CASE STUDY

CONTENTS

# The course of COVID-19 in a multiple sclerosis: a case report

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## ABSTRACT

The authors present the case of a prolonged course of COVID 19 disease in a 37-year-old patient with multiple sclerosis on anti-CD20 monoclonal antibodies immunotherapy.

This publication presents a clinical case of the course of COVID-19 disease in a multiple sclerosis patient receiving ublituximab therapy. The use of disease-modifying anti-CD20 monoclonal antibody therapy was associated with a protracted wave-like course of COVID-19 with the addition of a bacterial infection. This publication illustrates the key mechanisms and approaches to the treatment of such a cohort of patients.

The use of highly effective multiple sclerosis treatment methods may be associated with an increase in the incidence of COVID-19 and worsening of its course. Multiple sclerosis patients receiving anti-CD20 therapy are at particular risk of a wave-like course of COVID-19, caused by immunosuppression, creates a basis for bacterial and fungal coinfection.

**KEY WORDS:** immunotherapy, COVID-19, multiple sclerosis, monoclonal antibody therapy

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## INTRODUCTION

The course and treatment of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), may have significant specific features in patients with multiple sclerosis (MS), causing additional risks of severe course of the disease with development of acute respiratory distress syndrome (ARDS) [1].

Population-based data indicate significantly increased risk of severe course of disease and mortality from COVID-19 in patients with MS [2]. On the contrary, in other studies the course of COVID-19 and mortality depended mostly on age and co-morbidities, such as obesity, diabetes, heart and lung diseases [3]. Furthermore, it is assumed that there is an associative relationship between the adverse course of COVID-19 and progressive course of MS, higher rate of disability and certain methods of treatment, in particular, the chronic use of immunosuppressive agents [4]. Although MS is mostly diagnosed in young patients, in clinical practice there are many 60+ patients with MS.

Modern immunomodulatory therapy for MS, treatment with immunosuppressive drugs in particular, can increase the risk of an infectious process, especially with regard to viruses and development of bacterial coinfection [5]. A target therapy for MS, including the use of anti-CD20 monoclonal antibodies, is primarily aimed at the suppression of immune response. Hence, patients may become more prone to complications caused by COVID-19 due to an insufficient immune system response to the virus. However, immunosuppression has been reported to play a protective role against COVID-19 and its severe course in MS patients treated with anti-CD20 agents [6].

This paper presents a clinical case of COVID-19 in a patient with MS treated with ublituximab (a humanized monoclonal antibody targeting the CD20 B-lymphocyte antigen), who had a protracted wave-like course of the disease with prolonged SARS-CoV-2 replication [7].

## CASE REPORT

Patient N., 37 years o/age, Caucasian, diagnosed with secondary progressive MS (according to the McDonald criteria [8]) in 2016. She received pulse therapy with methylprednisone (years 2016-2018), and disease-modifying therapy with glatiramer acetate and fingolimod (years 2018-2020). In January 2020, due to a highly active course of MS, and considering the current evidence [9, 10], treatment with ublituximab was initiated (one injection was done). The prescribed treatment favored the absence of exacerbation and neuroradiological stabilization of MS (Expanded Disability Status Scale (EDSS) [11] = 2 points).

On 19 March 2021, the patient developed a sore throat, fever up to 37.6°C, SARS-CoV-2 was detected by PCR, and COVID-19 was diagnosed. From day one until day 17 of the disease she was under the outpatient supervision, receiving amoxicillin protected with clavulanic acid for 7 days, and then 400 mg moxifloxacin for 10 days. The patient was admitted to the hospital for further treatment on day 18 of the illness due to hectic hyperthermia, which was not corrected with antipyretic drugs within the last 5 days, shortness of breath with a decrease in saturation according to pulse oximetry data ($SpO_2$ 89-90 %), combined with asymptomatic episodes of atrial fibrillation (according to ECG monitoring data). The patient had positive repeated PCR test for SARS-CoV-2. Spiral computed tomography (CT) of the lungs showed viral bilateral pneumonia, with the pronounced pathological changes in 25-50 % of the lung parenchyma (stage 2 [12]; Fig. 1). Taking into account the severity of the patient's condition, a critical decrease in the absolute count of lymphocytes to $0.4x10^9$/l, intravenous administration of human immunoglobulin in a dosage of 32 g (0.4 g/kg/day) and pulse therapy with methylprednisone 750 mg per day for 3 days was prescribed, with the following gradual reduction of the daily dose to 40 mg. Since PCR test was positive, antiviral drug remdesivir was prescribed intravenously for 4 days according to the regimen: a loading dose of 200 mg/day on day 1, followed by 100 mg/day. Concomitant heparin, antiarrhythmic drugs, antibiotics (taking into account the significant increase in procalcitonin values), prophylactic antifungal treatment were used.

In the course of treatment, the patient showed normalization of the inflammatory markers' levels, body temperature decreased to 36.6°C, $SpO_2$ increased to 96 %, and general

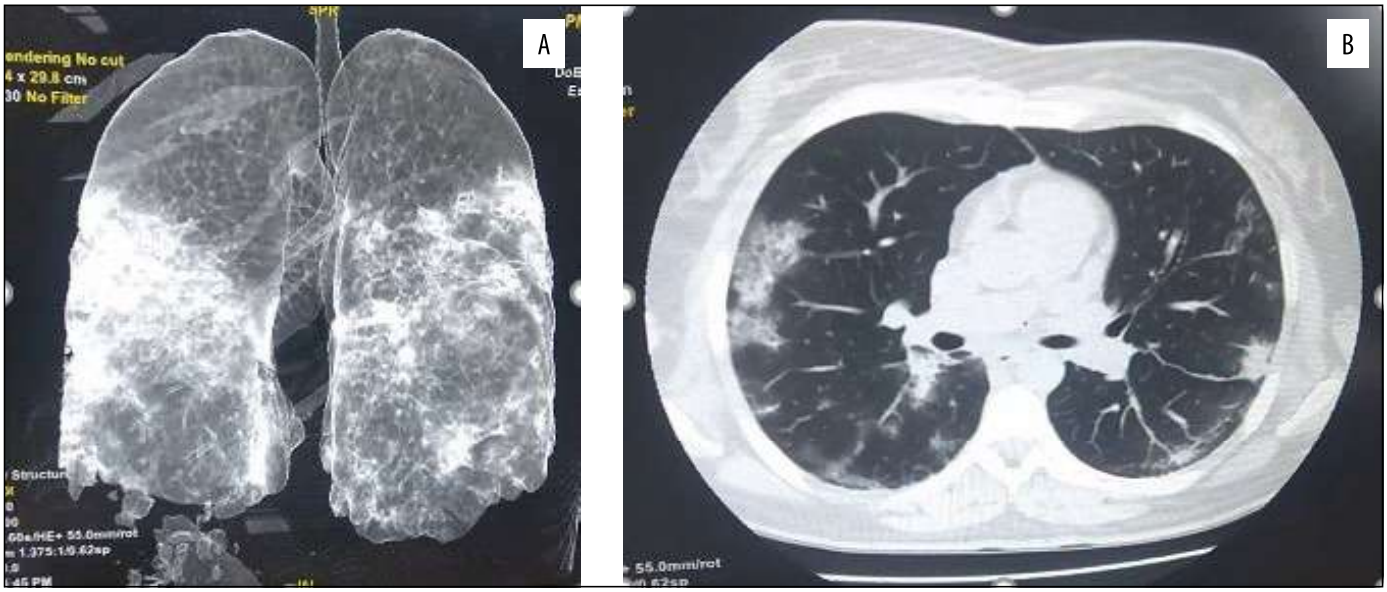


**Fig. 1.** Lung CT scan of the patient N. (day 18 of illness), demonstrating the signs of viral bilateral pneumonia, with involvement of 25-50 % of the lung parenchyma (stage 2 [12]). (A) 3D reconstruction; (B) axial plane.

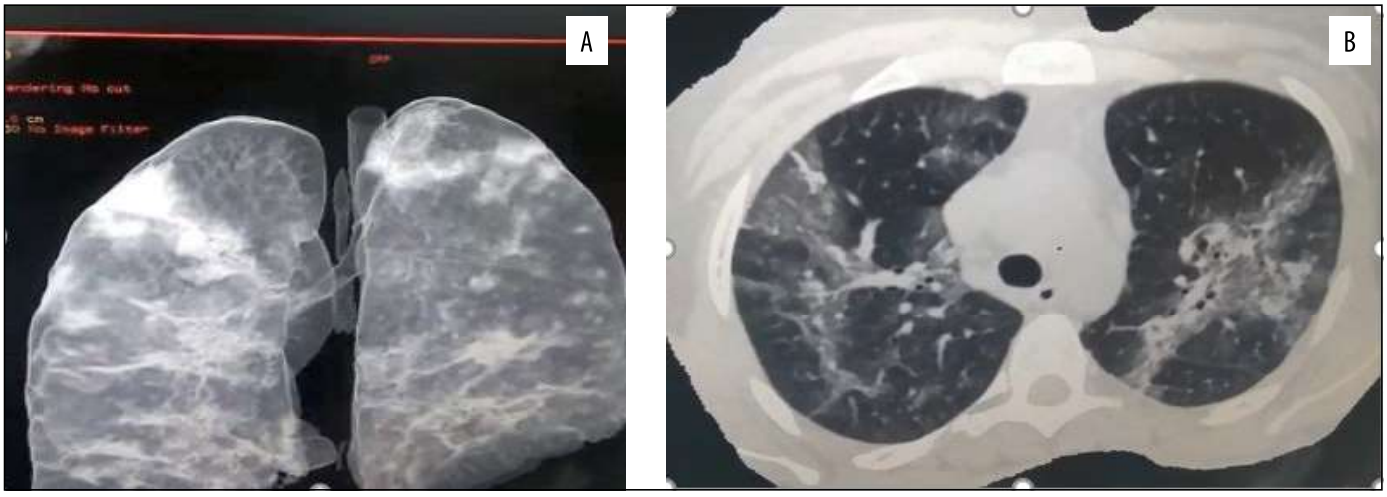


**Fig. 2.** Lung CT scan of the patient N. (day 32 of illness), demonstrating the signs of viral bilateral pneumonia with coalescent foci, with involvement of 50-75 % of the lung parenchyma (stage 3 [12]). (A) 3D reconstruction; (B) axial plane.

weakness regressed. On day 26 of the illness, the patient was transferred to the daytime in-patient ward, where she received anticoagulant rivaroxaban and antiarrhythmic agent, while the dose of steroids was further gradually reduced.

However, on day 32 of disease, the patient was re-admitted to the hospital with complaints of shortness of breath, a decrease in $SpO_2$ to 88-90 %, and an increase in body temperature up to 38.5°C. PCR testing revealed again a positive result for SARS-CoV-2. The increased inflammatory markers indicated exacerbation of the disease, while repeated CT of the lungs revealed bilateral viral pneumonia with coalescent foci with damage of 50-75 % of the lung parenchyma (stage 3 [12]; Fig. 2). Considering the severity of the condition and the data of clinical, laboratory and instrumental evaluation, the patient was repeatedly given pulse therapy with methylprednisone 500 mg for 3 days, followed by a gradual dose reduction, and antiviral therapy with remdesivir for 3 days according to the regimen described above. Additionally, meropenem and fluconazole were prescribed. Upon re-admission to the hospital, the patient had her blood culture tested for sterility, with no bacterial growth found.

The patient's condition improved on day 42 of the disease: shortness of breath, general weakness and fatigue regressed, while pro-inflammatory blood markers, such as C-reactive protein, ferritin, fibrinogen, interleukin-6, procalcitonin, got back to normal. However, repeated PCR test for SARS-CoV-2 was negative only on day 52. The patient was discharged home under the supervision of a family doctor and a neurologist with adherence to quarantine measures. After the viral infection, the patient had no signs of clinical and neuroradiological MS activity. Blood test for the subpopulation of lymphocytes, conducted on 4 April 2021, showed a slight increase in the relative and absolute count of B-lymphocytes (CD3-CD19+) up to 0.9 % (10 cells/**μL**). Due to this it was decided to postpone administration of the next doses of ublituximab.

It has been suggested that immunocompromised individuals, particularly MS patients receiving immunosuppressive therapy to modify the course of the disease, are at increased risk of developing severe COVID-19 [13, 14]. However, many patients receiving immunosuppressive therapy for MS, have uncomplicated COVID-19. Patients with MS and a severe form of COVID-19 are usually older and, accordingly, have a greater number of comorbidities, including the decompensated ones. At present, several immunosuppressive drugs for COVID-19 treatment are being tested, such as fingolimod (a S1P modulator) and emapalumab (an anti-interferon-gamma monoclonal antibody) [15]. Trials of tocilizumab (an antagonist of interleukin-6 receptors) have been completed for the treatment of severe forms of COVID-19 [16], and now it is included in the international guidelines as an effective drug for the therapy of patients with SARS-CoV-2 infection progression, including those with MS [17, 18].

In MS patients receiving immunomodifying therapy, the ability of the drugs to suppress the hyperactive cascade reaction of the immune system should be considered. Taking into account the mechanism of action of almost every monoclonal antibody used to treat MS, some of them should contribute to a mild, uncomplicated course of COVID-19 [19]. During SARS-CoV-2 infection, a powerful expressive immunological response occurs with massive production of pro-inflammatory cytokines (in particular, interleukin-6), which triggers the development of a «cytokine storm» and ARDS [20]. Data were obtained on the positive effect of interferon-beta medications in the treatment of COVID-19, especially in the case of their early adminisration [21]. Glatiramer acetate and fumarate, which are used to treat MS, increase the expression of circulating natural killer cells, providing additional protection against COVID-19 and its severe course in such patients [22]. The effect of glatiramer fumarate in inhibiting the function of macrophages, which play an important role in the development of ARDS, is also considered [1].

There is still insufficient evidence for the effectiveness of anti-B cell therapy in patients with MS and COVID-19. However, studies on ocrelizumab drug noted a high risk of addition and development of bacterial infections [23]. It is not fully understood whether there is a temporal relationship between the use of ocrelizumab and the risk of infection with COVID-19 and the severe course of the disease. Some studies indicate the risks of severe disease, with increased need for an in-hospital treatment, but no increase in mortality [18, 24, 25]. The use of ocrelizumab results in CD20+ B-lymphocytes depletion, which, in turn, leads to a decrease in cytokine production, a decrease in antigen-presenting function and differentiation of B-lymphocytes into plasma cells [26].

Initial antiviral immune responses are provided primarily by T-cells, in particular CD8+ cytotoxic T-lymphocytes, natural killer cells and, to a lesser extent, B-cells [27]. This allows us to explain why patients receiving anti-CD20 therapy have a relatively good response to treatment of viral infections, but on the other hand, the addition of a bacterial infection complicates the recovery process. Ocrelizumab and other anti-CD20 agents have relatively insignificant effect on T-cell counts and have not been associated with severe viral infections [28]. In the registration studies of MS treatment with ocrelizumab, infections were slightly more frequent compared to similar groups (interferon-beta-1a or placebo) [29]. In these studies, the viral infection that could be identified was mild-to-moderate. Infections were most likely bacterial, i.e. pneumonia, urinary tract infections and cellulitis. However, there are always rare exceptions to the rule; for example, an individual case of fulminant hepatitis

associated with an unusual ECHO virus-25 infection in a patient receiving ocrelizumab therapy [30].

The clinical case described above shows a prolonged course of COVID-19 with pneumonia, relapses of the immunopathological phase of the disease and the addition of bacterial superinfection, which may have been caused by the use of immunomodulatory therapy in connection with the underlying disease and longer replication of the virus. The use of ublituximab can lead to depletion of B-cells, which, in turn, impairs the formation of anti-SARS-CoV-2 antibodies. Regarding the further treatment of MS, the existing guidelines indicate a delay in the re-administration of immunosuppressive drugs, and vaccination is not a contraindication to its implementation [1].

## CONCLUSIONS

The use of highly effective MS treatment methods may be associated with an increase in the incidence of COVID-19 and worsening of its course. MS patients receiving anti-CD20 therapy are at particular risk and require careful clinical evaluation and consideration of an atypical immune response with the formation of a protracted course of the disease. Such a wave-like course of COVID-19, caused by immunosuppression, creates a basis for bacterial and fungal coinfection. However, immunosuppression with anti-CD20 drugs does not exclude the possibility of pulse therapy with steroids. What concerns the following MS treatment, guidelines suggest a delay in re-administration of immunosuppressive drugs, and vaccination against COVID-19 makes sense after six months with subsequent antibody testing.

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## CONFLICT OF INTEREST

The Authors declare no conflict of interest

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