Case Report: Convalescent Plasma Achieves SARS-CoV-2 Viral Clearance in a Patient With Persistently High Viral Replication Over 8 Weeks Due to Severe Combined Immunodeficiency (SCID) and Graft Failure

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INTRODUCTION

We describe a 25-year-old female patient with severe combined immunodeficiency (SCID) due to a RAG1 variant (1, 2) with persistently high SARS-CoV-2-RNA concentrations in respiratory samples over 60 days. Immunocompromised patients have not only an increased risk of acquiring severe Corona virus disease 2019 (COVID-19) (3, 4) but may fail to achieve viral clearance with prolonged shedding of viable virus (5, 6).
Our patient was first treated with remdesivir and subsequently received convalescent plasma (CP), which achieved sustained viral clearance.

**CASE DESCRIPTION AND DIAGNOSTIC ASSESSMENT**

The patient was diagnosed with T-/B-/NK⁺ SCID and received unconditioned haploidentical hematopoietic stem cell transplantation (HSCT) from her father at 4 months of age (7). Due to incomplete immune reconstitution with poor T cell- and no B cell-engraftment she received a stem cell boost without preconditioning at 4 years of age, repetitive donor lymphocyte infusions (5 times, last infusion 11/2019) and regular immunoglobulin substitution therapy.

She suffered from recurrent bronchopulmonary infections and chronic obstructive pulmonary disease. Due to progressive graft failure she was scheduled for another HSCT.

After a close friend tested positive for SARS-CoV-2, testing was performed while she was asymptomatic and results were positive for SARS-CoV-2 on 30th of April 2020 (day 0). Since patients with SCID are prone to severe systemic viral infections (e.g. cytomegalovirus, adenovirus, parainfluenza virus) (8–10) she was admitted for clinical observation.

Upon admission, her physical examination, vital signs, chest radiography and a CT scan were unremarkable (Figure 1). The patient experienced a mild headache for one day but no other COVID-19 associated symptoms. The initial SARS-CoV-2-RNA concentration in the nasopharyngeal swab was 4.89 x 10⁸ copies/ml. SARS-CoV-2 could not be PCR-amplified from the patient’s EDTA blood, bone marrow, urine and stool samples. Over the course of 30 days, the patient did not develop any overt symptoms despite persistent high-level viral replication.

On initial admission (day 0) the patient had a reduced neutrophil count (nadir of 115/µl on day 4), lymphopenia (389/µl) with reduced T-cells 250/µl (CD⁴⁺CD⁴⁵⁺RA⁻ T-cells 6.4/µl; CD⁴⁺CD⁴⁵⁺RO⁻ T-cells 63/µl; CD⁸⁺CD⁴⁵⁺RA⁻ T-cells 29/µl; CD⁸⁺CD⁴⁵⁺RO⁻ T-cells 68/µl). NK-cells (CD3 CD⁵⁶⁺) were reduced to 1.3% (4.8/µl). Monocytes were 285/µl and B-cells were absent, which was in line with undetectable IgA and IgM levels (IgG was substituted). Neutrophils were reduced shortly after infection and recovered preceding development of pneumonia (Table 1). The patient received prophylactic antibiotic and antifungal treatment.

On d33 of follow-up the patient presented without overt symptoms, but oxygen saturation was 93% and a CT-scan showed signs of COVID-19 pneumonia (Figure 1). SARS-CoV-2-RNA was 1.95 x 10⁷ and 4.07 x 10⁶ copies/ml in nasopharyngeal and bronchial fluid samples, respectively. Thus, COVID-19 pneumonia was diagnosed and the patient received remdesivir (200 mg i.v. on d33, 100 mg/d i.v. d34-42) over 10 days (11). Remdesivir treatment reduced viral concentrations from 1.95 x 10⁷ copies/ml to 5.35 x 10⁴ copies/ml (Figure 2). Whole genome sequencing of SARS-CoV-2 showed no remdesivir resistance development. Clinical symptoms of pneumonia improved, however, virus concentrations increased again to levels of 1.48 x 10⁶ copies/ml on d54. To achieve viral clearance, the patient received two units of convalescent plasma (CP, 250 ml each) from donor-1 on day 55 (12). This contained spike-specific IgA- and IgG-antibodies (OD-ratios were 1.94 and 3.26, respectively) and had a neutralizing antibody titer (NT-titer) of 1:80. On d57 a third unit of donor-1 CP was administered. Viral concentration dropped from 3.8 x 10⁷ copies/ml (d55) to 6.75 x 10⁴ copies/ml (d59, 2.75-log reduction). Infusion of three additional units of CP from a different donor (donor-2; d60, d62, d64; IgA/IgG OD-ratio: 8.58/6.44; NT-titer: 1:80) resulted in undetectable viral concentration on NP swabs and increased anti-SARS-CoV-2 antibodies in the patient’s serum above the detection limit (IgA/IgG OD-ratio: 2.78/2.96) (Figure 1). The patient’s symptoms cleared completely and SARS-CoV-2 RNA remained negative even after anti-SARS-CoV-2 antibodies decreased below the detection limit on day 111. The patient received the planned second HSCT on day 138 following conditioning with treosulfan (42g/m²). Despite this immunosuppressive and -modulatory procedure, the SARS-CoV-2-RNA was not detected by PCR on NP swabs or in the patient’s blood (last test from day 158).
DISCUSSION

This unique case illustrates the course of COVID-19 in a situation where the functionality of innate and especially adaptive humoral and cellular immunity is severely limited. Development of COVID-19 pneumonia was significantly delayed despite high viral concentrations and only developed after partial recovery of the cellular immune response. As expected, viral clearance is not achieved with severely impaired T-cell and absent B-cell mediated responses (13, 14). This case and the detection of viral replication in cell culture beyond d50 highlights the need for prolonged quarantine measures and monitoring in patients with immune defects (6).

While remdesivir treatment reduced virus concentrations by 2.6-log, however, after stopping of the drug virus concentrations quickly recovered. CP administration from two different donors achieved sustained viral clearance even after anti-SARS-CoV-2 antibodies dropped below the detection limit, which is in line with reports from patients with primary and secondary immunodeficiency as well as with hematological malignancies (15–17). This therapeutic effect was retained even during a second HSCT on day 138. This case report underscores the importance of the humoral immune response, substituted here by CP transfusions, to successfully clear SARS-CoV-2 infection.

DATA AVAILABILITY STATEMENT

The datasets presented in this study can be found in online repositories. Consensus Sequences are available on GISAID: EPI_ISL_572330, EPI_ISL_572331, EPI_ISL_572333, EPI_ISL_573152, EPI_ISL_574259, EPI_ISL_572397. See also Supplementary Material.
ETHICS STATEMENT

The examinations were carried out in accordance with the Declaration of Helsinki and the patient gave written informed consent for use of CP as well as for publication of the pseudonymized results and patient history.

AUTHOR CONTRIBUTIONS

VK, JB, TF, and BJ initiated this work, supervised the study, and drafted the manuscript. VK, JB, TF, BJ, AKu, CK, AKi, TL, AM, AS, MH, PA, GA, JN, SM, and SE took care of the patient, analyzed the clinical data and phenotype, determined diagnostic procedures and treatment plan, and interpreted treatment responses. AW, LM, TS, JT, PO, MD, NL, OA, and HS developed virological test strategies (ELISAs, testing for neutralizing SARS-CoV-2 antibodies, viral sequencing), and performed and interpreted virological data. All authors critically revised the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fimmu.2021.645989/full#supplementary-material

REFERENCES

1. Notarangelo LD, Kim MS, Walter JE, Lee YN. Human RAG Mutations: Biochemistry and Clinical Implications. Nat Rev Immunol (2016) 16(4):234–46. doi: 10.1038/nri.2016.28
2. Fischer A, Notarangelo LD, Neven B, Cavazzana M, Puck JM. Severe Combined Immunodeficiencies and Related Disorders. Nat Rev Dis Primers (2015) 1:15061. doi: 10.1038/nrdp.2015.61
3. Goodall JW, Reed TAN, Ardissino M, Bassett P, Whittington AM. A Retrospective Cohort Study. Epidemiol Infect (2020) 148:e251. doi: 10.1017/S0950268820002472
4. Kim L, Garg S, O’Halloran A, Whitaker M, Pham H, Anderson EI, et al. Risk Factors for Intensive Care Unit Admission and In-hospital Mortality Among Hospitalized Adults Identified Through the U. S. Coronavirus Disease 2019 (Covid-19)-Associated Hospitalization Surveillance Network (Covid-Net). Clin Infect Dis (2020). doi: 10.1093/cid/ciaa1012
5. Avanzato VA, Matson MJ, Seifert SN, Pryce R, Williamson BN, Anzick SL, et al. Case Study: Prolonged Infectious SARS-CoV-2 Shedding From an Asymptomatic Immunocompromised Individual With Cancer. Cell (2020) 183:1901–12. doi: 10.1016/j.cell.2020.10.049
6. Aydillo T, Gonzalez-Reiche AS, Aslam S, van de Guchte A, Khan Z, Obla A, et al. Shedding of Viable Sars-CoV-2 After Immunosuppressive Therapy for Cancer. N Engl J Med (2020) 383:2586–8. doi: 10.1056/NEJMoa2013670
7. Pai SY, Logan BR, Griffith LM, Buckley RH, Parrott RE, Dvorak CC, et al. Transplantation Outcomes for Severe Combined Immunodeficiency, 2000–2009. N Engl J Med (2014) 371(5):434–46. doi: 10.1056/NEJMoa1401177
8. Ruffner MA, Sullivan KE, Henrickson SE. Recurrent and Sustained Viral Infections in Primary Immunodeficiencies. Front Immunol (2017) 8:665. doi: 10.3389/fimmu.2017.00665
9. Dropulic LH, Cohen JL. Severe Viral Infections and Primary Immunodeficiencies. Clin Infect Dis (2011) 53(9):897–909. doi: 10.1093/cid/cir610
10. Al-Herz W, Essa S. Spectrum of Viral Infections Among Primary Immunodeficient Children: Report From a National Registry. Front Immunol (2019) 10:1231. doi: 10.3389/fimmu.2019.01231
11. Grein J, Ohmagari N, Shin D, Diaz G, Asperges E, Castagna A, et al. Compassionate Use of Remdesivir for Patients With Severe Covid-19. N Engl J Med (2020) 382(24):2327–36. doi: 10.1056/NEJMc2015312
12. Bloch EM, Shoham S, Casadevall A, Sachais BS, Shaz B, Winters JL, et al. Deployment of Convalescent Plasma for the Prevention and Treatment of COVID-19. J Clin Invest (2020) 130(6):2757–65. doi: 10.1172/JCI138745
13. Vardhana SA, Wolchok JD. The Many Faces of the anti-COVID Immune Response. J Exp Med (2020) 217(6):e20200678. doi: 10.1084/jem.20200678
14. Liu STH, Lin HM, Baine I, Wajnberg A, Gumprecht JP, Obla A, et al. Convalescent Plasma Treatment of Severe COVID-19: A Propensity Score-Matched Control Study. Nat Med (2020) 26:1708–13. doi: 10.1038/s41591-020-1088-9
15. Senefeld JW, Klassen SA, Ford SK, Wiggins CC, Rostrom BC, Thompson MA, et al. Therapeutic Use of Convalescent Plasma in COVID-19 Patients With Immunodeficiency. medRxiv (2020) 2020.11.08.20224790. doi: 10.1101/2020.11.08.20224790
16. Thompson MA, Henderson JP, Shah PK, Rubinstein SM, Joyner MJ, Choueiri TK, et al. Convalescent Plasma and Improved Survival in Patients With Hematologic Malignancies and COVID-19. medRxiv (2021) 2021.02.05.21250953. doi: 10.1101/2021.02.05.21250953
17. Hueso T, Pouderoux C, Pérez H, Beaumont A-L, Raillon L-A, Ader F, et al. Therapeutic Use of Convalescent Plasma for B-cell-depleted Patients With Protracted COVID-19. Blood (2020) 136(20):2290–5. doi: 10.1182/blood.2020008423

Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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