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Case Report

Post-acute COVID-19 syndrome after reinfection and vaccine breakthrough by the SARS-CoV-2 Gamma variant in Brazil

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ABSTRACT

We describe a case of prolonged COVID-19 caused by the SARS-CoV-2 Gamma variant in a fully vaccinated healthcare worker, 387 days after an infection caused by lineage B.1.1.33. Infections were confirmed by whole-genome sequencing and corroborated by the detection of neutralizing antibodies in convalescent serum samples. Considering the permanent exposure of this healthcare worker to SARS-CoV-2, the waning immunity after the first infection, the low efficacy of the inactivated vaccine at preventing COVID-19, the immune escape of the Gamma variant (VOC), and the burden of post-COVID syndrome, this individual would have benefited from an additional dose of a heterologous vaccine.

Introduction

With the ongoing pandemic, long-term manifestations are being observed in COVID-19 recovered patients. This is defined as Post-acute COVID-19 syndrome, characterized by the persistence of symptoms after 4 weeks from the onset of the disease. It presents a broad spectrum of manifestations, which may encompass all organs and systems and nonspecific symptoms (Nalbandian et al., 2021). The diagnosis is often hard to establish, the exact underlying pathophysiology mechanisms remain unknown (Greenhalgh et al., 2020), and the frequency of occurrence is not established.

As of August 2021, Brazil has the third-highest number of cumulative cases of COVID-19 worldwide (Oswaldo Cruz Foundation, 2021). In December 2020, the first confirmed case of reinfection was reported in the country, followed by several other cases, mostly caused by the Gamma variant of concern (VOC) among unvaccinated individuals (Brazilian Ministry of Health, 2021). Brazil's vaccination campaign started in January 2021, with adsorbed (inactivated) SARS-CoV-2 vaccine (CoronaVac-Sinovac/Butantan), administered in a two-dose schedule, with doses separated by a 28 day

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interval (Oswaldo Cruz Foundation, 2021). CoronaVac was the first vaccine available in Brazil, when healthcare workers (HCW) immunization was prioritized. By the end of August 2021, 27% of the country's population of 230 million had been fully vaccinated. Effectiveness of CoronaVac was around 65.9% for the prevention of COVID-19 in Chile (Jara et al., 2021) and 49.4% (95% CI 13.2 to 71.9) effective in the prevention of COVID-19 in HCW, in a setting of high prevalence of the Gamma VOC in Manaus, Brazil (Hitchings et al., 2021). These results were similar to that of a nationwide study of 61 million Brazilians which demonstrated that complete vaccination with CoronaVac in the general population was associated with a 54.2 (95% CI 53.4-55.0) lower risk of infection (Cerqueira-Silva et al., 2021).

The emergence of SARS-CoV-2 VOCs, facilitated by factors such as low vaccination coverage globally and sustained virus transmission, raised questions regarding the extent of protection provided by vaccination programs. Moreover, primary and secondary failure of inactivated vaccine to efficiently neutralize VOCs after complete vaccination course have already been described (Hunsawong et al., 2021; Yigit et al., 2021). Thus, genomic and immune response follow-up are crucial in evaluating the impact of VOCs while the pandemic persists. The present report describes a case of prolonged COVID-19 after breakthrough infection by SARS-CoV-2 Gamma VOC (P.1) more than a year after clinical infection by the B.1.1.33 lineage in a HCW fully vaccinated with CoronaVac in Brazil.

Case description

A healthy 43-year-old male HCW presented with fever, headache, rhinorrhea, and dry cough on April 5, 2020. Clinical manifestations disappeared after 14 days, and no hospitalization was necessary. COVID-19 was confirmed by RT-PCR of a nasopharyngeal sample, as previously described (Konrad et al., 2020). The SARS-CoV-2 B.1.1.33 lineage was identified by whole-genome sequencing. Briefly, the SARS-CoV-2 genome was assembled using established Illumina protocols (Resende et al., 2020). FASTQ reads were imported into the CLC Genomics Workbench version 20.0.4 (QIAGEN), trimmed, and mapped against the reference sequence EPI_ISL_402124 from the EpiCoV database at GISAID (www.gisaid.org): hCoV-19/Brazil/RJ-FIOCRUZ-1691-R1/2020 (EPI_ISL_2196361) and hCoV-19/Brazil/RJ-FIOCRUZ-21373-R2/2021 (EPI_ISL_2196251). The lineages were classified using the Pango Lineages tool (O'Toole et al., 2021).

On January 27, 2021 (nearly 9 months later), the patient received the first dose of CoronaVac followed by a second dose 28 days later. On April 26, 67 days after the second dose of CoronaVac, and 387 days after the first episode of COVID-19, the HCW developed a new episode of COVID-19 confirmed by RT-PCR (Figure 1. A-B). The lineage Gamma was identified by whole-genome sequencing more than a year after B.1.1.33 infection (Figure 1. C-D) (Guindon et al., 2010). The patient presented the same clinical manifestations and duration as in the first episode of COVID-19, except for headache and blurred vision, which persisted for 18 weeks beyond the acute infection episode with Gamma VOC. These findings were not attributable to any alternative diagnoses.

Spike protein specific immunoglobulin G (anti-S IgG) was under the detectable range five months after the initial infection (September 9, 2020), but still present two months after the second dose of vaccine (April 27, 2021) and ten days after reinfection (May 6, 2021) (Figure 1.B). The humoral response to SARS-CoV-2 after reinfection was confirmed by a highly specific plaque reduction neutralization test ($PRNT_{90}$) for SARS-CoV-2. Inactivated serum samples presented high neutralizing antibodies (Nabs) titers for B.1.1.33 (320), Gamma (320), and Delta (160).

Discussion

This case illustrates that even after complete vaccination the continuous exposure of HCWs to SARS-CoV-2 can lead to breakthrough infection. Furthermore, unlike the first infection, the clinical presentation of SARS-CoV-2 upon reinfection was characterized by persistent neurological symptoms.

Our data suggest rapid waning of binding antibodies by the absence or low levels of anti-S IgG after the infection with B.1.1.33, but presence of highly specific Nabs for B.1.1.33, Delta and Gamma VOCs, after complete vaccination following a second episode of COVID-19.

Whether the HCW developed Nabs after full immunization with CoronaVac remains unknown. Usually, individuals with pre-existing immunity develop uniformly high neutralizing antibody responses (Reynolds et al., 2021). Although it is not clear which qualitative and quantitative parameters could be used as an adequate correlate of protection and its duration, this HCW was not protected against reinfection. We hypothesize that this is probably due to absent post-infection virus neutralizing activity, a short-lived humoral immune response, and the circulation of new variants capable of escaping immune responses generated by the first infection (Fintelman-Rodrigues et al., 2021), and by the immunity rendered by two doses of CoronaVac. Although Nab appears to protect against symptomatic infection, the minimum titers necessary for conferring immunity to SARS-CoV-2 are a topic of ongoing research.

The patient had no known comorbidities. The only factor that could explain the multiple episodes of COVID was his permanent exposure to SARS-CoV-2. His reinfection occurred more than a year after the primary infection, time expected for waning of protection following natural infection by SARS-CoV-2 (Hall et al., 2021). As expected in vaccinees, the patient did not develop acute critical illness, confirming the efficacy of CoronaVac in reducing the risk of severe disease and death at a time when the Gamma variant accounted for 96% of circulating genotyped SARS-CoV-2 specimens (Hitchings et al., 2021). Nevertheless, the patient required long-term specialized care because of post-COVID-19 syndrome.

As of August 2021, social distancing measures were relaxed and vaccinated individuals have engaged more frequently in social activities, increasing their risk of exposure to SARS-CoV-2 and breakthrough infections globally. Moreover, it is of concern that vaccines currently being used in Brazil, including CoronaVac, barely prevent infection and transmission, contributing to the persistence of the pandemic, particularly in the current scenario of predominantly highly transmissible Delta VOC, the prevalence of which has increased from 48% in July to 86% in August 2021. It is thus highly advisable that SARS-CoV-2 surveillance and intervention programs aimed at reducing viral exposure continue until an adequate proportion of the population is fully vaccinated, especially considering the emergence of new VOC that may compromise vaccine efficacy.

Considering the permanent exposure of this healthcare worker to SARS-CoV-2, the waning immunity of first infection, the low efficacy of inactivated vaccine in the prevention of COVID-19, the immune escape of Gamma variant (VOC), and the burden of post-COVID syndrome, this individual would have benefited from an additional dose of a heterologous vaccine.

In the epidemiological setting of low immunization rates and high transmission rates of SARS-CoV-2, the breakthrough reinfection with a VOC in an HCW is particularly timely and may presage trends in reinfection and hospitalization across Latin America, as we enter the third year of the pandemic. As vaccine supply chain limitations ease, evidence-based decisions about boosting are urgently required. In addition, better understanding of immune factors potentially associated with persistence of COVID-19 symptoms might help the management of this condition.

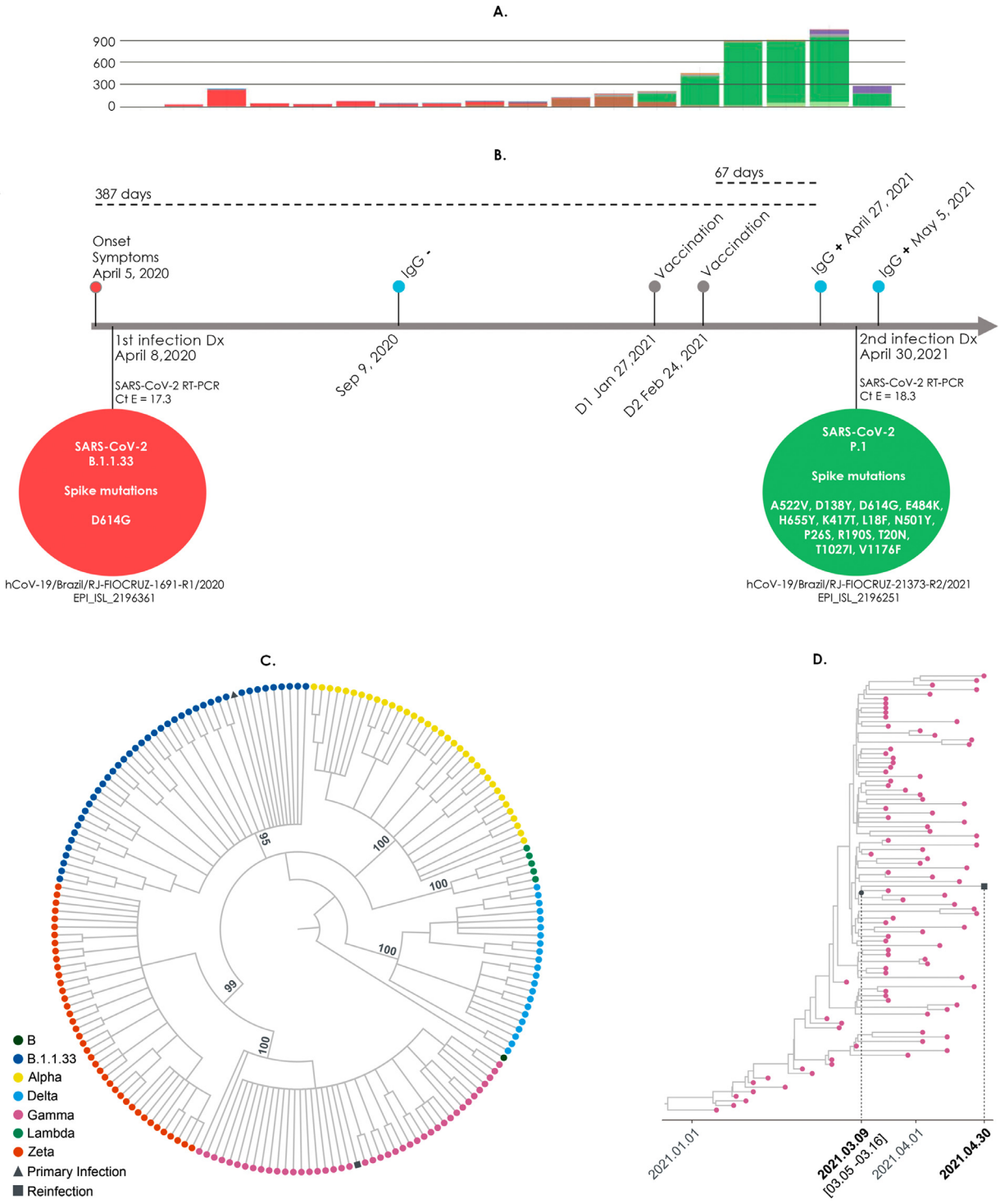

Figure 1. A. Frequency of SARS-CoV-2 lineages in the state of Rio de Janeiro (Source COVID-19 FIOCRUZ Genomic Network http://www.genomahcov.fiocruz.br/presenca-das-linhagens-por-estado/). **B.** Timeline of SARS-CoV-2 P.1 Gamma reinfection case and antibody status. **C & D** Phylogenetic and temporal characterization of SARS-CoV-2 genomes recovered from primary infection and from reinfection episode. **C.** Maximum Likelihood tree (n = 189) constructed with IQ-TREE2 of Brazilian SARS-CoV-2 whole genome sequences (29,415 nts.) (*6*). Primary infection and reinfection samples are highlighted by their shapes. B.1.1.33, Alpha (B.1.1.7), Delta (B.1.617.2), Gamma (P.1), Lambda (C.37) and Zeta (P.2) lineages have their statistical support (aLRT, average likelihood ration test) indicated in their corresponding branches. The tree was rooted with a B lineage reference sequence from Wuhan, China. **D.** Time-scaled Bayesian MCC tree of whole genome sequences inferred with Beast 1.10 from Brazilian SARS-CoV-2 Gamma variant (n = 100). The reinfection sample and its MRCA (Most Recent Common Ancestor) are both highlighted by their shapes. The collection date and the date to which the MRCA was traced back to (alongside its 95% HPD interval) are both annotated in the timeline in the bottom of the tree. The MRCA (Most Recent Common Ancestor) of the reinfection genome was traced back to early March 2021 [2021.03.09 (95%HPD: 2021.03.05 – 2021.03.16)], therefore significantly distinct, even its lower limit, from the patient's first notified SARS-CoV-2 infection.

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Potential conflict of interest

The authors have indicated they have no potential conflicts of interest to disclose.

Financial disclosure

The authors have indicated they have no financial relationships relevant to this article to disclose.

Ethical considerations

This case is part of a cohort study of COVID-19 patients where immunity and genomic surveillance of SARS-CoV-2 are evaluated, with systematic collection of blood and respiratory tract samples. Informed consent was obtained from all the participants. The study was approved by the Brazilian National Ethics Committee (CONEP) under register number 30639420.0.0000.5262.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2021.10.048.

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