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SARS-CoV-2 reinfection across a spectrum of immunological states

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Abstract

Purpose: Several cases of symptomatic reinfection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) after full recovery from a prior episode have been reported. As reinfection has become an increasingly common phenomenon, an improved understanding of the risk factors for reinfection and the character and duration of the serological responses to infection and vaccination is critical for managing the coronavirus disease 2019 (COVID-19) pandemic.

Methods: We described four cases of SARS-CoV-2 reinfection in individuals representing a spectrum of healthy and immunocompromised states, including (1) a healthy 41-year-old pediatrician, (2) an immunocompromised 31-year-old with granulomatosis with polyangiitis, (3) a healthy 26-year-old pregnant woman, and (4) a 50-year-old with hypertension and hyperlipidemia. We performed confirmatory quantitative reverse transcription-polymerase chain reaction and qualitative immunoglobulin M and quantitative IgG testing on all available patient samples to confirm the presence of infection and serological response to infection.

Results: Our analysis showed that patients 1 and 2, a healthy and an immunocompromised patient, both failed to mount a robust serologic response to the initial infection. In contrast, patients 3 and 4, with minimal comorbid disease, both mounted a strong serological response to their initial infection, but were still susceptible to reinfection.

Conclusion: Repeat episodes of COVID-19 are capable of occurring in patients regardless of the presence of known risk factors for infection or level of serological response to infection, although this did not trigger critical illness in any instance.

KEYWORDS

antibody, COVID-19, immunity, reinfection, SARS-CoV-2

1 | INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in over 260 million cases and 5 million deaths worldwide.[1] While prior infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been shown to be highly protective against re-infection,[2,3] increasing reports have surfaced over the course of the pandemic about cases of patients who have retested positive for SARS-CoV-2 infection after resolution of symptoms and viral shedding from their initial episode.[4–12] Our understanding of the immune mechanisms that define protection, and the reason certain patients are more susceptible to reinfection than others, remains incomplete. Gathering additional data about these rare cases may help further our understanding of reinfection and immunity and is essential for optimizing our responses to this ongoing crisis. The following report details four cases of SARS-Co-V-2 reinfection in patients with different medical backgrounds.

2 | CASE 1

The first case is a 41-year-old Hispanic-Latina female pediatrician with no known chronic medical conditions who developed respiratory symptoms, fever, headaches, fatigue, anosmia, and ageusia in March 2020 in the setting of a household exposure (her husband) who tested positive for SARS-CoV-2 2 days before her. Three days after her symptom onset, her nasopharyngeal (NP) swab sample was positive for SARS-CoV-2 by reverse transcription-polymerase chain reaction (RT-PCR). Besides a persistent loss of smell and taste, her symptoms resolved without hospitalization or treatment. She was enrolled in an observational study and underwent serial NP swab sampling seven times from April to September 2020, with negative quantitative RT-PCR results each time. In September, she developed respiratory symptoms and chest tightness and was again found to be positive for SARS-Co-V-2 by RT-PCR, which was further confirmed by quantitative RT-PCR testing (viral load (VL) 22,800 copies/ml). Like her first episode, she recovered without hospitalization or treatment. Her husband was also enrolled in the observational study and had NP and serum samples drawn at similar time points. However, the husband never retested positive for SARS-CoV-2 or had symptoms after his initial episode in March. Thus, it is possible that the patient's occupation as a physician may have increased her susceptibility to reinfection due to a higher risk of workplace exposure to SARS-CoV-2. The period between the patient's first and second episodes was 174 days. Qualitative immunoglobin M (IgM) and quantitative IgG was measured in samples obtained from April to October 2020 for both the patient and her husband (Figure 1). In April, 4 weeks after her initial positive SARS-CoV-2 test, low but detectable levels of anti-Spike IgM and IgG were present in her serum. Her IgG level peaked at 123 arbitrary units (AU)/ml in April and declined persistently thereafter (IgM > 1.0 and IgG >50 AU/ml are considered positive). In September, during her second COVID-19 episode, she no longer had detectable levels of IgM, and her IgG level had dropped below 50 AU/ml. In contrast, the husband had detectable levels of IgM and IgG from April to October, and his levels of IgG peaked at 919.7 AU/ml in April and remained over 182 AU/ml through October. With this patient's lack of comorbidities or evidence of prior infections, it is unclear why her antibody response was

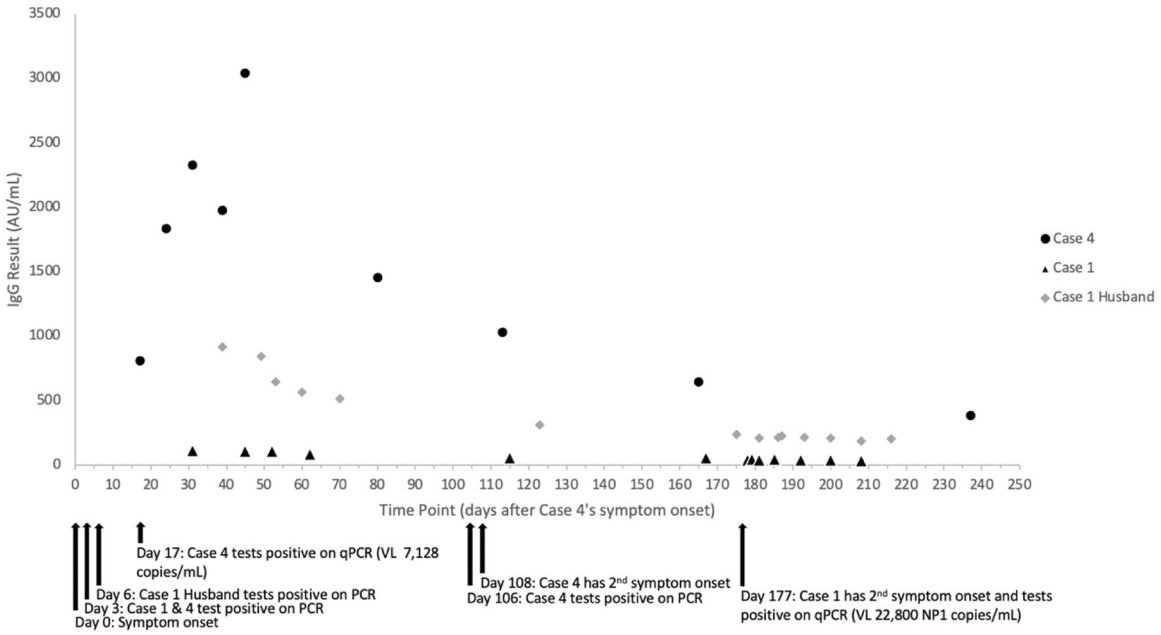

FIGURE 1 Serologic responses over time. IgG antibody levels against the SARS-CoV-2 spike receptor-binding domain (RBD) at each time point in Case 1, the husband of Case 1, and Case 4 relative to each individual's first infection symptom onset (Day 0) are shown. Case 1 and her husband had serial serological testing from April to October 2020 and Case 4 had serial serological testing from March to October 2020

less robust and quicker to decline, although this may explain part of her susceptibility to reinfection. While available studies suggest that total anti-SARS-CoV-2 Ig is a reasonable correlate of protection, the literature and these cases also suggest that the presence of antibodies alone does not necessarily indicate protection from reinfection.[13]

3 | CASE 2

The second case consists of a more severe case of COVID-19 in an immunocompromised 31-year-old African-American female with hypertension, hyperlipidemia, congestive heart failure, and end-stage renal disease (on hemodialysis since 2013 after renal transplant failed) in the setting of granulomatosis with polyangiitis (treated with rituximab every 4 months, administered in February and June 2020). She first tested positive for SARS-CoV-2 by RT-PCR from a sample obtained in March of 2020 when she was admitted to the hospital for fever, myalgias, and cough, and a chest computed tomography showed small bilateral pleural effusions and bibasilar atelectasis/consolidation. At the time of admission, RT-PCR testing was delayed such that results did not return until after her 3-day hospitalization ended, during which she was treated empirically for bacterial pneumonia. Subsequent screening testing for SARS-CoV-2 during hospital encounters for other medical needs was negative by RT-PCR in June and early August. In mid-August, she developed new dyspnea, fever, and fatigue, and her chest X-ray showed mild pulmonary edema and trace bilateral pleural effusions. A point-of-care SARS-CoV-2 RT-PCR test was negative, and she was admitted for evaluation. After extensive workup for ongoing fever without an identifiable cause, she was retested for SARS-CoV-2 by RT-PCR and found to be positive 9 days after symptom onset, a result that was later confirmed with quantitative RT-PCR (qRT-PCR) (VL 167,000,000 copies/ml). She received supportive treatment and was discharged 10 days after her positive test on a 2 L/min oxygen requirement. Due to the delay of over a week after her initial presentation in diagnosing her SARS-CoV-2 reinfection, she was not placed on COVID-19 isolation precautions, resulting in the infection of three healthcare workers involved in her care. Serological testing on three samples taken over the course of her second hospitalization all resulted negative for IgG and IgM to SARS-CoV-2. Rituximab, an anti-CD20 antibody, is known to deplete B cells and has been suggested to impair viral clearance of SARS-CoV-2 for prolonged periods in some cases,[14,15] but in this case, multiple negative tests over the 154 days between her episodes support true reinfection instead. Whether she had an initial serologic response to SARS-CoV-2 that rapidly waned or never developed effective antibodies at all is unknown.

4 | CASE 3

The third case describes a 26-year-old obese (body mass index > 30 kg/m^2) African-American female with no known chronic medical conditions who was 18 weeks pregnant (G1P0) when she presented complaining of a productive cough, chills, nausea, and vomiting, and her chest X-ray showed bibasilar air space opacities. Her SARS-CoV-2 RT-PCR was positive (subsequently confirmed with qRT-PCR VL 1,518,000,000 copies/ml), and she was admitted to the hospital. She improved after receiving supportive treatment for her symptoms and was discharged 2 days later, remaining clinically well for almost 4 months. She was exposed to a patient with COVID-19 at her place of work in mid-October, but tested negative by RT-PCR at that time. Three days later, now 36 weeks pregnant, she developed congestion, cough, and dyspnea and tested positive for SARS-CoV-2 by RT-PCR. She recovered at home without treatment and had a spontaneous vaginal delivery of a healthy baby in November. While no interim samples were available for testing, prolonged viral shedding seems unlikely given the long period (4 months) between the two episodes and the development of new typical symptoms with her second event. Pregnant patients are known to be more susceptible to respiratory viral infections in general, thought to be due to a complex combination of hormonal and other immunomodulatory changes in the presence of the fetus, as well as alterations in the upper respiratory tract brought about by pregnancy.[16] This trend is also seen with both severity and infection risk in COVID-19, potentially related alterations in anatomy, various hormonal and immunological changes, and increased expression of angiotensin-converting enzyme 2 in pregnancy.[17] However, pregnant patients have not been shown to exhibit a greater risk of infection or mortality with SARS-CoV-2[18] like that seen with the H1N1 influenza pandemic of 2009. Given the lack of reported cases of reinfection during pregnancy to date, it does not seem to convey any substantially increased risk for reinfection, although whether pregnancy modulates humoral responses to SARS-CoV-2 infection or vaccination remains unclear.

5 | CASE 4

The final case describes a 50-year-old White male patient with a history of hypertension and hyperlipidemia who presented in March 2020 after developing respiratory symptoms, fever, chest pain, and myalgias a week following a COVID-19 exposure at his place of work. He returned 2 days later, had a normal chest X-ray, but tested positive for SARS-CoV-2 by RT-PCR. He was admitted to the intensive care unit for persistent fever and progressive shortness of breath, although he was never hypoxic. He was treated empirically with azithromycin for suspected superimposed community-acquired pneumonia and discharged home 2 days later. He was enrolled in an observational study and had an NP sample taken 2 weeks after his initial positive test that was still positive for SARS-CoV-2 by qRT-PCR (VL 7128 copies/ml). He had lingering symptoms of cough, fatigue, and sore throat from April to June, but five serial NP samples throughout April and May tested negative by qRT-PCR. During a clinical follow-up visit in June, he had a routine NP swab that tested positive for SARS-CoV-2, and he developed a dry cough and loss of taste 2 days later. He recovered without the need for hospitalization or treatment and tested negative for SARS-CoV-2 a week later.

TABLE 1 Summary table describing demographics, comorbidities, symptoms, and viral loads of both the initial and repeat episodes of COVID-19 of each of the four cases

Demographics	Comorbidities	Initial COVID-19 episode symptoms	Reinfection episode symptoms	Initial COVID-19 viral load	Reinfection episode viral load	Initial Sx duration (days)	Reinfection Sx duration (days)
Case 1—41-year-old Hispanic-Latina female pediatrician	None	Respiratory symptoms, fever, headaches, fatigue, anosmia, ageusia	Respiratory symptoms, chest tightness	Unknown	22,800 copies/ml	105	15
Case 2—31-year-old African-American female	Hypertension, hyperlipidemia, congestive heart failure, end-stage renal disease (on hemodialysis), granulomatosis with polyangiitis (treated with rituximab)	Fevers, myalgias, coughing	Dyspnea, fevers, fatigue	Unknown	167,000,000 copies/ml	22	14
Case 3—26-year-old African-American G1P0 female	Obesity (BMI > 30 kg/m^2), 18 weeks pregnant at the time of first infection	Productive cough, chills, nausea, vomiting	Congestion, cough, dyspnea	1,518,000,000 copies/ml	Unknown	17	16
Case 4—50-year-old white male	Hypertension, hyperlipidemia	Respiratory symptoms, fever, chest pain, myalgias, lingering symptoms of cough, fatigue, and sore throat for 2 months	Dry cough, loss of taste	7128 copies/ml	Unknown	43	11
Demographics	Comorbidities	Initial COVID-19 episode symptoms	Reinfection episode symptoms	Initial COVID-19 viral load	Reinfection episode viral load	Initial Sx duration (days)	Reinfection Sx duration (days)
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Case 3—26-year-old African-American G1P0 female	Obesity (BMI > 30 kg/m^2), 18 weeks pregnant at the time of first infection	Productive cough, chills, nausea, vomiting	Congestion, cough, dyspnea	1,518,000,000 copies/ml	Unknown	17	16
Case 4—50-year-old white male	Hypertension, hyperlipidemia	Respiratory symptoms, fever, chest pain, myalgias, lingering symptoms of cough, fatigue, and sore throat for 2 months	Dry cough, loss of taste	7128 copies/ml	Unknown	43	11

Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; Sx, Symptoms.

The interval of about 3 months in between his two positive tests as well as five negative quantitative PCR test results in this interim period suggest true reinfection. In terms of serologic responses, he had detectable levels of IgG from March to October, which peaked at 3040.6 AU/ml in April and remained over 385 AU/ml through October. While IgM levels were no longer detectable in this patient after May, he had IgG anti-spike protein levels of 1030.2 AU/ml in late June during his second COVID-19 infection (Figure 1). While this patient lacked significant comorbidities other than hypertension that might explain why he was more susceptible to reinfection and demonstrated a strong overall serologic response to infection, there is mounting evidence suggesting that males are more susceptible to severe SARS-CoV-2 infection through multiple purported mechanisms including variable Toll-like receptor 7 activation and mucosal-associated invariant T-cell responses.[19]

In summary, we report four cases of SARS-CoV-2 reinfection in patients across the spectrum of age and health. For Cases 1 and 2, a clear lack of serologic response to initial infection may have contributed to their risk, although why the healthy patient in Case 1 failed to mount an effective antibody response is unclear. However, for Case 4, a strong serological response was measured after his first infection event which persisted during and after his reinfection, suggesting that anti-spike receptor-binding domain (RBD) antibodies alone are not sufficient for protection. These findings support the mounting evidence that antibody levels measured in routinely collected tests are not accurate indicators of protection from reinfection and suggest other immunological factors, including neutralizing antibody levels and cell-mediated immunity, play a large role in defining reinfection risk.[20]

On average, COVID-19 symptoms last between 1 and 4 weeks,[21] although only two of the cases described in our paper had initial episodes of COVID-19 symptoms that resolved within this average timeframe. The subjects with longer initial symptom duration may have even met the criteria for postacute sequelae of COVID-19. Importantly, symptoms were less severe and of shorter duration during the repeat episodes for all of the patients, and long-lasting symptoms were not noted on reinfection in any of the cases, regardless of varying serologic responses across the group, consistent with the reported literature.[22]

Unfortunately, samples were not available to demonstrate differences in viral strains across episodes for these patients, but there is no data indicating widespread circulation of substantially different SARS-CoV-2 variants in North Carolina during these timeframes. This suggests that immunologic variables rather than virologic causes are primarily responsible for these reinfection cases. It is also worth noting that differences between reinfection and breakthrough infections in vaccinated hosts continue to be explored. As reinfection becomes an increasingly common phenomenon in the current pandemic, with an estimated rate of reinfection of 0.3%,[23] an improved understanding of the character and duration of protective immunity and risk factors for poor serologic responses to infection and vaccination has major consequences for our handling of the pandemic moving forward (Table 1).

6 | METHODS

6.1 | qRT-PCR

SARS-CoV-2 copies of NP1 in nasal swab viral transport medium (VTM) were quantified by qRT-PCR using the CDC-recommended kit (CDC-006-00019, Revision: 03). Viral RNA was extracted according to the manufacturer's instructions (QiaAmp Viral RNA kit). Regression analysis of threshold cycle number versus a serial dilution of a NP1 gene standard (Integrated DNA Technologies) was used to determine NP1 copy number. Data were normalized to input RNA and reported as copy/ml of VTM.

6.2 | Serology

IgG and IgM antibodies against the SARS-CoV-2 spike RBD were measured using the AdviseDx SARS-CoV-2 IgM and IgG II (Abbott) chemiluminescent microparticle immunoassays on the Alinity platform. The threshold for positive on the qualitative IgM assay: index ≥1.0 AU is positive and <1.0 AU is negative (from kit instructions). Index is relative fluorescence of the sample, divided by relative fluorescence of calibrator, or index (S/C). The threshold for positive on the quantitative IgG assay is ≥50 AU/ml.

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

ETHICS STATEMENT

All human studies have been approved by the appropriate ethics committee and have therefore been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The analysis of the cases was approved by the Duke University Health System Institutional Review Board under the Analysis of possible COVID-19 reinfection protocol (Pro00107410) and the Molecular and Epidemiological Study of Suspected Infection protocol (MESSI, Pro00100241).

AUTHOR CONTRIBUTIONS

All authors have read and approved the final version of the manuscript. Justine M. McKittrick had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed significantly to this study.

DATA AVAILABILITY STATEMENT

The authors confirm that the data supporting the findings of this study are available within the article and its Supporting Information Materials.

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