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# Successful Treatment of Persistent SARS-CoV-2 Infection in an Immunocompromised Patient

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## Introduction

The COVID-19 pandemic has been marked by long-term persistence of SARS-CoV-2 in immunocompromised patients receiving B-cell-depleting therapies, with many individuals experiencing fatal COVID-19.

- People infected with SARS-CoV-2 typically do not have detectable virus in their upper airway 14 days after symptom onset.[1]
- Long-term infections are characterized by:
  - SARS-CoV-2 RNA that remains detectable several months after disease initiation, and
  - the accumulation of high numbers of mutations demonstrating within-host genomic variation.[2]
- Rituximab, a B-cell-depleting therapy, targets the CD20 antigen expressed on the surface of B lymphocytes & can decrease the number of B-cells for over 6 months.[3]
  - Rituximab can increase the risk of infection, cause a delay in clearance of some infections, and has been shown to interfere with the development of specific antibodies to influenza and hepatitis B vaccinations.[4]
- Examples of positive outcomes can drive improved outcomes from infection in this population.

## Methods

### Sample Collection

- Nasopharyngeal swab specimens were collected on day 167 and day 185 of the patient's clinical course.

### Sequencing viral genomes

- Amplified viral genomes using ARTIC v4 and v4.1 primer sets.
- Amplicons were sequenced using Next-Generation Sequencing (NGS) with backup sequencing on a nanopore platform.
- Aligned the raw FASTQ files to the Wuhan Hu-1 reference sequence.
- Analyzed sequences for genomic variance over time at the consensus and sub-consensus level using SAMtools and LoFreq v2.1.3.1.

### Phylogenetic tree generation

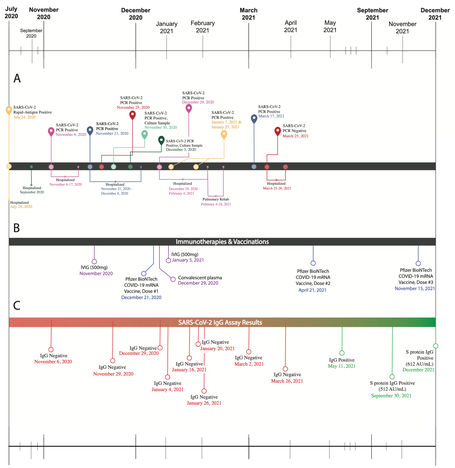
- All GISAID sequences labeled as B.1595.3 [N=39] were pulled on July 26, 2022.
- Retained sequences with lengths between 29000 and 31000 bp and fewer than 600 ambiguous sites (Ns) [N=35, including the patient's samples].
- Aligned sequences [N=35] using Nextclade.
- Generated the tree using default settings in IQtree.

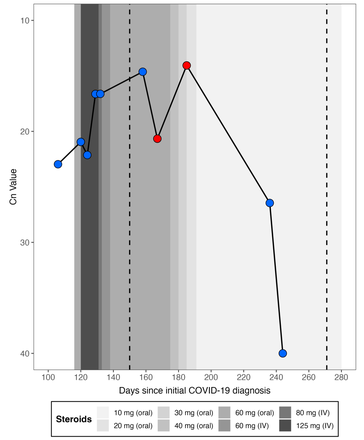
## Results

An individual with rheumatoid arthritis (RA) treated with azathioprine & rituximab (last dose in July 2020) was diagnosed with COVID-19 in July 2020 & admitted with pneumonia.

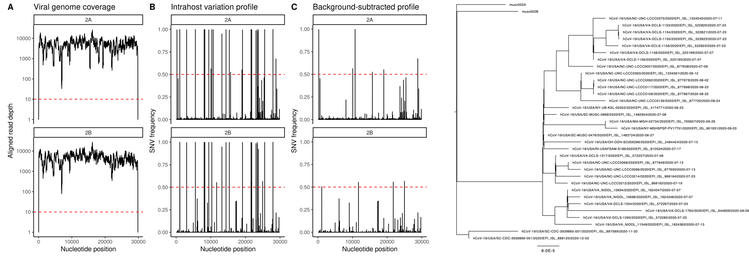
- **COVID-related treatments/vaccinations**: a 5-day treatment of remdesivir, intravenous immune globulin (IVIG), and corticosteroids for organizing pneumonia.
  - Readmitted to the ICU in December 2020 with persistent infection, and treated with a single dose of convalescent plasma, a second 5-day treatment of remdesivir, and baricitinib.
  - Received 3 doses of mRNA vaccine (Pfizer BioNTech) in December 2020, April 2021, and November 2021.
- Hospital course was complicated by CMV pneumonitis & *P. aeruginosa* bacteremia

**Figures**: Timelines of patient disease course, therapies & vaccinations, and results from assessment of antibody-based immune responses to SARS-CoV-2 (left); Cn Values Over Patient's Clinical Course of COVID-19 (right).




**Figures**: Sequencing coverage & variant accumulation in sequenced samples (left); Tree showing MUSC genomes in relation to other B.1.595.3 variants (right).




Viral sequencing over the course of illness indicated a persistent infection with a lineage B.1.585.3 virus that accumulated 14 mutations throughout the infection.

- Two mutations (S494P, S D737Y) are associated with therapy resistance and are similar to those found in other immunocompromised individuals with persistent COVID-19.
- Additional mutations were of unknown consequence.

## Conclusion

SARS-CoV-2 was able to establish persistent infection and accumulated mutations associated with therapeutic resistance.

- Cessation of B-cell-depleting therapy and weaning of corticosteroids was critical in achieving viral clearance of SARS-CoV-2 after more than 200-days of persistent COVID-19 infection.
- Repeated vaccination was associated with a delayed seroconversion in this patient with reversibly immunosuppression.

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