



Case Report

A prolonged Delta SARS-CoV-2 infection during the Omicron wave in an HIV immunosuppressed patient

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ARTICLE INFO

Article history:

Received 2 September 2025

Revised 14 November 2025

Accepted 14 November 2025

Keywords:

SARS-CoV-2

Immunosuppressed patient

Viral variants

Prolonged infection

ABSTRACT

Here, we describe a fatal, prolonged Delta SARS-CoV-2 infection lasting 55 days during the Omicron wave in a severely immunosuppressed HIV patient. We observed persistent viral replication, high within-host mutation rates, and emergence of rare spike mutations. Findings suggest prolonged infections may drive SARS-CoV-2 evolution and reintroduce variants presumed extinct into immune-evasive forms.

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Case description

We present the case of a 52-year-old man originally from the United Kingdom, resident in Tenerife (Canary Islands, Spain), diagnosed with a deep subcutaneous abscess in the left hemiface. After progressive worsening, the patient was hospitalized, and antibiotic treatment was started. On the same day, SARS-CoV-2 was first detected in a nasopharyngeal swab. However, he was not initially treated for COVID-19 as he had no respiratory or gastrointestinal symptoms.

During the same admission, he was diagnosed with HIV (T-CD4 lymphocyte count of 6/μL and a viral load of 2,700,000 copies/mL) and cytomegalovirus DNAemia (3,803 IU/mL). Treatment was initiated with tenofovir/emtricitabine/raltegravir and ganciclovir. Twenty-nine days after admission, a biopsy of the oral mucosa revealed diffuse large B-cell lymphoma, activated immunophenotype with multifocal involvement of the lungs, liver,

and brain, with treatment pending. The sample from the abscessed oral area was deparaffinized and tested positive for SARS-CoV-2 by PCR, although sequencing was not possible due to high cycle threshold (Ct) values.

Despite persistently testing positive for SARS-CoV-2 (Figure 1a), he received a 3-day course of remdesivir (day 30 after first SARS-CoV-2 detection) and a second 10-day course (day 50), but never tested negative by PCR. Infectious SARS-CoV-2 was cultured from samples collected on day 0 and 43, confirming active viral replication (see Supplementary material, Figure S1). Exitus occurred on day 55 after progressive clinical deterioration, persistent fever, and acute renal failure. More details on the clinical case are included in the Supplementary Materials.

Ten SARS-CoV-2-positive samples were sequenced during the patient's admission (Figure 1a). All sequences were classified as AY.7, a Delta sublineage that circulated in the Canary Islands from December 2021 to March 2022 (Supplementary material, Figure S2). All sequences showed an accumulation of mutations compared to the Wuhan-Hu-1/2019 reference, with 32 mutations present in the Spike (S) gene only (Figure S3). Viral mutation rate was high throughout infection (median mutation rate, defined as the number of nucleotide mutations of a sequence compared to the first

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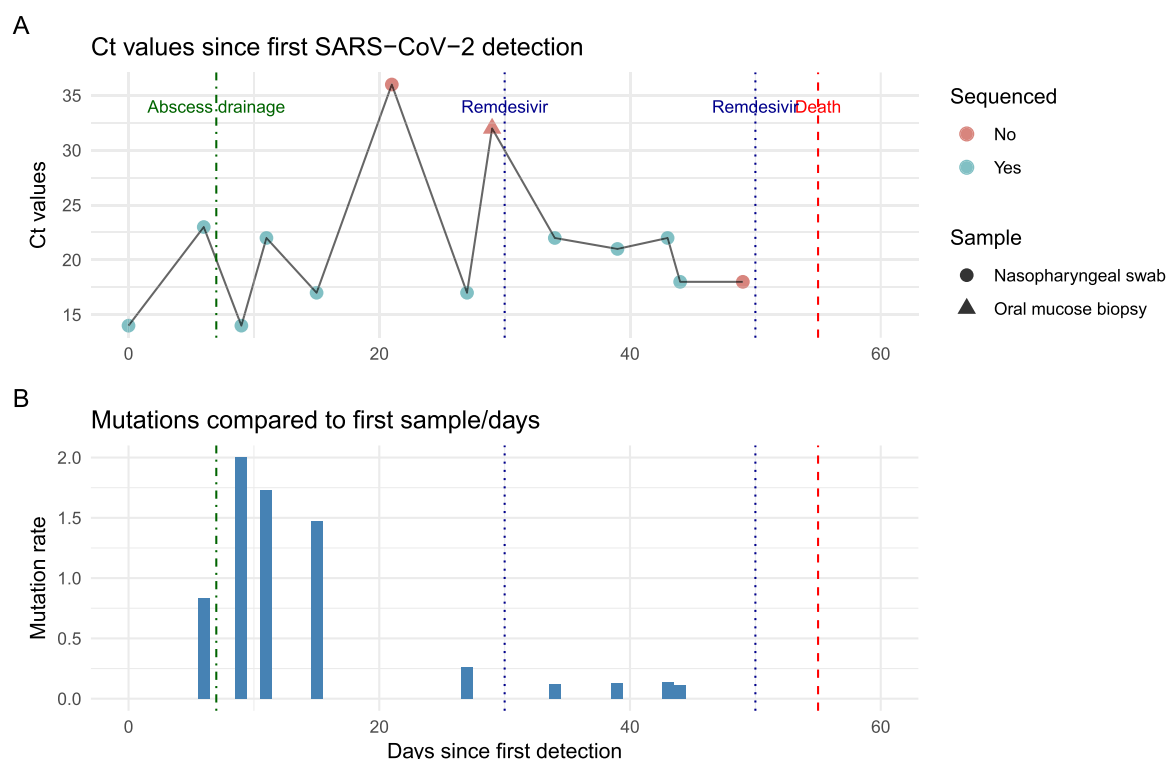


Figure 1. Longitudinal dynamics of SARS-CoV-2 cycle threshold (Ct) values and within-host mutation accumulation. (A) Temporal evolution of PCR Ct values obtained from respiratory and nonrespiratory samples. Each point represents a PCR result, colored by sequencing status and shaped by sample type. (B) Number of within-host mutations detected over time relative to the consensus sequence of the first sequenced sample. Dot-dash, dashed, and dotted vertical lines indicate the day of abscess drainage (green), remdesivir treatment (blue), and exitus (red), respectively.

collected sample, divided by days from detection of infection, was 0.26), with a peak reached between day 9 and day 15 (Figure 1b).

Phylogenetic analysis, including additional AY.7 sequences from the Canary Islands, placed the patient-derived sequences on a distinct, distant branch (Figure S4), suggesting independent evolution or prolonged within-host diversification. To rule out co-infection with multiple lineages, Viralflow analysis confirmed that only the AY.7 lineage was present in all samples. Almost all genomic positions corresponding to the Delta B.1.617.2 lineage-defining mutations showed an allele frequency of one, further supporting the presence of a single lineage (Figure S3). Of note, the Delta B.1.617.2 lineage-defining mutations S:T19R and S:T478K, and the additional mutation S:L452R, were replaced by S:T19K, S:T478E, and S:L452Q, respectively, in these samples (Figure S3). The co-occurrence of S:L452Q and S:T478E mutations in the receptor-binding domain (RBD) is extremely rare globally (33 sequences worldwide, according to outbreak.info; queried on 17/06/2025). The S:T477N and the S:T478E substitutions were only present in the consensus sequences corresponding to the samples at days 0, 9, 11, and 15. However, other aligned sequences show a drop in coverage in the region overlapping these two amino acids. Therefore, we cannot exclude that these mutations were also present in the sequences from the other time points. Other relevant mutations were present in the viral sequences isolated from this patient. The S:R346T and the S:N460K substitutions on the S gene RBD sequence were also present. These two mutations are usually found in Omicron sub-lineages - being the latter the lineage-defining mutation of BA.2.75 lineage - and are associated with neutralizing antibody escape [1,2]. The S:N439K change, although rare in Delta variants [3], confers resistance to monoclonal antibody treatment [4], as well as the S:V483A amino acid substitution [5,6]. Finally, the S:E484K mutation, widely recognized for its role in immune escape, was also detected [7] (Figure S3).

We did not detect any *de novo* amino acid substitutions over the course of infection (Figure S3). Instead, the apparent increase in mutation rate observed at days 9 to 15 (Figure 1b) could be explained by the temporary loss of pre-existing amino acid substitutions, followed by their reemergence at later stages. Allele frequency analysis supports this observation, showing that mutations not present in the consensus sequence remained detectable at lower allele frequencies at these time points (Figure S4, Figure S5), indicating that they persisted within the viral population rather than representing newly emerging mutations.

Discussion

We present a case of a prolonged Delta SARS-CoV-2 infection in an immunosuppressed patient with HIV during the Omicron wave in Tenerife (Canary Islands, Spain). The detection of a Delta variant case nearly a year after its last transmission in the community in the region is remarkable. Our data suggest the existence of a human reservoir, as previously described [8], and highlight the risk of reintroducing variants that are considered extinct or against which population immunity might have waned. The presence of 32 amino acid substitutions accumulated in the Spike is also notable. This S gene sequence resembles more the profile of an Omicron variant, described as having 26 accumulated amino acid substitutions, than that of a Delta variant, which presented only seven amino acid substitutions compared to the reference genome [9]. Furthermore, some of the amino acid substitutions are typical of an Omicron variant, suggesting the emergence of these mutations during infection progression. Patients with HIV are often characterized by prolonged SARS-CoV-2 infections, especially those with advanced disease, as having low CD4+ T cell counts leads to impaired adaptive immunity and viral clearance [10]. The resulting sustained viral replication provides opportunity for the virus to

evolve towards immune-evasive phenotypes, giving rise to mutations present in variants of concern (VOCs) that confer resistance to neutralizing antibodies [11,12]. Our findings support the hypothesis of the emergence of novel VOCs in prolonged infection in immunocompromised patients [11–13].

We did not see the emergence of novel amino acid substitutions throughout infection, something that was previously observed in other longitudinal studies in immunosuppressed patients [12–14]. This could be because we only captured a brief, end-stage of the infection, where all amino acid substitutions had already accumulated into the sequence during an earlier stage before December 27, 2022. The presence of a Delta lineage in a period where only Omicron was circulating supports this hypothesis, suggesting that this patient had a persistent infection starting earlier before attending the ED. In a recent study [15], the authors observed convergent amino acid changes characteristic of Omicron in an untreated HIV-positive patient originally infected with a B.1. lineage virus throughout an infection lasting more than two years. Our findings, together with prior research, highlight the importance of monitoring infections in immunosuppressed individuals, as these cases can provide valuable insights into viral evolutionary dynamics. They also underscore the need for effective treatment in these patients to limit opportunities for the emergence and spread of novel VOCs in the community.

Among the limitations of the study are that we could not capture earlier stages of infection to have a better picture of viral evolution, since this was limited by the time the patient sought medical attention. Furthermore, we cannot completely rule out that a Delta/Omicron coinfection occurred in this patient at any time, since genome sequencing was performed using a tiling PCR approach and all downstream analyses were based on consensus sequences and not on a sequence read basis.

Data availability

Generated consensus sequences were deposited to GISAID under the EPI_SET_250708ob available at <https://doi.org/10.55876/gis8.250708ob>.

Funding

This work was supported by Cabildo Insular de Tenerife [CGIEU0000219140, CGIAC0000014697 and Apuestas científicas del ITER para colaborar en la lucha contra la COVID-19]; by the agreements OA17/008 and OA23/043 with Instituto Tecnológico y de Energías Renovables (ITER) to strengthen scientific and technological education, training, research, development and innovation in Genomics, Epidemiological surveillance based on sequencing, Personalized Medicine and Biotechnology; Fundación Canaria Instituto de Investigación Sanitaria de Canarias [PIFIISC21/37, EMER24/06]; Fundación DISA [OA23/074]; Instituto de Salud Carlos III [PI20/00876, CD22/00138, CB06/06/1088], co-funded by the European Regional Development Fund, A way of making Europe from the EU; European Health and Digital Executive Agency [HADEA, 101113109 RELECOV 2.0]; and by Cabildo Insular de Tenerife and Consejería de Educación, Gobierno de Canarias [A0000014697].

Ethical approval

This study was approved by the Ethics Committee of the Hospital Universitario de Canarias in accordance with institutional and international ethical standards (CHUNSC_2024_48).

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

DGMA, LC, JAF and CF conceptualized and coordinated the study. RGM, NRG performed the sequencing experiments. JMLS and AMB conducted the bioinformatics analysis. LAV and SM carried out the viral culturing experiments. DGMA and LC performed data analysis and drafted the initial version of the manuscript. CF, JAF, RGM and LC obtained funding. All authors contributed to data interpretation and reviewed the manuscript.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ijid.2025.108233](https://doi.org/10.1016/j.ijid.2025.108233).

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