



SARS-CoV-2 late shedding may be infectious between immunocompromised hosts

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ABSTRACT

Background: Immunocompromised patients shed SARS-CoV-2 for extended periods, but to our knowledge person-to-person transmission from late shedding has not been reported.

The case: We present a case in which a COVID-19 patient infected another over 28 days after the patient's initial symptoms, past current guideline recommendations of 20 days for length of isolation in immunocompromised patients. Whole genome sequencing of their viruses was performed to ascertain the transmission.

Discussion: Severely immunocompromised patients, whose clearance of the virus is impaired, may remain infectious for extended periods. Caution should be taken particularly in hospital settings where lapses in isolation procedures might pose increased risk, especially to other immunocompromised patients.

KEYWORDS

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The world has been in the grip of a pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) and its associated disease (COVID-19) for over a year now. Several reports have been published showing that some patients shed the virus for prolonged periods [1–3]. Patients receiving chemotherapy are generally severely immunosuppressed and, as such, susceptible to a wide variety of infections also with poorer outcomes. It is, therefore, not surprising that the same applies for cancer patients faced off with COVID-19 [4]. When compared to immunocompetent patients, immunocompromised patients also shed the virus for longer periods of time [1,3,5]. Nonetheless, to our knowledge no studies to date have reported cases of person-to-person transmission in this late shedding and, hence, the clinical and epidemiological significance has therefore remained unclear. However, there is evidence from other viral infections such as influenza and noroviral diarrhoea showing that severely immunocompromised patients may shed the virus and remain infectious for extended periods of time due to impaired clearance [6,7]. Current CDC [8] and ECDC [9] guidelines recommend the duration of isolation for severely immunocompromised COVID-19 patients to be up to 20 days. We present a case that infers prolonged infectiousness, even past 20 days, to be possible with immunosuppressed patients and posits it to be a matter of consequence especially in hospital settings.

Description

Patient A, a 73-year-old woman with diffuse large B-cell lymphoma and Waldenström macroglobulinemia, was exposed to COVID-19 on the 11th of December 2020. The patient had received her third course of rituximab, cyclophosphamide, doxorubicin and prednisone on the 1st of December and was chronically cytopenic due to the treatment and the bone marrow-affecting

malignancy itself. The patient developed fatigue on the 15th of December and on the 21st of December she was admitted to Tampere University Hospital (TaUH) oncology ward with fever and tested positive for COVID-19 (cycle thresholds [Ct] 28.71 for ORF1a/b target and 29.37 for envelope gene [E] target). The patient initially improved, and was discharged to home isolation.

On the 12th of January, 28 days after the onset of symptoms the patient was admitted to TaUH oncology ward to continue lymphoma treatment. The patient still reported fatigue and malaise. The 13th of January the patient became febrile and ceftriaxone was initiated. The patient shared a room with Patient B, a 77-year-old woman scheduled to receive radiotherapy together with rituximab and temozolomide for primary central nervous system lymphoma, for a total of 7 days.

On the 20th of January, Patient B was transferred to a secondary treatment facility where the patient had also resided prior to her visit to the oncology ward. On the 24th of January Patient B became febrile and tested positive for COVID-19 (Ct 13.20 for ORF1a/b and 13.31 for E). Patient A was still COVID-positive on the 30th of January (Ct 24.8 for E and 23.9 for RdRp) and was also found to be seronegative for IgG-antibodies against SARS-CoV-2 on the 25th of January, which may indicate an insufficient immune response. Eventually both patients succumbed to COVID-related respiratory failure.

Whole genome sequencing of the SARS-CoV-2 samples from these patients was performed using the ARTIC protocol [10] (Table 1), followed by phylogenetic analysis with Nextstrain [11] by the Expert Microbiology Unit of the National Institute for Health and Welfare. Both viruses were of the genetic lineage B.1.1.241 and nearly identical. Patient A's second sample, taken over a month after the first, was also nearly identical to the first and to patient B's sample. The sequences will be submitted to Gisaid database. These analyses support our postulate that Patient A, over 28 days after her initial symptoms,

Table 1. Sequence comparison: The variations on the left were observed in both samples when compared to the Wuhan reference strain.

Nucleotide variations in both samples vs Wuhan reference							Individual variations between samples			
C241T	C2695T	C3037T	C8092T	A11782G	C14408T	A17615G	Patient	Date of sample	Nt variations	Aa variations
G18538T	T21570G	C21575T	G22616T	A23403G	G24586T	T25473C	A	Dec 21st	0	0
G25526T	C28253T	C28472T	G28881A	G28882A	G28883C		B	Jan 24th	C5178T	ORF1a:T1638I
Amino acid variations in both samples vs Wuhan reference									C9491T	ORF1a:H3076Y
N:P67S	N:R203K	N:G204R	ORF1b:P314L	ORF1b:K1383R	ORF1b:V1691L	ORF3a:W45L	A	Jan 30th	C11454T	ORF1a:A3730V
									C5178A	ORF1a:T1638N S:S50L
									C21711T	
									C27911T	
S:V3G	S:L5F	S:A352S	S:D614G							

The variations on the right were observed between the individual samples. The first sample obtained from patient A serves as reference. Patient B's sample, obtained a month later, has very little variation suggesting direct progeny. Patient A's second sample obtained over a month after the first has acquired only three nucleotide variations, one of which is at the same locus as in Patient B's virus, further supporting A having remained infectious and infecting B, and opposing the possibility of reinfection from an unrelated source. The sequences will be submitted to Gisaid database.

infected patient B. Furthermore, contact tracing did not reveal any other possible sources for Patient B's infection since the Patient B's hospitalisation on the 21st of Dec. Patient A's reinfection was considered as a possibility, but is unlikely, since Patient B's strain was almost identical to Patient A's both samples and the two had not previously met.

Discussion

The implication is that severely immunocompromised patients, whose clearance of the virus is impaired, may remain infectious for extended periods. Caution should be taken particularly in hospital settings where lapses in isolation procedures might pose increased risk, especially to other immunocompromised patients. In the COVID-19 case described here, the 20 days of isolation was not sufficient. Furthermore, prolonged shedding may increase potential accumulation of point mutations up to emergence of new SARS-CoV-2 variants. Further studies are needed to ascertain this implication and to determine a sufficient duration of isolation for severely immunosuppressed patients. A reverse transcriptase polymerase chain reaction (RT-PCR) test may remain positive for a long time with poor correlation to infectivity or shedding of viable virus [2] and could lead to unnecessarily long isolation periods and delays in chemotherapy. SARS-CoV-2 antibodies may be of additional value in assessing a patient's ability to contain shedding and, thus, help determine the length of the isolation. Additionally, a new onset of fever on an immunocompromised individual, whose isolation has ended fairly recently, should prompt a reassessment of the duration of isolation procedures.

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Disclosure statement

None to declare.

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References

- [1] Cogliati Dezza F, Oliva A, Cancelli F, et al. Determinants of prolonged viral RNA shedding in hospitalized patients with SARS-CoV-2 infection. *Diagn Microbiol Infect Dis*. 2021; 100(2):115347.
- [2] Zapor M. Persistent detection and infectious potential of SARS-CoV-2 virus in clinical specimens from COVID-19 patients. *Viruses*. 2020;12(12):1384.
- [3] Hensley MK, Bain WG, Jacobs J, et al. Intractable Coronavirus Disease 2019 (COVID-19) and prolonged severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) replication in a chimeric antigen receptor-modified T-cell therapy recipient: a case study. *Clin Infect Dis*. 2021: ciab072.
- [4] Liang W, Guan W, Chen R, et al. Cancer patients in SARS-CoV-2 infection: a nationwide analysis in China. *Lancet Oncol*. 2020;21(3):335–337.
- [5] Aydililo T, Gonzalez-Reiche AS, Aslam SA, et al. Shedding of viable SARS-CoV-2 after immunosuppressive therapy for cancer. *N Engl J Med*. 2020;383(26):2586–2588.
- [6] Roosenhoff R, van der Vries E, van der Linden A, et al. Influenza A/H3N2 virus infection in immunocompromised ferrets and emergence of antiviral resistance. *PLoS One*. 2018;13(7):e0200849.
- [7] Davis A, Cortez V, Grodzki M, et al. Infectious norovirus is chronically shed by immunocompromised pediatric hosts. *Viruses*. 2020;12(6):619.
- [8] Centers for Disease Control and Prevention guidance for Discontinuation of Transmission-Based Precautions and Disposition of Patients with SARS-CoV-2 Infection in Healthcare Settings [updated 2021 Jun 2]. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/disposition-hospitalized-patients.html>.
- [9] European Centre for Disease Prevention and Control guidance for discharge and ending of isolation of people with COVID-19 [updated 2020 Oct 16]. Available from: <https://www.ecdc.europa.eu/sites/default/files/documents/Guidance-for-discharge-and-ending-of-isolation-of-people-with-COVID-19.pdf>.
- [10] Artic Network protocols for sequencing SARS-CoV-2. Available from: <https://artic.network/ncov-2019>.
- [11] Nextstrain database for pathogen genome data. Available from: <https://nextstrain.org>.