CASE REPORT

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Transfusion-Related Acute Lung Injury (TRALI) After Convalescent Plasma Therapy in COVID-19 Patient

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ABSTRACT

The coronavirus disease 2019 (COVID-19) continues to spread all around the world. Mortality and morbidity rates are increasing-up to now. Although convalescent plasma therapy can be thought to be useful in the treatment of COVID-19, it carries potential risks, such as transfusion-related acute lung injury (TRALI). In COVID-19 infection, tachypnea, tachycardia, increased need for oxygenation, and the presence of bilateral widespread infiltrates on radiological imagings are evaluated as acute respiratory distress syndrome (ARDS). This clinical situation may develop independently from disease progression in patients receiving convalescent plasma therapy and it is called TRALI. We aimed to present our case to discuss the difficulty of this situation to differentiate from COVID-19 related ARDS.

Keywords: COVID-19, Convalescent Plasma, Transfusion-Related Acute Lung Injury, Acute Respiratory Distress Syndrome

Introduction

Since the first reported case of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in China in December 2019, the disease continues to increase its effect and the disease was defined as coronavirus infectious disease 2019 (COVID-19). According to the data of the end of April 2021, 160 million infected cases and 3 million 200 thousand deaths occurred all around the world (1). Antiviral drugs such as remdesivir, lopinavir/ritonavir and favipiravir, immunmodulatory drug hydroxychloroquine which is an antimalarial, interleukin-6 receptor bloker tocilizumab and steroids were used for treatment (2-6). Supportive treatments including high flow nasal oxygen, mechanical ventilatory support, extracorporeal membrane oxygenation are also used (7). One method that had been used among these potential treatments was convalescent plasma therapy. Convalescent plasma therapy has a historical background (8-10). Also, it is an easily accessible source of antibodies in COVID-19, as the number of people who have been infected and recovered is high. This treatment has been included in the treatment approaches in COVID-19 from the beginning (11, 12). However, it brings some risks one of them defined as transfusion-related acute lung injury (TRALI).

TRALI is a leading cause of transfusion-related morbidity and mortality. It is characterized by tachypnea, tachycardia, cyanosis, dyspnea and fever occurring in the first 12 hours following the administration of plasma and plasma-rich blood products. The diagnosis is made by the team following the patient, if it is considered within pre-diagnoses (13). Our patient, we followed up in our intensive care unit with COVID -19 pneumonia, suddenly deteriorated after convalescent plasma treatment. The results of the examinations were accepted as TRALI. Therefore, we wanted to discuss this differential diagnosis based on our case.

Case Report

A 42-year-old man was admitted to COVID-19 emergency department of our hospital for chills, weakness, fever ongoing for five days. Shortness of breath had been added in the last two days. He had been smoking for ten years and was diagnosed with Hepatitis B carrier. On physical examination, blood pressure was 120/60 mm Hg, heart rate was 130 beats/min, fever was 38.7°C, oxygen saturation was 80%. Laboratory values as follow: White blood cell count 10.630/mm^3, lymphocyte cell count 2.73/mm^3, C-reactive protein 21.3 mg/L, D- dimer 0.87 µg/ml, fibrinogen 487.59

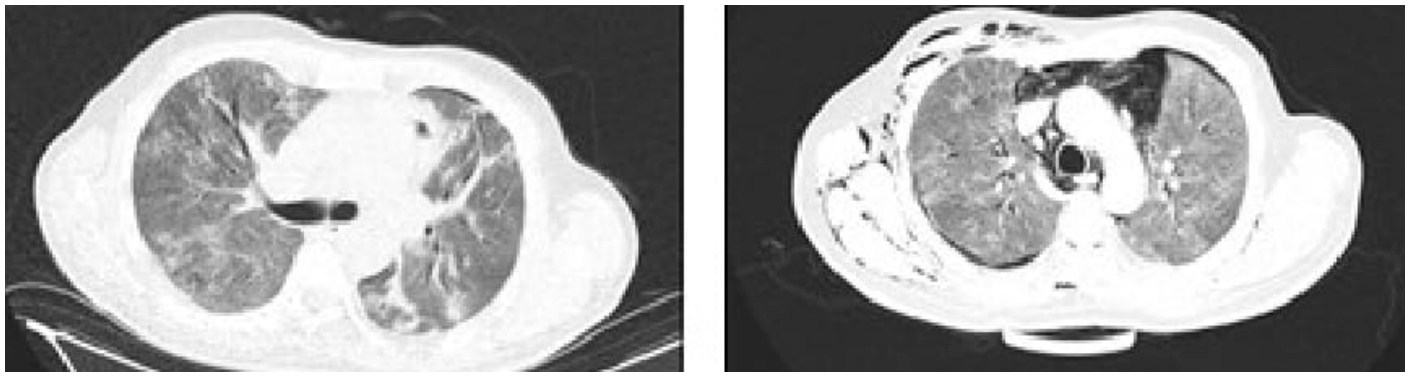

Figure 1. Thoracal computed tomography scan showing consolidated areas with ground glass opacities at the time of admission (left) and ground glass opacities widely covered the whole lung after administration of convalescent plasma treatment (right).

mg/dl, ferritin 423.31 ng/ml. On room air pH: 7.41, paO2: 42,6 mmHg, paCO2: 34,2 mmHg, HCO3: 22 mEq/L were detected in arterial blood gas test. PaO2/FiO2 ratio was 203. Levels of electrolytes and cardiac parameters, and liver and kidney function test results were normal. There were consolidated areas with patchy ground glass opacities in the thorax computed tomography (CT) (Figure1). Real-time reverse transcriptase polymerase chain reaction (RT-PCR) of the patient's pharyngeal swab for SARS-CoV-2 nucleic acid was positive.

The patient was admitted to the COVID-19 intensive care unit (ICU). High flow nasal oxygen therapy (flow rate: 30 L/min) and NIMV (12 cmH2O CPAP) were started to support respiration of patient. First loading, then maintenance doses of Favipiravir, prophylactic LMWH (Low molecular weight heparin), N-asetylcysteine treatments were started. As the oxygenation of patient still did not improve on the 4th day of ICU and the fibrinogen and d-dimer levels increased, convalescent plasma treatment was administered to treatment. A 250 mg/day methylprednisolone and 400 mg/12 hours, total two doses tocilizumab treatment was applied on the 5th day. Approximately 6 hours after plasma treatment initiation, an increase in respiratory rate (40/min), worsening of oxygen saturation despite NIMV support (75%), tachycardia (150/min), and fever (38°C degrees) were developed. PaO2/FiO2 ratio was 57 (Table 1). Thorax CT was performed to exclude possible differential diagnoses due to this sudden deterioration (such as pulmonary tromboembolism, pneumothorax etc). It was observed that ground glass opacities widely covered the whole lung areas at CT (Figure 1). The results of cardiac enzymes, electrocardiography and subsequent ECHO at the bedside were normal. Therefore, the patient was accepted as TRALI.

Oxygenation support was increased compared with the needs of the patient at the begining. HFNO flow rate increased. Oxygen support therapy was provided alternately with NIMV. Since the patient was conscious and fully cooperative with oxygen supplements, observation for a few hours and if necessary, intubation was planned afterwards. The clinic and oxygenation values started to improve within hours. Therefore the process was managed without the patient being intubated. Appropriate fluid

Table 1. Comparation of arterial blood gas analyses and laboratory findings at the time of admission and after convalesent plasma treatment.

	At the time of admission	After administration of convalescent plasma
WBC (cells/mm^3)	10.630	11.510
Lymphocyte (cells/mm^3)	2.73	2.82
Ferritin (ng/mL)	423.31	895.54
D-dimer (µg/L)	0.87	3.47
Fibrinogen (mg/ dl)	487.59	594.45
CRP (mg/dL)	21.3	36.5
Arterial blood gas test		
pH	7.41	7.24
paO2(mmHg)	42.6	28
paCO2(mmHg)	34.2	46
HCO3 (mEq/L)	22	19
SpO2		49
PaO2/FiO2 ratio	203	57

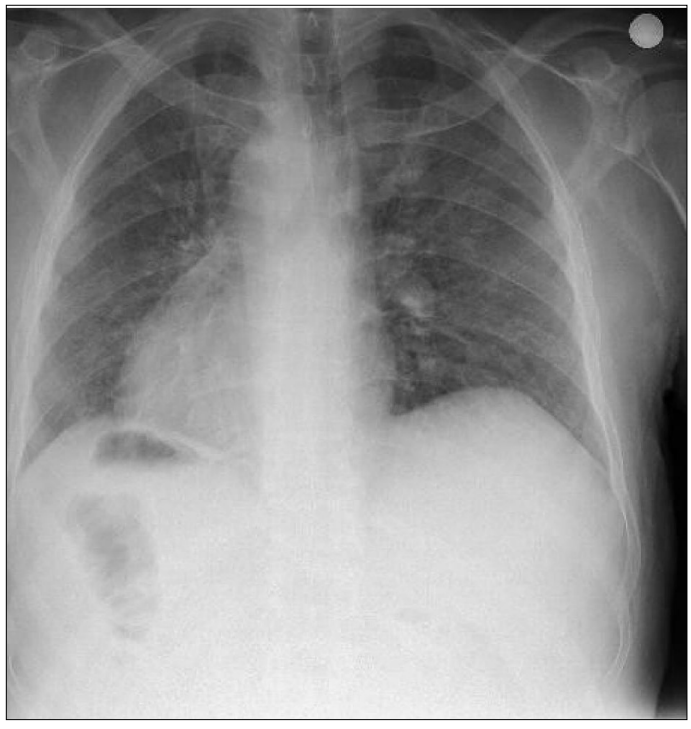

Figure 2. Chest X-rays showing resolution before discharge.

replacement was given to correct hypotension, steroid therapy was continued. The patient was followed up in the ICU for 10 more days, and his respiratory failure and oxygen need improved within days. He was discharged at the day of 23rd ICU admission. When he was discharged was shown in Figure 2.

Approval was obtained from our patient in order to use the data obtained by clinical condition, laboratory values and imaging methods.

Discussion

We presented a patient with COVID 19 pneumonia in whom we considered TRALI due to the sudden clinical deterioration after convalescent plasma treatment and the presence of progression with radiological imaging.

The use of convalescent plasma in COVID-19 pneumonia was proposed from data of previous pandemias such as Spanish flu, H1N1, Ebola, Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) (14-17). If we reviewed the datas of previous publications created based on the case series to date, it seems to be an effective method in COVID-19 (11,12). In our hospital, we apply convalescent plasma treatment on the base of the recommendations of the Ministry of Health of Turkey COVID-19 treatment guide. In COVID-19 infection, tachypnea, tachycardia, increased need of oxygenation, and the presence of bilateral widespread infiltrates with imaging methods are evaluated as acute respiratory distress syndrome (ARDS). This situation may develop independently of disease progression in patients receiving convalescent plasma therapy and it is called TRALI. This serious transfusion event is either underreported or underestimated. One of the main reasons is the low awareness of TRALI among clinicians (16,17).

TRALI is a clinical syndrome characterized by respiratory distress that begins after any blood pruduct transfusion. It usually occurs within the first 6 hours after transfusion. There are dyspnea, tachycardia, hypoxia, fever and bilateral diffuse infiltrates on chest radiography, not due to cardiac pathologies. Severe hypotension and acute renal failure accompanied by renal tubular necrosis can be seen. Most accepted theories in the mechanism of TRALI were as follow; After transfusion of plasma-containing blood products, allo-antibodies (anti-HLA class I and II, antineutrophil antibodies) from the donor activate the recipient's neutrophils, monocytes, tissue macrophages. Capillary damage, increased permeability and inflammatory process begins as a result of the activation of granulocytes. Fluid ponding occurs in the alveolar space (18).

It is named according to the presence or absence of risk factors causing acute lung injury as TRALI and possible TRALI. Pathologies that cause direct lung damage such as aspiration, pneumonia, toxic gas inhalation, drowning in water and indirect damage factors such as septic shock, anaphylaxis, drug intoxications, acute pancreatitis, burns, multiple trauma are held responsible as risk factors (16). It would be appropriate to evaluate our patient as possible TRALI because of pneumonia as a risk factor. In 2019, a research group proposed to devide TRALI differently. TRALI Type I (without an ARDS risk factor) and TRALI Type II (with an ARDS risk factor or with existing mild ARDS (19). The result of a study was 11.6% of patients with existing ALI worsened after transfusion concluded that pre-transfusion respiratory comorbidity poses a risk for possible TRALI (20). This should be taken into account when planning transfusion therapy in patients with respiratory dysfunction. The clinical diagnosis of TRALI is made by excluding other differential diagnoses. Differential diagnoses are established by evaluating the patient's history, physical examination, electrocardiogram, ECHO, cardiac enzymes, chest radiographs, fluid balance and hemodynamic data. Before TRALI diagnosis fluid overload, heart failure, myocardial infarction should be considered.

If we compare ARDS due to COVID-19 and TRALI; tachypnea, tachycardia, cyanosis, dyspnea and fever are clinical findings also seen in COVID-19. However, in TRALI, these findings develop within hours after transfusion. Radiological findings in COVID-19 include areas of consolidation and intermittent ground-glass appearances in places. However, diffuse and dense ground glass areas are seen in the lung after TRALI.

Considering all the differential diagnoses in our patient, we made the necessary examinations, and as a result, we called the TRALI. TRALI is fatal if not diagnosed and intervened. TRALI has no specific treatment. Immediate cessation of the transfusion and appropriate oxygenation support are the first treatment. Mechanical ventilation should be applied if necessary. Effective fluid therapy and vasopressor support should be given to the patient to correct hypovolemia. Advantage or disadvantage of steroids has not been clarified (17). We followed the patient by applying all these treatments.

Conclusion

The COVID-19 pandemic continues, and convalescent plasma therapy is a frequently used treatment method among existing treatments. Physicians who perform this application should definitely include TRALI in their differential diagnosis and follow the patient in this respect.

AUTHOR CONTRIBUTIONS:

Concept: BMC; **Design:** BMC, SA; **Supervision:** BMC; **Fundings:** SA; **Materials:** BMC, SA; **Data Collection and/or Processing:** BMC, SA; **Analysis and/or Interpretation**: SA; **Literature Search:** BMC; **Writing Manuscript**: BMC; **Critical Review:** BMC, SA.

Informed Consent: Approval was obtained from the patient (Ağa Bitiktaş) and his son (Cezmi Bitiktaş).

Peer-review: Externally peer-reviewed.

Conflict of Interest: Authors have no conflicts of interest to declare.

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