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Clinical Infectious Diseases

BRIEF REPORT

Severe Acute Respiratory Syndrome Coronavirus 2 Reinfection: A Case Series From a 12-Month Longitudinal Occupational Cohort

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Findings are described in 7 patients with severe acute respiratory syndrome coronavirus 2 reinfection from the National Basketball Association 2020–2021 occupational testing cohort, including clinical details, antibody test results, genomic sequencing, and longitudinal reverse-transcription polymerase chain reaction results. Reinfections were infrequent and varied in clinical presentation, viral dynamics, and immune response.

Keywords. SARS-CoV-2; COVID-19; reinfection; asymptomatic; surveillance.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection was diagnosed in >30 million individuals in the United States between 1 March 2020 and 30 May 2021 [1]. The strength and duration of immunity after infection, vaccination, and in response to SARS-CoV-2 variants remain key unknowns that will shape the future of coronavirus disease 2019 (COVID-19) spread. To date, the majority of reported SARS-CoV-2 reinfection cases have limited clinical details [2, 3]. A deeper understanding of the patterns and factors influencing COVID-19 reinfection is important to inform clinical and public health policy decisions. This report presents 7 cases of COVID-19 reinfection observed from the National Basketball Association (NBA) occupational COVID-19 testing program, with relevant clinical details.

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METHODS

The NBA occupational COVID-19 testing program provides an opportunity to detect and diagnose SARS-CoV-2 infections and reinfections, even among asymptomatic individuals [4]. NBA players, staff and vendors who participated in the US-based 2020–2021 NBA season as well as associated household members were tested for SARS-CoV-2 using frequent serial reverse-transcription polymerase chain reaction (RT-PCR) testing of combined anterior nasal and oropharyngeal swab samples and other testing platforms as part of occupational health and safety protocols during the COVID-19 pandemic. Testing frequency depended on an individual's role, but for many the testing cadence was daily. This longitudinal data set includes RT-PCR results, demographics, clinical information, infection history, antibody titer levels, SARS-CoV-2 variant information, and the presence and nature of symptoms for individuals who experienced a reinfection between 1 December 2020 and 30 May 2021. This retrospective observational study was approved by the Advarra Institutional Review Board.

RESULTS

Of 7980 individuals monitored during the 6-month study period, 768 team staff, arena staff, third-party vendors, players, or household members of any of these groups reported or were found to have recovered from a prior infection, defined as a confirmed positive RT-PCR test result plus symptoms, sequential positive RT-PCR results, and/or presence of antibodies (in unvaccinated individuals) at any point since the emergence of the COVID-19 pandemic; 7 of these experienced reinfections after a documented first infection. The reliable documentation of first infection coupled with serial testing, during and after reinfection, maximized the likelihood of detecting reinfections.

We observed variation in symptoms, viral dynamics as measured by RT-PCR cycle threshold (Ct) values (open reading frame [ORF] 1 a/b nonstructural region), and the levels of anti–SARS-CoV-2 antibodies among the 7 people with diagnosed reinfection (Table 1). All patients with reinfection were male, and their ages at reinfection ranged from 19 to 44 years (mean, 30 years). Six of the 7 individuals (86%) were asymptomatic at the time of reinfection; patient 7, who was immunocompromised, experienced headaches, myalgia, and an altered sense of taste and smell at the time of reinfection. In addition, patient 4 experienced gastrointestinal symptoms 9 days from the first positive test linked to his reinfection. Six of 7 patients (86%) had detectable SARS-CoV-2 antibodies at or soon before the time of reinfection, with a mean level of 23.0 arbitrary units (AU)/mL (range, 6.7–37.9 AU/mL), noting that the time interval from

Table 1. Clinical Characteristics of Reinfection

Patient	Time From Initial Positive Test to Reinfection, d	Symptomatic During Initial Infection	Antibody Titer Before Reinfection, AU/mL[a]	Time From Antibody Titer to Reinfection, d	Nadir Ct During Reinfection[b]	Symptomatic During Reinfection	SARS-CoV-2 Variant at Reinfection[c]	Antibody Titer After Reinfection, AU/mL[a,d]	Time From Reinfection to Antibody Titer, d	Time From Reinfection to Clearance, d[e]
1	204	No	35.2	1	28.47	No	NA	22.0	63	5
2	196	No	9.0	40	25.36	No	B.1.2	20.8	8	11
3	198	No	23.1	80	28.98	No	B.1.1.7	155.0	23	11
4	101	No	6.7	79	32.56	Yes	NA	NA	NA	14
5	156	No	379	66	35.24	No	NA	NA	NA	6
6	182	No	25.9	106	33.57	No	NA	NA	NA	4
7	25	Yes	ND	0	16.75	Yes	B0.1.2	22.5	33	15

Abbreviations: AU, arbitrary units; Ct, cycle threshold; d, days; NA, not available; ND, not detected; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]Antibody tests were conducted using one of the following platforms, which differed in the target antigen of SARS-CoV-2: the DiaSorin LIAISON system, which detects immunoglobulin (Ig) G antibodies to the S1/S2 antigens; the Roche Elecsys system, which detects IgG antibodies to the nucleocapsid antigen; the Abbott Architect system, which detects IgG antibodies to the nucleocapsid antigen; and the Ortho VITROS system, which detects IgG antibodies to the S1 antigen. All listed titer values correspond to the DiaSorin LIAISON platform. Dates of initial infection were self-reported by individuals; while most were confirmed by documentation of a positive test result with a date of collection, initial infection dates were approximated by patients 5 and 6, owing to lack of documentation for the collection date.

[b]Target 1 for the Roche Cobas diagnostic platform, open reading frame (ORF) 1, which is specific to the detection of SARS-CoV-2.

[c]Variants listed use Phylogenetic Assignment of Named Global Outbreak Lineages (Pangolin) nomenclature.

[d]Antibody titer obtained ≥7 days after the onset of reinfection.

[e]Two consecutive negative test results after reinfection is the key clinical criterion defining recovery from/clearance of reinfection.

the most recent antibody measurement to reinfection varied (range, 0–106 days). In 2 of the 7 patients (29%; patients 2 and 3), anti–SARS-CoV-2 antibody levels increased after reinfection by 11.8 and 131.9 AU/mL. Patient 7 did not have detectable antibodies on the day of reinfection but exhibited seroconversion by day 33 after reinfection, with an antibody titer of 22.5 AU/mL. The remaining patients (patients 4, 5, and 6) did not undergo antibody testing after recovery from their reinfection (Supplementary Table 1).

The timing of the antibody tests varied, because these were optional tests performed for clinical or diagnostic reasons (eg, real-world use) rather than as part of a research protocol. The presence of antibodies at time of reinfection in these patients highlights the question of how much certain quantitative results from commercially available antibody tests indicate protection from SARS-CoV-2 infection. Spike protein–directed antibody levels correlate well with virus-neutralizing titers [5], but the precise level of neutralizing antibodies necessary for protection from reinfection, and the translation of such levels to commercially available antibody tests, remains unclear. SARS-CoV-2 genomic sequencing was not performed on isolates from the primary infections. Among the 3 reinfected individuals whose samples were sequenced, 2 variants were detected: B.1.1.7 (patient 3) and B.1.2 (patients 2 and 7). Genomic sequencing results support a common transmission pathway between these patients and their exposure contacts, sharing the same variants and similar genomes. The viral genome for the close contact of patient 7 could not be sent for sequencing.

DISCUSSION

The viral trajectories of the reinfections differed from the patterns observed in this population among those with primary infections, with mean nadir Ct (representing peak viral load) of 28.70 (range, 16.75–35.24) during reinfection, compared with the previously reported mean nadir of 22.4 Ct (95% credible interval, 20.2–24.5) (Supplementary Figure 1) [6]. While the intervals overlap, the difference in means suggests lower viral loads during reinfection compared with primary infection. This difference could indicate reduced viral replication during infection for individuals who already have antibodies to SARS-CoV-2, compared with COVID-19–naive individuals. Although this is a limited sample size, findings in the patients presented here suggest that immune responses and viral control may vary among individuals, whether owing to pharmacokinetics, undiagnosed immunodeficiencies, and/or other factors. The mean time between primary infection and reinfection was 152 days (median, 182 days; range, 25–204 days, including the immunocompromised patient), consistent with findings of a previous study on reinfection [2].

Among the 7 detected reinfections, 6 (86%) were subclinical at the time of the first positive test, and likely undetectable

without the serial testing program. Despite the lack of clinical symptoms, 4 of these individuals had nadir Ct values ranging from 16.75 to 28.98 during reinfection, which may have been sufficient for viral transmission to others [8]. To date, there is limited evidence on the transmission risk for recovered individuals who are reinfected [9], although there have been reports of Ct values <30 in cases of reinfection [10, 11].

The patients discussed here fit the clinical pattern of reinfection based on longitudinal RT-PCR surveillance results, symptoms, and serology (Supplementary Figure 2) although lack of longitudinal genomic sequencing cannot rule out viral persistence. All patients, except patient 1, were known to have unmasked exposure to an individual who tested positive for SARS-CoV-2 within 1 week before their reinfection (each of the presented cases were distinct and unrelated). Although it is possible that these are not all true reinfections, the quality and reliability of the epidemiological and longitudinal data offer strong evidence of reinfection and provide a complete clinical illustration of these cases.

Patient 7, the only patient who lacked detectable SARS-CoV-2 antibodies at the time of reinfection, was reinfected within 30 days of the initial RT-PCR–confirmed primary infection. The rapid reinfection led to an evaluation for immunocompromising conditions and subsequent diagnosis of a mild immunodeficiency disorder, which likely explains the lack of antibodies after initial infection. This individual had distinct COVID-19 symptoms during the primary infection (moderate respiratory symptoms) compared with the reinfection (headaches, myalgia, anosmia, and dysgeusia) and had completely recovered from his initial symptoms before reinfection, supportive of the COVID-19 diagnosis as well as clinically suggesting 2 separate infections.

It is possible that these cases could represent false-positive results, transient virus, or a continuation/reactivation of the primary infection rather than reinfection; to some extent, diagnostic uncertainty is clinically instructive, as we work to better understand reinfection.

The population assessed in this study was predominantly male, unvaccinated, relatively young, and healthy compared with the general population. As noted by Váncsa et al, younger patients may display a longer period of viral shedding, but also may present with a second infection later than older patients [11]. In this population, we did not observe intermittent positive RT-PCR results between the initial and the second infection, despite frequent testing, except in patient 6, who tested positive with a high Ct value (the same sample was reprocessed and was negative on a less sensitive machine), 10 days before reinfection, and negative 3 times before reinfection. Ct values were not available for initial infection, and owing to the small number of individuals here, the effect of emerging variants and the impact of vaccination on reinfection rates could not be assessed.

Clinically relevant COVID-19 reinfections, both symptomatic and asymptomatic, do occur, although infrequently in this longitudinal cohort. The diversity of patterns observed here presents interesting immunological questions, relevant to current vaccine and preparedness plans. As SARS-CoV-2 variants emerge, cases of COVID-19 reinfection present an opportunity to understand real-world effectiveness of vaccines and postinfection immunity beyond clinical trial settings. Such insights are critical to inform infection prevention efforts. These case studies and discussion are intended to stimulate others to consider this information, to build knowledge of reinfection, and to inform clinical management and policy.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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