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CASE REPORT

Prolonged Viral Shedding and Multiple Admissions Due to SARS-CoV-2-Associated Pneumonia in a Patient with Chronic Lymphocytic Leukemia: A Case Report

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ABSTRACT

We describe a case of a patient who experienced recurrent COVID-19 pneumonia over a period of 123 days. Neither remdesivir nor convalescent plasma were temporally associated with viral clearance or increased plasma neutralization capacity. Antibody levels remained low until day 151 and cellular immunity increased overtime with no viral evolution.

Keywords: SARS-CoV-2; Prolonged viral shedding; Chronic lymphocytic leukemia

Abbreviations

PaO₂/FiO₂ ratio: Ratio of arterial oxygen partial pressure (PaO₂ in mmHg) to fractional inspired oxygen (FiO₂ expressed as a fraction, not a percentage); CRP: C-Reactive Protein; LDH: Lactate Dehydrogenase; IL-6: Interleukin 6; DXM: Dexamethasone; CP: Convalescent Plasma; VL: Viral Load

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Introduction

While most non-immunocompromised subjects effectively clear SARS-CoV-2 infection in less than 10 days [1], there are several reports of prolonged viral shedding associated with immunosuppressive status [2,3]. The adaptive immune system (B cells, CD4⁺ and CD8⁺ T-cells) and neutralizing antibodies are important factors to control viral infections, including SARS-CoV-2 [4]. Chronic Lymphocytic Leukemia (CLL) is a cause of immunosuppressive status due to impaired humoral and cellular immunity [5], involving both innate and adaptive immune responses. In addition, type, duration, number and combinations of therapies, including rituximab or venetoclax [6,7], also contribute to immune suppression in subjects with CLL.

Many uncertainties persist around the management of COVID-19 in immunocompromised patients with hematological malignancies [8]. We report a case of recurrent SARS-CoV-2 infection in a patient with CLL with previous exposure to rituximab and following third-line treatment with venetoclax, a selective BCL-2 inhibitor molecule and BH-3-only mimetic [6]. We describe the clinical characteristics of this patient, as well as the evolution of humoral and cellular mediated immune responses over time.

Material and Methods

SARS-CoV-2 viral load was quantified from nasopharyngeal swab samples by reverse transcription quantitative PCR (RT-qPCR). The presence of anti-SARS-CoV-2 antibodies in plasma samples was evaluated using an in-house sandwich-ELISA. Both HIV reporter pseudoviruses expressing SARS-CoV-2 spike protein and luciferase were used for the virus neutralization assay. The T-cell response was determined by IFN γ ELISpot assay using 30 peptide pools covering the spike, membrane, nucleocapsid and nsp3 regions of SARS-CoV-2 proteome. Viral genome sequencing was performed to evaluate the development of spike mutations and intra-host virus evolution (supplementary methods). Every convalescent plasma unit was obtained by plasmapheresis procedure from donors, containing a volume of 220–315 mL, anti-SARS-CoV-2 anti-Spike IgG ($\geq 20,000$ AU/ml) and residual leukocytes ($< 1 \times 10^6$ /L). Blood group and Rh (D) and negative infectious markers were identified prior to infusion, according to current regulations and recommendations. The patient provided written informed consent before sampling.

Case Description

Patient was a 64-year-old female with medical history of chronic hypertension and left lung tumorectomy secondary to stage Ib lung adenocarcinoma, in remission since 2015. She was diagnosed with CLL in 2015 and was treated with

rituximab, fludarabine and cyclophosphamide in 2016, acalabrutinib between September 2017 and March 2020, and venetoclax (400 mg QD) from July 2020 onwards.

A nasopharyngeal RT-PCR test for SARS-CoV-2 was positive on February 7 2021, following a contact-tracing study. The patient started presenting with fever up to 39°C and cough on February 18. After experiencing worsening symptoms, she was admitted on February 27 with bilateral opacities revealed by chest X-ray (Figure 1a). Treatment with remdesivir (five days), dexamethasone (6 mg/day) and prophylactic enoxaparin were administered. Subsequently, the patient experienced clinical improvement and was discharged on March 3, her treatment thereafter being dexamethasone for ten days and prophylactic enoxaparin.

Forty-eight hours after discharge, the patient started feeling shortness of breath on exertion, asthenia and fever up to 39.3°C, being admitted with ARDS and new radiographic opacities (Figure 1b) on March 14. RT-PCR testing for SARS-CoV-2 was still positive (Cycle Threshold (Ct): 22). During the following days, non-invasive mechanical ventilation was started with a fraction of inspired oxygen (FiO₂) of 100%. Oxygen, remdesivir and dexamethasone were started again, and prophylactic enoxaparin was maintained. The subsequent evolution was satisfactory, and she was discharged for a second time on March 20, with radiological improvement and without supplementary oxygen.

On April 1, the patient again experienced fever up to 39°C, chills, profuse sweating, asthenia and cough. She was admitted to hospital for a third time on April 7 because of a new COVID-19 pneumonia and ARDS (Figure 1c). A SARS-CoV-2 RT-PCR test was positive (Ct: 23.5). The same treatment regimen with oxygen, remdesivir and dexamethasone was followed and, additionally, one unit of Convalescent Plasma (CP) was administered on April 10. After experiencing progressive improvement, she was discharged asymptomatic on April 18.

Once again, on April 27 she presented with asthenia, dysthermia, dyspnea and cough. A new RT-PCR test result was positive (Ct: 25.7) and, due to clinical aggravation, she was admitted on April 30 with ARDS and radiological progression compared to previous findings (Figure 1d). **Supplementary** oxygen, remdesivir, dexamethasone and prophylaxis with enoxaparin were administered, followed by a second unit of CP on April 29. She was discharged on May 5 after a favorable evolution, with two more scheduled CP infusions every fourteen days. Finally, on July 6 2021, 151 days after the first positive RT-PCR test for SARS-CoV-2 and following four hospital stays in which the patient underwent the standard treatment regimen for COVID-19 pneumonia and the administration of four units of CP, a non-detectable RNA result was confirmed, accompanied by complete clinical recovery.

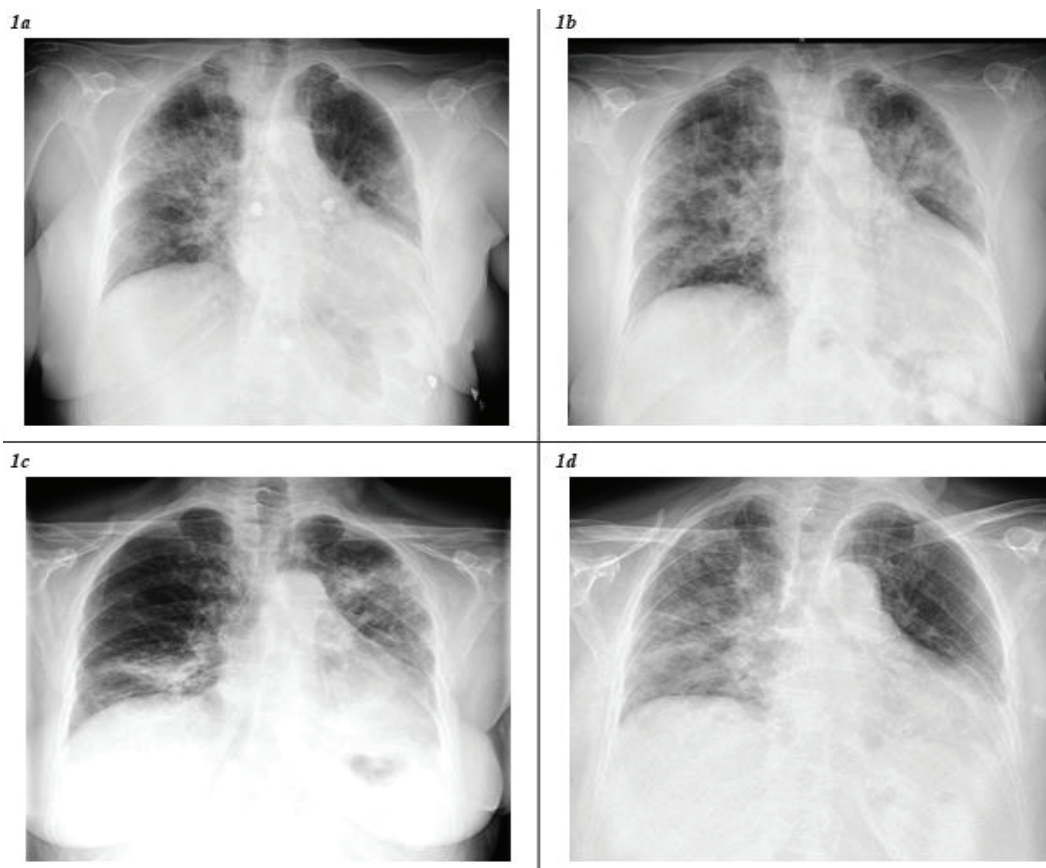


Figure 1 Radiological evolution of SARS-CoV-2 infection at each hospital admission.

1a). February 27, 2021: PaO₂/FiO₂ ratio 248; Lymphocytes 0.551/x10³/μl; CRP 125.6 mg/L; D-Dimer 923 ng/ml; LDH 440 U/L; IL-6 36.32 pg/ml; Ferritin 174 ng/ml.
1b). March 14, 2021: PaO₂/FiO₂ ratio 238; Lymphocytes 0.5/x10³/μl; CRP 209.4 mg/L; D-Dimer 1203 ng/ml; LDH 574 U/L; IL-6 36 pg/ml; Ferritin 329 ng/ml.
1c). April 7, 2021: PaO₂/FiO₂ ratio 276; Lymphocytes 0.703/x10³/μl; CRP 152.9 mg/L; D-Dimer 695 ng/ml; LDH 416 U/L; IL-6 30.74 pg/ml; Ferritin 328 ng/ml.
1d). April 30, 2021: PaO₂/FiO₂ ratio 257; Lymphocytes 0.585/x10³/μl; CRP 132.5 mg/L; D-Dimer 864 ng/ml; LDH 393 U/L; IL-6 37.5 pg/ml; Ferritin 352 ng/ml.

Discussion

In the case of SARS-CoV-2 infection described here, whereas consecutive treatments with remdesivir and dexamethasone in accordance with international guidelines were associated with clear clinical improvements consistent with clinical trial results [9,10], neither remdesivir nor CP infusion were associated with SARS-CoV-2 Viral Load (VL) reductions (Figure 2a). Nasopharyngeal RT-PCRs showed fluctuating but persistent, high-level viremia up to 123 days after the initial diagnosis, becoming aviremic by day 151. In fact, SARS-CoV-2 VL at hospital discharge was higher than VL at admission in at least three of the four COVID-19 episodes. This incomplete viral clearance of SARS-CoV-2 could be due to secondary impairments in the humoral and cellular adaptive immune responses associated with CLL, as well as previous treatments including rituximab [7]. In addition, immunosuppressive effects of dexamethasone could have also contributed to increase and/or prolong viral shedding [11].

Limited data from case reports and observational studies suggest a potential benefit of CP in immunosuppressed

patients, including those with CLL [6,12]. In our patient, however, IgG/A/M anti-S2 + RBD SARS-CoV-2 antibodies (in-house sandwich ELISA) remained low until day 151, when IgG and IgM (but not IgA) increased. CP infusion was not associated with increased plasma neutralization capacity as titers remained mostly < 3.0log₁₀ (Figure 2b), and it did not have a discernible clinical impact, which calls into question its usefulness for preventing new relapses. This is consistent with results from clinical trials in which CP was not effective for the treatment of hospitalized patients with COVID-19 [13].

A progressive increase in serum levels of first IgM and then IgG was found. This, however, was observed later than usually observed in non-immunosuppressed subjects [14] and in spite of there being undetectable levels of B lymphocyte in peripheral blood during monitoring. This suggests that B-lymphocytes located in compartments other than the blood, despite being dysfunctional, may be able to produce antibodies against SARS-CoV-2, albeit later than in the immunocompetent population (Figure 2c). In addition, an increase in the cell-mediated immune response both in magnitude and breadth was observed starting from day 105 after the first positive RT-PCR test. This improvement

took place parallel to the increase in humoral immunity and coincided with a complete viral shedding and the patient's clinical improvement, with a response to nucleocapsid proteins proving to be greater than the response to other viral proteins (Figure 2d).

Patients with underlying immunosuppression may constitute a scenario that facilitates viral evolution, as has been reported in several cases [15]. Moreover, intra-host evolution and the development of viruses with mutations in the spike glycoprotein have been considered to be one mechanism for the emergence of SARS-CoV-2 variants [16]. In our patient, virus genome sequencing from a sample obtained at first admission was performed, and an Alpha Variant (officially referred to as B.1.1.7) was identified. Additionally, several samples were subsequently obtained and sequenced at every admission at the hospital, revealing the presence of four mutations in four regions (ORF1a:Q3332L, ORF1a:T1001I, ORF1b:T2537I, ORF7a:Q62S) which appeared alternately without any clear evidence of viral evolution over the course of the infection. This lack of intra-host virus evolution suggests an absence of endogenous or exogenous selective pressure on the virus in upper respiratory airways in this immunosuppressed patient.

In summary, subjects with CLL are susceptible to developing a prolonged SARS-CoV-2 infection with the consequent pneumonia and ARDS, even on multiple occasions. Similarly, to what occurs in the general population, consecutive treatments with remdesivir and dexamethasone, as well as prophylaxis with enoxaparin

and supplementary oxygen, seemed to be useful to treat pneumonia and ARDS episodes, while delayed and effective humoral and cellular-mediated responses led to definitive viral clearance. By contrast, infusion of CP did not seem to play a useful role in achieving good clinical outcomes. Well-designed randomized clinical trials of new antiviral drugs are urgently needed to provide personalized treatment for COVID-19 hospitalized subjects at risk of viral clearance delay, as well as to explore whether SARS-CoV-2 RNA levels could predict clinical outcomes and recurrences in immunosuppressed patients.

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Conflict of Interest

J. R. Santos has received research funding, consultancy fees and lecture sponsorships from and has served on

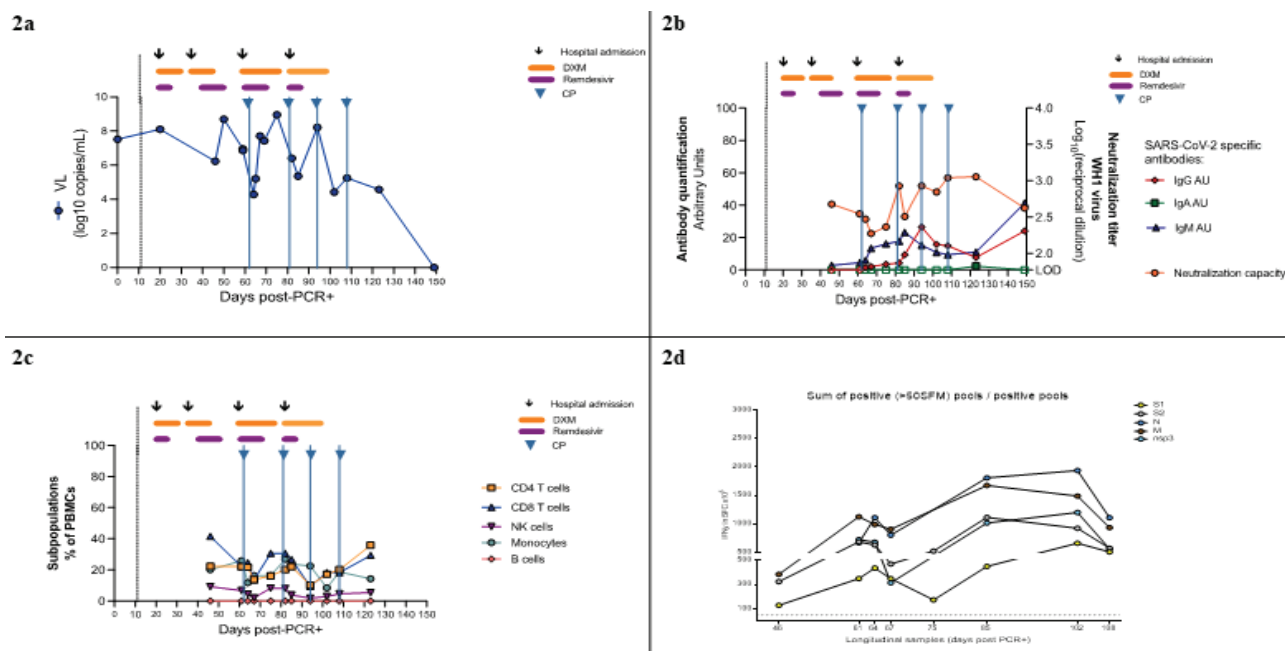


Figure 2 Viral kinetics and immunologic evolution during SARS-CoV-2 infection.

2a). SARS-CoV-2 viral load in nasopharyngeal swabs.

2b). IgG/A/M antibody quantification and plasma neutralization capacity.

2c). Peripheral blood mononuclear cells subpopulations.

2d). T-cell response to S, M, N and nsp3 proteins of SARS-CoV-2.

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