ARP Rheumatology 2024;2:145-150
https://doi.org/10.63032/MNQF7735

CASE BASED REVIEWS

A Case Report and Literature Review of a Triple-Vaccinated, Rituximab-Treated Systemic Lupus Erythematosus patient with COVID-19 pneumonia

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ABSTRACT

Introduction: Patients being on immunosuppressive treatment of any reason, along with other risk factors such as smoking and obesity, are vulnerable to be infected from SARS-CoV2. Aim of this report is to describe a case of a female patient under Rituximab therapy who experienced episodes of lung infection due to Severe Acute Coronavirus 2 (SARS-CoV-2) invasion although fully vaccinated.
Case report: A 50-year-old woman, with a past medical history of lupus nephritis on rituximab was diagnosed with lung infection due to SARS-CoV-2. Eight months later, following her last infusion of Rituximab (RTX), she developed moderate Coronavirus Disease 2019 (COVID-19). After a partial recovery, she exhibited exacerbation of respiratory symptoms leading to readmission and invasive oxygenation. She was eventually discharged home after 31 days. Her monthly neurological evaluation did not reveal evidence of disease activity. She later received intravenous immunoglobulin and a decision was made to restart rituximab.
Conclusions: This case raises the possibility of persistent virus shedding and reactivation of severe acute respiratory syndrome coronavirus in a patient with SLE and Rituximab therapy. We emphasize a precise consideration of management of patients with autoimmune disorders during the COVID-19 pandemic.

Keywords: COVID-19; Vaccination; Systemic lupus erythematosus; Immunosuppression; Rituximab treatment.

INTRODUCTION

The use of immune-modulatory agents in the related diseases is challenging for the development of possible infections. As the COVID-19 pandemic continues to affect all type of populations worldwide without distinction, clinicians are faced with some complex cases in regards to management and therapeutic decisions. Herein, we present a case of a 50-year-old female being under long-lasting immune-suppression treatment including rituximab for lupus nephritis, who developed COVID-19 respiratory failure despite being fully vaccinated against SARS-CoV-2.

CASE REPORT

A 50 years-old woman was hospitalized in the COVID-19 section of the Department of Internal Medicine in the University Hospital of Patras, Greece. She had been diagnosed with Systemic Lupus erythematosus (SLE) after suffering episodes of hematuria, proteinuria and hypertension by renal biopsy in 2019, with no other systematic symptoms. She had no other significant medical condition instead of a BMI=28 and 20 pack years of smoking. Since then, the patient had received corticosteroids (prednisolone 5mg 1 – 0 - ½ od, after dosing modifications and tapering, initiating with 10mg bid), azathioprine 100mg od, mycophenolate mofetil 1g bd, tacrolimus 1mg bd and hydroxychloroquine (200mg od) regularly and no disease flares were reported. Additionally, the patient was treated with RTX 1g every 6 months (July-February) starting from July 2019, as a maintenance treatment.

During the COVID-19 pandemic, the patient was vaccinated against SaRS-CoV-2 as per her family doctor's advice. She received the first and second dose of SaRS-CoV-2 (mRNA vaccine from Biontech, Pfizer) in April 2021, when the vaccine became available in Greece and 3 months after the last Rituximab administration. She received the booster dose (Biontech, Pfizer) on November 5th, 2021. No side effects were reported from the patient after application of each dose of the vaccine. The patients had no measurement of antibodies level after vaccination.

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Submitted: 04/01/2024
Accepted: 04/05/2024

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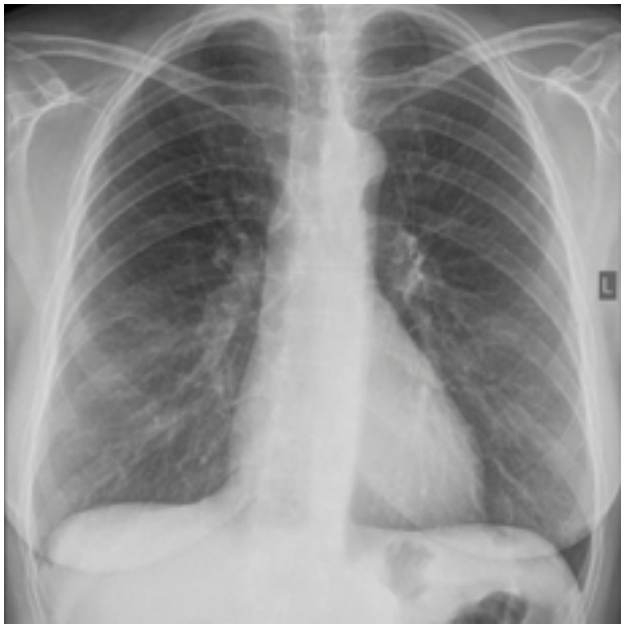

Figure 1. Chest X-ray findings on first ED visit. Mild bilateral infiltrates suggesting possible COVID-19 pneumonia

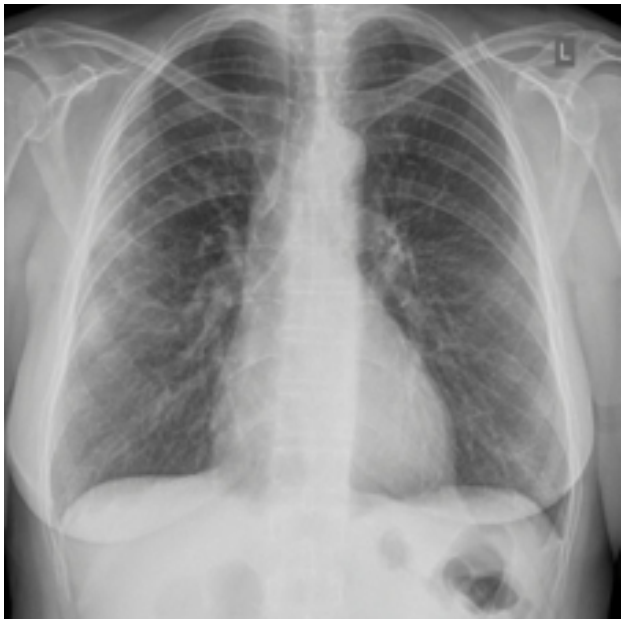

Figure 2. Chest X-ray finding on second ED visit. Worsening infiltrates validating the diagnosis of COVID-19 pneumonia

On November 27th and December 1st 2021, she visited the Emergency Department (ED) with persistent cough and tested positive for SaRS-CoV-2 RT-PCR, but was discharged due to the absence of hypoxemia, despite an X-ray showing mild bilateral infiltrates (Figure-1), been informed from clinicians to observe her clinical status for the case of deterioration. Immunosuppression along with the absence of any strict criterion for hospitalization as per local guidelines and treatment strategies at that time, led to the decision to avoid exposure to hospital environment. On December 20th, the patient visited the ED, this time presenting with worsening symptoms, including fever (39° C with armpit measurement), dyspnea, headache and fatigue. A new chest X-ray demonstrated slightly worsening infiltrates (Figure-2). In initial assessment the patient had SpO2 92% on room air, which increased up to 97% with low flow nasal oxygen support with PO_2/FiO_2=366 and Arterial Blood Gases (ABGs) as shown on Table I. The RT-PCR for SaRS-CoV-2 results was positive and she was admitted in an isolated ward for further treatment. First day laboratory findings are presented on Table II. The patient responded well to oxygen therapy, requiring up to 3 litres via low-flow nasal cannula with a rapid reduction of fever. She was also under piperacillin-tazobactam 4.5g qid, Remdesivir (200 mg IV on day 1 and 100 mg daily IV for the next 4 days), low weight molecular heparin (enoxaparin) (40 mg od SC) corticosteroid nebulizers (budesonide) and dexamethasone (6 mg od IV) while her immunosuppressive treatment was suspended. At the 4th day of hospitalization, the patient tested negative for SaRS-CoV-2 and was discharged on the 5th day, without need for oxygen support, in improved clinical condition. Following her hospitalization, an anti-SARS-CoV-2 IgG antibody test was requested, which was negative (1RU/ml). Patient's clinical course is summarized on Figure 3. A chest CT scan was recommended within one month since discharge and an appointment for post-COVID health clinic was appointed to assess the results.

DISCUSSION

SLE is a chronic rheumatoid disease able to produce among others a great number of blood abnormalities including lymphopenia and increased risk of recurrent infections. Additionally, the fact that immunosuppressive drugs are the cornerstone of its treatment, especially RTX, a question has been raised on whether vaccination against SaRS-COV-2 is effective in those patients, especially considering the interval between vaccination and RTX administration. The need of a booster dose soon after the primary vaccination has also been described especially for this group of patients[1, 2].

RTX, a recombinant monoclonal antibody against the protein CD20, is primarily found on the surface of immune system B-cells. RTX destroys B-cells and is therefore used in the treatment of diseases which are characterized by excessive production of B-cells, over-

active or dysfunctional B-cells. These are lymphomas, leukemias, and autoimmune disorders[3]. Additionally, among patients with autoimmune disorders, such as Multiple Sclerosis (MS), RTX reduces disease relapse[4].

TABLE I. Patient's ABGs on low-flow nasal oxygen supply, 3lt/min (FiO2=27%)

Variable	Value
pH	7.45
pCO2	39 mmHg
pO2	99 mmHg
HCO3	27 mEq/L
Lac	0.4 mmol/L
PO_2/FiO_2	366

CO2: carbon dioxide, O2: oxygen, HCO3: bicarbonate, Lac: lactate

This case constitutes real world evidence, that patients with an underlying condition treated with Rituximab should receive personalized care when presenting with prolonged symptoms of COVID-19, even if they have been fully vaccinated against SARS-COV-2. Fortunately, our patient developed only mild to moderate COVID-19 pneumonia, but a similar case report of a patient with neuromyelitis optica spectrum disorder treated with RTX required intensive care unit (ICU) admission[5]. Below, we present a rapid review of the current literature on vaccination efficacy in patients treated with RTX.

Patients with autoimmune disease are described to develop adequate humoral response after COVID-19 vaccination, especially SLE patients (90% seropositive) compared to other autoimmune diseases, such as Rheumatoid Arthritis and vasculitis (approximately 70% se-

TABLE II. Laboratory findings during patient's hospitalization.

Variable	Value day 1	Value day 2	Value day 3	Value day 4	Value day 5	Reference Values
WBC (K/μL)	4,650	3,350	-	3,320	-	4,000 - 11,000
Hemoglobin (g/dL)	11.8	10.8	-	11.2	-	11.8 – 17
Platelets (/μL)	182,000	172,000	-	194,000	-	150K – 400K
D-dimers (μg/mL)	0.59	-	-	-	-	0.0 - 0.5
Fibrinogen (mg/dL)	453	-	-	-	-	200 – 400
Creatinine (mg/dL)	1.0	0.9	-	0.9	-	0.9 - 1.6
Urea (mg/dL)	34	29	-	36	-	15 – 54
LDH (U/L)	253	227	-	623	-	120 – 230
SGOT (U/L)	15	12	-	21	-	< 40
SGPT (U/L)	12	9	-	14	-	< 40
albumin (g/dL)	4.4	3.7	-	3.5	-	3.5-5.5
CPK (U/L)	54	55	-	187	-	< 190
TnI (pg/mL)	0.4	-	-	0.6	-	0 – 15.6
CRP (mg/dL)	26.49	17.31	-	9.85	-	< 0.5
Ferritin (ng/dL)	>1675	875	-	205	-	17-390
ESR	108	74	-	50	-	0-10

WBC: white blood cells, LDH: lactate dehydrogonase, SGOT: serum glutamic-oxaloacetic transaminase, SGPT: Serum Glutamate Pyruvate Transaminase, CPK: Creatine phosphokinase, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate

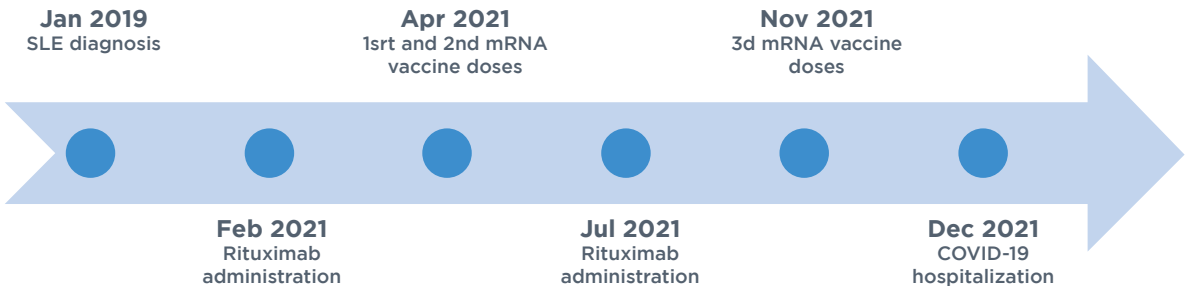

Figure 3. Summary of patient's clinical course.

ropositive)[6]. Seropositivity is decreased below 40% in patients on RTX with autoimmune diseases6. Our case report is in line with previous studies which demonstrate that humoral response is affected by CD20+ cell depleting therapies such as RTX[7, 8], which is proven to be an independent prognostic factor for that phenomenon, when it constitutes a compound of the last 12-month treatment[9]. Herein we briefly summarize some results referring to the humoral response in patients receiving anti-CD20 agents, some risk factors that seem to be related to the antibody production after vaccination and the cellular response of this patient group.

In a multi-center study, patients with rheumatic disease on Rituximab found to be 61% seronegative for anti-spike IgG after vaccination[10]. Ferri *et al.* also describe increased seronegativity among patients with Autoimmune diseases on RTX compared to patients receiving other treatments[11], while a nation-wide study in Austria described increased seronegative response to the vaccine in Multiple Sclerosis (MS) patients on anti-CD20 therapy with an OR=0.15[12]. That increase could be 20-fold higher when comparing MS patients on Rituximab vs healthy volunteers according to Sormani *et al.*[13]. This patient group is found to develop eliminated anti-RDB Ab, anti-spike specific Ab and memory B-cell response compared to healthy volunteers[14]. Among immune mediated disease patients who were twice vaccinated, only 43% vs 80% and 24% vs 77% were IgG seropositive compared to healthy volunteers and patients receiving other treatment, respectively[15, 16]. Hematologic patients on CD-20+ cell depleting therapy are also found to have eliminated humoral response compared to healthy volunteers[17, 18] and decreased neutralization capacity[19].

Some studies describe that detectable B lymphocyte count is important to predict the effect of vaccination on producing antibodies. Higher lymphocyte count is related to expanded response rates[20] and patients with detectable B-cell count can present with positive anti-RBD Abs even when that count is low[21, 22]. Jinich *et al.* estimated that B-cell reconstitution after depleting therapy has 91.3% positive predictive value on serologic response to vaccination[23]. Contrariwise, undetectable B-cells are independent factor for seronegativity after 2 doses of the vaccine ($p<0.001$)[24].

Time since last therapy seems to be crucial for seropositivity after vaccination. Longer interim is analogue to increased seropositive IgG response[25]. Patients who received Rituximab <6months before vaccination are observed to develop decreased anti-spike antibody response compared to those who had >6months interval[7]. Another study demonstrated that, among a cohort with rheumatic diseases patients, the seropositive group for SARS-COV-2 antibodies, received CD20+ cell depleting therapy median 704.5 days after treatment, while seronegative group had median 98 days interval[26]. RituxiVac study described that >7.6 months interval has positive predictive value for positive humoral response along with >643 CD4+ cells/μL[27]. Affirmatively to those data, the Singapore Chapter of Rheumatologists recommended a 6 month interval between vaccination and anti-CD20+ treatments[28]. RTX should be re-administered at least one month after Covid-19 vaccination[29]. The aforementioned data could explain our patient's seronegative result, considering her treatment/vaccination timeline. Moreover, our patient's timeline is line with current literature which describes that time between RTX administration and COVID-19 mild disease is 6.1 months median and 4.6 months median between RTX administration and COVID-19 disease that needed hospitalization[30].

COVID-19 severity and RTX treatment is further investigated in multiple studies. Patients with rheumatic diseases do not seem to have increased risk for COVID-19 infection except of those receiving RTX, who have worsen prognosis[31]. Studies on MS patients on disease modifying therapies demonstrated that only RTX can increase COVID-19 infection frequency[32, 33]. RTX treatment on those patients is a risk factor for severe disease and can predict worse outcomes[32, 33, 34]. Particularly for mortality rates, RTX therapy is described to increase the risk among MS/ Neuromyelitis Optica Disorder (NMOD) patients compared to other treatments[4, 35].

In contrary to pessimistic data on humoral response in that patient group, literature supports that cellular response remains intact[7, 14, 22], as they can produce CD4+/CD8+ S-protein specific T-cells in amounts comparable to healthy volunteers after 2 doses of vaccination[36]. The third dose may also increase T-cell response, but humoral non-responders tend to remain seronegative[37]. That could explain our patient's optative course and full recovery. In case a patient does not improve with standard of care, IVIG and convalescent plasma infusion may improve prognosis[38].

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