic function were showed: levels of alanine aminotransferase (81 U/L, normal range: 9-50 U/L) and aspartate aminotransferase (94 U/L, normal range: 15-40 U/L) were elevated, and CD3 and CD4 cell counts were markedly decreased (Supplemental Table) on day 10. Chest CT indicated multiple ground-glass opacities in bilateral lungs on day 11 (Supplemental Figure 1. A-C). The peak of temperature was 38.5˚C up to date. His vital signs remained clinically stable except oxygen saturation was 97% while providing oxygen at 3 L/min. IL-6 (198.66 pg/ml) was almost 10 folds of normal range (≤5.9 pg/ml) which indicated an initiation of cytokine storm on day 12 (Figure 1). The EBP, including double plasma molecular adsorption system (BS330 and HA330II, Jafron, China) and plasma exchange (2000 ml each), was thus applied to remove the cytokines on day 13. The BS330 and HA330II were installed in series after the plasma separator (EC-4W, Asahi) with a blood flow velocity of 80-100 ml/min and a separating speed of 20-25ml/min, and the duration of the treatments was 6 hours. The plasma exchange was then conducted. Intravenous methylprednisolone (40 mg daily) was used to suppress the inflammation reaction. The patient was largely stable until the chest distress exacerbated and blood in phlegm developed on day 14. He then progressed to type I respiratory failure (partial pressure of oxygen 51 mmHg, partial pressure of carbon dioxide 32 mmHg) with 89% oxygen saturation while the oxygen flow was 3 L/min. High-flow oxygen (40 L/min) was initiated to keep the oxygen saturation values between 96-99%. Hydroxychloroquine was discontinued due to a long QT interval. The EBP therapy continued on days 14 and 15 respectively.

The patient was transferred into ICU on day 15. Given the acute inflammatory reaction, methylprednisolone was improved to 60 mg twice daily, and piperacillin-tazobactam (4.5 g administered intravenously every 8 hours) was initiated concerning about the hospital-acquired pneumonia. Acetylcysteine was used to dilute the phlegm. The human serum albumin and other supportive care were also administered. The clinical condition of the patient was improved on day 16 and was stable

thereafter, and his hepatic function was back to normal as well. The body temperature returned to normal on day 17. The IgM of anti- SARS-CoV-2 was identified (77.11 AU/mL, normal value <10 AU/mL) at the same day. Methylprednisolone was gradually reduced and discontinued on day 23. The lesions on chest CT was confined on day 17 and further alleviated on day 21 and almost disappeared on day 33 (Supplemental Figure 1). Low flow rate of oxygen (2 L/min) was delivered instead of high-flow oxygen on day 26 then discontinued on day 36. He was asymptomatic at rest and had no shortness of breath while doing activity training. His renal function was unaffected and immunoglobulin levels including IgG, IgM, IgA and IgE were normal throughout the clinical course. Complement C3 level was staying below the normal range (0.9-1.8 g/L) during the hospital duration (Supplemental Table 1). C4 level (<0.06 g/L, normal range: 0.1-0.4 g/L) was reduced at day 16 and was back to normal (0.15 g/L) on day 31. The nucleic acid testing of SARS-CoV-2 was negative in four different times. He was discharged on day 38.

Discussion

The management of COVID-19 in critical cases is still challenging nowadays. Respiratory and circulation supports, such as mechanic ventilation and extracorporeal membrane oxygenation (ECMO), were almost the last defense for severe COVID-19[5]. Although specific methods to intervene the progression of critical cases are unknown, the effects of EBP in treatment of COVID-19 associated cytokine storm have not been emphasized. The outcome of the present case of COVID-19 with ARDS is promising. Pulmonary fibrosis was not observed up to date.

EBP was suggested to interrupt the inflammation cascade and stop the progression of cytokine storm in this case. There were obvious peak levels of cytokines and bent over after the initiation of EBP on day 13. HA330 improved oxygenation and lung mechanics by removing circulating and alveolar cytokine levels[6], and BS330 adsorbed bilirubin so as to attenuate liver injury[7].The EBP that combined the double plasma molecular adsorption system and plasma exchange can directly reduce the cytokines. Although methylprednisolone was also administered synchronously, it has been identified that the significant time point of IL-6 reduce was the seventh day rather than the first three days in ARDS[8]. In addition, there was a very short time window to manipulate the acute inflammatory state. The patient turned to be unstable all of sudden without changes of clinical

symptoms or subjective discomfort until day 14. Fortunately, we noticed the elevation of cytokine levels on day 12. Therefore, the proper time for intervention based on the levels of cytokines needs further validation.

Similar features were found in this case as previous literatures[9,10], for instance, low level of lymphocyte, high level of cytokines and D-dimer. More interestingly, we found that the changes of fibrinogen degradation products (FDPs) (Figure 1) were correlated with cytokines. It returned to normal range even earlier than cytokines and D-dimer. Besides, rising in the D-dimer over time was observed in non-survivors with more stable levels in survivors[10]. Taken together, employing FDPs as sensitive marker of injury and prognosis of COVID-19 is also warranted.

The present patient has completely recovered from severe COVID-19. Other factors should also be considered: (1) no chronic complication and relative younger age; (2) no development of other organ failure; (3) the existence of antibody to SARS-CoV-2.

Conclusion

The prognosis of critical cases of COVID-19 might be changed if the intervention of EBP was performed timely.

Conflicts of Interest statement: The authors declare that they have no relevant financial interests.

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Ethical Approval: This study has been approved by Qilu Hospital, Cheeloo College of Medicine, Shandong University.

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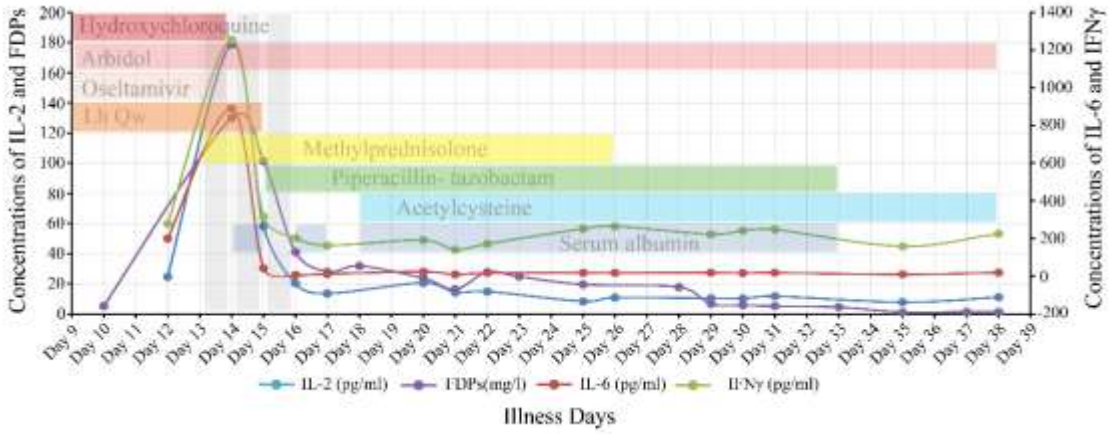
Figure and figure legend

Figure. 1 The changes of cytokines and FDPs and the medications applied



The left vertical axis represents the levels of interleukin 2 (IL-2, blue dot) and fibrinogen degradation products (FDPs, purple dot). The right vertical axis represents the levels of interleukin 6 (IL-6, red dot) and interferon γ (INF γ, green dot). The horizontal axis shows the illness days. The gray vertical bar shows the artificial liver therapy. The horizontal bars with different colors represent the medications, and the lengths represent the corresponding duration. Lh Qw denotes Lianhua Qingwen capsule.