

Case Reports of COVID 19 Recurrence

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Abstract

CASE REPORT OF COVID 19—Recurrence We describe as case series of 7 patients who presented with a recurrence of COVID 19 by PCR test an average of 94.9 days after their initial symptomatic presentation of illness. Patients had tested negative by PCR or had evidence of antibodies in between the 2 episodes. The majority of patients were asymptomatic on the second presentation and were found incidentally on prescreen for procedures, surgery. The subsequent positive COVID-19 PCR tests resulted in cancellations of clinic, procedures, surgery, and impacted patients' home and employment status. Further studies are needed to understand the mechanisms and ultimate outcomes of these recurrences.

Keywords

COVID-19, Clinical Recurrences, disease management, Testing results, disease outcomes

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Background

The first confirmed case of COVID-19 reinfection in the United States occurred the week of October 14, 2020 in a 25 year-old Nevada man who tested positive for the virus in April, recovered, then fell ill and tested positive again in June. In his case the second presentation was more serious and he was hospitalized and given oxygen. Genetic sequencing turned up significant differences between the virus samples taken in April and June indicating a second infection rather than the virus lingering dormant in the system after the first bout of illness.¹ Other documented cases of patients have similarly been presented.² In these infections genomic sequences were able to confirm infections as distinct isolates of SARS-CoV-2. None of the individuals had known immune deficiencies and one had pre-existing antibody (IgM) against SARS-CoV-2. In other instances, because of the wide range of serological testing platforms used, it is impossible to compare results from one assay to another and since genomic information isn't always available, it is difficult to determine if these are new infections or resurgence of dormant virus. Antibody levels are also highly dependent on the timing after exposure so even they may not assist in determining the true reinfection versus recurrence. PCR tests for the virus can remain positive up to 3 months. That too doesn't determine infectiousness. There are multiple proxies for determining infectiousness.³ However, most of them

require biosafety level 3 facilities and are not routinely done in clinical labs.⁴

While reinfection rates of coronavirus have been the focus, they are rare and repeat bouts of illness, are a reality in patients who previously presented with symptoms and tested positive months earlier. For the patients and their health care providers they portend a nightmare of uncertainty for the future effectiveness of vaccines, quarantines and lockdowns. This is distinct from “Long-haul” COVID syndrome since these patients were asymptomatic between the presentations. These cases are very challenging to determine if this is a real reinfection. More than likely it is a resurgence of symptoms connected to the original infection. The virus may set off an inflammatory response that flares up later or perhaps even a chronic low grade infection that smolders for weeks. For clinicians and patients alike, it is important to understand these occurrences since they may lead to anxiety over whether this will lead to hospitalization, a prolonged illness and long-term sequelae. Additionally, how should these patients be treated? Can they still transmit the virus to others? Are masks necessary?

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Table 1. Patients Who Presented with Recurrence of Covid-19 Test Positive.

Age	Initial symptoms	Interim covid19 test	Subsequent presentation	#Days between 1st and 2nd test	Conditions	Resolution covid retest
38	Cough, fever, loss taste/smell	NEG.	ASX	62	MDEPRESSION, PTSD	RESOLVED-1 WEEK
60	Cough	NEG	ASX	75	MDEPRESSION PTSD, Hx BLADDER CA	Positive PCR
60	Acute renal failure	NEG	FATIGUE	72	DIABETES	POSITIVE PCR
27	Fever, "flu-like"	Antibody +	FATIGUE,LOSS TASTE	79	PSORIATIC ARTHRITIS	RESOLVED—106 days
33	Fever, cough, diarrhea	Antibody +	Fever, headache	172	PTSD, Allergic rhinitis	RESOLVED—3 days
71	Fever, pneumonia respiratory insufficiency	NEG	ASX	93	Renal/liver transplant HIV, CHF,DIABETES,CRD	RESOLVED—17 days
72	Dyspnea, fatigue, headache	NEG	FATIGUE	111	Pulmonary/Cardiac Sarcoidosis	No Retest

What procedures should be used for quarantine to help protect communities? More knowledge of these presentations and their course is needed to answer these questions.

Method

A total of 600 patients who tested positive at the Miami Veterans Health System were followed during the period of April 12, 2020 to October 21, 2020. The SARS-CoV-2 RNA was detected from nasopharyngeal swab (NPS) during the acute phase of infection. The agent was detected by the BioFire RP2.1. A COVID-19 follow-up clinic was established and all patients were then followed serially daily, by telephone encounter by an Internal Medicine provider until symptoms improved, the patient was hospitalized and until resolution of the disease. This report summarizes a group of 7 veterans who presented PCR positive for COVID 19 and after 2 months or more re-presented with a positive PCR test of the SARS-CoV-2. The same provider followed these patients again (Table 1).

Results

The patients re-tested were COVID19-PCR positive again an average of 94.9 days (Range 62-172 days) from their original presentation and first COVID 19-PCR positive test. In the majority of the cases, patients were asymptomatic at the time of the second presentation and would have gone undetected if not for hospital prescreening requirements for procedures/surgery. Only 1 patient, a young woman, had typical symptoms (fever, headache) at the time of the second presentation which resolved in less than a week. Two other patients did complain of fatigue in the month prior to subsequent positive test and 1 noted persistence of loss of taste and smell for the previous 2½ months.

We do not have laboratory evidence of reinfection however, we have each patient's acknowledgement that they had not violated social distancing, use of masks, handwashing and no recent travel or animal exposure. Additionally, they indicated that family members in the same household have tested negative for the virus. Four of the patients had tested negative by PCR between their first and second attacks and in 2 other cases, the patients had evidence of immune response. Their ages varied widely from 27 to 72 years of age. None of the patient were from community living centers or assisted living facilities. There were 2 women, 2 African Americans, and 4 Hispanics. Their underlying conditions were also variable. Three patients could be considered immunocompromised (psoriatic arthritis, renal/liver transplant and HIV (undetectable viral load), and sarcoidosis). Two of those patient were receiving long-term immunosuppressive therapy (Adalimumab, Tacrolimus/Sirolimus). Three patients were insulin-requiring diabetics. Their initial presentation included typical symptoms of cough, fever, "flu-like" illness, loss of taste, smell, and fatigue. One patient had diarrhea; 1 had acute renal failure on top of chronic renal insufficiency. Only 1 patient was hospitalized during the initial presentation for GI bleeding and small bowel obstruction. During that hospitalization he developed respiratory failure with bilateral pneumonia and tested positive for COVID-19. He did not require intubation or surgery and recovered. He remained COVID positive for 2 months; tested negative the third month and re-tested positive 4 months later as part of routine screening. Since he was asymptomatic at that time, it was determined that there was no suspicion for new acute COVID infection and that he would test positive due to his immunosuppressed state. Five months later he tested negative . None of the patients received hydroxychloroquine, Remdesivir, dexamethasone at the time of their initial COVID-19 presentation. Only the

patient with HIV was chronically receiving antiviral drugs—Dolutegravir and Lamivudine.

Discussion

Although this recurrence of positive SARS-CoV-2 test result occurred rarely in only 1.2% of the patients that we were following, it is an important occurrence for providers to be aware of. It has also been described by a French national series of 11 COVID-19 patients who also experienced a second clinically—and virologically—confirmed acute COVID-19 episode.⁵ In their series, the patients presented the second time with at least 1 major clinical sign of COVID-19, including fever, chills, flu-like syndrome, dyspnea, anosmia or dysgeusia, and a positive SARS-CoV-2 RT-PCR test. Their patients had radiographic signs of acute COVID-19 and averaged 10 days median duration of symptoms for their second episode. Four of their 11 patients were health care workers who had a first mild COVID-19 episode with complete recovery, returning to work in COVID units. All of them experienced a clinical relapse requiring sick-leave but no hospitalization after a median symptom-free interval of 9 days. In contrast, none of our patients were health care workers and all but 1 were either asymptomatic or had recent presentation of fatigue, and loss of taste/smell.

COVID-19 recurrences are different from secondary complications, “long-haul” symptoms or persistence of traces of viral RNA that can be detected in respiratory samples up to 6 weeks after onset of symptoms in clinically-cured patients. All of our patients had tested negative by PCR tests and 2 had evidence of antibodies in between their initial infection and the subsequent episode. While antibody responses to SARS-CoV-2 are detected in most infected patients within 2 weeks of COVID-19 symptoms, it is not known how long they remain or will provide protection from re-infection. What studies have shown is that the magnitude and maintenance of the response of the antibody are dependent on the severity of the disease. The more severe the disease the higher the level of the antibody and the longer the presence of antibody in the follow-up period (>60 days). The amount and length of time of the presence of antibody is very important to the possibility of reinfection, resurgence, and the durability of vaccine protection.^{6,7} While disease severity has been found to correlate with the level of serum neutralizing capacity, in the patients reported 3 of the 7 were asymptomatic, the rest had mild to moderate disease, only 1 developed pneumonia with respiratory insufficiency. While immunosuppressive factors such as drugs or pathological conditions

could contribute to impaired viral clearance and favor viral reactivation, the 3 patients who met this criteria had tested negative by PCR and averaged 79, 93, and 111 days between their initial illness and second positive test. The presentations highlight the wide heterogeneity of SARS-CoV2 infections. Further study of the presence and types of neutralizing antibodies is needed to understand the complexity of the disease and the resurgence described.

Although the patients did not have significant symptoms on second presentation, the finding of testing positive for COVID-PCR again did have significant implications for them. They all had anxiety and had to deal with the uncertainty of the meaning of the positive re-test. Additionally, it led to cancellations of necessary procedures and surgery and clinic follow-up appointments which further intensified the impact on these patients’ health. Patients were advised, based on an abundance of caution, to re-quarantine for 10 days. This had untoward impact on their families and their employment. The majority of the patients expressed frustration and anger at the occurrence primarily because of the impact on their scheduled procedures. Despite diagnoses of major depression and PTSD in 4 of the patients, there was no exacerbation of symptoms related to these diagnoses. On follow-up, to date, only 4 have been retested and are negative, 1, has not been retested and 2 remain positive (one-20 days after his second positive test and 72 days from the original presentation; the second-90 days from the original presentation. Our case series has limitations. The limited number of observations is important. Additionally, the resolution of the initial infection was primarily clinically-defined and only 5 of the patients tested negatively for the virus by PCR and only 2 had antibody testing prior to the subsequent positive test. Additionally, viral culture was not performed on any of the patients to determine if this was re-infection, smoldering viral carriage, or an inflammatory response.

More research is needed and long-term assessment of these patients. The question of reinfection versus resurgence of the infection could have significant implications for our understanding of COVID-19 immunity and outcomes.


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