A case of COVID-19 Reinfection and Systematic Review of Patterns of Reinfection

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Abstract: We present a case of a middle age Hispanic patient with COVID-19 reinfection. We conducted a systematic review of the literature of reinfection cases and found that women represent the majority of the cases and that reinfection usually presents with more severe disease, particularly among healthcare workers.

Key Words: COVD-19, reinfection, systematic review

(*Infect Dis Clin Pract* 2021;29: e409–e411)

A little over a year into the COVID-19 pandemic, there has been close to 100 million cases and approximately to 2.4 million deaths worldwide. Most patients who recover from a natural infection are protected from future infections either through T-cell memory or measurable neutralizing antibody titers. Several studies have already documented a decline in the seroprevalence of antibodies.[1]

Several reports of possible coronavirus reinfection have been published.[2] Little is known about the patterns of clinical presentation of COVID-19 reinfection. Our aims are to present a reinfection case and to conduct a systematic review of the literature of the clinical patterns of presentations among reinfected COVID-19 patients.

CASE REPORT

We report a 58-year-old Hispanic man whose initial COVID-19 presentation was flu-like symptoms and loss of smell with fever and chills. A nasopharyngeal real-time reverse transcription polymerase chain reaction (RT-PCR) confirmed a diagnosis of COVID-19. He confirmed an exposure to a COVID-19–positive patient. Characteristics of his initial presentation included a 12-day history of mild symptoms that did not require hospitalization and that resolved with supportive care while he self-isolated. Three weeks after the initial positive COVID-19 test, he was seen in clinic and a repeat RT-PCR was reported as negative, and he had no COVID-19–related symptoms or post–COVID-19 syndrome.

A month later, during a follow-up telehealth visit he reported undergoing an elective shoulder surgery. A month after this elective procedure, he presented to the emergency department with a 2-week history of pleuritic chest pain, dyspnea, and diarrhea. His medical history includes coronary artery disease, smoking, and bipolar disorder. His social history is relevant for cigarette smoking. He is divorced and is estranged from his 3 daughters. On physical examination, he had normal temperature, normal blood pressure, and an oxygen saturation of 97%. He had scattered rales and no wheezing. On admission, his chest x-ray had no infiltrates and his laboratory data were remarkable for an elevated white blood cell count (12.1 cells/mL^3—35% lymphocytes), a D-dimer of 568 ng/mL, lactic acid of 2.4 mmol/L, and a lactate dehydrogenase of 337 U/L. His troponins and creatinine were normal.

An RT-PCR for COVID-19 was reported as positive. The patient was admitted to the hospital and started on azithromycin, ceftriaxone, and steroids as well as famotidine for noncardiac chest pain. He was discharged after 2 days of hospitalization with no symptoms. Because of the rapid improvement, a chest computed tomography scan was not performed. All COVID-19 tests were repeated to confirm accuracy, and neither of them reported cycle threshold values.

Systematic Review of Reinfection Case Reports or Series

We conducted a search of the literature on November 18, 2020, using the MEDLINE database through PubMed. The search terms included COVID-19 AND reinfection OR reactivation. We included COVID-19 case reports or case series of reinfection published as either letters to the editor or original studies. We excluded reviews and all other study designs and included preprints in PubMed. Two investigators (L.T. and A.P.) reviewed the abstract of each citation and identified abstracts for full-text review. When either selected an article for full-text review, it was evaluated by both investigators. One investigator (L.T.) was responsible for completing the evidence table, and a second investigator (A.P.) verified the accuracy of the data collected. From each case report, we collected the demographic characteristics, comorbidities, severity of the initial and recurrent infection, and time between infections. We defined severe COVID-19 disease if the patient was hospitalized, complained of dyspnea, had pulmonary infiltrates, or had hypoxemia.

Our search strategy revealed 123 citations, of which we included 40 for full-text review. We included 17 articles reporting a case report or a case series of COVID-19 reinfection.

To date, 35 COVID-19 reinfection cases have been published. Table 1 reports the relevant clinical characteristics of those patients. The median age of reinfection cases was 54 years; interquartile range 36–72 years, 54%; 95% confidence interval of 36 to 71 of reinfection cases occurred in women and 40% confidence interval of 23 to 57 of the cases occurred in healthcare workers. Regarding severity, 69% of the cases had mild symptoms during initial presentation compared with 37% with mild symptoms during the second presentation. Thirty-one percent of cases with mild symptoms during initial presentation had severe disease after reinfection, and 34% had mild disease on both presentations. The median time to reinfection was 2 months (interquartile range, 1.5–3 months). Older age and the presence of comorbidities were more common among those with severe initial presentation or second presentation, whereas younger age was more common among those with mild symptoms

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The authors have no funding or conflicts of interest to disclose.

ISSN: 1056-9103

TABLE 1. Reported Cases of COVID-19 Reinfection and Comparison of the Severity of the Presentation

Author	Age	Sex	Risk of COVID-19 Exposure	Initial Presentation	Reinfection	Time Between Infections in Months
Selvaraj[9]	70	Male	Obesity, OSA, hypertension, asthma	Mild disease	Severe disease	7
AlFehaidi[10]	46	Female	Asthma	Mild disease	Mild disease	2
Torres[11]	36	Female	Healthcare worker	Mild disease	Severe disease	3
De Brito[12]	40	Male	Healthcare worker	Mild disease	Mild disease	1.5
	48	Female	Healthcare worker	Mild disease	Mild disease	1
Nachmias[13]	20	Female	None	Mild disease	Mild disease	3
Moore[14]	63	Female	Lymphoma	Mild disease	Severe disease	2
Lancman[15]	55	Female	Diabetes, CAD, asthma, leukemia	Mild disease	Severe disease	2
Goldman[16]	60	Female	Hypertension, COPD, nursing home resident	Severe disease	Mild disease	5
Bonifacio[17]	24	Female	Healthcare worker	Mild disease	Mild disease	1
Munoz[18]	51	Male	ESRD	Mild disease	Severe disease	2
Bentivegna[19]	69	Female	Diabetes, cancer	Severe disease	Severe disease	1
Duggan[2]	82	Male	Parkinson's, diabetes, hypertension	Severe disease	Severe disease	1
Bongiovanni[20]	48	Female	Healthcare worker	Mild disease	Mild disease	4
Tillett[21]	25	Male	None	Mild disease	Severe disease	
Lafaie[22]	84	Female	Hypertension, cancer, heart disease	Severe disease	Severe disease	1.5
	90	Female	Diabetes, hypertension	Severe disease	Severe disease	1.5
	84	Female	Hypertension, heart disease	Severe disease	Severe disease	1
Gousseff[23]	19	Female	Healthcare worker	Mild disease	Severe	NR
	32	Female	Healthcare worker	Mild disease	disease	
	33	Female	Pregnancy	Mild disease	Mild disease	
	43	Male	Healthcare worker	Mild disease	Mild disease	
	85	Male	Bronchiectasis, CAD	Severe disease	Severe disease	
	54	Male	Hypertension	Severe disease	Severe disease	
	91	Female	CAD, diabetes	Severe disease	Severe disease	
	55	Male	Cirrhosis	Mild disease	Severe disease	
	72	Male	Inflammatory neuropathy	Severe disease	Severe disease	
	73	Male	Lymphoma	Severe disease	Severe disease	
	84	Female	CAD, diabetes	Severe disease	Severe disease	
Fernandes[24]	29	Male	Healthcare worker	Mild disease	Mild disease	2
	63	Male	Healthcare worker, hypertension	Mild disease	Severe disease	2
	40	Female	Healthcare worker, asthma	Mild disease	Mild disease	2
	67	Male	Healthcare worker, hypertension	Mild disease	Severe disease	2
	47	Male	Healthcare worker	Mild disease	Mild disease	2
	31	Male	Healthcare worker	Mild disease	Severe disease	2

CAD indicates coronary artery disease; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; OSA, obstructive sleep apnea.

after reinfection or reactivation. Among health care workers, 44% had a severe disease after reinfection.

DISCUSSION

The patient presents as a COVID-19 reinfection or reactivation. This pattern, although uncommon, has been reported in several countries. Potential mechanisms include suboptimal control of the SARS-CoV-2 infection due to inappropriate T-cell response,[3] allowing a second episode of viral replication, an insufficient production of antibodies due to mild illness or immune dysfunction, or the loss of the antibodies over time.[4]

Our patient's initial mild illness may be consistent with the lack of antibody production or loss of antibodies over time theories; however, because antibodies were not measured after his initial presentation, all hypotheses are speculative. An alternative explanation to our patient's presentation could be persistence of the positivity of the PCR. Both age and severity of the initial infection may correlate with prolonged shedding. However, his presentation was 3 months later and unlikely to be explained by prolonged viral shedding, and he also had a negative PCR when asymptomatic during an outpatient visit.

The source of the reinfection is unclear. He could have been reinfected in the hospital as he had an elective procedure, and we are unsure about his social distancing as well how much he adhered to masking. A potential contributor to the reinfection could have been postsurgical stress, there is growing evidence that stressful stimuli lead to disruptions in the hypothalamic-pituitary-adrenal cortisol axis, and this can impact immunological and neuroendocrine pathways.[5]

Our review of the literature found interesting trends that will need to be evaluated and confirmed in observational studies. First, many cases had mild initial presentations and more severe reinfections, and this was particularly true for healthcare workers. Second, there may be particular comorbidities, such as respiratory diseases or leukemia, which could predispose to reinfection. Third, age seems to be the most important predictor of reinfection and of

the severity of the reinfection. Fourth, slightly more reinfection cases were reported among women. Evaluation of these patterns using case reports seems to be the best evaluation at this time as reinfection is an uncommon presentation and a critical factor limiting conducting a cohort study.

Our case report is limited by the lack of SARS-CoV-2 antibody testing to document possible immunity or lack thereof. We also lack genetic sequencing of the SARS-CoV-2 virus to determine whether the same genetic strain caused the infection as a possible explanation for reactivation, and we are also unclear whether the reinfection occurred by a different strain. These issues limit our ability to prove that this was reinfection; however, the newly positive test in a symptomatic patient points to the likelihood of reinfection. Our systematic review is limited as we only included case reports found on PubMed.

Our SARS-CoV-2 testing did not report a cycle threshold value. This value represents a measure of the viral load in the sample and could inform clinical decision making regarding infectivity. No study to date reports using cycle threshold values to decide on potential reinfections. However, repeated testing with changes in values of cycle threshold could be used as a marker of reinfection with increasing viral load after documenting recovery with values near the cycle threshold cutoff.

Certainly, COVID-19 reinfections are rare events, and 2 issues have to be considered. First, to establish true reinfections, viral genomes from the first and second infection have to have enough differences, particularly with the emergence of the United Kingdom, South Africa, and Brazilian strains, which have much higher ability to infect.[6] Second, immunological memory after an infection should assure that a second COVID-19 event be milder. That is not what we found in our or other cases. The worse reinfection presentation could be mediated by disproportionate immune responses or antibody-dependent enhancement.

Our patient initially presented with mild COVID-19 and later presented 3 months with a more symptomatic infection that did not prove to be pneumonia or pulmonary embolism. A potential explanation for the timeframe of the severe presentation could be that as reported by others, protective antibodies decrease after 3 months after infection but an activated innate immunity can lead to hyperinflammatory cytokine storm and severe disease.[7]

Many of the case reports in this systematic review were healthcare workers. Previous studies have documented that healthcare workers have a higher chance of reporting a positive SARS-CoV-2 test compared with the general community. The factors that impact the possibility of a positive test are the adequacy of protective personal equipment, ethnicity, and clinical setting.[8] It is intuitive that healthcare workers have more reinfections as they are repeatedly exposed; however, it was surprising to learn that healthcare workers had significantly more severe disease when reinfected.

In conclusion, we report an ethnic minority patient with a COVID-19 reinfection after an initial mild disease. Our literature review suggests that a combination of age, sex, comorbidities, and severity of initial infection could predispose people to COVID-19 reinfection and that reinfection is usually more severe than the initial illness. Observational studies should continue to evaluate the impact and biological underpinnings of various predisposing factors.

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