Case Report

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TANAFFOS

Long COVID in Patients with Multiple Sclerosis Treated with Rituximab: A Report of Two Cases

Payam Tabarsi [1], Abdolreza Mohamadnia [2], Pardis Shahabinejad [3], Sara Haseli [2], Elham Askari [2], Naghmeh Bahrami [4], Shadi Shafaghi [5], Maryam Hajimoradi [5]

[1] Clinical Tuberculosis and Epidemiology Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [2] Chronic Respiratory Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran, [4] Department of Tissue Engineering and Applied Cell Sciences, School of Advanced Technologies in Medicine, Tehran University of Medical Sciences, Tehran, Iran, Craniomaxillofacial Research Center, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran, [5] Lung Transplantation Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran

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Correspondence to: Askari E
Address: Chronic Respiratory Diseases Research Center, NRITLD, Shahid Beheshti University of Medical Sciences, Tehran, Iran
Email address: dr_elham_askari@yahoo.com

COVID-19 symptoms may persist for more than 12 weeks in some infected patients, a condition described as long COVID-19 in these cases. These patients have symptoms attributed to impairment of multiple organs. Scientists have discovered the lengthy COVID-19 etiology, risk factors, and treatments. It has been observed that immunosuppression may prolong COVID-19 symptoms. Patients with multiple sclerosis (pwMS) are generally treated with disease-modifying treatments, which suppress the immune system and predispose patients to infections like COVID-19. Also, these drugs may increase not only the morbidity and mortality of infection but also the risk of developing long COVID-19 in these patients. We have described two cases of multiple sclerosis patients who were diagnosed with long COVID-19. Both patients were under treatment with rituximab, so we discussed treatment choices and strategies for pwMS patients under rituximab who had symptoms of long COVID. Our data would further add to the information on managing long COVID-19 in pwMS under treatment with rituximab.

Keywords: COVID-19; long COVID; multiple sclerosis; rituximab; post-COVID syndrome

INTRODUCTION

COVID-19, an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), first emerged in Wuhan, China, in December 2019. Since then, the lives of many people around the globe have been affected by this disease. Recent evidence suggests that a subset of patients infected with the SARS-CoV-2 virus will continue to have symptoms for longer than expected. Although the recovery time from COVID-19 infection varies among individuals, most patients recover after an average of two to three weeks (1, 2). However, some patients might experience persistent COVID-19-related symptoms. COVID-19 symptoms may persist for up to five weeks or longer in about 20 percent of cases, half of whom may experience the symptoms for more than 12 weeks (3). Studies have shown that this group of patients, who are known to have long COVID, have symptoms attributed to impairment of multiple organs such as the lungs, heart, brain, kidneys, spleen, and liver (4).

It has been estimated that about 2.8 million patients are diagnosed with multiple sclerosis (MS) worldwide as of 2020 (5). Patients with MS (pwMS) are generally treated

with disease-modifying treatments (DMTs), which have the potential to suppress the immune system and predispose patients to infections such as COVID-19. To date, most of the published studies have focused on the impact of DMTs on developing COVID-19 in pwMS, some of which show an increased risk of COVID-19-associated mortality and morbidity among pwMS receiving certain DMTs (6). Information about the effects of these medications on long COVID, however, remains limited. In this article, we describe two patients with a prior history of multiple sclerosis who were diagnosed with long COVID. As both our patients were under treatment with rituximab, we specifically discussed the treatment options for pwMS receiving rituximab who manifest symptoms of long COVID.

CASE SUMMARIES

Case 1

A 31-year-old woman with a history of MS presented to the emergency department due to a cough and fever lasting for three months. She had been on treatment with rituximab (500 mg every six months) for the past four years. On initial examination, she was febrile (39°C) with a respiratory rate of 24 breaths/minute, heart rate of 120 beats/minute, blood pressure of 130/70 mmHg, and oxygen saturation of 75% on ambient air. Cardiovascular examination was normal; however, rales were heard bilaterally on auscultation of the lungs. The main laboratory findings are shown in Table 1. On peripheral blood flow cytometry, B-cell biomarkers (CD20+, CD19+) were remarkably decreased (<1%), resulting from RTX treatment. As part of the initial evaluation, the patient underwent chest radiography, which revealed bilateral nodular opacities (Figure 1a). Chest computed tomography (CT) demonstrated bilateral multifocal nodular infiltration compatible with COVID-19 bronchopneumonia (Figure 1b). Subsequently, a positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-PCR) was detected using nasopharyngeal specimens. According to the patient, she had had several positive COVID-19 tests within the past few months. Based on the patient's past medical history, laboratory, and radiologic findings, a diagnosis of long COVID was made. Assisted non-invasive ventilation (NIV) was started along with broad-spectrum antibiotics, steroids, low-dose heparin, and antiviral therapy (Remdesivir). Due to her hypogammaglobulinemia (IgG= 393 mg/dl, IgA= 39 mg/dl, IgM= 39 mg/dl), a single dose of IVIg was started for the patient (400 mg/kg). Over the following weeks, she gradually recovered and was discharged with a neurology outpatient follow-up.

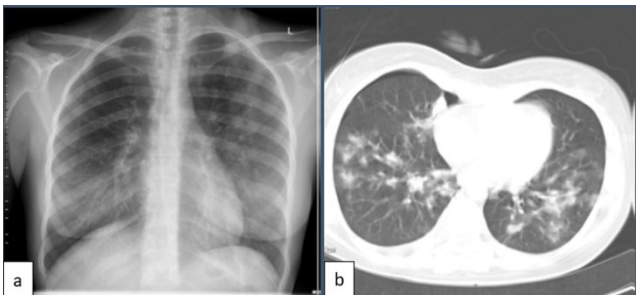

Figure 1. (a) Chest x-ray shows bilateral nodular opacities. Likewise, (b) chest CT scan shows bilateral multifocal nodular infiltration

Case 2

A 26-year-old female with a prior history of relapsing-remitting MS, diagnosed four years ago, had initially visited a hospital due to fever and chills, followed by a productive cough and dyspnea. She was treated with rituximab for the last three years. She had tested positive for COVID-19 on that visit, for which she had received supportive care. About seven weeks after the onset of her symptoms, she presented to our hospital with a worsening of her condition. On arrival, vital signs were as follows: temperature 40°C, heart rate 128 beats/minute, respiratory rate 28 breaths/minute, blood pressure 110/70 mmHg, and oxygen saturation 78% (on room air). Respiratory and cardiovascular examinations were unremarkable. Laboratory investigations are shown in Table 1. Flow cytometry revealed a dramatic reduction in CD20+ (<1%) and CD19+ (<1.1%) cells. Non-contrast enhanced images of

the lungs showed peribronchovascular consolidation and ground glass opacities more prominent in the right upper lobe, which was compatible with COVID-19 bronchopneumonia (Figure 2). She was treated immediately with broad-spectrum antibiotics, intravenous steroids, antiviral therapy (Remdesivir), and supplemental oxygen. Due to hypogammaglobulinemia (IgG= 678 mg/dl, IgA= 38 mg/dl, IgM= 39 mg/dl, IgE= 7 mg/dl), she received a single dose of IVIg (400 mg/kg). Her symptoms gradually improved over the next three weeks, and she was discharged without sequelae. Also, she was advised to follow up with the neurology outpatient clinic to substitute her MS medication.

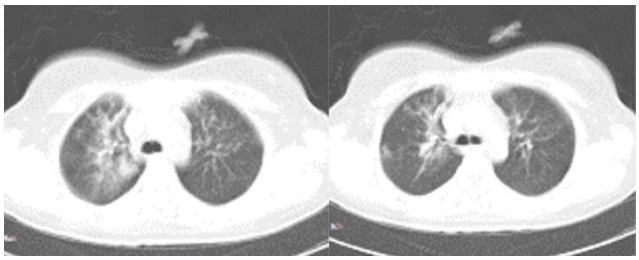

Figure 2. Chest CT scan shows peribronchovascular consolidation and ground glass opacities, particularly in the right upper lobe

Table 1. Laboratory findings of the patients

Laboratory test		Patient 1	Patient 2
WBC	Total count, cells/μl	6100	5100
	Neutrophil, %	68	72
	Lymphocyte, %	21	26
CRP, mg/L		79	51
D-dimer, ng/mL		800	1370
ALT, U/L		38	14
AST, U/L		29	32
LDH, U/L		315	496
Ferritin, ng/ml		283	2150
ESR, mm/hr		52	70

WBC, white blood cell count; CRP, C-reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LDH, lactate dehydrogenase; ESR, erythrocyte sedimentation rate.

DISCUSSION

Long COVID was initially introduced by Dr. Paul Garner in May 2020, after he revealed that he had been experiencing symptoms lasting for more than six weeks following the onset of his COVID-19 diagnosis (7). The term then grew popular among the research community, and there were many articles published with regard to long COVID. Since then, other terms such as post-COVID syndrome, post-COVID conditions (PCC), or post-acute sequelae of SARS-CoV-2 infection (PASC) have been used interchangeably to describe patients with persistent symptoms after an acute SARS-CoV-2 infection (8). According to the Centers for Disease Control and Prevention (CDC), long COVID is defined as having ongoing symptoms of COVID-19 that persist beyond four weeks from initial infection (9). Importantly, long-COVID can be seen in both patients with and without a history of hospitalization for COVID-19 infection.

The most common symptoms among individuals with long COVID are fatigue, dyspnea, cough, sleep disturbances, and headache. Based on current reports, factors associated with an increased risk of developing long COVID are not well-established. Some studies have proposed that female sex, age, presence of comorbidities such as hypertension, obesity, and diabetes, as well as an immunosuppressive state, may be associated with long COVID (10). However, other studies have found contradictory findings (11, 12).

With the emergence of the COVID-19 pandemic, there was concern that patients with MS might have higher SARS-CoV-2 infection, hospitalization, and mortality rates. Many studies investigated the effect of disease-modifying therapies (DMTs), which are widely used in pwMS, on developing COVID-19 infection. Rituximab, a chimeric monoclonal antibody targeted against CD20+ B cells, is a mainstay of therapy in pwMS. In general, studies have not reached a specific conclusion with regard to the role of rituximab in COVID-19 morbidity and mortality (6).

It is not well known whether pwMS undergoing treatment with immunomodulators/immunosuppressors will develop antibodies against SARS-CoV-2 following infection. The long-term consequences of COVID-19 infection in pwMS are also a matter of debate. In addition, studies have suggested that COVID-19 infection may be

linked to MS exacerbation and relapse (6). For all the above reasons, management of pwMS infected with SARS-CoV-2 remains extremely challenging. Here, we provide a guideline for the management of pwMS receiving rituximab who are suspected of having long COVID (Figure 3).

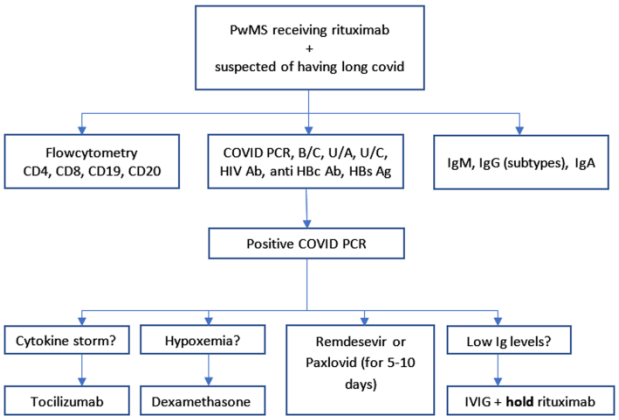

Figure 3. This algorithm shows how to approach patients with multiple sclerosis who are suspected of having long COVID

Some studies have shown a decreasing trend in immunoglobulin levels, specifically IgG, during rituximab treatment in patients with MS. Patients with MS might also have lower baseline IgG levels compared with healthy controls (13). A study by Cervia et al. investigating the risk factors for PASC found that low IgM and IgG3 levels during the acute phase of infection were significantly associated with developing PASC (14). The effects of rituximab on long COVID disease courses have not been studied yet. However, we suggest that rituximab be substituted with another medication in pwMS who present with long COVID and are found to have low immunoglobulin levels.

Declaration

Written informed consent was obtained from the patient to publish this report following the journal's patient consent policy.

Competing interests

None

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