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Anti-Infective Agents, **XXXX,** *XX,* **exxxxx**

CASE REPORT

Successful Combination of Remdesivir and Convalescent Plasma to Treat a Patient with Rituximab-Related B-Cell Deficiency and Prolonged COVID-19: A Case Report

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Abstract: ***Background*:** Treatment of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in immuno-compromised patients with complete B cell depletion can be really challenging due to the lack of seroconversion and long-lasting disease.

***Case Report*:** We describe a case of long-lasting coronavirus disease (COVID-19) in a female patient with rheumatoid arthritis who was treated with rituximab and continued to show B-cell depletion. An ongoing replication of SARS-CoV-2 was demonstrated for a period of 8 months when nasopharyngeal swabs were tested. She was treated once with remdesivir but without lasting resolution, and she was then treated with convalescent plasma but with a similar effect. Only with a combination of both treatments was clinical resolution achieved. The patient's lack of seroconversion and the prolonged course of the disease illustrate the importance of humoral immunity in resolving SARS-CoV-2 infection. This case report highlights challenges in managing immunocompromised hosts, who may act as persistent shedders and sources of transmission.

***Conclusion*:** The combination of remdesivir and convalescent plasma resulted in successfully achieving clinical resolution of SARS-CoV-2 infection in our patient.

Keywords: SARS-CoV-2, COVID19, immunocompromised, rituximab, convalescent plasma, rheumatoid arthritis.

1. INTRODUCTION

Since the emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the causative agent of coronavirus disease 2019 (COVID-19), there has been an ongoing effort to define viral kinetics, host immune responses, and transmission dynamics. The average incubation period in individuals who develop symptoms is approximately 5 days (interquartile range, 2-7 days). The viral load in the respiratory tract peaks around the time of symptom onset, and the shedding of infectious virus occurs for 2-3 more days [1]. While peak viral loads in asymptomatic and symptomatic individuals are similar, those with symptoms appear to shed viral RNA in greater quantities for longer periods. Individuals can test positive for nucleic acids for up to 6 weeks after symptom onset [2]. When evaluated, infectious virus is generally not detected after 7 days or more after symptom onset and contact tracing studies suggest that individuals are most infectious within 5 days of symptoms [3, 4]. The resolution of symptoms often coincides with seroconversion, with immunoglobulin G (IgG) levels increasing between 7- and 14-days post infection [5]. Immuno-com-promised individuals are underrepresented in most studies, and patients with primary or secondary immunodeficiencies may differ in their degree of shedding, kinetics of immune clearance, and disease severity. Considerable variability in these features is also likely based on the type and severity of underlying immune deficit. Among patients treated with immunosuppressive agents and/or biological drugs, B-cell-depleting agents such as rituximab have been particularly associated with severe disease or a long-lasting course [6, 7]. Here, we describe the clinical and virological course of a patient with complete B-cell depletion and COVID-19.

2. CASE REPORT

A 50-year-old woman with a 10-year history of rheumatoid arthritis refractory to traditional disease-modifying antirheumatic drugs (DMARDs) and previously treated with etanercept, adalimumab and abatacept without achieving disease control underwent the first course of anti-CD20 monoclonal antibody rituximab (RTX) in 2019, and in February 2020, another course of 2 injections (1000 mg intravenous, two weeks apart) was given.

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Exposure to SARS-CoV-2 likely occurred on the same day of RTX infusion. She later presented to the emergency department 8 days after the RTX course, complaining of fever, cough and flu-like symptoms for 4 days. A nasopharyngeal (NP) swab was positive for SARS-CoV-2 by reverse-transcription polymerase chain reaction (RT–PCR). She was diagnosed with SARS-CoV-2 interstitial pneumonia, and a chest HRCT scan showed multiple round and oval ground-glass opacities in both lungs, with a crazy-paving pattern (Fig. **1**). No mediastinal lymphadenopathy or pleural effusion was present. Based on the preliminary data on COVID-19 treatment available at that time, she was treated with hydroxychloroquine 200 mg per day and intravenous methylprednisolone 0,5 mg/kg for 10 days with little improvement in symptoms. Of note, peripheral blood flow cytometric phenotyping showed a complete depletion of B lymphocytes, counted as CD19+ B cells (Table **1**).

Table 1. Cellular counts related to therapies.

-	TIME	Total lymphocyte count cells/µL	CD4/CD8 cells/µL	CD4 T cells cells/µL	CD8 T cells cells/µL	B cells cells/µL	Neutrophil count cells/µL	Total IgG mg/dl	Total IgM mg/dl	Total IgA mg/dl	CRP mg/L	Ferritin ng/ml	IL-6 pg/	SARS-CoV-2 IgG CLIA AU/ml	Cycle threshold
ADMISSION	Day 0	-	-	-		-	4500	-	-	-	97	-	-	-	-
REMDESIVIR	Day 15	572	1,78	366	206	0	3200	545	109	43,09	120	674	36,6	0,7	19
-	Day 48	1136	1,16	610	526	0	7100	569	78,2	37	30	270	-	-	Not detectable
-	Day 75	1895	2,07	1289	622	0	5000	632	105	38,04	18	175	-	0,2	Detectable only in Sputum but not in NP
CONVALESCENT PLASMA	Day 90	1070	1,9	700	370	0	9100	569	78,2	37	97,6	722	-	-	30
-	Day 125	451	1,88	294	157	0	10000	-	-	-	7	-	-	-	Not detectable
-	Day 134	735	1,12	388	347	0	9000	-	-	-	33,8	-	-	7,9	
REMDESIVIR + CONVALESCENT PLASMA	Day 194	670	1,23	662	376	0	8000	-	-	-	50	-	-		33
-	Day 210	1602	1,02	808	794	0	3700	-	-	-	2,5	322	-	8,4	Not detectable

(Table 1) contd….

-	Day 260	-	-	-	-	-	-	-	-	-	-	-	-		Not Detectable
1st DOSE OF VACCINE	Day 350		-	-	-	10	-	-	-	-	-	-	-	-	Not Detectable

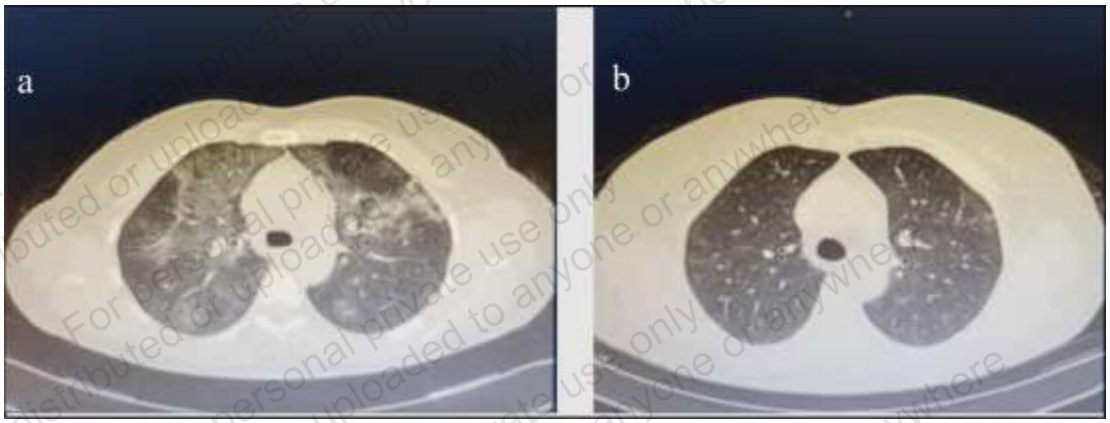

Fig. (1). Chest HRCT scans on Day 09 after admission (**a**) showing COVID-19 pneumonia, and after Remdesivir + convalescent plasma admnistration on Day 210 (**b**). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Over the following week, she continued to have fatigue and a mild cough but remained afebrile. She began to experience mld dyspnea without the need for supplemental oxygen. An NP swab again tested positive for SARS-CoV-2 by RT–PCR on Day 15 from admission and then on Day 26, when NP and sputum samples were again positive for SARS-CoV-2 by RT–PCR. On Days 26 and 34, serological testing did not detect antibodies to SARS-CoV-2 (EUROIMMUN anti-SARS-CoV-2 IgG enzyme-linked immunosorbent assay), and peripheral B lymphocytes were still depleted. Thus, remdesivir was initiated (5-day course at a dose of 200 mg intravenously on the first day and 100 mg on the remaining days).

According to WHO severity definitions of SARS-CoV-2 infection, she had a nonsevere SARS-CoV-2 infection because of the absence of signs of critical severe disease [8].

Sputum samples remained positive for SARS-CoV-2 by RT–PCR, but her condition improved, and on Day 41, chest HRCT showed a significant improvement and reduction in the COVID-19-related ground-glass pattern. Repeated serologic testing 66 days after initial symptoms did not detect IgG antibodies against SARS-CoV-2 (Roche Elecsys Anti-SARS-CoV2, outside hospital report). She was discharged on Day 69 of her illness with an NP swab still positive. On Day 77, the patient presented again to the emergency department with fever, cough, and shortness of breath. A chest radiograph showed new bilateral lung opacities. Two days after admission, she had a worsening chest radiograph and increasing oxygen requirement. She was treated with methylprednisolone and piperacillin/tazobactam for 12 days and oxygen at a maximum flow of 4 l/min. On Day 97, the patient again presented with fever and cough. On Day 108, she received 600 cc of COVID-19 convalescent plasma (CCP) in a compassionate use program, which was well tolerated.

Convalescent donors were eligible for plasma donation 15 days after the resolution of COVID-19. Collected apheresis plasma underwent standard testing, as per current regulations in Italy. Additionally, anti–SARS-CoV-2 antibody content was assessed in each donation, with a requirement for a SARS-CoV-2 Sero neutralization titer ≥ 160.

Her fever disappeared within 24 hours after the infusion, she showed a progressive improvement of dyspnea, and oxygen was stopped 3 days after the infusion. On Day 128, anti SARS-Cov2 IgG and IgM were 7.91 AU/ml and 0,87 AU/ml (CLIA), respectively. During the following weeks, her condition continued to improve, despite episodes of intermittent fever, and on Day 159, she was discharged without oxygen in good condition with a positive NP swab. On Day 192, she returned to the emergency department with fever, cough, and shortness of breath. A chest HRCT scan again revealed a pattern of typical COVID-19 interstitial pneumonia. On Day 194, she received 600 cc of convalescent plasma, and on Day 195, she started a concurrent course of remdesivir for 5 days (at a dose of 200 mg intravenously on the first day and 100 mg on the remaining days). Her fever disappeared within 24 hours, and the oxygen administered with nasal cannulas at a flow of 4 liters/min was slowly weaned off in a few days. She was discharged home on Day 203 of her illness. During the following weeks, she remained afebrile, and her chest radiograph improved from prior evaluations. On Day 260, she had her first NP swab negative for SARS-CoV-2, and an HRCT scan showed that resolution of SARS-CoV-2-related pneumonia was achieved (Fig. **1**).

At 350 days after the beginning of SARS-Cov-2 infection, she underwent vaccination with two doses of the BNT162b2 (Pfizer–BioNTech) mRNA vaccine.

The prefacing anti-spike antibody titer was undetectable, and one month after the first vaccine injection, it was still undetectable by two different assays for SARS-CoV-2 (Snibe on the Maglumi platform and DiaSorin, CLIA assays). Peripheral blood CD19+ lymphocytes were 10 cells per microliter and thus still partially depleted. The second injection of BNT162b2 was administered after 3 months, and the anti-spike IgG titer was 130 BAU/ml (DiaSorin assay, positive > 33.8 BAU/ml) indicating a seroconversion. Between admission and the first negative swab on Day 260, any recovery of B cells was observed. B cells were detected (for the first time since rituximab administration) on Day 440 after admission and after the second injection of the BNT162b2 vaccine.

3. DISCUSSION

The persistence of viral RNA and long-term replication are increasingly recognized as sequelae of acute viral infections. In most cases, these phenomena are attributable to incomplete immune clearance and/or ongoing viral replication in immune-privileged sites. Several studies have described the effect of rituximab on B cells and mainly on B effector and B regulator cells, with a secondary influence on the T helper cell response [9, 10].

Some studies have reported a higher risk of infection in RA patients treated with rituximab than in those treated with other biologic DMARDs [11, 12], but these data come from registries and retrospective studies, which may contain bias due to their observational designs. The effects of rituximab on the immune system response to SARS-CoV-2 infection have yet to be elucidated. A systematic report on SARS-CoV-2 infection among IMID patients who were treated with rituximab exhibited a high rate of severe infections requiring hospitalization (61.5%), with bilateral pneumonia and hyperinflammation leading to a high mortality rate (23.1%). Therefore, treatment with rituximab should be considered a possible risk factor for unfavorable outcomes in COVID-19 patients with IMID [13]. However, further study is necessary to confirm this association. Adults with primary and secondary immunodeficiencies are at increased risk of morbidity and mortality from COVID-19 compared to the general population [14].

Variable degrees of hypogammaglobulinemia (mostly profound) have been reported in patients with prolonged COVID-19 treated with anti-CD20 drugs and complete depletion of peripheral B cells [15].

It has also been reported that delayed viral clearance and a prolonged disease course may be independent of baseline Ig levels [16]. According to this, the total IgG levels of our patient were only slightly under normal values, with normal IgM and IgA (Table **1**), and although extremely prolonged, the clinical course was moderate in severity, with no progression to severe disease or multiorgan involvement.

At the time of the first and second waves of the pandemic, there were limited treatments for COVID-19. Remdesivir is a ribonucleotide analog that inhibits SARS-CoV-2 RNA-dependent RNA polymerase and arrests viral RNA synthesis by acting as a delayed chain terminator [17]. Concordant with previous case reports, we found that the administration of remdesivir was associated with significant improvements in immunological and physiological biomarkers of SARS-CoV-2 infection. However, the rapid recrudescence of symptomatic COVID-19 following the cessation of remdesivir supports the hypothesis that remdesivir monotherapy is insufficient to support virological clearance and the resolution of COVID-19 in patients with humoral immunodeficiency. In our patient, like other reports, combined treatment with remdesivir and convalescent plasma achieved virological clearance and persistent resolution of symptoms. We noticed an improvement in the patient's clinical condition and radiological assays (Fig. **1**) both after remdesivir and convalescent plasma. Overall, rapid defervescence and less need for oxygen are due to the action of both treatments in reducing lung inflammation, leading to persistent clinical improvement and sustained virological clearance. The efficacy of convalescent plasma in the treatment of COVID-19 in patients has been reported in a small case series of individuals with both congenital and acquired B-cell defects [18-21].

Of note, two reports demonstrated that viral persistence could occur despite the generation of CD4 and CD8 T-cell responses to viral antigens and that the magnitude of ex vivo antiviral T-cell responses is augmented following the administration of convalescent plasma [5].

The first cycle threshold measured from an NP swab collected from our patient had a value of 19 (Table 1); during the disease, multiple RT-PCRs were performed on NP and sputum samples after the first administration of remdesivir, and viral RNA was not detectable in NP samples but sputum only. Then, it was detectable again 3 weeks after administration, with a cycle threshold value of 33. We observed a similar course after the first CP administration.

In this patient, when CP was administered alone, it led to an immediate clinical improvement that lasted 79 days and faded when immunoglobulins from CP had probably completely waned off and not replaced because of the humoral deficiency of the patient (Fig. **2**).

On Day 128, Sars-cov2 IgG and IgM were, respectively 7.91 AU/ml and 0,87 AU/ml (CLIA). These were the only SARS-CoV2 IgG ever detected in the patient. We propose that the source of those antibodies was the convalescent plasma administered.

These data point to a nonredundant role for humoral immunity in the immunological control of SARS-CoV-2, potentially *via* mechanisms such as antibody-dependent cellular cytotoxicity or opsonization and suggest that convalescent plasma might be a rational therapeutic choice for individuals with humoral immune deficiencies, particularly when current immunoglobulin replacement products lack SARS-CoV-2-specific antibodies [21]. However, the administration of convalescent plasma to immunodeficient patients has been associated with the emergence of novel genomic variants within SARS-CoV-2 encoding spike proteins that demonstrate reduced susceptibility to neutralization *in vitro* [22].

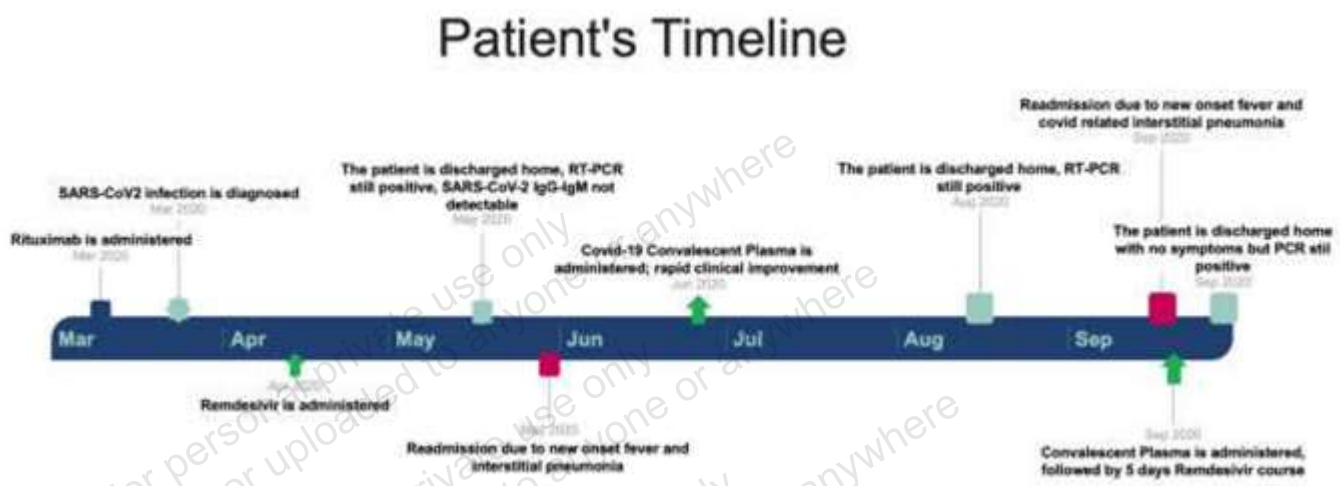

Fig. (2). Patient's timeline. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

Thus, combination treatments that simultaneously suppress viral RNA synthesis and facilitate viral clearance might be useful in immunocompromised individuals, as they may also reduce the emergence of novel viral variants.

Human neutralizing monoclonal antibodies against the SARS-CoV-2 spike protein used in a combined cocktail (REGN-COV2) have been shown to reduce the risk of the emergence of treatment-resistant mutant viruses protecting against SARS-COV2 mutational escape [23].

CONCLUSION

Combined treatment with remdesivir and convalescent plasma could be an important resource to effectively treat immunocompromised patients affected by COVID-19, leading to faster viral clearance and allowing them to return to a normal life.

A more comprehensive understanding of the mechanisms through which convalescent plasma mediates its therapeutic effect and how these mechanisms are defective in primary and secondary immune deficiency may facilitate the selection of individuals who would benefit from such interventions. We hypothesize that rituximab antibody-mediated depletion of B cells is primarily responsible for prolonged viral shedding and long-lasting COVID-19.

This humoral defect explains the absence of detectable seroconversion and may be associated with a lack of seroconversion after vaccination for SARS-CoV-2.

Our experience may be useful when caring for patients with COVID-19 and B-cell depletion in whom other treatments, such as monoclonal antibodies to SARS-CoV-2 targets, are not indicated. Further focused studies are required to gain insight into the safety and efficacy of this treatment combination in such a clinical condition.

AUTHORS' CONTRIBUTIONS

GR, GA and WC provided the concept and design of the study and cared for the patient. GR, WC and DF extracted the clinical and laboratory data and acquired the data. GR, GA, WC, DF and SDG analysed and interpretated the data, GR, DF and WC drafted the manuscript and GA and SDG critically revised the manuscript. All authors read and worked on the manuscript.

LIST OF ABBREVIATIONS

CP	=	Convalescent Plasma
IMID	=	Immune-mediated inflammatory diseases
NP	=	Nasopharyngeal
RA	=	Rheumatoid Arthritis
RTX	=	Rituximab

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This study has been approved by Ethics Committee of ATS SARDEGNA, Sassari, Italy, (Approval no. 237/2020/CE; title "CONVAPLA-COVID-19").

HUMAN AND ANIMAL RIGHTS

No animals were used in this research. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or research committee and with the 1975 Declaration of Helsinki, as revised in 2013.

CONSENT TO PARTICIPATE

The patient gave her consent for participation and publication.

According to Italian bylaws, a record of written informed consent of the patient to be treated with convalescent plasma according to the above referenced "CONVAPLA-COVID-19" protocol is kept on file and included in the clinical record of each patient.

STANDARDS OF REPORTING

CARE guidelines were followed.

AVAILABILITY OF DATA AND MATERIALS

The data and supportive information are available within the article.

FUNDING

None.

CONFLICTS OF INTEREST STATEMENT

Dr. Davide Firinu is the Editorial Advisory Board Member for the journal Anti-Infective Agents.

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Declared none.

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