A Patient with X-Linked Agammaglobulinemia and COVID-19 Infection Treated with Remdesivir and Convalescent Plasma

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To the Editor:

Over the past year, the coronavirus disease 2019 (COVID-19) has resulted in a worldwide pandemic. The disease results in a wide range of clinical presentations that range from asymptomatic to respiratory failure and death. To date, only two agents have been shown to be efficacious in disease treatment: dexamethasone and remdesivir. Convalescent plasma, obtained from individuals who have recovered from COVID-19, contains polyclonal antibodies that may assist with viral clearance. There are few reports in the literature about the natural history and effect of these therapies in patients with primary immunodeficiency who develop COVID-19.

We report a case of a patient with X-linked agammaglobulinemia (XLA) who was diagnosed with COVID-19 and required a prolonged hospital admission including transfer to the intensive care unit (ICU). His condition worsened with initial supportive therapies, but improved after receiving remdesivir and convalescent plasma.

This 28-year-old male was diagnosed with XLA at 1 year of age after presenting with a septic hip. Flow cytometry showed complete absence of B-cells and agammaglobulinemia. His history was notable for a chronic multifocal cellulitis of his leg secondary to helicobacter species that had been successfully treated without recurrence in 2019. His infectious history was otherwise unremarkable. He has one maternal male 1st cousin who died of an infection at the age of 12. The patient has never had confirmatory sequencing of the Bruton's tyrosine kinase

gene, though his diagnosis of XLA is strongly suspected by his clinical history of early onset infections and absence of B-cells. He was receiving 10 g of subcutaneous immunoglobulin (SCIG) weekly. He presented to the hospital with a 1-week history of fevers, chills, hyposmia, and worsening productive cough and dyspnea. He had received a throat swab prior to presentation that was positive by RT-PCR for COVID-19.

On presentation, the patient was tachycardic, tachypneic, and required 2 l of oxygen by nasal prongs. A chest X-ray revealed evidence of bilateral airspace opacities suggestive of pneumonia. He had hyponatremia, leukopenia, thrombocytopenia, transaminitis, and elevated inflammatory markers (Table 1).

The patient was admitted to the general internal medicine unit and was started on dexamethasone 6 mg daily and a normal saline infusion. Despite these measures, the patient continued to have worsening hypoxia and increased work of breathing. By day 4, he required 5 l of oxygen by nasal prongs and had a respiratory rate of 22. He was then started on a 5-day

Table 1 Laboratory values

Parameter	Admit	Peak	Discharge	Normal adults
WBC	2.31	9.5	9.5	4.0–11 × 10 ³ /μL
HGB	137	146	145	130–170 g/L
PLTS	93	264	250	140–400 × 10 ³ /μL
Neutrophils	1.96	6.67	6.67	2.0–6.3 × 10 ³ /μL
Lymphocytes*	0.160	1.78	1.78	1.0–3.2 × 10 ³ /μL
Na	124	137	137	135–145 mmol/L
ALT	96	96	56	10–45 U/L
AST	104	104	30	7–40 U/L
Ferritin	>1500	>1500	–	30–280 μg/L
CRP	127	127	–	0.0–5.0 mg/L
d-Dimer	608	608	–	<500 ng/mL

*Lymphocyte counts on days 5 and 8 were 0.25 and 1.25 × 10³/μL respectively. These values were drawn on the day of convalescent plasma treatment (day 5) and 3 days following this treatment (day 8)

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course of remdesivir. He self-administered his scheduled SCIG dose on day 4. On day 5, he required 60% oxygen by high flow nasal cannula and was transferred to the intensive care unit. He then received 500 mL of convalescent plasma. On day 8, a CT thorax was performed showing multifocal ground glass opacities and extensive pneumomediastinum with pneumopericardium and subpleural extension resulting in pleural dehiscence (Fig. 1).

On day 9, the patient began showing signs of clinical improvement, and his oxygen requirements had improved. He was transferred back to the ward with daily chest X-rays to monitor for progression to pneumothorax. By day 11, he had been completely weaned off of oxygen and the pneumomediastinum had resolved. He was discharged on day 13.

Patients with primary immunodeficiencies are suspected to be at elevated risk for more severe infections due to COVID-19, yet there are few reports in the literature that discuss these cases. One early study reported 2 patients with agammaglobulinemia (one with XLA) and 5 patients with CVID that had COVID-19 infection [1]. Compared to the patients with CVID, patients with agammaglobulinemia had very mild courses. This was further supported by a second report of 2 XLA patients who had quick recovery following COVID-19 infection without requirement for intensive care [2]. An international study of patients with inborn errors of immunity and COVID-19 infection described 6 with XLA. These XLA patients all had mild disease, though 2 received convalescent plasma during their treatment course [3]. These studies led to a hypothesis that B-lymphocytes might be directly involved in COVID-19-related inflammation, and their absence may result in milder disease. However, this hypothesis has now come into question after a recent case series documented 3 XLA patients who required more protracted hospital courses

refractory to supportive therapy alone [4]. All 3 of these patients had rapid recovery after infusions of convalescent plasma.

Our case, when combined with the recent case series, supports the theory that patients without B-lymphocytes can still mount a strong inflammatory response when infected with COVID-19. In contrast to earlier case reports, our case demonstrates that XLA patients remain at risk of severe complications during infection with COVID-19. The rapid recoveries seen in XLA patients following administration of convalescent plasma is suggestive that antibodies may be important for viral neutralization. However, a recent randomized trial of 334 adult patients with severe COVID-19 pneumonia showed administration of convalescent plasma compared to placebo resulted in no difference in clinical outcomes or mortality [5]. Whether convalescent plasma has a unique mechanism of effect in patients with absence of B-lymphocytes remains unknown. While we cannot discount the role of remdesivir, the rapid response to this convalescent plasma in our patient suggests that humoral immunity is an important factor in recovery from COVID-19. Further studies and reports are needed to determine whether the observed response to convalescent plasma is unique to patients who lack B-lymphocytes.

Authors' Contributions All authors contributed to the study conception. The first draft and manuscript was written by Aled Iaboni, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data Availability All data collected for the purposes of this study comply with field standards.

Declarations

Ethical Approval This is a case report. Upon review of The Unity Health Research Ethics Board protocols and guidelines, it was determined that ethics approval was not required for this type of submission.

Consent to Participate The case subject freely gave informed consent to participate in this research.

Consent for Publication The case subject has consented to have their data published in this journal article and has filled a consent form to this effect. This is available for review upon request.

Conflict of Interest The authors declare no competing interests.

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Fig. 1 Coronal CT chest image performed on day 8 of admission revealing multifocal ground glass opacities, pneumomediastinum, and pneumopericardium

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