

Reinfection with SARS-CoV-2: An inconvenient truth?

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ABSTRACT

Data show that antibody-related immunity against SARS-CoV-2 may not be long-lasting. We report two cases regarded as cured from COVID-19, which presented again with symptoms and a positive SARS-CoV-2 RT-PCR test. Case one, a 60-year-old male, had a biphasic presentation of symptoms compatible with COVID-19 infection, associated with a positive RT-PCR test. Case two, a 25-year-old female, had a first positive RT-PCR test during hospital screening, and months later a symptomatic presentation of COVID-19, associated with a positive RT-PCR test. All cases were immunocompetent. Anti-IgG-SARS-CoV-2 blood samples were negative in both. Elevation of analytical inflammatory markers suggested new infection in both cases. COVID-19 reinfection may be a differential diagnosis and primary care physicians should acknowledge it. Previously cured patients should be encouraged to comply with health public preventive measures.

Keywords: Family medicine, infectious diseases, public health

Introduction

Knowledge regarding COVID-19 epidemiology and clinical presentation has been evolving over the past year,^[1] with dramatic consequences to human population. Since the advent of the first COVID-19 vaccine, many countries had been endeavouring to achieve group immunity. An obstacle to group immunity, despite controversial, would be the risk of reinfection in patients recovered from COVID-19. Globally, there have been some case reports suggesting reinfection with SARS-CoV-2. Some of these reports had managed to sequence viral genome, showing that reinfection may occur with different virus' strains. Implications to public health management, namely the likelihood of transmissibility, of a possible reinfection remain unknown.^[2,3] Hereby, we report two cases recovered from COVID-19, followed in primary care that showed once again

symptoms and a positive SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test. These cases expand the scarce published data, highlighting the importance of taking preventive measures, and enhance the role of primary care as the first line against COVID-19 reinfection.

Cases History

Case one

A 60-year-old male, caucasian and immunocompetent, presented with fever, myalgia and abdominal pain for the past 7 days. Past medical history revealed a partial nephrectomy. Physical examination did not show any relevant findings. A nasopharyngeal swab test (NST) was performed for RT-PCR analysis, which was positive. Considering his clinical stability, he was managed as an outpatient and monitored by telephone call every day. He became asymptomatic 26 days post-onset. He repeated two NSTs, both negative and achieved discharge criteria [Table 1]. Ninety-five days after first onset he presented with fever (axillary temperature of 39.0°C) and

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Received: 24-07-2021

Revised: 11-10-2021

Accepted: 20-10-2021

Published: 31-01-2022

Access this article online

Quick Response Code:



Website:
www.jfmpc.com

DOI:
10.4103/jfmpc.jfmpc_1490_21

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How to cite this article: Sonié P, Manuel-Silva J, Rafael A, Amorim-Alves L. Reinfection with SARS-CoV-2: An inconvenient truth? J Family Med Prim Care 2022;11:366-9.

sore throat. Laboratory findings showed leukocytosis with neutrophilia and an elevated C-Reactive Protein. He was empirically medicated with amoxicillin/clavulanate. A NST was also performed and the result was positive. Two days after he became asymptomatic. Given these two episodes, he was referred to an infectious diseases' appointment where he performed NST and blood serology tests, which were all negative. None of the high-risk patients' contacts were infected after the second episode.

Case two

A 25-year-old female, caucasian, immunocompetent with no relevant medical history performed a NST in the context of hospital screening, which was positive. Until that moment, she was asymptomatic. Considering her status, she was managed as an outpatient and monitored by telephone call every day. She repeated two NSTs, both negative, and achieved discharge criteria [Table 2]. One hundred and three days post-onset, she performed blood serology tests, which were all negative. One hundred and forty-five days post-onset she presented with fever, generalized myalgia and lumbago for 2 days. She described a close contact with a COVID-19's confirmed case 4 days ago. Laboratory findings showed elevation of C-Reactive Protein and the NST performed was positive. None of the high-risk patients' contacts were infected after the second episode.

Discussion

We report two cases with a compatible biphasic presentation of COVID-19. In each case there was an asymptomatic period, which lasted for 2 months and 4 months, respectively, after discharge criteria were met. Every episode had an associated positive RT-PCR test. We also observed an increase in inflammatory markers in the second episode, measured by C-Reactive Protein value, which is highly associated with a new infection. Furthermore, the presence of anosmia and ageusia anew, two hallmark symptoms of COVID-19, without rhinorrhoea or compatible past medical history, increases the probability for a reinfection.

SARS-CoV-2 reinfection seems to be a rare phenomenon.^[4,5] Reinfection can only be confirmed using genomic sequencing to establish that the infections were caused by two different strains.^[5] Poor methodological data and, more often, insufficient logistic resources make it difficult to establish a reinfection case.^[2] Until December 2020, there were only 17 confirmed cases of reinfection, all by genetic sequencing.^[5] Prolonged respiratory shedding of viral RNA following acute infection is a well-documented cause of false RT-PCR positive tests.^[6] However, the actual evidence suggests that are features that increase the likelihood of a reinfection: Immunosuppressive conditions, new variants of concern, a longer time interval since the first infection, a high viral RNA level on repeat testing

Table 1: Evolution of case one's symptoms and performed RT-PCR results. A vertical line represents onset of symptoms and duration, and a horizontal line represents its end. A "+" sign represents a positive RT-PCR test, and a "-" sign a negative one

| Day after onset | RT-PCR | Fever | Abdominal Pain | Myalgia | Anosmia | Ageusia | Sore Throat | Cough | Asthenia |
|-----------------|--------|-------|----------------|---------|---------|---------|-------------|-------|----------|
| 0 | | | | | | | | | |
| 1 | | | | | | | | | |
| 2 | | | | | | | | | |
| 3 | | | | | | | | | |
| 4 | | | | | | | | | |
| 5 | | | | | | | | | |
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| 7 | + | | | | | | | | |
| 8 | | | | | | | | | |
| 9 | | | | | | | | | |
| 10 | | | | | | | | | |
| 11 | | | | | | | | | |
| 12 | | | | | | | | | |
| ... | | | | | | | | | |
| 26 | | | | | | | | | |
| ... | | | | | | | | | |
| 30 | - | | | | | | | | |
| ... | | | | | | | | | |
| 33 | - | | | | | | | | |
| ... | | | | | | | | | |
| 95 | + | | | | | | | | |
| 96 | | | | | | | | | |
| 97 | | | | | | | | | |
| ... | | | | | | | | | |
| 105 | - | | | | | | | | |

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Table 2: Evolution of case two's symptoms and performed RT-PCR results. A vertical line represents onset of symptoms and duration, and a horizontal line represents its end. A "+" sign represents a positive RT-PCR test, and a "-" sign a negative one

| Day after onset | Evolution of symptoms and RT-PCR results | | | | | | | |
|-----------------|--|-------|----------|---------|----------|-------|---------|---------|
| | RT-PCR | Fever | Dyspnoea | Myalgia | Headache | Cough | Anosmia | Ageusia |
| 0 | + | | | | | | | |
| 1 | | | | | | | | |
| 2 | | | | | | | | |
| 3 | | | | | | | | |
| 4 | | | | | | | | |
| 5 | | | | | | | | |
| 6 | | | | | | | | |
| 7 | - | | | | | | | |
| 8 | | | | | | | | |
| 9 | | | | | | | | |
| 10 | | | | | | | | |
| 11 | - | | | | | | | |
| ... | | | | | | | | |
| 143 | | | | | | | | |
| 144 | | | | | | | | |
| 145 | + | | | | | | | |
| 146 | | ┆ | | | | | | |
| 147 | | | | ┆ | | | | |
| 148 | | | | | | | | |
| 149 | | | | | | | ┆ | |
| 150 | | | | | | | | |
| 151 | | | | | | | ┆ | |
| 152 | | | | | | | | ┆ |

or undetectable blood anti-IgG antibodies.^[3,4] Our cases match two of these features: They had no detectable blood anti-IgG antibody and a long interval since first infection, at the time when reinfection was considered. Given that both diagnoses were done at a primary care level and symptoms were not severe, we were not able to measure viral RNA level or request genomic sequencing, which are not available at this level of care. Although we are not able to confirm a reinfection, we have strong clinical and analytical data that support this hypothesis.

Globally, reports of compatible reinfection among healthcare workers are becoming increasingly more frequent.^[7-10] In some of these, the second episode seems to be more severe.^[10] A large-scale observational study conducted in Denmark concluded that a previous infection with SARS-CoV-2 would decrease the likelihood of reinfection by 77-83%, although this "protection" decreased to below 50% in people with 65 years or older.^[11] The same results were observed in other cohort studies that estimated the risk reduction between 83 and 95%.^[12,13] This information highlights that although being rare, reinfection by SARS-CoV-2 is possible.

Despite having a small sample, we did not identify transmission of COVID-19 in our high-risk patients' contacts by the time of the second episode. All high-risk contacts were isolated and routinely tested for COVID-19 and symptoms until completed 14 days after first contact. However, until the risk of transmissibility in reinfected patients is properly addressed by

high-quality methodological studies, we advise to keep health public preventive measures that are known to reduce the risk of transmission.

In conclusion, we documented two cases of highly suspected COVID-19 reinfection. This report highlights the importance of retesting after a first infection if the clinical and epidemiological context for a second COVID-19 episode is plausible. Primary care physicians should regard this as a differential diagnosis when facing a respiratory infection. In the future, we will be able to provide more accurate public health recommendations regarding reinfected patients and their risk of transmissibility.

Key Messages

- COVID-19 reinfection may occur, and primary care physicians should consider this diagnosis when facing a patient with a respiratory infection.
- Recovered patients should be encouraged to comply with health public preventive measures until further evidence is provided.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients

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understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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