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Convalescent plasma for COVID-19 complicated by ARDS due to TRALI

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SUMMARY

Convalescent plasma, which contains antibodies from recovered individuals, has been used as an effective treatment for infectious diseases in the past and is currently being used as a potential treatment option for COVID-19. Multiple studies have reported this treatment to be safe. We report a case of a patient who developed acute respiratory distress syndrome (ARDS) with features suggestive of transfusion-related acute lung injury after being treated with convalescent plasma for COVID-19. We emphasise the need to be aware of the potential risk of transfusion reactions and disease worsening with convalescent plasma administration and to weigh the risk and benefits of this therapy before administration to patients and propose that further study be done regarding the potential risks of convalescent plasma.

BACKGROUND

The COVID-19 has led to a severe strain on the healthcare system of the USA. Research and clinical investigations are actively attempting to find therapeutic agents to combat COVID-19. Convalescent plasma transfusions have been used as treatment for prior SARS-related viruses and are emerging as a treatment option in COVID-19. While its efficacy is still being studied, numerous studies have reported this to be a safe treatment option for COVID-19. We present a case of an adverse reaction to this therapy in a patient with COVID-19.

CASE PRESENTATION

We are reporting a case of a 28-year-old female gravida 2, para 1 at late third trimester with no medical history presenting to the hospital with worsening dyspnoea and intermittent fevers after a positive COVID-19 PCR 6 days prior to presentation. The patient endorsed experiencing fevers, myalgia and dyspnoea for about a week prior to her presentation prompting her to check her COVID-19 PCR. Given the trajectory of her symptoms and based on a study of hospitalised patients in Wuhan for pneumonia due to SARS-CoV-2, the patient did appear to be well within the median time period for onset of symptoms and according to the same study about 20% of patients developed respiratory failure secondary to ARDS within a median of 8 days after the onset of symptoms, which was also within the time period of the patient's presentation.¹ In the emergency room, the patient was hypoxic with an oxygen saturation (SpO₂) of 90%–91% on room air while at rest, decreasing to 87% on ambulation. Saturation improved to 96% on 2L nasal cannula. She was tachycardic to 110s and tachypneic with

a respiratory rate 22. Chest X-ray showed bilateral opacities consistent with a viral pneumonia. The patient was admitted with a presumed diagnosis of COVID-19 pneumonia.

The clinical team believed that maternal risks of worsening COVID-19 outweighed fetal risks of prematurity and decision was made to induce labour with oxytocin and misoprostol. However, during induction of labour, cord prolapse was identified and an emergency c-section was performed without complications. A male infant was born with appearance, pulse, grimace, activity, and respiration (APGAR) scores of 9 and 9 at 1 and 5 min, respectively, and tested COVID-19 negative. No blood products were given to the patient during the surgery but she did receive 1.7 L of crystalloid fluid. Four hours following surgery, the patient became hypoxic with oxygen saturation in the 80s. The patient's oxygen requirements escalated to high-flow nasal cannula (HFNC) at 40% fraction of inspired oxygen (FiO₂). The patient was also given Lasix and was prone. The patient's oxygen saturation improved to 95%.

Given the patient's increased susceptibility to infection postoperatively, the decision was made to treat the patient's COVID-19 pneumonia with convalescent plasma over other immunosuppressive therapies like tocilizumab. The patient received 1 unit of convalescent plasma (approximately 200 cc in volume) transfused over 1 hour. The patient had no adverse reactions during the transfusion. However, 10 min post-transfusion, the patient developed erythema of the upper chest, neck and lower face. She also had increased dyspnoea, was febrile to 100.4, hypoxic with an oxygen saturation of 60% on 40% HFNC and hypotensive to 82/52. Rales were heard bilaterally on auscultation, no distended neck veins were noted and no peripheral oedema was noted.

INVESTIGATIONS

The acute respiratory failure required emergent endotracheal intubation. The patient was also started on a Levophed infusion for shock and was transferred to the intensive care unit (ICU). A chest X-ray showed significantly worsened bilateral opacities compared with chest X-ray prior to convalescent plasma. Given the constellation and timing of symptoms, a diagnosis of transfusion-related acute lung injury (TRALI) induced ARDS was made and the patient was treated with intravenous solumedrol, diphenhydramine and fluid resuscitation with crystalloids. With this therapy, the patient's rash resolved in a few hours and the patient's blood pressure stabilised. Haematological



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workup revealed no alloantibodies or signs of haemolytic anaemia.

Pro-brain natriuretic peptide (Pro-BNP) measured before convalescent plasma administration was 195 increased to 400 after administration. A point-of-care ultrasound (POCUS) after initial therapy revealed bilateral pleural effusions. Transthoracic echocardiogram conducted a day after convalescent plasma administration revealed normal biventricular function. The patient's white cell count trended up to 22 000 postconvalescent plasma and slowly trended down to around 10 000 within the next few days.

DIFFERENTIAL DIAGNOSIS

While TRALI was our most likely diagnosis, other differentials for patient's presentation include transfusion-associated circulatory overload (TACO), anaphylaxis, pulmonary embolism and worsening of COVID-19 pneumonia. TACO and anaphylaxis are other transfusion reactions that can occur during or following a transfusion reaction that may lead to acute respiratory distress. TACO causes a clinical picture similar to congestive heart failure with physical examination findings of distended neck veins, peripheral oedema and lab findings of elevated pro-BNP. However, in our case, pro-BNP was not significantly elevated, no peripheral oedema was observed, and echocardiogram was normal, which suggests against TACO. Anaphylaxis can also cause respiratory distress and can be associated with a new rash, fever and hypotension, which occurred in our patient. However, other common physical examination findings including stridor and wheezing was not seen. Furthermore, chest X-ray in anaphylaxis would not show worsening or new infiltrates and ultrasound would not show new pleural effusions. Another consideration that we had in this patient was pulmonary embolism. Given the patient's thrombotic state the cause of her hypoxia could have been from a massive/saddle embolus. However, given the temporal connection of her symptoms with her transfusion along with lack of imaging evidence of POCUS of evidence of right heart strain along with evidence of bilateral pleural effusions the concern for pulmonary embolism was lower than a transfusion associated event. Lastly, worsening COVID-19 pneumonia is a consideration as that can also lead to worsening respiratory distress, worsening infiltrates, hypotension. However, given the temporal relationship of the transfusion to our patient's symptoms, worsening COVID-19 pneumonia is less likely.

TREATMENT

After initial fluid resuscitation and with daily Lasix and Solumedrol, patient's ARDS improved on the ventilator, increasing from an initial ratio of arterial oxygen partial pressure to fractional inspired oxygen (P/F ratio) of 80 after intubation to 340. The patient was weaned off the ventilator and extubated after 5 days. The patient was subsequently weaned to room air and discharged from the hospital 4 days after extubation.

OUTCOME AND FOLLOW-UP

The patient and her baby appear healthy and well in a 2-week follow-up at outpatient clinic.

DISCUSSION

Originating in Wuhan, China, SARS-CoV-2, which causes COVID-19 has now become widespread across the world with the USA currently considered to be the epicentre of the pandemic.² Given the novelty of COVID-19 along with the lack of proven therapeutic options and active vaccinations, one

therapy that is being studied is the administration of convalescent plasma from recovered COVID-19 patients. The mechanism by which passive antibody administration is believed to work is through viral neutralisation. Other mechanisms proposed include antibody-dependent cellular cytotoxicity and/or phagocytosis. While passive transference of antibodies is most effective as a means for prophylaxis, in a patient with the active infection it is considered effective when the inoculum of the virus is its lowest shortly after exposure/onset of symptoms.

The origins of the use of convalescent plasma dates back to the 1890s, prior to the advent of antibiotics to treat various infectious diseases.³ Studies and medical literature from as early as the 1920s during the Spanish influenza A (H1N1) infection indicate clinically important reduction in the risk for death and improvement in clinical signs and symptoms.⁴ More recently, convalescent serum used during the 2009–2010 influenza H1N1 pandemic showed reduced mortality along with symptom improvement.⁵ In 2013, during the West African Ebola epidemic a small nonrandomised study in Sierra Leone revealed significantly improved survival for those treated with convalescent whole blood relative to those who received standard treatment.⁶ The efficacy of convalescent plasma in treating coronavirus illnesses has also shown promise. The SARS-CoV-2 in 2003 and Middle East respiratory syndrome (MERS) in 2012 were both outbreaks in which convalescent plasma was used as treatment. Systematic reviews and an exploratory meta-analysis of 32 studies of SARS coronavirus infection and severe influenza which involved 699 treated patients and 568 untreated 'controls' (and 60 patients with unknown status) revealed evidence for a consistent reduction in mortality with plasma therapy. The post hoc meta-analysis showed a significant reduction in the pooled odds of mortality following treatment, compared with placebo or no therapy (OR, 0.25; 95% CI: 0.14 to 0.45; with limited heterogeneity: $I^2=0\%$).⁷

However, like any therapy, convalescent plasma is not without risk. Anecdotal cases of TRALI have been reported after administration of convalescent plasma in patients with MERS and the ebola virus.^{8,9} TRALI is believed to be caused by the result of patient and blood component factors which lead to neutrophil activation and endothelial cell damage and capillary leak in the lung causing pulmonary oedema and hypoperfusion. Most cases likely require the confluence of multiple factors to form a 'perfect inflammatory storm' which leads to significant lung injury.¹⁰ A systematic review and meta-analysis determining the efficacy and safety of convalescent plasma for severe COVID-19 based on evidence in other severe respiratory viral infections showed that in one non-randomised study of patients with SARS-CoV-2 or Ebola virus infections and one randomised control trial in patients with influenza reported no serious adverse events related to intravascular volume overload and TRALI or serious allergic reaction due to plasma transfusion.¹¹ Pooled estimates from four randomised control trials with patients with severe influenza ($n=576$) suggested that convalescent plasma caused few or no serious adverse effects (RR 0.85, 95% CI 0.56 to 1.29).¹¹ Two randomised control trials reported no significant difference in transfusion-specific serious adverse reactions, with an incidence of 6% of patients in the convalescent plasma arm vs 6% in the control arm.¹¹

While transfusion reactions have been reported in convalescent plasma administration to treat other viruses, multiple studies focusing on convalescent plasma transfusion in COVID-19 have not reported any transfusion reactions. For convalescent plasma therapy in the COVID-19 population, in order for a donor to donate convalescent plasma they must

meet the following criteria; lab confirmed positive test for COVID-19 (documentation of positive test required). All types of positive tests are accepted, including a positive antibody test. The donor's symptoms must be gone for 14 days. Four preliminary studies of the safety and efficacy of convalescent plasma (consisting of 10, 25, 6, and 5 patients, respectively) with severe COVID-19 concluded that there were no adverse reactions to convalescent plasma such as TRALI.^{11–14} It is important to note, however, that these preliminary studies may not capture rare reactions that may have been missed because of the small sample sizes.

Given these studies, we believe that our patient may be one of the first documented cases of transfusion reaction from convalescent plasma for treatment of novel COVID-19 SARS-CoV-2 infection. TRALI is a clinical diagnosis seen in patients with a new acute lung injury within 6 hours after transfusion associated with bilateral chest radiograph infiltrates and hypoxaemia ($\text{PaO}_2/\text{FiO}_2 \leq 300$ or $\text{SpO}_2 < 90\%$) on room air, no evidence of left atrial hypertension (oedema not purely hydrostatic), and no acute lung injury before the transfusion.¹⁵ Other possible findings include leucopenia, fever and hypotension. Our patient had an existing acute lung injury from COVID-19 but chest X-ray showed worsening of infiltrates after transfusion, worsening of hypoxia, fever and hypotension, which are signs supporting a diagnosis of TRALI. However, given the current definition of TRALI, our patient did not meet criteria for TRALI due to the nature of her existing lung injury from COVID-19 pneumonia. Because convalescent plasma is being used to treat COVID-19 induced lung injury, TRALI may be underdiagnosed in the COVID-19 population given its current definition. The criteria for TRALI may need to be re-examined in patients with COVID-19 who already have pre-existing lung injury, receive plasma products, and then show worsening of lung injury. Certainly more studies need to be performed to better assess the risk of transfusion reactions and adverse events related to convalescent

plasma to treat COVID-19 and a risk–benefit analysis should be performed prior to its administration.

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Learning points

- ▶ Transfusion-related acute lung injury (TRALI) is a clinical diagnosis and may be under-diagnosed in the COVID-19 population.
- ▶ TRALI can be a rare respiratory complication of transfusion, including from convalescent plasma.
- ▶ It is important to weigh the risks and benefits of convalescent plasma administration with the potential for transfusion reactions such as TRALI.

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