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Research Article
Persistent SARS-CoV-2 Beta Variant Infection in Patients with Follicular Lymphoma

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Abstract

Background and Objective: Immunosuppressed patients with COVID-19 can experience prolonged viral shedding, allowing SARS-CoV-2 to evolve into multiple mutational variants due to the lack of immune pressure and antiviral treatments. However, no standardized treatment protocol exists for managing such cases. This study investigates treatment strategies for persistent COVID-19 in immunosuppressed patients by reviewing existing literature and analyzing a clinical case. **Materials and Methods:** The study focuses on a 48-year-old woman with follicular lymphoma (FL) who experienced multiple COVID-19 episodes despite prior treatments. The patient was treated with a 10-day intravenous remdesivir regimen, oxygen therapy and trimethoprim/sulfamethoxazole prophylaxis while undergoing genomic monitoring. Clinical evaluation included CT scans, chest X-rays, RT-PCR tests and genomic sequencing to track viral mutations. No statistical tests were applied, but the study provides a detailed clinical assessment of disease progression and treatment response. **Results:** The combination of remdesivir, oxygen therapy and antibiotics successfully improved the patient's condition, leading to a non-oxygen-dependent SpO_2 of 94% by discharge. Genomic sequencing identified the B.1.177 variant, carrying multiple spike protein mutations, suggesting immune escape mechanisms. Despite an initial negative antigen test after 16 days, the patient remained SARS-CoV-2 positive in subsequent tests, emphasizing the virus's adaptability in immunosuppressed hosts. The study highlights the importance of genomic monitoring in optimizing treatment strategies. **Conclusion:** This case study demonstrates the effectiveness of remdesivir, oxygen therapy and antibiotic prophylaxis in treating persistent COVID-19 in immunosuppressed patients. However, the findings are limited by the single-patient analysis, lack of control groups and absence of long-term follow-up. Future research should focus on larger cohorts and randomized controlled trials to evaluate antiviral and immune-modulatory therapies. Genomic surveillance should also be prioritized to understand viral evolution and its impact on treatment outcomes.

Key words: COVID-19, SARS-CoV-2, beta variant, remdesivir, immunocompromised

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Competing Interest: The authors have declared that no competing interest exists.

Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) can cause prolonged viral shedding in immunosuppressed patients, lasting several months[1,2]. Factors contributing to prolonged high viral loads include host immune status, virological factors and the type and extent of immunosuppression[3]. In addition, there is evidence that patients with hematological malignancies have a higher risk of death from severe COVID-19 compared to patients with solid tumors or those without cancer[4]. During prolonged COVID-19 infection, the virus evolves rapidly by generating multiple mutational variants[1]. This genetic variation is thought to result from the lack of immunological pressure and the treatments used against COVID-19. Therefore, immunosuppressed patients may contribute to the increased genetic diversity of SARS-CoV-2 and play a significant role in the emergence of variants of concern, such as B.1.1.7 (alpha), B.1.351 (beta), P.1 (gamma) and B.1.617.2 (delta)[1]. These new variants can evade both naturally induced and vaccine-induced immunity[5]. There is no established standard treatment protocol for the management of COVID-19 in immunosuppressed hosts. However, a case series analysis of prolonged SARS-CoV-2 infection in patients with follicular lymphoma (FL) diagnosed before COVID-19 demonstrated the efficacy of combination treatment with dexamethasone, remdesivir and convalescent plasma[6]. This study aims to address the challenge of managing prolonged SARS-CoV-2 infections in immunosuppressed patients by evaluating effective therapeutic strategies. It documents the clinical case of a follicular lymphoma patient with recurrent COVID-19, highlighting the efficacy of combination therapy with remdesivir, oxygen therapy and antibiotic prophylaxis. Additionally, it emphasizes the need for genomic monitoring and enhanced infection control to prevent viral transmission.

MATERIALS AND METHODS

Study design: This observational case study examines the clinical course and treatment outcomes of a 48-year-old non-smoking woman diagnosed with follicular lymphoma in 2020, previously treated with steroids and suffering from persistent COVID-19.

Patient selection and clinical history: The patient had a history of repeated SARS-CoV-2 infections, with prolonged antigen test positivity during hospitalizations in May and July 2021.

Data collection and clinical assessment: On 19 February, 2022, she was admitted to the hospital via emergency medical services due to increasing dyspnea over 1.5 weeks, asthenia and hypoxia (SpO_2 87%). Physical examination findings included crackles over the lung bases.

Diagnostic imaging and laboratory investigations: The CT imaging demonstrated bilateral focal consolidation lesions, interstitial thickening and ground-glass opacities, with the most severe involvement in the paracentral lobes and a 50% estimated pulmonary parenchymal involvement. A small 4 mm subpleural calcification was also noted in the right lung. Chest X-ray findings suggested less severe lung involvement compared to CT imaging (Fig. 1). Laboratory tests and administered medications are summarized in Fig. 2.

Treatment protocol: The patient received passive oxygen therapy via a 12 L reservoir mask, intravenous remdesivir for 10 days, thromboprophylaxis, anti-ulcer therapy and antibiotic prophylaxis with trimethoprim/sulfamethoxazole. Clinical improvement was noted, with SpO_2 increasing to 94% on room air.

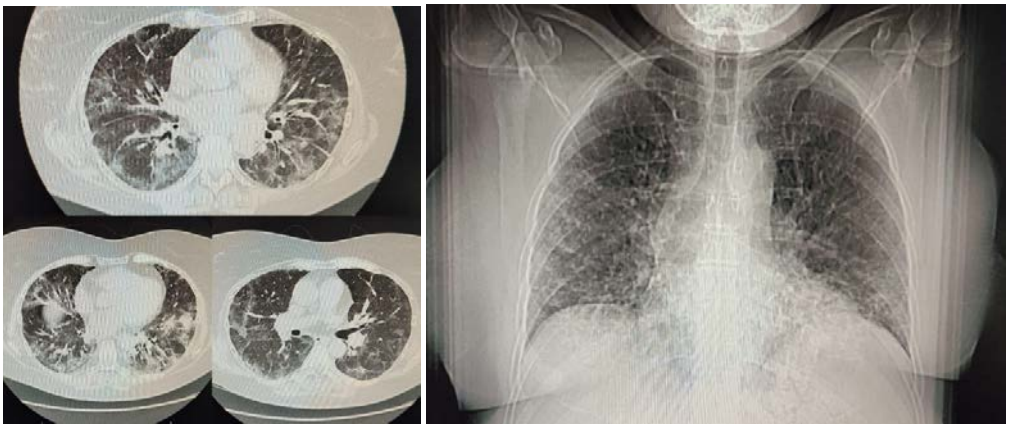

Fig. 1: Medical imaging of the patient: CT scan dated 22.02.2022 and X-ray dated 19.02.2022

Virological and genomic analysis: To monitor treatment efficacy, SARS-CoV-2 RT-PCR and antigen tests were performed. A positive RT-PCR result on February 28, followed by inconclusive tests on March 2 and 4, led to genomic sequencing, which identified the B.1.177 variant with multiple spike protein mutations. The listed mutations are consistent with the laboratory results. Sequencing performed using Oxford Nanopore technology (with >2590x coverage) confirmed the presence of a 4-nucleotide deletion at reference position 25432, a 16-nucleotide deletion at position 27968, and the NS8_ins27stopF mutation, resulting in a 78.5% truncation of the protein sequence. The viral genome also contained a 35-nucleotide gap relative to the WIV04 reference strain, with 0.07% unique mutations.

Outcome assessment: On March 7, the antigen test turned negative and the patient was discharged home. This study focuses on a single case, with no statistical analysis, emphasizing detailed clinical documentation of treatment response and viral genomic evolution.

Ethical consideration

Ethical approval: This study was conducted in accordance with ethical guidelines and patient rights regulations. Given that it is a retrospective observational case study based on standard diagnostic and therapeutic procedures, formal approval from an ethics committee was not required.

Statement of human and animal rights: The study adhered to the ethical principles outlined in the Declaration of Helsinki. No experiments involving animals or invasive procedures beyond routine clinical care were performed.

Statement of informed consent: Written informed consent was obtained from the patient for participation in this study and the publication of relevant medical data in an anonymized manner.

RESULTS

Immunosuppression was associated with an increased risk of developing persistent SARS-CoV-2 infection. Genotyping revealed that the patient had been infected with the B.1.177 variant of SARS-CoV-2, which contained multiple spike protein mutations. Although there was no consensus on the management of persistent COVID-19. Observations indicate that a combined therapy consisting of a 10-day remdesivir regimen, oxygen therapy and antibiotic prophylaxis was effective in combating the SARS-CoV-2 infection, ultimately leading to positive clinical outcomes for the patient (Fig. 2). The patient had experienced multiple episodes of SARS-CoV-2 infection in the past, as confirmed by previous positive tests (August 2021, February 2022) and hospitalizations related to these infections. The hospitalization in February 2022, which began on February 19, was longer and more intensive, lasting 10 days, which may indicate a more severe course of infection or an increased inflammatory response (Fig. 3). The patient initially exhibited elevated levels of inflammatory markers, such as CRP and IL-6, indicating an active phase of infection. In response, treatment with

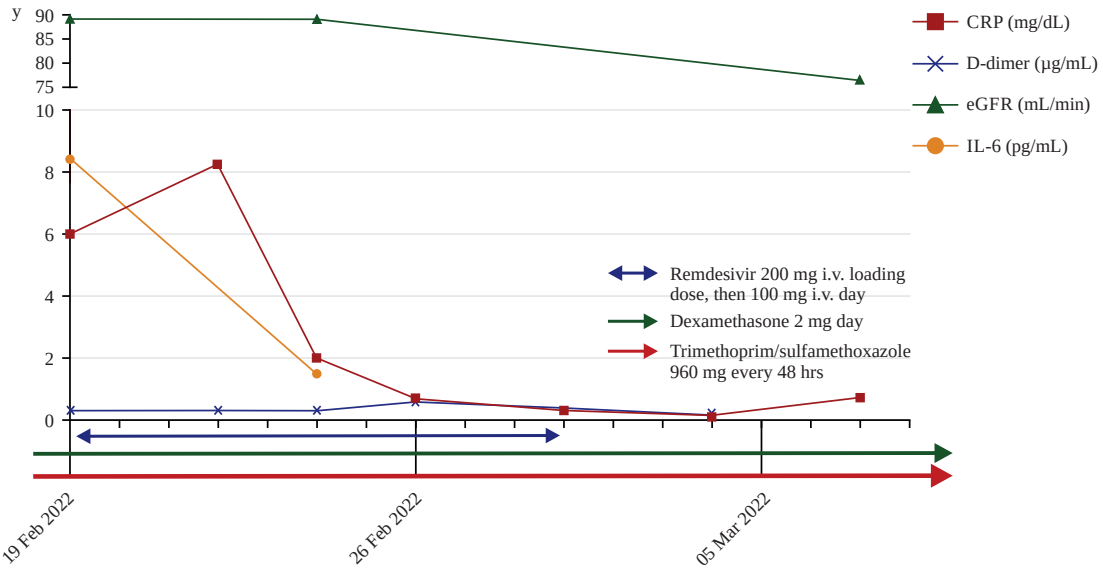

Fig. 2: Laboratory tests and selected drugs of the patient from the period of hospitalization
y: Concentration level of biomarkers (CRP, D-dimer, IL-6) and eGFR

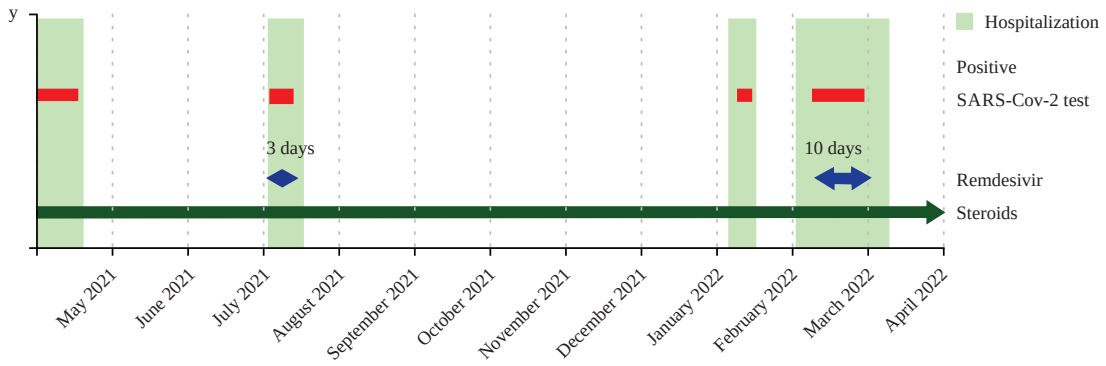

Fig. 3: Course of SARS-CoV-2 infections and treatments of the patient
y: Patient status and therapy

Table 1: Treatment options for persistent SARS-CoV-2 in patients with lymphoma

Therapeutic options for people at high risk of COVID-19 progression	Dosage	Indications	Efficiency
Monoclonal antibodies			
Casirivimab-imdevimab	i.v./i.m.	Pre-exposure prophylaxis, post-exposure prophylaxis, treatment of mild/moderate COVID-19 in people at high risk of progression	Reduction in hospitalization and mortality by 70-85%
Tixagevimab-cilgavimab	i.v.	Pre-exposure prophylaxis, early treatment of infected patients at high risk of disease progression/severity	COVID-19 symptomatic risk reduction of 76.7%
Sotrovimab	i.v.	Treatment of mild/moderate COVID-19	Reduction in hospitalizations and mortality
Antiviral drugs			
Remdesivir	i.v.	Treatment of COVID-19 with oxygen-requiring pneumonia, mild-moderate COVID-19 with risk of progression	Reduction in risk of hospitalization and death
Nirmatrelvir enhanced with ritonavir	p.o.	Treatment of mild/moderate COVID-19 with high risk of progression	Reduction in risk of hospitalization and death
Molnupiravir	p.o.	Treatment of mild/moderate COVID-19 with high risk of progression	Reduction in risk of hospitalization and death

i.v.: Intravenous, i.m.: Intramuscular and p.o.: By mouth

remdesivir was initiated with a 200 mg intravenous loading dose, followed by 100 mg daily for 10 days. Additionally, the patient received dexamethasone (2 mg daily) and prophylactic antibiotic therapy with trimethoprim/sulfamethoxazole (960 mg every 48 hrs). By February 26, 2022, a significant decline in CRP and IL-6 levels was observed, suggesting an effective suppression of the inflammatory response. The D-dimer levels remained stable throughout the hospitalization period, indicating no thromboembolic complications. Although eGFR values showed a gradual decline, no severe impairment was noted, allowing the continuation of therapy without the need for modification. A comprehensive analysis of laboratory parameters up to March 5, 2022, confirms that the chosen therapeutic strategy successfully controlled the infection, stabilized the patient's condition and contributed to a favorable clinical recovery (Fig. 2). Long-term follow-up may provide additional insights into potential post-infection complications and the effectiveness of the implemented therapy in preventing further episodes of illness (Fig. 3). Our case showed that the combination of a 10-day remdesivir therapy together with oxygen therapy and antibiotic prophylaxis was capable of resolving the SARS-CoV-2 infection and resulted in positive patient outcomes. This aligns with treatment strategies for high-risk patients, where remdesivir oral antivirals (nirmatrelvir/ritonavir, molnupiravir) and monoclonal antibodies like sotrovimab and casirivimab-imdevimab reduce hospitalization and mortality risks. Additionally, monoclonal antibodies like casirivimab-imdevimab and tixagevimab-cilgavimab are used for prophylaxis and early treatment (Table 1). Additionally, close genomic monitoring and reinforced infection control measures to avert transmission among immunosuppressed patients, who might have shed older SARS-CoV-2 variants for longer, were necessary.

DISCUSSION

Immunocompromised patients are particularly vulnerable to prolonged COVID-19 infection, as Ko *et al.*[7] describe in their observational study. This is due to the intensive replication of

the virus and the use of pharmacotherapy, which puts selection pressure on the virus. Mutations in the spike protein are particularly dangerous, as it is the main target for both COVID-19 vaccines and certain drugs. In this particular case, the patient with a history of follicular lymphoma underwent treatment for over 10 months, as illustrated in Fig. 3.

Hodgkin lymphoma is a malignant neoplasm originating from the B cells of the lymphatic system. The incidence is approximately 2-3 cases per 100,000 person-years. It is usually benign, although about 20% of patients have progression or relapse within 2 years of starting treatment[8]. Risk factors for the development of the disease appear inconclusive. A systematic review by Park *et al.*[9] found a higher risk of papular lymphoma in women with Sjogren's syndrome or women who smoke, among others. Patients with hematological malignancies are at increased risk of death in COVID-19. The EPICOVIDEHA study, describing patients with hematological malignancies with a confirmed diagnosis of COVID-19, showed that patients with non-Hodgkin's lymphoma constituted the largest group of COVID-19 patients, highlighting the important presence of this disease group among patients with haematological malignancies who developed COVID-19. The mortality rate for COVID-19 and follicular lymphoma was 31.8%[10]. Diagnosis of lobular lymphoma involves an excisional biopsy of the lymph node along with assessment of prognostic biomarker levels[8]. Treatment of early-stage lymphoma usually includes radiotherapy, which provides a median survival of approximately 19 years. However, patients diagnosed at stage I/II represent only about 10% of cases. Close follow-up is recommended for asymptomatic advanced-stage follicular lymphoma. The combination of rituximab with chemotherapy increases treatment efficacy and prolongs progression-free survival, but does not extend overall survival[11]. In patients with relapsed follicular lymphoma, CAR-T therapy, especially using T cells targeting the CD19 antigen, appears promising. A study by Schuster *et al.*[12] reported a 71% response rate in patients treated with this method.

Such patients, especially those with cancer, on immunosuppressive therapies like CAR T-cells or anti-CD20, those on long-term corticosteroids or organ transplant recipients, are particularly vulnerable to prolonged SARS-CoV-2 infections. Additionally, individuals with untreated or poorly managed HIV infections are also at risk[1]. These infections can result in multi-mutant variants characterized by rapid evolutionary changes, possibly due to partial immune control in these patients[8].

The viral variants found in immunosuppressed patients share features with known variants of concern, including B.1.1.7, B.1.351, P.1 and B.1.617.2. Many of these variants exhibit convergent mutations in the spike protein, suggesting adaptive evolution and selection pressure, which facilitates their rapid spread[1].

In this case, the patient was infected with the B.1.1777 variant. The SARS-CoV-2 B.1.177 lineage emerged in Spain in the summer of 2020 and spread across Europe through travel. This lineage was prevalent in Spain until February 2021, when it was overtaken by the Alpha variant, first identified in Spain around October 2020. Between December 21 and January 4, 2021, 397 sequences of Alpha (frequency 0.24) and 993 sequences of B.1.177 (frequency 0.61) were recorded[13].

The patient's lymphoma and long-term steroid treatment may have increased the risk of developing multi-mutational escape variants. The Beta lineage of SARS-CoV-2 is associated with higher transmissibility, virulence and resistance to neutralization by sera from vaccinated and convalescent individuals[8]. Literature suggests that convalescent plasma and monoclonal antibody (mAb) treatments contribute to the emergence of new mutant variants with immune escape mutations, facilitating reinfection in immunosuppressed patients[14]. Consequently, serum was not used in this patient's treatment. Previous hospitalizations did not include RT-PCR tests to identify the virus type and optimize treatment. Genomic monitoring in high-risk patients can be beneficial, allowing for therapy adjustments based on potential mutations and aiding in the monitoring of emerging variants to protect public health.

Remdesivir has been shown to significantly reduce recovery time and inhibit viral replication[15]. In this immunocompromised patient, 10 days of remdesivir therapy had a notable antiviral effect, resulting in a negative antigen test after 16 days of hospitalization and clinical improvement. Dexamethasone, known to lower mortality in mechanically ventilated patients, was also used in this case[16]. Recommendations for managing patients with lymphoma and COVID-19 are summarized in Table 1[17,18].

This study is limited by a small sample size, lack of long-term follow-up and the observational nature, which prevents establishing causality. The impact of lymphoma treatments on viral persistence was not fully explored and genomic sequencing at specific time points may have missed mutations. Future research should include larger cohorts, extended follow-up and frequent whole-genome sequencing to track viral evolution. Studies should also assess the role of different treatments and immune responses in persistent SARS-CoV-2 infection among immunocompromised patients.

CONCLUSION

Immunosuppressed patients can experience prolonged SARS-CoV-2 shedding, lasting for months. The risk of prolonged infection is influenced by factors such as the immune status of the host, virological factors and the type and degree of immunosuppression. Additionally, SARS-CoV-2 can rapidly evolve in these patients, generating multi-mutational variants and increasing viral genetic diversity. Despite the absence of a standardized treatment protocol for COVID-19 in immunosuppressed individuals, a combination of dexamethasone, remdesivir and convalescent plasma has shown efficacy in some cases. Close genomic monitoring is recommended to adjust therapy and prevent the transmission of older SARS-CoV-2 variants. Among these treatments, remdesivir significantly reduces recovery time and inhibits viral replication, as evidenced by the patient's negative antigen test and improved clinical status. Dexamethasone has been shown to reduce mortality in mechanically ventilated patients and proved beneficial in this case. Managing patients with lymphoma and COVID-19 requires genomic monitoring, therapy adjustments for potential mutations and strict infection control measures. Enhanced infection control is crucial to prevent the transmission of SARS-CoV-2 among immunosuppressed patients.

SIGNIFICANCE STATEMENT

Immunosuppressed patients, particularly those with hematological malignancies, are at an increased risk of prolonged SARS-CoV-2 infections, which can lead to the emergence of new viral variants due to reduced immune pressure. This case study highlights the clinical course of a patient with follicular lymphoma experiencing persistent COVID-19 and demonstrates the efficacy of a combined treatment strategy including remdesivir, oxygen therapy and antibiotic prophylaxis. Study findings emphasize the necessity of genomic monitoring in immunocompromised individuals to detect emerging variants early and guide treatment decisions. Understanding the interplay between host immune status, treatment regimens and viral evolution is critical for improving therapeutic strategies and mitigating the spread of SARS-CoV-2 variants in vulnerable populations.

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