Successful treatment of plasmapheresis followed by interferon beta-1a in a child with severe COVID-19

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COVID-19 outbreak has become a global health concern due to challenges in treatment and high mortality rate; therefore, its therapeutic approaches play an important role in reducing the mortality rate and resolving this concern. Different therapies have been introduced, including interferon beta-1a and purification methods, for instance, plasmapheresis. In this article, we reported a child with severe COVID-19 who fully recovered after receiving plasmapheresis and interferon beta-1a.

Key words: COVID-19, interferon beta-1a, pediatric infectious disease, plasmapheresis

INTRODUCTION

Coronavirus disease 2019 (COVID-19) has become a global health concern due to pandemic and relatively high mortality rates, especially in severe and critical cases. Despite the lower incidence rate in children than in adults and the lower severity, COVID-19 in children could cause critical illnesses and even septic shock.

There is no consensus on the management of children with COVID-19. However, different treatment recommendations have been introduced and are being used in hospitals and ICUs based on patient’s condition.[1] Furthermore, supportive care, such as oxygen therapy, organ function support, maintaining water-electrolyte balance, and homeostasis are suggested.[2] One of the controversial treatment is blood purification methods, for example, plasmapheresis. Some studies revealed a significant effect of blood exchange on cytokine/chemokine levels reduction.[3,4] On the other hand, it was shown that hyperinflamation and cytokine storm played great roles in severe cases.[5] However, there is no study on the treatment of plasmapheresis efficacy on children with COVID-19, based on our literature review.

In this article, we reported the first case of severe COVID-19 who fully recovered after receiving plasmapheresis and interferon beta-1a in addition to the Iranian protocol of COVID-19 treatment for children in Isfahan, Iran.

CASE REPORT

A 13-year-old girl was admitted with fever for 5 days, productive cough, hemoptysis, and diarrhea. In initial physical examinations, she was alert with respiratory distress and tachycardia. Chest indrawing and decrease lung sound on the right side were two obvious signs in the chest examination. The rest of the examinations was...
unremarkable. Her blood tests at the admission time showed lymphopenia and elevated C-reactive protein, procalcitonin, and lactate dehydrogenase [Table 1].

In order to confirm COVID-19, a chest computed tomography (CT) scan was done, and a nasopharyngeal swab sample was collected for the reverse transcription polymerase chain reaction (RT-PCR) test. The result of the RT-PCR test and chest CT scan findings confirmed the diagnosis of COVID-19 [Figure 1].

Therefore, based on the Iranian protocol of COVID-19 treatment, therapy began [Table 2]. Furthermore, she went on BiPAP because of respiratory distress and decreased arterial oxygen saturation. Due to hemoptysis and suspicion of acute respiratory distress syndrome, she was admitted to ICU, and Atazanavir and interferon beta-1a were prescribed. Despite the therapy, signs worsened and arterial oxygen saturation decreased. Thus, plasmapheresis was performed four times in 2 days, and each time the patient received fresh-frozen plasma as replacement fluid.

After 2 days, a chest X-ray revealed a significant change in her lungs [Figure 2], and her general condition improved. Arterial oxygen saturation with BiPAP changed from 80% before the plasmapheresis to 94% after the fourth time of plasmapheresis. After that, interferon beta-1a was injected every 48 h for three times between the 3rd and 7th day of hospitalization. Tachypnea and tachycardia disappeared on the 5th day.

Serial laboratory tests revealed an elevated WBC count with a predominance of PMNs in the 7th day. This leukocytosis remained until discharge time [Table 1]. Furthermore, repeated chest CT scans represented a dramatic change in pulmonary infiltrates compared to the 1st day [Figure 2].

The patient was transferred from the ICU to ward after the 8th day of hospitalization. On the 9th day, her oxygen therapy changed from BiPAP to a nasal cannula. Over the next 5 days, respiratory distress disappeared gradually which allowed tapering of supplemental oxygen.

Finally, she was discharged from the hospital after 14-day hospitalization with good condition, normal

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**Table 1: Daily physical examination and laboratory tests findings**

| Parameters                          | Day 1 | Day 2 | Day 4 | Day 7 | Day 9 | Day 14 |
|-------------------------------------|-------|-------|-------|-------|-------|--------|
| Pulse rate (/min)                   | 121   | 110   | 70    | 86    | 80    | 82     |
| Respiratory rate (/min)             | 40    | 65    | 38    | 30    | 28    | 24     |
| Arterial oxygen saturation (%)      | 81    | 80    | 88    | 98    | 98    | 98     |
| WBC (×10^3//μl)                     | 6300  | 6800  | 6700  | 20,400| 21,200| 18,700 |
| Neutrophil (%)                      | 89.8  | 92.5  | 90    | 88    | 90    | 85     |
| Lymphocyte (%)                      | 8     | 6     | 9     | 7     | 7     | 11     |
| Hemoglobin (g/dl)                   | 13.4  | 13    | 12.6  |       | 13.2  | 12     |
| Platelet count (×10^3//μl)          | 181,000| 186,000| 201,000| 314,000| 270,000|
| AST (IU/L)                          | 37    | 31    | 117   | 41    | 37    | 36     |
| ALT (IU/L)                          | 18    | 14    | 108   | 87    | 57    | 206    |
| T-Bilirubin (mg/dl)                 | 3     | 0.8   |       |       |       |        |
| D-Dimer (ng/mL)                     | 3240  |       | 1575  |       |       |        |
| Ferritin (ng/mL)                    | 410   |       |       |       |       |        |
| Lactate dehydrogenase (IU/L)        | 701   |       | 988   | 988   |       |        |
| C-reactive protein (mg/dL)          | 46    |       |       |       | 47    |        |
| ESR 1st h                           | 19    |       |       |       | 69    |        |
| Procalcitonin (μg/l)                | 10    |       |       |       |       |        |
| Creatinine (mg/dl)                  | 0.9   | 0.9   | 0.8   |       |       |        |
| pH*                                 | 7.46  | 7.38  | 7.48  | 7.48  | 7.48  |        |
| Bicarbonate* (mmol/L)               | 21    | 22.2  | 32    | 25.1  |       |        |
| pCO₂* (mmHg)                        | 30    | 38.5  | 43    | 34    |       |        |

*Findings were resulted of venous blood gas tests. WBC: White blood cell, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase
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Figure 2: Serial chest X-rays revealing response to treatment, (a) 1st day, (b) 2nd day, (c) 3rd day, (d) 10th day, (e) 11th day, and (f) 13th day of admission

Table 2: Daily supportive care and treatment

| Treatments                  | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|-----------------------------|-------|-------|-------|-------|-------|-------|-------|-------|-------|--------|--------|--------|--------|--------|
| Intensive care unit         | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Oxygen therapy              | BiPAP | BiPAP | BiPAP | BiPAP | BiPAP | BiPAP | BiPAP | BiPAP | BiPAP | Nasal cannula | nasal cannula | nasal cannula | nasal cannula | Room air |
| Plasmapheresis              | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Interferon beta 1-a         |       |       |       |       |       |       |       |       |       | ✓      | ✓      | ✓      | ✓      | ✓      |
| Hydroxychloroquine          | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Lopinavir/ritonavir*         | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Ceftriaxone/cefotaxime       | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Vancomycin                  | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Atazanavir*                 | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |
| Ciprofloxacin               | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓     | ✓      | ✓      | ✓      | ✓      | ✓      |

*Atazanavir and lopinavir/ritonavir were discarded, because liver function tests and bilirubin level became abnormal at the 2nd day

oxygen saturation in room air, and without fever. She had a good condition without any problem in a 2-week follow-up.

DISCUSSION

We reported the child with severe COVID-19 that received plasmapheresis in addition to standard therapy and ultimately was discharged in good condition. Her clinical characteristics, including respiratory rate, arterial oxygen saturation, and lymphopenia, were consistent with the literature review. However, her platelet count is normal, contrary to the literature review. Her diagnosis was made after the positive result of RT-PCR and typical lesions seen in the chest CT scan.

Up to the present, COVID-19 treatment consists of supportive care and reducing the severity of injuries caused by virus infection. Hyperinflammation and cytokine storm are among the causes of SARS-CoV-2 infection-associated lesions. On May 15, 2020, the World Health Organization announced the diagnostic criteria of multisystem inflammatory syndrome related to COVID-19 ( multisystem inflammatory syndrome in children [MISC]). At that time, we did not know this term in pediatric patients and now following this knowledge, the presented case suffered from MISC because of persistent fever, diarrhea, and elevated D-Dimer.

Early control of MISC can improve outcomes. In this regard, different theoretical methods, including IFN-α, corticosteroid therapies, intravenous immunoglobulin, IL-1 family antagonists, TNF blockers, chloroquine and blood purification treatments, are recommended. Few studies introduced blood purification treatment as a therapeutic method for severe and critical adult cases. A case report showed convalescent plasma therapy as an efficient treatment in severe COVID-19 cases. Furthermore, plasma exchange and plasmapheresis are among new treatments in patients with severe COVID-19 based on theories; however, their outcomes are not completely known, especially in children. In our case, we performed two times/day plasmapheresis in the first 2 days of admission for our case, which caused a significant
diminishing of lung infiltration in chest X-ray. A single-center clinical trial showed that interferon beta-1a positively affected on adult patients’ conditions. In our case, three doses of interferon beta-1a in 6 days were administered after performing plasmapheresis. Furthermore, hydroxychloroquine was introduced to reduce the severity of cytokine storm, and it was prescribed for our case. All of these, along with the Iranian protocol of COVID-19 treatment and respiratory support [Table 2] improved her severe COVID-19.

**CONCLUSION**

Up to now, there is no established treatment for COVID-19. Reports from the different parts of the world showed that children with MISC need immunomodulatory treatment. Control of them can survive patients’ lives. In this article, we reported the successful use of plasmapheresis to control MISC and prevent its consequences.

RS contributed in the conception of the work, revising the draft, approval of the final version of the manuscript, and agreed for all the aspects of the work. HR contributed in revising the draft critically for important intellectual content, approval of the final version of the manuscript, and agreed for all aspects of the work. AD contributed in the conception of the work, drafting, revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. AS contributed in revising the draft, approval of the final version of the manuscript, and agreed for all aspects of the work. ZP contributed in revising the draft critically for important intellectual content, approval of the final version of the manuscript, and agreed for all aspects of the work.

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**Declaration of patient consent**

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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**Conflicts of interest**

There are no conflicts of interest.

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