

## Convalescent (Immune) Plasma Followed by Intravenous Immunoglobulin Infusion in an Adolescent with Severe COVID-19

Şiddetli COVID-19'lu Ergende Konvalesan (İmmün) Plazmayı İzleyen İntravenöz İmmünoglobülin İnfüzyonu

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### ABSTRACT

Coronavirus disease 2019 (COVID-19) pandemic has drawn attention over old immunotherapeutic agents such as convalescent (immune) plasma (CIP). Here, an adolescent with severe COVID-19 case requiring CIP and intravenous immunoglobulin (IVIG) treatments is described. A 17-year-old male patient was brought to the emergency room with complaints of fever, fatigue, and severe cough. Two doses of CIP were infused to the patient because of the increase in persisting fever, dyspnea, and acute phase reactant levels after the third day of routine protocol treatment. IVIG therapy was begun for 2 days at a dose of 1 g/kg/day due to resurgence in acute phase reactants and progressing radiological findings following CIP transfusion. Our patient avoided mechanical ventilation and showed immediate clinical and radiological improvement with CIP transfusion followed by IVIG therapy. Timely initiation of CIP treatment followed by IVIG prevented the disease from worsening and helped to reduce the requirement for mechanical ventilation.

**Keywords:** Convalescent (immune) plasma; COVID-19; intravenous immunoglobulin.

### ÖZ

Koronavirüs hastalığı 2019 (coronavirus disease 2019, COVID-19) pandemisi konvalesan (immün) plazma (CIP) gibi eski immünoterapötik ajanların üzerine dikkati çekmiştir. Burada, CIP ve intravenöz immünoglobülin (IVIG) tedavisi gerektiren şiddetli COVID-19 hastalığı olan bir adolesan olgu sunulmaktadır. 17 yaşında erkek hasta ateş, yorgunluk ve şiddetli öksürük yakınmalarıyla acil servise getirildi. Hastaya rutin protokol tedavisinin üçüncü gününden sonra devam eden ateş, nefes darlığı ve akut faz reaktan düzeylerindeki artış nedeniyle iki doz CIP infüzyonu uygulandı. CIP transfüzyonu sonrası akut faz reaktanlarında yeniden artış ve ilerleyen radyolojik bulgular nedeniyle 2 gün süreyle 1 g/kg/gün dozunda IVIG tedavisine başlandı. Hastamız CIP transfüzyonunu takiben IVIG tedavisiyle hemen klinik ve radyolojik iyileşme gösterdi ve mekanik vantilatör uygulamasından kurtuldu. CIP tedavisinin zamanında başlatılması ve ardından verilen IVIG, hastalığın kötüleşmesini önlemiş ve mekanik ventilasyon ihtiyacının azaltılmasına yardımcı olmuştur.

**Anahtar kelimeler:** Konvalesan (immün) plazma; COVID-19; intravenöz immünoglobülin.

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### INTRODUCTION

The immune response is vital for the control and improvement of viral infections. The literature reports different immunotherapeutic modalities including convalescent (immune) plasma (CIP) therapy and intravenous immunoglobulin (IVIG) and their beneficial outcomes in coronavirus disease 2019 (COVID-19) (1-7). Here, an adolescent case with severe COVID-19 disease requiring CIP and IVIG treatments to recover is discussed under the light of current literature.

Received / Geliş Tarihi : 17.05.2021

Accepted / Kabul Tarihi : 12.07.2021

Available Online /

Çevrimiçi Yayın Tarihi : 26.07.2021

## CASE REPORT

A 17-year-old male patient without any known illness was brought to the emergency room with complaints of fever, fatigue, and severe cough. His complaints had started 22 days before hospitalization, with insistent weakness, sore throat, runny nose, and mild cough. No pneumonia signs were detected in computed tomography (CT) one week after symptoms onset, and symptomatic treatment was given. On the 11<sup>th</sup> day of his complaints, he represented with persistent nasal discharge, paroxysmal and severe cough, causing dyspnea; and antibiotherapy and 5-day methylprednisolone (1mg/kg/day) were given. Two days later, the patient had increased weakness, severe cough with phlegm, and a persistent fever of 38-39 °C despite acetaminophen intake. He was hospitalized to our general pediatric wards due to positive (severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) polymerase chain reaction (PCR) test and nonspecific pneumonia findings (diffuse nodular consolidations in both hemithorax) in thorax CT scan (Figure 1a, 1b).

At the admission his general condition was moderate; physical examinations demonstrated decreased lung sounds and diffuse crackles on both lungs. Mild lymphopenia (1290/ $\mu$ L), transient elevation of AST/ALT, high CRP (115, n: <5) mg/L, and normal D-dimer were detected. The patient was started on ceftriaxone 4 g/bid (50 mg/kg/day) and hydroxychloroquine 400 mg/bid (5 mg/kg base/day) for 5 days.

On the third day of admission, subcostal-intercostal retractions and dyspnea began with exercise and talking. Lymphopenia deepened as 945/ $\mu$ L, CRP increased up to 147 mg/L. The postero-anterior chest x-ray showed an increase in bilateral lung infiltration areas. Hydroxychloroquine therapy was changed to favipiravir 3200 mg/day at two doses of loading and 1200 mg/day for maintenance in a total of 5 days. Vancomycin 2 g/day and azithromycin 250 mg/day were added. High flow nasal cannula (HFNC) oxygen therapy was initiated after being transferred to pediatric intensive care unit.

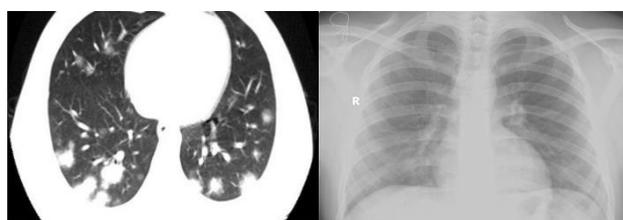
On the fourth day of his admission, increase in dyspnea was observed with exercise and talking. Fibrinogen was 462 (n: 202-430) mg/dl, ferritin: 1036 (n: 4.6-204) ng/mL and IL-6: 21.95 (n: 0-7) pg/mL were elevated (Table 1). First dose of CIP was administered because of the increase in persisting fever, dyspnea, and acute phase reactant levels. Enoxaparin 4000 IU/day was added into his treatment.

On the fifth day, postero-anterior x-ray showed increased infiltration in the right lung. On the sixth day, pathologic lung sounds in the right were increased, considered as consolidation. A second dose of CIP was administered, because the consolidation developed in the right lung and the acute phase reactants were still above the normal, despite a decreasing trend.

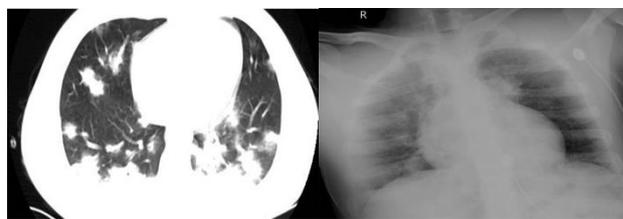
On the seventh day, pathologic right lung sounds were decreased and there were crackles in the left lung. Blood gas analysis showed high lactate level (3.4 mmol/L). The thorax CT demonstrated an increase of infiltration extending through to upper segments (Figure 2a, 2b). Since resurgence in acute phase reactants and progressing radiological findings, IVIG therapy was begun for 2 days at a dose of 1 g/kg/day.

On the eighth day, the patient stated significant regression in his exercise dyspnea and cough. Blood gas analysis

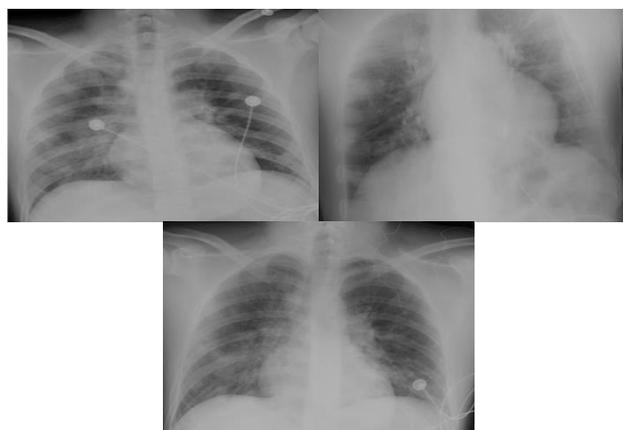
showed mild respiratory alkalosis (pH: 7.48, pCO<sub>2</sub>: 32.8 mmHg). On the ninth day, following the second dose of IVIG, auscultation findings of both lungs were significantly lessened, the patient started to be able to eat comfortably, and activity increase was observed. The HFNC oxygen flow was started to reduce. Chest X-rays progressively demonstrated diffuse consolidation regions containing air bronchograms in both lungs at the 8<sup>th</sup> thru 9<sup>th</sup> day of admission (Figure 3a, 3b). On the tenth day, the pulmonary auscultation findings turned back to normal. Chest X-ray showed partial resolution of consolidation regions in both lungs (Figure 3c). On the eleventh day, he was transferred to general pediatric wards. He was discharged on 14<sup>th</sup> day and ceftriaxone was discontinued.



**Figure 1a.** Although CT shows diffuse nodular consolidations in both hemithorax (nonspecific findings for COVID-19 pneumonia); **1b.** chest X-ray seems to be roughly normal at the day of hospitalization



**Figure 2a.** CT shows diffuse peripheral and central focal patchy ground-glass opacities and air bronchograms in both hemithorax (specific for COVID-19 pneumonia) at the 7<sup>th</sup> day of hospitalization; **2b.** Chest X-ray also demonstrates diffuse consolidation regions containing air bronchograms at the same day of admission



**Figure 3a.** Chest X-rays progressively demonstrate diffuse consolidation regions containing air bronchograms in both lungs at the 8<sup>th</sup> and **3b.** 9<sup>th</sup> day of admission; **3c.** it shows partial resolution of consolidation regions in both lungs at the 10<sup>th</sup> day of admission

**Table 1.** Change in acute phase reactants of our patient during hospitalization

	Day 1	Day 3	Day 4	Day 5	Day 6	Day 7	Day 8	Day 9	Day 10
<b>WBC</b> (/μL)	13300	5130	4800	5520	5170	5880	7430	5540	4640
<b>Neutrophil</b> (/μL)	10800	3690	3280	3210	3510	3270	5550	3740	2900
<b>Lymphocyte</b> (/μL)	1290	945	1080	1580	1230	2030	1260	1290	1170
<b>CRP</b> (mg/L, n: <5)	115	147	95	65	58	48	87	72	48
<b>Procalcitonin</b> (ng/mL, n: <0.5)			0.33	0.19	0.15	0.11	0.10	0.06	0.04
<b>D-dimer</b> (μgFEU/L, n: <500)	154	266	494	327	316	931	434	716	2630
<b>Fibrinogen</b> (mg/dL, n: 202-430)			462	462	443	434	614	417	380
<b>Ferritin</b> (ng/mL, n: 4.6-204)			1036	890	694	979	1230	780	634
<b>hsTn-I</b> (ng/L, n: 0-15.6)		4.7	5.4	3.7	1.9	2.2	2.7	1.2	1.3

WBC: white blood cell, CRP: C-reactive protein, hsTn-I: high sensitivity troponin I, n: normal

## DISCUSSION

Systematic reviews evaluated many studies providing clinical outcome data on the utilization of immunotherapies for the treatment of COVID-19, including CIP and IVIG administration. It seemed that immunotherapy as a supplementary therapy together with other routine cares could be an effective and safe method (6-8). However, Cochrane review by Chai et al. (9) stated that they are uncertain whether CIP is beneficial for people admitted to hospital with COVID-19.

Although there are no strict guidelines for IVIG use in COVID-19, the FDA approved the application of CIP to the severe or immediately life-threatening COVID-19 cases (10). According to the guidelines, severe disease is described as one or more of the following: Dyspnea, tachypnea  $\geq 30$ /min, blood oxygen saturation  $\leq 93\%$ ,  $PaO_2/FiO_2 < 300$  and pulmonary infiltrates  $> 50\%$  within 24-48 hours. Since our patient had started to have obvious dyspnea and tachypnea despite routine treatment, first dose of CIP transfusion was given on the fourth day of his admission.

IVIG might also be therapeutic option by the way of its nonspecific antiviral and immunomodulator actions. Even antibodies cross reacting with SARS-CoV-2 have been shown to be currently available IVIG preparations (11). Subgroup analysis of a research demonstrated that a high dose ( $> 15$  g/day) IVIG administration in the early phase ( $\leq 7$  days after admission) revealed significant decline in 60-day mortality in the critical cases (12). However, some reviews still conclude that the present data is inadequate to advocate the efficacy or safety of IVIG administration in the COVID-19 therapy (5).

Both CIP and IVIG could be used as a part of combined immunomodulatory therapies in COVID-19 (13-15). Successful management with plasma exchange subsequently IVIG administration in a critically ill COVID-19 case was described (16). However, in the literature, to the best of our knowledge, successful use of IVIG following CIP treatment in the same patient has not been described.

## CONCLUSION

Immunotherapeutic agents as a supplementary therapy together with other routine cares in COVID-19 cases seem to be an effective and safe method. Earlier CIP transfusion followed by IVIG administration even in an adolescent with severe COVID-19 cases could be helpful to prevent mechanical ventilation and recover rapidly from COVID-19.

**Informed Consent:** Written informed consent was obtained from the parents of the patient for publication.

**Conflict of Interest:** None declared by the authors.

**Financial Disclosure:** None declared by the authors.

**Acknowledgements:** None declared by the authors.

**Author Contributions:** Idea/Concept: ÖÖ, BE, MCD, HS; Design: ÖÖ, BE, MCD, HS; Data Collection/Processing: ÖÖ, BE, MCD, HS; Analysis/Interpretation: ÖÖ, BE, MCD, HS; Literature Review: ÖÖ, BE, MCD, HS; Drafting/Writing: ÖÖ, BE, MCD, HS; Critical Review: ÖÖ, BE, MCD, HS.

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