Prolonged Viral Shedding in Three Young Adult Cases of COVID-19

Wen-Yi Dong¹, Ming-Ju Zhou²,³, Lei Huang³, Chao Zhang¹,³, Fu-Sheng Wang¹,²,³, Zhou-Hua Xie¹,*

¹ Guangxi AIDS Clinical Treatment Centre, The Fourth People’s Hospital of Nanning, Nanning 530013, China; ² Beijing Ditan Hospital, Capital Medical University, Beijing 100015, China; ³ Medical Department of Infectious Diseases, The Fifth Medical Centre of Chinese PLA General Hospital, National Clinical Research Centre for Infectious Diseases, Beijing 100039, China.

Abstract

Severe acute respiratory syndrome coronavirus-2 infection is usually self-limited, with a short duration for viral shedding within several weeks. However, prolonged viral shedding has been observed in severe or immune-compromised coronavirus disease 2019 (COVID-19) cases. Here, we reported that three young adult cases of COVID-19 patients, who were either immunosuppressed nor severe, showed prolonged viral RNA shedding from the upper respiratory tract for 58, 81, and 137 days since initial diagnosis. To our knowledge, this is the longest duration of viral shedding reported to date in young adult patients. Further studies on factors relevant to prolonged viral positivity, as well as the correlation between viral positivity and transmission risk are needed for the optimal management of COVID-19 patients with prolonged nucleic acid positive.

Keywords: COVID-19; Immune-competent; Prolonged viral shedding; SAR-CoV-2

Introduction

The outbreak of coronavirus disease 2019 (COVID-19), caused by novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), was declared as a global pandemic by WHO due to the widespread infectiousness and high contagion rate, resulting in a severe threat to public health and safety worldwide.[1] More than 200 million confirmed cases of the COVID-19 have been reported to World Health Organization (WHO) on November 2021, with an average fatality rate of almost 2.0%.

The viral ribonucleic acid (RNA) detection by polymerase chain reaction (PCR) is widely used for determining an appropriate period of quarantine, and is important for determining control strategies to manage the disease and to reduce transmission. Most people who have COVID-19 recover within a few weeks, while a number of patients exhibit prolonged virus shedding in the body, with the longest duration for over 110 days. The median duration of viral shedding from the time of symptoms onset were 17 days (95% CI 15.5–18.6) in upper respiratory tract samples and 21.8 days (95% CI 16.4–27.1) in feces.[2]

The factors associated with prolonged SARS-CoV-2 RNA shedding in COVID-19 patients have not been well understood. Several risk factors including administration of immunosuppressant drugs (such as corticosteroids and B cell-depleting antibodies), delayed admission to the hospital, severe illness at admission, male sex, as well as old age have been found to be responsible for prolonged viral shedding.[3] Moreover, recent reports suggested that impaired CD8+ T cells and lower NK cell count correlates the most with a longer duration of viral shedding.[4,5] However, persistent viral positivity was rarely observed in immune-competent individuals.

Here, we reported three young adult cases of COVID-19 patients with prolonged SARS-CoV-2 RNA shedding, for 58, 81, and 137 days from initial diagnosis, and the three patients were strictly quarantined before re-admission, which excludes environmental contamination or reinfection. Notably, the manifestations of these cases were mild or asymptomatic, with no relevant risk factors mentioned above. Therefore, a better understanding of the factors and impacts associated with prolonged viral shedding is warranted, which can facilitate better individual well-being and healthcare.

Case presentation

The study was approved by the Institutional Review Board of the Fourth People’s Hospital of Nanning, and written informed consents were obtained from the participants.

Case 1

The patient was a 26-year-old female who was living in Wuhan and identified as a close contact with confirmed COVID-19 patients on January 2020. She was admitted to hospital on January 22, with symptoms of rhinorrhea, sore muscles, and asthenia for 3 days. She had no history of clinically significant underlying conditions, and no indications of compromised immunity. After hospitalization, the computed tomography (CT) scan revealed inflammation of the lower lobe of the left lung. She was tested positive for SARS-CoV-2 RNA on January 30. The patient received antiviral therapy including piperacillin, oseltamivir, and...
moxifloxacin and had remission of symptoms. Then, she was discharged from the hospital after two negative PCR results. Then she was quarantined at home, but tested positive again in the 4-week visit after discharge and showed asymptomatic. On re-admission, she was asymptomatic and received traditional Chinese medicine. SARS-CoV-2 serology was positive by chemiluminescent immunoassay (CIA) on re-admission. Moreover, the CT scan revealed a significant improvement in pulmonary infection compared to the first admission. After two negative PCR results performed 24 hours apart, she was discharged on March 21 and the timeline events for her were shown in Figure 1A. Laboratory results are shown in Table 1.

Case 2
The patient was a 25-year-old male who was working in Jakarta, Indonesia. On July 24, 2020, he complained of cough, fever, and fatigue with no medical history of immunodeficiency-related diseases. After the diagnosis of SARS-CoV-2 related pneumonia, the patient was admitted to local hospital. On August 17, he was asymptomatic and considered clinically recovered. After leaving the hospital, he was isolated in a single room arranged by the company. On September 16–18, after 55 days post initial diagnosis, three consecutive nasopharyngeal swabs (NPS) nucleic acid tests were reported negative at the local hospital, and then he returned to China but tested positive again at the customs outpatient department on September 22, 2020, but showed clinical asymptomatic. After hospitalization, the patient received antiviral treatment including arbidol tablets and Lianhuaqingwen (a Chinese herbal medicine) according to Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment. SARS-CoV-2 serology was positive by CIA. The patient was kept continuous nucleic acid tests and discharged from the hospital after two negative PCR results 86 days after initial diagnosis as shown in Table 1. Laboratory results are shown in Table 1.

Case 3
A 37-year-old male returned to China from Jakarta, Indonesia on December 29, 2020. He was tested NPS positive without clinical symptoms at entry. Then he was admitted to hospital and given interferon atomization, arbidol, Lianhuaqingwen, and traditional Chinese medicine decoction for treatment. Two consecutive swabs of the throat and NPS were negative for PCR after treatment. The patient was discharged from hospital on February 28 and quarantined at home, but tests positive again 2 weeks later with asymptomatic. SARS-CoV-2 serology was positive by CIA on re-admission. After re-admission, antiviral treatment was continued, but the nucleic acid tests were positive for several times. He was discharged on March 21, 24 hours after two NPS negative intervals. The timeline events for him were shown in Figure 1. Laboratory results are shown in Table 1.

Discussion
The viral RNA shedding patterns in COVID-19 patients are diverse due to the heterogeneously clinical spectrum of the disease. Prolonged SARS-CoV-2 shedding in cases of immunodeficiency or older age has been reported.[3] Recent research reports that prolonged SARS-CoV-2 shedding leads to viral evolution and reduced sensitivity to neutralizing antibodies in an immunosuppressed individual treated with convalescent plasma.[6] In this report, we describe prolonged viral shedding duration in three young individuals without immunodeficiency-related diseases, and one of them was up to 137 days from the initial positive PCR test of COVID-19. Since these patients were strictly quarantined from the first discharge to re-admission, and cycle threshold (Ct) values for positive PCR test during rehospitalization were high [Figure 1], it is not likely they were reinfected. In addition, no new confirmed cases were reported in relation to these three cases reported here. Our data suggested that prolonged SARS-CoV-2 shedding can be found in mild or even asymptomatic cases, highlighting the need for evaluating transmission risk in COVID-19 patients with prolonged nucleic acid positive.

The RNA positivity is widely used as a marker of infectivity to guide the duration of quarantine.[7] Currently, China applies a strict strategy for patient discharge and de-isolation. For discharge, the criteria are two consecutively negative PCR (interval ≥ 24 hours), improved respiratory symptoms, and obvious absorption of inflammation in pulmonary imaging. For de-isolation, the criteria are RNA negative 2 weeks after discharge. However, it remains unclear whether the prolonged viral shedding is associated with lasting infectivity. Prolonged hospital stays and quarantine can be a

### Table 1: Clinical characteristics of patients

|                      | Case 1        | Case 2        | Case 3        |
|----------------------|---------------|---------------|---------------|
| Age (years)          | 26            | 25            | 37            |
| Sex                  | Female        | Male          | Male          |
| BMI (kg/m²)          | 19.0          | 26.2          | 20.3          |
| Symptoms             | Rhinobyon, fatigue, sore muscles | Cough, fever, fatigue | Asymptomatic |
| Onset to admission (days) | 3             | 3             | N/A           |
| Disease severity     | Mild          | Mild          | Asymptomatic  |
| Re-admission         |               |               |               |
| CRP (mg/L)           | <0.5          | 4             | 1             |
| CD4+ T cells (cells/mL) | 426          | 773           | 847           |
| CD8+ T cells (cells/mL) | 558          | 891           | 560           |
| IgG                  | Positive      | Positive      | Positive      |
| IgM                  | Negative      | Positive      | Negative      |
| Ct values            | N/A           | 27.35         | 31.65         |
| Treatment            | Traditional Chinese medicine | Arbidol, Lianhuaqingwen | Arbidol, Lianhuaqingwen |

BMI: body mass index; CRP: C-reactive protein; Ct: Cycle threshold; IgG: Immunoglobulin G; IgM: Immunoglobulin M; N/A: Not available.
significant challenge to healthcare resources, as well as to patients’ mental health outcomes, such as fears, frustration, boredom, inadequate information, financial loss, anxiety, and stigmatization.

The confirmation of SARS-CoV-2 infection mainly depends on PCR, which can only detect part of viral genome, and cannot distinguish infective virus from inactive virus. Virus culture assays,

---

Figure 1: (A) Timeline of events for the three cases with prolonged viral shedding in this study. (B) The dynamic information of PCR Ct values and (C) IgG or IgM antibody titers of re-admission for case-2 and case-3. Ct: cycle threshold.
which are the gold standard for verification of infectivity, but live virus culture is time-consuming, require high stringent biosafety measures, and there is also the problem of potentially low detection rates. Therefore, it is urgent to develop new strategies for infectious assessment to manage patients with prolonged viral shedding. For example, it was recommended to detect subgenomic SARS-CoV-2 RNA to monitor the shedding of infectious virus.\(^9\) In addition, studies have shown that infectious virus particles mainly exist in the early stage of infection, although nucleic acid is positive in the later stage, but the possibility of infectivity is low.\(^10\) Moreover, the Ct values of PCR can be used as quantitative measure for predicting the infectivity of shedding virus.

In conclusion, in this study, we presented three non-severe cases of COVID-19 with prolonged viral shedding. Although lack of insight for exact mechanism, our observations called for developing strategies to evaluate viral infectivity in persistently SARS-CoV-2-positive individuals, which might have significant implications on current isolation/quarantine and work restriction policies.

**Funding**

This study was supported by the Key Research and Development Program of Guangxi (AB20059001).

**Author Contributions**

Zhou-Hua Xie conceived and designed the study. Wen-Yi Dong and Zhou-Hua Xie took care of patients and provided the clinical information. Ming-Ju Zhou and Chao Zhang drafted the manuscript. Lei Huang and Fu-Sheng Wang provided comments on the study. All authors revised the manuscript and approved the final manuscript.

**Conflicts of Interest**

None.

Editor note: Chao Zhang and Fu-Sheng Wang are the editors of Infectious Diseases & Immunity. The article was subject to the journal’s standard procedures, with peer review handled independently by these editors and their research groups.

**References**

[1] Wang GQ, Zhao L, Wang X, et al. Diagnosis and treatment protocol for COVID-19 patients (tentative 8th edition): interpretation of updated key points. Infect Dis Immun 2021;1(1):17–19. doi: 10.1097/ID9.000000000000002.

[2] Cevik M, Tate M, Lloyd O, et al. SARS-CoV-2, SARS-CoV, and MERS-CoV viral load dynamics, duration of viral shedding, and infectiousness: a systematic review and meta-analysis. Lancet Microbe 2021;2(1):e22. doi: 10.1016/S2666-5247(20)30172-3.

[3] Feng Z, Li J, Yao S, et al. Clinical factors associated with progression and prolonged viral shedding in COVID-19 patients: a multicenter study. Aging Dis 2020;11(3):1069–1081. doi: 10.14336/AD.2020.0630.

[4] Turner JS, Day A, Alsoussi WB, et al. SARS-CoV-2 viral RNA shedding for more than 87 days in an individual with an impaired CD8+ T cell response. Front Immunol 2020;11:618402. doi: 10.3389/fimmu.2020.618402.

[5] Luo C, Tao X, Cui W, et al. Natural killer cells associated with SARS-CoV-2 viral RNA shedding, antibody response and mortality in COVID-19 patients. Exp Hematol Oncol 2021;10(1):5. doi: 10.1186/s40164-021-00199-1.

[6] Kemp SA, Collier DA, Datin RP, et al. SARS-CoV-2 evolution during treatment of chronic infection. Nature 2021;592(7853):273–277. doi: 10.1038/s41586-021-03291-y.

[7] Welb CR, Townsend JP, Pandey A, et al. Optimal COVID-19 quarantine and testing strategies. Nat Commun 2021;12(1):356. doi: 10.1038/s41467-020-20742-8.

[8] van Kampen JJA, van de Vijver DAMC, Fraaij PLA, et al. Duration and key determinants of infectious virus shedding in hospitalized patients with coronavirus disease-2019 (COVID-19). Nat Commun 2021;12(1):267. doi: 10.1038/s41467-020-20568-4.

[9] Advandato VA, Matson MJ, Seifert SN, et al. Case study: prolonged infectious SARS-CoV-2 shedding from an asymptomatic immunocompromised individual with cancer. Cell 2020;183(7):1901–1912 e1909. doi: 10.1016/j.cell.2020.10.049.

[10] Kim MC, Cui C, Shin KR, et al. Duration of culturable SARS-CoV-2 in hospitalized patients with Covid-19. N Engl J Med 2021;384(7):671–673. doi: 10.1056/NEJMc2027040.

Edited By Haijuan Wang