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### SARS-CoV-2 symptomatic reinfection among patients with primary antibody deficiency

Nufar Marcus, MD<sup>a,b,c,d</sup>, Liat Ashkenazi-Hoffnung, MD<sup>b,e,f</sup>,  
Adi Ovadia, MD<sup>b,c,g,h</sup>, Ilan Dalal, MD<sup>b,c,g,h</sup>,  
Siril Yoffe, MD<sup>a,b,c</sup>, Nesia Kropach, MD<sup>b,d,i</sup>,  
Neta Zuckerman, PhD<sup>j</sup>, and Oded Scheuerman, MD<sup>b,d,f</sup>



#### Clinical Implications

Our data show a high rate of symptomatic reinfection with severe acute respiratory syndrome coronavirus 2 in patients with primary antibody deficiency. This highlights the susceptibility of this patient population, supporting the need for continued isolation, prophylactic treatment, and further development of therapeutic options.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has appeared as a global threat to human health, with more than 280 million confirmed cases and more than 5 million deaths so far.<sup>1</sup> However, true reinfection with pre-micron strains is rare.<sup>2-6</sup> Estimated rates of reinfection of 0.6% to 1% were suggested in international and Israeli studies.<sup>2-6</sup>

Patients with B-cell abnormalities and lack of antibody production are more susceptible to SARS-CoV-2 infection.<sup>7</sup> It is therefore presumed that such patients, particularly those with primary antibody deficiency (PAD) who rely on intravenous immunoglobulin replacement therapy (IGRT) for protection against other viruses, would likely be more susceptible to reinfection with SARS-CoV-2.

Herein, we describe 5 patients with PAD from 2 immunology services in Israel who reported having a symptomatic SARS-CoV-2 infection in July 2020 and January 2021 with a full clinical recovery. All patients had several negative SARS-CoV-2 polymerase chain reaction (PCR) testing after their initial infection. During the delta variant (B.1.617.2) wave occurring in September 2021 in Israel, all 5 patients suffered from a new distinct SARS-CoV-2 symptomatic reinfection. None of the described 5 patients received the Pfizer-BioNTech COVID-19 vaccine because of apprehension of vaccine-related side effects.

Patient 1 diagnosed with X-linked agammaglobulinemia (XLA) presented with SARS-CoV-2 infection in January 21. He developed pneumonia needing prolonged hospitalization and treatment with antiviral medication and convalescent plasma. After complete recovery, he was hospitalized again with a new SARS-CoV-2 infection during the delta wave variant. He again suffered from pneumonia (Figure 1), and a similarly severe course complicated by diabetic ketoacidosis. Patient 2 also diagnosed with XLA had his first infection with SARS-CoV-2 in January 2021. He had 5 days of fever and cough. He was not hospitalized. On September 2021, 8 months after the initial disease, he developed fever and cough with positive SARS-CoV-2 PCR. Symptoms resolved after a few days; however, viral PCR testing was positive at day 25 of illness (CCT 24), necessitating

prolonged isolation. Patient 3 with hyper-IgM syndrome presented with SARS-CoV-2 infection with fever and cough and respiratory distress in July 2020, and was isolated for 8 weeks because of prolonged positive PCR. His second infection occurred in September 21 again with fever and cough. Patient 4 diagnosed with RelB deficiency had 2 SARS-CoV-2 infections, the first on September 20 and the second on October 21, presenting with cough, upper respiratory symptoms, and fever. Patient 5 diagnosed with XLA presented with fever and diarrhea and was first diagnosed with SARS-CoV-2 infection on January 2021. During his acute illness, he was hospitalized and treated with fluids and ceftriaxone for 2 days. Symptoms resolved; however, PCR testing remained positive for 5 weeks, necessitating prolonged isolation. On September 2021, he developed his second SARS-CoV-2 infection with high fever, cough, headache, and gastrointestinal symptoms. He was hospitalized for 2 days and was treated with ceftriaxone and fluids.

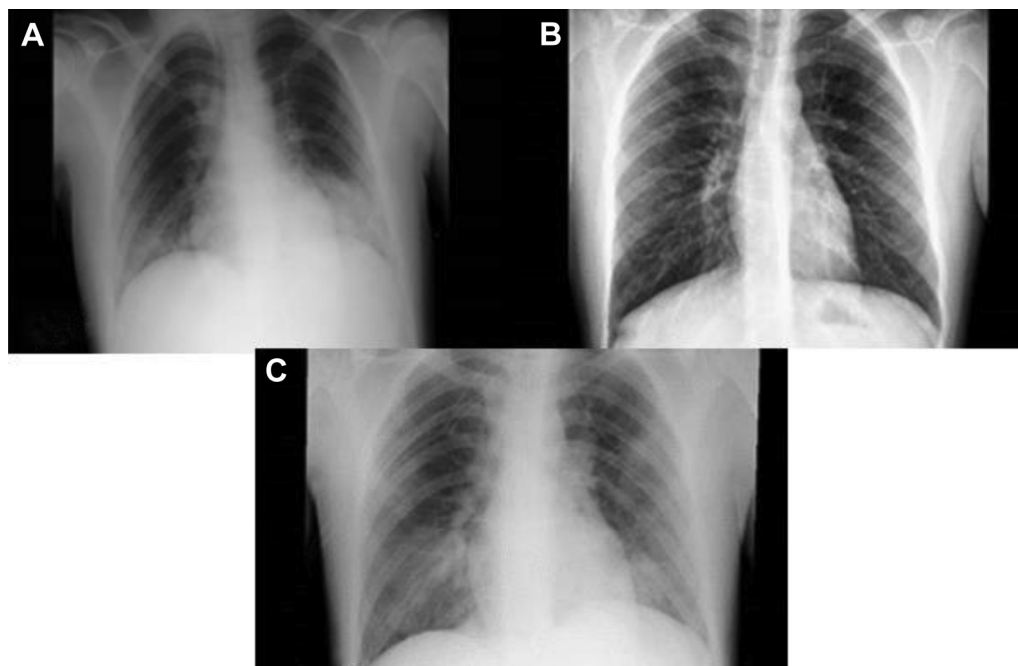
Details of these 5 patients are shown in Table I.

In this report, we describe 5 patients aged 9 to 31 years with PAD, adequately treated with IGRT, who suffered a SARS-CoV-2 symptomatic reinfection during the delta variant (B.1.617.2) wave. This description is exceptional because of the low rates of reinfection previously reported among immunocompetent hosts.<sup>2-6</sup> Our cohort included 65 patients with PAD followed at the Schneider's Children Medical Center of Israel and at the Edith Wolfson Medical Center; 11 of 65 (17%) patients with PAD suffered from SARS-CoV-2 infection and 5 of the 11 (42%) patients infected suffered from reinfection during the delta variant wave. This is despite meticulous immunoglobulin replacement therapy protecting them from other infections.

Tang et al<sup>5</sup> described a low risk for SARS-CoV-2 recurrent infection in the general population. Of a total of 113,715 patients described in different publications around the world, only 1% suffered from SARS-CoV-2 reinfection. Another study that analyzed 9119 COVID-19 recovered patients found that only 0.7% became reinfected.<sup>4</sup> Moreover, a significant reduction of 80% to 100% risk of reinfection with SARS-CoV-2 infection during the delta variant wave was shown in those who were previously infected.<sup>4</sup> Similarly, data from Austria showed low rates of hospitalization (5 of 14,840; 0.03%) and death (1 of 14,840; 0.01%) due to reinfection.<sup>3</sup>

Data on SARS-CoV-2 in patients with PAD are limited. In an early report after the first 2 waves of SARS-CoV-2 infection in Israel, Marcus et al<sup>7</sup> reported a low impact of the SARS-CoV-2 infection in patients with inborn errors of immunity (IEI), likely due to adherence to hygiene measures and social isolation. Although this study included patients with all types of IEI, it also showed that most patients who were infected were patients with PAD.<sup>7</sup> Our findings support that these patients are truly susceptible to this virus and do not mount a protective immune response after a naturally occurring illness.

Interestingly, Hagin et al<sup>8</sup> described a good cellular response to the Pfizer-BioNTech COVID-19 vaccine among patients with IEI, including some patients with PAD. Whether this confers clinical protection against SARS-CoV-2 infection or reinfection in patients with PAD is yet to be determined.



**FIGURE 1.** (A) Chest X-ray of patient 1 in January 2021 during his first SARS-CoV-2 infection, when he had presented with fever, hypoxemia, and respiratory distress showing pneumonia. (B) Chest X-ray performed in April 2021 showing complete resolution in the interim when he had serial negative PCR tests. (C) Chest X-ray performed on his second infection in September 2021 showing new infiltrates.

**TABLE I.** Demographic and clinical data of 5 patients with primary antibody deficiency who suffered from SARS-CoV-2 reinfection

Patient no.	1	2	3	4	5
Age/sex	17.5 y/M	13 y/M	31 y/M	16 y/F	9.5 y/M
Underlying PAD diagnosis	XLA	XLA	HIGMS CD40L-def	RelB	XLA
Date of first infection	January 21	January 21	July 20	September 20	January 21
Last day of +PCR test after infection	30 d	30 d	60 d	21 d	3 d
Course of first infection	Severe pneumonia Hypoxemia	Mild	Moderate Respiratory distress	Mild	Moderate
Hospitalization days	8 d	None	3 d	None	3 d
Treatment of first infection	Dexamethasone Remdesivir Enoxaparin Convalescent plasma	None	Dexamethasone	None	Fluids Ceftriaxone
Date of second infection	September 21	September 21	September 21	October 21	September 21
Last day of +PCR test after infection	11 d	30 d	N/A	14 d	35 d
Course of second infection	Severe pneumonia Hypoxemia DKA (IDDM1)	Moderate	Moderate	Moderate	Moderate
Hospitalization days	5 d	None	None	3 d	3 d
Treatment of second infection	Ceftriaxone Insulin/fluids Enoxaparin Convalescent plasma	None	None	Monoclonal anti-SARS-CoV-2 antibodies (Regeneron)	Ceftriaxone Fluids IVIG

30d+PCR, 30 days of positive SARS-CoV-2 PCR test after initial positive PCR; CD40L-def, CD40 ligand deficiency; DKA, diabetic ketoacidosis; HIGMS, hyper-IgM syndrome; IDDM1, insulin-dependent diabetes mellitus; IVIG, intravenous immunoglobulin; N/A, not applicable; PCR, polymerase chain reaction; RelB, transcription factor RelB deficiency; XLA, X-linked agammaglobulinemia.

The rate of SARS-CoV-2 reinfection was extremely high among our patients with PAD (42%), despite regular immunoglobulin replacement therapy. Farcet et al<sup>9</sup> showed that

neutralizing antibody levels in intravenous immunoglobulin lots released since September 2020 are increasing. They extrapolated that lots released after July 2021 should have protective levels of

anti-SARS-CoV-2 antibodies.<sup>9</sup> However, such lots may not be readily available, and their clinical effectiveness is yet to be validated. Therefore, additional treatment options, such as prophylactic monoclonal antibodies, should be considered to prevent reinfection during SARS-CoV-2 high-transmission periods.

In conclusion, patients with PAD may be at increased risk for SARS-CoV-2 reinfection and therefore should be guided for stringent infection control measures despite past COVID-19 disease with consideration for other prophylactic pharmacological regimens. Whether or not vaccination with anti-SARS-CoV-2 vaccines or monoclonal antibody prophylactic therapy can protect these patients from reinfection with new emerging SARS-CoV-2 variants and will the newly approved antiviral medications be effective is yet to be determined.

<sup>a</sup>Allergy and Immunology Unit, Schneider Children's Medical Center of Israel, Felsenstein Medical Research Center, Kipper Institute of Immunology, Petah Tikva, Israel

<sup>b</sup>Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

<sup>c</sup>The Jeffrey Modell Foundation Israeli Network for Primary Immunodeficiency, New York, NY

<sup>d</sup>Pediatrics B, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

<sup>e</sup>Department of Day Hospitalization, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

<sup>f</sup>Pediatric Infectious Disease Unit, Schneider Children's Medical Center, Petah Tikva, Israel

<sup>g</sup>Pediatric Allergy Unit, E. Wolfson Medical Center, Holon, Israel

<sup>h</sup>Pediatric Department, E. Wolfson Medical Center, Holon, Israel

<sup>i</sup>Department of Genetics, Schneider Children's Medical Center of Israel, Petah Tikva, Israel

<sup>j</sup>Central Virology Laboratory, Israel Ministry of Health, Chaim Sheba Medical Center, Tel Hashomer

No funding was received for this work.

Conflicts of interest: The authors declare that they have no relevant conflicts of interest.

Received for publication January 7, 2022; revised April 27, 2022; accepted for publication May 2, 2022.

Available online May 19, 2022.

Corresponding author: Nufar Marcus, MD, Kipper Institute for Immunology, Schneider Children's Medical Center of Israel, Kaplan St 14, Petah Tikva 4920235, Israel. E-mail: [NOFARMK@clalit.org.il](mailto:NOFARMK@clalit.org.il)

2213-2198

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<https://doi.org/10.1016/j.jaip.2022.05.004>

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