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Persistent COVID-19 Infection In A B-Cell Depleted Patient With Successful Viral Clearance After Tixagevimab-Cilgavimab

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Abstract

Background: Patients receiving B-cell depleting regimens are at increased risk of persistent COVID-19. Selecting effective treatments for these patients becomes challenging with new viral mutations conferring resistance to available targeted therapies.

Case presentation: We describe a case of persistent COVID-19 in a patient under rituximab for ANCA-associated vasculitis. She obtained a first positive PCR test in April 2022. Over the following 115 days, she was hospitalized twice for worsening fever and respiratory symptoms which resolved transiently with remdesivir. PCR tests were positive for the Omicron BA.2 variant of SARS-CoV-2 throughout the two hospitalizations. Viral persistence rather than re-infection was confirmed using viral genomic sequencing. The patient received tixagevimab-cilgavimab at the end of her second hospitalization, and subsequently obtained negative PCR results.

Conclusion: Persistent COVID-19 should be rapidly suspected in immunocompromised individuals with symptom recurrence following recent COVID-19 infection. Anti-SARS-CoV-2 monoclonal antibodies may be a potentially effective treatment of persistent infections in this patient population.

Keywords: COVID-19; Rituximab; Antibodies, Monoclonal

Introduction

Prolonged SARS-CoV-2 viremia and increased mortality have been documented in immunosuppressed hospitalized individuals [1-3]. B-cell depleting regimens are commonly used in the treatment of autoimmune diseases and malignancies. Since the beginning of the pandemic, authors have reported impaired vaccine antibody response[4,5] and cases of persistent COVID-19 infections [6,7] in patients receiving anti-CD20 agents. Selecting effective therapies for viral clearance in these patients is difficult with emerging viral mutations and resistance against existing therapies [8]. Previously reported treatments achieving clinical recoveries include various combinations of viral nucleoside analogs, convalescent plasma, corticosteroids, immunomodulatory and anti-SARS-CoV-2 monoclonal antibodies (MoAb). Herein we describe the case of a patient receiving rituximab for ANCA-associated vasculitis who developed persistent infection with SARS-CoV-2 Omicron BA.2 variant despite sotrovimab and remdesivir. The infection subsequently resolved after administration of tixagevimab-cilgavimab, an anti-spike MoAb recently introduced for COVID-19 prophylaxis in individuals at increased risk of

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inadequate response to vaccines and for COVID-19 inpatient treatment [9,10]. Viral persistence throughout the clinical course, rather than re-infection, was confirmed by viral genotyping. In view of evolving patterns of viral resistance, our case highlights the need for effective treatment of SARS-CoV-2 infection in severely immunocompromised hosts.

Methods

Patient consent

Informed verbal and written consent was obtained from our patient during her hospitalization.

Case Presentation

Clinical presentation

A female patient in her fifties was referred for hospitalization for a non-resolving COVID-19 infection. She had a history of controlled granulomatosis with polyangiitis (GPA) for which she was immunosuppressed with rituximab every 6 months, methotrexate, and prednisone. She received four doses of monovalent mRNA COVID-19 vaccines, the last dose on February 15th, 2022. She developed progressive dyspnea, cough, myalgias and anosmia and first tested positive for SARS-CoV-2 by PCR on April 10th, 2022. Her last dose of rituximab was on March 16th 2022, 25 days prior to this first positive test. Symptoms persisted despite treatment with sotrovimab on day 4 following her positive test. She received azithromycin and levofloxacin for possible bacterial pneumonia on days 18 and 41, and was hospitalized on day 45 for worsening symptoms. Figure 1 illustrates the patient's clinical evolution and administered treatments.

Upon hospital admission, she was febrile and had an oxygen saturation of 93% at room air. She had no symptoms of GPA flare-up. Initial chest radiographs showed increased multifocal ground glass opacities and left peri-hilar alveolar infiltrates compatible with bacterial superinfection of the initial COVID-19 pneumonia. Piperacillin-tazobactam was initiated. A nasopharyngeal SARS-CoV-2 PCR test was positive. Blood serology showed positive COVID-19 anti-spike IgG (NADAL COVID-19). Despite broad spectrum antibiotics, c-reactive protein (CRP) levels increased to 134 mg/L. A chest CT-scan showed bilateral multilobar alveolar and ground glass opacities, without parenchymal nodules to suggest a vasculitis. ANCA titers were negative. On day 48, the patient became hypoxemic and needed 1.5 L/min of oxygen. CRP increased to 233 mg/L, and repeated chest radiograph showed marked progression of lung infiltrates. Persistent or recurrent COVID-19 infection were considered the most likely diagnoses, and a dose of tocilizumab 560 mg was administered. PCR test was positive again, with a cycle threshold (Ct) of 21. An angio-scan was performed, showing no pulmonary embolism and further progression of lung opacities. Bronchoscopy was performed and ruled out alveolar hemorrhage. Cultures for common bacteria, viruses and opportunistic pathogens in the broncho-alveolar lavage were negative. A 10-day course of dexamethasone and remdesivir was started, with rapid decrease of CRP levels and weaning of supplementary oxygen. The patient was discharged home at the end of the treatment.

Five days after discharge, the patient came back to the hospital for recurrent symptoms of malaise, cough and dyspnea. Her temperature was 40 °C, oxygen saturation was 92% at room air and CRP levels were at 162 mg/L. SARS-CoV-2 PCR test was positive again (Ct 25.1). Chest radiograph showed a new right upper lobe alveolar consolidation. Administration of piperacillin-tazobactam and azithromycin resulted in no improvement. A second 10-day course of remdesivir led to gradual resolution of fever and respiratory symptoms. After treatment with remdesivir, a dose of tixagevimab-cilgavimab 300-300 mg was administered and the patient was discharged home.

After this second hospitalization, the patient presented no recurrence of fever nor respiratory symptoms. However, she developed persistent hearing impairment in her left ear, was diagnosed with post-COVID-19 sensorineural hearing loss and treated with steroids. She obtained positive SARS-CoV-2 PCR tests on days 94 (Ct 30.8), 101 (Ct 28.5) and 108 after her first positive test. She obtained first negative PCR test on day 115. A second dose of tixagevimab-cilgavimab was given in December 2022, 6 months after her first dose. Her maintenance Rituximab therapy, initially scheduled in September 2022, was held and planned to be reassessed after her second dose of tixagevimab-cilgavimab.

Complementary microbiological analyses

SARS-CoV-2 viral genomic sequencing was performed to support or refute the COVID-19 infection persistence hypothesis (Figure 2). Three distinct positive clinical samples temporally covering both hospitalizations could be retrieved and sequenced. All samples were confirmed to contain Omicron BA.2 variant. We observed sequential accumulation of single nucleotide polymorphisms (SNPs) in the infective strain but within host diversity remained below previously proposed thresholds of transmission, suggesting persistence rather than reinfection with multiple distinct viral strains [11,12]. All viral sequence files are accessible on GenBank (Accession No OQ305820, OQ305821 and OQ305822).

Discussion

Previous reported cases of persistent COVID-19 infections in immunocompromised patients [3,6-8] illustrate the challenges in the diagnosis and treatment of COVID-19 in this population. Fever or respiratory symptoms in such patients present a large differential diagnosis with many infectious and auto-immune causes, prompting the start of time-consuming empirical treatments and investigations.

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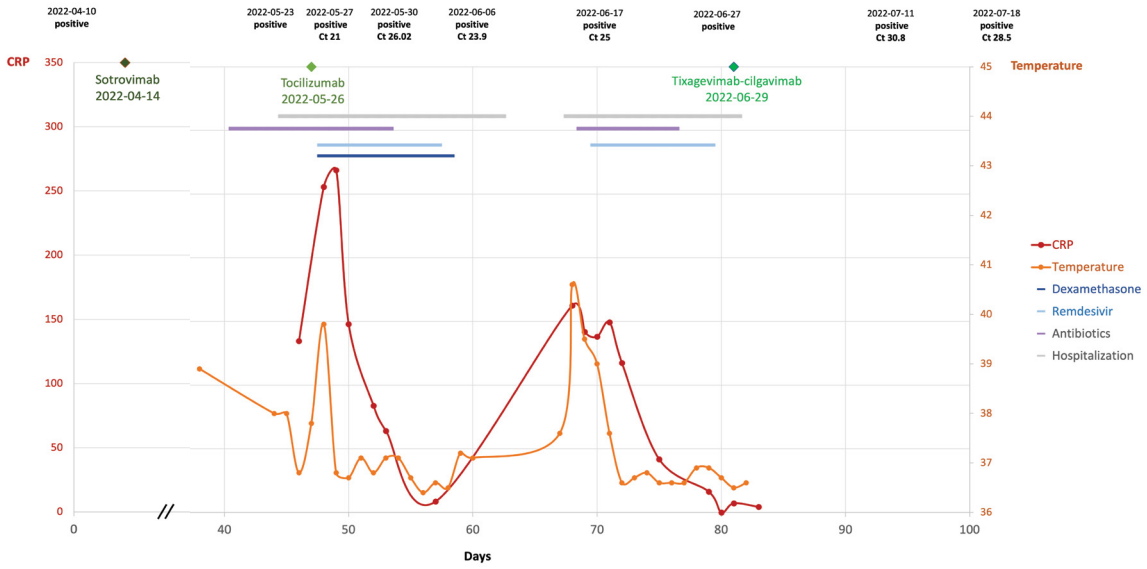

Figure 1: Clinical course, laboratory evolution and treatments. Figure 1 - Ct; cycle threshold.

A.

	Wuhan Reference	Patient BA.2 / 2022-05-30	Patient BA.2 / 2022-06-17	Patient BA.2 / 2022-06-22
Wuhan Reference	0			
Patient BA.2 / 2022-05-30	47	0		
Patient BA.2 / 2022-06-17	70	1	0	
Patient BA.2 / 2022-06-22	44	2	1	0

B.

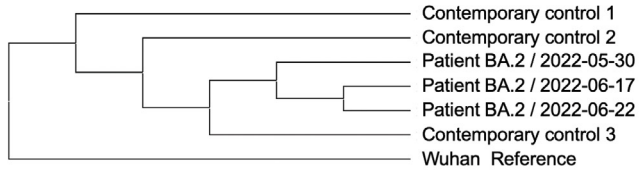

Figure 2: SARS-CoV-2 viral genomic analysis. Figure 2-Viral genomic distance matrix (A) and most likelihood phylogenetic tree (B). Patient's viral SARS-CoV-2 strain sequentially accumulated 1 (2022-06-17) and 2 (2022-06-22) single nucleotide polymorphisms compared to the anterior (2022-05-30) sequenced isolate. As expected, the patient's 3 sequenced isolates are clustered together among randomly selected contemporary hospital and community isolates.

COVID-19, whether a first, recurrent or persistent episode, should be rapidly suspected in these patients. We demonstrated by viral sequencing that our patient presented a persistent infection with Omicron BA.2 variant despite treatment with sotrovimab and two courses of remdesivir, and that effective viral clearance was finally achieved 115 days after her initial infection, following an infusion of tixagevimab-cilgavimab.

Immunocompromised patients' responses to various antiviral agents generate interesting hypotheses on the mechanisms of their impaired viral clearance. Remdesivir is a widely used nucleotide analog targeting SARS-CoV-2 viral replication reducing the time to recovery and progression towards severe forms of COVID-19 in hospitalized patients [13,14]. Our patient, like other patients under chemotherapy with COVID-19 [15,16], showed transient symptom resolution with remdesivir and recurrence of disease shortly after discharge. This clinical evolution suggests a marginal benefit of remdesivir in viral clearance, potentially serving as an adjunct to host immunity which likely plays a more central role.

Passive immunization is also important for viral clearance in immunocompromised individuals [17]. In patients under anti-CD20 therapies with persistent COVID-19, negative PCR results have been obtained after anti-spike monoclonal antibodies (MoAbs) casirivimab-imdevimab [6] and sotrovimab [7]. However, emerging variants are becoming resistant to previously effective MoAb. A work by Iketani et al. reported resistance of the Omicron BA.2 variant to 17 of

the 19 existing MoAb, including casirivimab-imdevimab and sotrovimab [8]. In concordance with these findings, our patient developed persistent infection with Omicron BA.2 despite sotrovimab. In Iketani's study, Omicron BA.2 remained sensitive to tixagevimab-cilgavimab. Although tixagevimab-cilgavimab was effective in preventing COVID-19 for up to 6 months as a prophylaxis [9], it did not lead to sustained recovery from COVID-19 in hospitalized patients (ACTIV-3 trial) [10]. However, this latter trial was conducted in the COVID-19 pandemic with the Delta variant. Furthermore, only 1% of patients were receiving biological agents for cancer or auto-immune disease. Its results thus may not reflect the potential benefits of tixagevimab-cilgavimab for Omicron BA.2 in this specific population. To our knowledge, our patient is the first reported patient under rituximab with persistent Omicron BA.2 infection obtaining negative PCR result after tixagevimab-cilgavimab, suggesting the potential role of this MoAb as a treatment of persistent infection with the Omicron BA.2 variant. Recent works demonstrated increased antibody evading properties for newer SARS-CoV-2 variants against existing MoAbs, highlighting the need and potential to develop new therapeutic MoAbs [18]. Studies including novel MoAb and larger numbers of patients under specific immunomodulating therapies are warranted to validate the efficacy of upcoming anti-SARS-CoV-2 MoAbs in these populations.

Lastly, our patient's lack of progression towards severe COVID-19 is also to be underlined. Although remdesivir likely contributed to this milder evolution, most reported cases of persistent COVID-19 in B-cell depleted patients are of light to moderate severity, with some describing short infections with little symptoms even without remdesivir [19,20]. While antibody responses seem to be key in viral clearance, they have also been hypothesized to mediate the hyperinflammation storms causing severe COVID-19 [17,21]. Impaired humoral immunity may therefore put patients at risk of persistent but milder infections. Further studies are required to clarify the specific mechanisms of humoral immunity in viral clearance and hyperinflammation.

Our case report presents several limitations. We did not perform serum viral RNA, which is correlated with active viral replication and severity of disease [22]. We performed serum anti-spike IgG once early in the disease course, but did not follow its variations. However, our early positive IgG result was possibly due to recent administration of sotrovimab, restricting its interpretation. We did not order Ct values on all our nasopharyngeal swabs, and thus obtained results are of limited value compared to other markers such as CRP and body temperature.

In conclusion, our patient is the first reported case of persistent COVID-19 infection with Omicron BA.2 variant in a patient under rituximab with viral clearance after tixagevimab-cilgavimab. We confirmed viral persistence rather than re-infection using viral genomic typing, highlighting the risk for persistent COVID infection in immunosuppressed patients. Our patient's recovery with postexposure tixagevimab-cilgavimab suggest the potentially effective role of anti-SARS-CoV-2 MoAbs as a treatment of persistent COVID-19 in immunocompromised patients. In view of the rapidly evolving resistance patterns of SARS-CoV-2, point-of-care viral genotyping to guide treatment is desirable for cases of persistent infections, especially in immunocompromised hosts.

Other Information

Data availability

All data underlying the results are available as part of the article and no additional source data are required.

Authorship Contribution

Conceptualization: Madeleine Durand, Qi Li, Simon Grandjean Lapierre, Karima Zerrouki

Data collection: Karima Zerrouki, Qi Li

Writing, original draft: Qi Li, Karima Zerrouki

Molecular analysis: Floriane Point, Simon Grandjean Lapierre

Reviewing and editing: Madeleine Durand, Simon Grandjean Lapierre

Supervision: Madeleine Durand, Simon Grandjean Lapierre

Disclosure

We disclose no financial or personal relationships with other people or organizations that could inappropriately influence this work. All authors qualify for authorship as per ICMJE recommendations.

All authors review the final manuscript before submission for peer review.

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