


Second Episode of COVID-19 in Health Professionals: Report of Two Cases

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Abstract: Although primary infection has been shown to prevent reinfection of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in animal models, gaps in the understanding of the immune response to the virus have not been adequately addressed, and some cases of possible reinfection have been reported; however, the frequency, relevance and proof of these events have yet to be determined. We report cases of two doctors who had two episodes of COVID-19 with positive RT-PCR (reverse transcriptase polymerase chain reaction) test results, raising the probability of reinfection. Case 1 was a 40-year-old male physician who presented fever and respiratory symptoms on April 10, with a positive RT-PCR test for SARS-CoV-2, with complete improvement of symptoms in five days. After 44 days, the patient presented the same symptoms of the previous episode, associated with anosmia and dysgeusia. The results of a new RT-PCR test performed two days later were positive for SARS-CoV-2. Case 2 was a 44-year-old female physician who worked in a reference clinic for COVID-19 (coronavirus disease 2019) and had onset of symptoms indicative of the disease on April 30. The RT-PCR test was positive for SARS-CoV-2, with improvement of symptoms in six days. On May 24, the patient presented fever, cough, and sore throat accompanied by headache, asthenia, myalgia, and diarrhea, and in this new episode, anosmia and dysgeusia were also present. A new RT-PCR test from nasopharyngeal swabs was performed with a positive result. Our two patients described here and other patients with possible reinfection who are now being observed in clinical practice reinforce the need to expand the investigation. Then, if the risk of reinfection is confirmed, these findings will be relevant from a clinical-epidemiological perspective to define isolation strategies and develop vaccines.

Keywords: COVID-19, SARS-CoV-2, reinfection, antibody

Introduction

Since the first reports of COVID-19 (coronavirus disease 2019) cases in China in December 2019, the disease has spread worldwide, and millions of people have been affected, resulting in thousands of deaths. Although it has been shown that primary infection prevents reinfection with SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) in animal models and that neutralizing antibodies are produced after infection in humans, some cases of possible reinfection have been reported.¹⁻⁵ These reports suggest the possibility of differences in the immune responses to the virus in some individuals; however, the frequency, relevance and proof of these events are yet to be determined.³⁻⁵

We report two cases of doctors from Pernambuco, northeastern Brazil, who presented a second episode of clinical manifestations of COVID-19 weeks after

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recovery from their initial infection. These doctors presented positive RT-PCR (reverse transcriptase polymerase chain reaction) results from nasopharyngeal swabs on both occasions, suggesting reinfection.

Case Reports

Patient 1 was a 40-year-old man without comorbidities who worked as a doctor in the emergency mobile care service and in a referral hospital for patients with COVID-19. On April 10, he developed symptoms of fever, cough, sore throat, fatigue, myalgia, headache and diarrhea. The results of an RT-PCR test from a nasopharyngeal swab performed four days later were positive for SARS-CoV-2. The patient's respiratory symptoms improved within five days. Following the local quarantine protocols, patient 1 returned to work after 14 days. IgM and IgG serology tests were performed four weeks later, and the results were negative. On May 26, patient 1 started to present the same symptoms he had reported forty-seven days earlier but now with the onset of anosmia and dysgeusia. The results of a new RT-PCR test performed from nasopharyngeal swabs two days later were positive for SARS-CoV-2. Despite the absence of dyspnea and normal O₂ saturation, a chest CT scan was performed two days later, and the results were normal. The symptoms regressed after five days. Six weeks after the second wave of symptoms, a RT-PCR test from nasopharyngeal swabs was negative, and the serology was positive for IgG and IgM (Table 1, Figure 1).

Patient 2 was a 44-year-old woman without comorbidities who worked as a doctor in a reference clinic for COVID-19. Patient 2 experienced the onset of symptoms on April 30, including a subjective sensation of fever (37.2°C), cough, sore throat, fatigue, myalgia, diarrhea and headache. The RT-PCR results from the nasopharyngeal swab test performed four days later were positive for SARS-CoV-2. The respiratory symptoms improved after five days, but the general symptoms of fatigue and headache persisted for another six days. After 14 days, she returned to her regular activities. On May 24, the patient had the onset of fever, cough, and sore throat accompanied by headache, asthenia, myalgia, and diarrhea, and in this new episode, anosmia and dysgeusia were also present. The patient's respiratory symptoms improved after seven days, but her anosmia and dysgeusia persisted for more than 60 days and had not yet improved by the time the case was reported. A new RT-PCR test from nasopharyngeal swabs was performed, with positive results. IgM and

IgG serology chemiluminescence tests were performed five days after the second wave of symptoms to assess whether there were previous antibodies produced in response to the first infection; these tests were positive only for IgG. A new RT-PCR test from nasopharyngeal swabs was performed after six weeks, with negative results, and the serology tests were positive for IgG (Table 1, Figure 1).

Discussion

We report two patients who had two episodes of symptoms related to COVID-19, both of which were confirmed by RT-PCR, with a long symptom-free period between episodes, suggesting reinfection. The cases occurred in two doctors who worked in reference health units caring for COVID-19 patients. Cases of medical professionals suspected of reinfection have been reported, and such reinfection could be related to an increased risk due to repeated exposure to infected patients.^{6,7}

Reports have been published suggesting reinfection in patients with two waves of clinical manifestations and positive RT-PCR in those waves. Bongiovanni and Basile reported two elderly patients who, after their previously positive RT-PCR results became negative and they recovered from the initial wave of symptoms of COVID-19, had symptom recurrence and new positive test results approximately thirty days after the initial test. The authors considered the possibility that age and the presence of comorbidities may have contributed to modifications in the immune responses of these patients, increasing the risk of new infection.⁴ Another three elderly patients with two waves of symptoms were reported by Lafaie et al, and the patients presented positive RT-PCR results in samples with an interval longer than 30 days; however, as the period without symptoms was short, the authors suggested a recurrence of infection and not infection with a new viral strain. According to the authors, the absence of IgG antibodies in two of the patients would justify the hypothesis of recurrence and may be related to the immunosuppression of elderly patients.³ Our two cases occurred in healthy young patients, without comorbidities, with a long asymptomatic period, which may suggest reinfection more than a reactivation of previous infection.

In the two episodes of the patients reported here, RT-PCR tests were not performed beyond the recommendations of the protocol in Brazil; the recommendation is only that health professionals should isolate for a period of 14 days after clinical recovery before returning to regular activities. Sun et al reported prolonged

Table 1 Demographic Data and Clinical Characteristics of Two Patients with Confirmed and Clinical-COVID-19

	Patient 1 First Episode	Patient 1 Second Episode	Patient 2 First Episode	Patient 2 Second Episode
Age (years) Sex Comorbidities	40 Male None		44 Female None	
Symptoms onset - date First and second RT-PCR - date	04/10/20 Pos - 04/14/ 20	05/26/20 Pos - 05/28/20	04/30/2020 Pos - 05/04/20	05/24/20 Pos - 05/29/20
First serology IgM and IgG - date Second serology Ig M and IgG - date Third RT-PCR - date Interval between symptom onset from the first to the second wave (days) Interval between the first and the second RT-PCR (days)	Neg IgM and IgG - 05/12/20 Pos -IgM and IgG - 07/14/20 Neg - 07/14/20 46 44		Neg IgM and Pos IgG- 06/01/20 Neg IgM and Pos IgG- 07/14/20 Neg - 07/14/20 25 25	
Instituted therapy	Symptomatic	Symptomatic+ hydroxychloroquine +azithromycin+ ivermectin	Symptomatic +azithromycin +ivermectin	Symptomatic+ hydroxychloroquine +azithromycin+ ivermectin
Symptoms (duration in days) Fever Maximum temperature °C Nonproductive cough Sputum production Rhinorrhea Sore throat Dyspnea Anorexia Fatigue Myalgia Arthralgia Anosmia Dysgeusia Headache Diarrhea Nausea Vomiting Chest X ray and CT - date	Yes (2) 38.5 Yes (3) No No Yes (4) No No Yes (5) Yes (2) No No No Yes (2) Yes (2) No No No Not performed	Yes (3) 38.3 Yes (4) No No Yes (4) No No Yes (4) Yes (2) No Yes (5) Yes (5) Yes (2) Yes (4) No No Normal - 05/28/20	No 37.2 Yes (3) No No Yes (5) No No Yes (11) Yes (10) No No Yes (11) Yes (4) No No Not performed	Yes (3) 37.8 Yes (7) No No Yes (7) No Yes (7) Yes (10) Yes (10) No Yes (60+) Yes (60+) Yes (7) Yes (3) Yes (3) No Normal - 05/24/20

Abbreviations: Pos, positive; Neg, negative; CT, computed tomography.

persistence of viral RNA in nasopharyngeal swab samples with medium time until clearance of 22.7 days and 33.5 in mild and severe cases, respectively.⁸ Lan et al found prolonged shedding of viral RNA material from throat swab samples of mild COVID-19 patients for 50 days at maximum.⁶ The persistence of positive RT-PCR test results detected by a sensitive method can only indicate the presence of residual viral particles and may not indicate viable

virus or reinfection. However, in the reported cases, the patients had symptoms in the second wave, which would indicate not only the persistence of detectable viral particles but also the presence of viable virus. Another factor that supports a new SARS-CoV-2 infection is the presence of anosmia and dysgeusia, which has shown high specificity and high positive predictive value for COVID-19 in outpatients.⁹

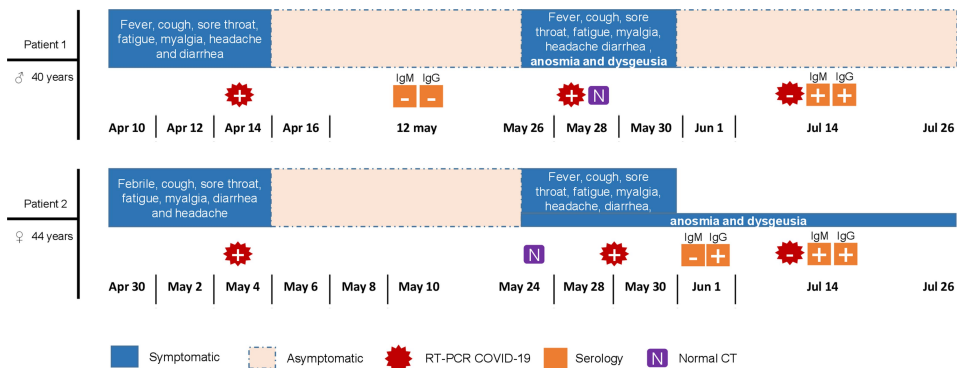


Figure 1 Timeline of symptoms and laboratory results in two cases of COVID-19.

Recurrence or positive RT-PCR retests in patients in the convalescence phase who recovered from a first episode of COVID-19 have been reported in some studies, but these patients have not become symptomatic.^{6,10} In a study by Lan et al, medical professionals who had clinical features of COVID-19 and were hospitalized had negative RT-PCR test results at the time of hospital discharge; after 5 to 13 days, another test was performed, yielding positive results, but these patients did not develop symptoms.⁶ There is the possibility that in these case reports, there were false-negative RT-PCR test results in the discharge, and in fact, these cases indicated the detection of persistent viral RNA and not reinfection.

One of the patients in this report did not have positive serology test results after the first wave of symptoms with RT-PCR positivity, which could indicate the absence of neutralizing antibodies capable of preventing a second infection; however, six weeks after the second wave of symptoms, the RT-PCR was negative, and the serology was positive for IgG, and IgM was still positive, indicating recent infection. However, the second patient had positive IgG test results in the first days of the second wave, indicating that antibodies were produced by a previous infection.

In animal models, it has been shown that primary infection prevents reinfection of SARS-CoV-2, increasing the production of neutralizing antibodies.¹ However, the presence of IgG antibodies may not indicate protection for all individuals. In a study by Ibarondo et al, the levels of IgG antibodies against the spike protein-binding receptor rapidly decreased to half the initial value 36 days after recovery; in mild cases of the disease, it was not possible to define whether immunoglobulins had prolonged protective effects.¹¹ Furthermore, the presence of IgG antibodies may not indicate protection for all individuals, being

necessary the presence of CD4+ T cells and memory CD8+ T cells, which produce effector cytokines and IFN- γ to induce effective protection in patients, as demonstrated in a SARS-CoV study.¹² Chaturvedi et al also considered that eventual “escape mutations” could lead to changes in the glycoprotein spike (S), leading to reduced antibody ability to neutralize the modified virus in a second exposure.¹³

The isolation of the virus in two episodes of symptoms and the demonstration of molecularly distinct viruses may contribute to the hypothesis of reinfection, distinguishing cases of reactivation of previous infection from cases of reinfection, which was not possible in the reported cases. Recently, researchers from the University of Hong Kong reported a case of a man with different strains of COVID-19 in samples collected with an interval of 4.5 months, reinforcing that events of reinfection are possible. The man was asymptomatic during the second infection, which was picked up by screening tests.¹⁴

Conclusion

Our two patients described here and other patients with possible reinfection who are now being observed in clinical practice, in association with the gaps in the understanding of the immune response to the virus that are not fully elucidated, reinforce the need to expand the investigation. Then, if the risk of reinfection is confirmed, these findings will be relevant from a clinical-epidemiological point of view to define isolation strategies and to develop vaccines.

Data Sharing Statement

All data generated or analyzed during this study are included in this published article.

Ethics Approval and Informed Consent

Both patients provided written informed consent for publication of the case details prior to collecting information. The patient provided written consent for inclusion of their personal or clinical details in this study.

The study was approved by the Research Ethics Committee of the Center of Medical Sciences, Federal University of Pernambuco (CAAE (Certificate of Presentation of Ethical Appreciation): 31047320.7.0000.5208).

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Author Contributions

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

Conflicts of Interests

The authors declare that they have no conflicts of interest for this work.

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