Pneumocystis jirovecii pneumonia complicated a case of SARS-CoV-2 infection and multiple sclerosis after treatment with rituximab

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Abstract

Immunodeficient patients are less prone to develop serious complications of COVID-19 and cytokine storm. However, they are more likely to develop opportunistic infections that can mimic the symptoms of the SARS-CoV-2. we presented a 27-year-old male case of SARS-CoV-2, who was complicated with Pneumocystis jirovecii pneumonia, following treatment with rituximab.

Introduction

In December 2019, the viral infection outbreak in Wuhan, China became a global pandemic that crossed borders and put the lives of populations in danger, especially those with immunodeficiency (1). During these challenging years and the management of COVID-19 disease, many questions have arisen regarding immunomodulatory and immunosuppressive therapies, especially, in patients with demyelinating disease (2). Given the reduced immune responses, immunodeficient patients are less prone to develop serious complications of COVID-19 and cytokine storm. However, they are more likely to develop opportunistic infections that can mimic the symptoms of SARS-CoV-2 infection (3).

Multiple sclerosis (MS), an autoimmune, demyelinating disease of the central nervous system (CNS), is mainly linked to the reaction of CD4+ T cells to the antigens of myelin membrane (4). Two previous randomized clinical trials (RCTs), has demonstrated that rituximab, a monoclonal anti-CD20 antibody, could be effective in primary progressive multiple sclerosis (PPMS) and relapsing-remitting multiple sclerosis (RRMS) (5). However, there are growing reports, introducing post-rituximab therapy Pneumocystis jirovecii pneumonia (PJP), in cases of systemic lupus erythematosus, Wegener's granulomatosis, rheumatoid arthritis, lymphoma, and humoral renal transplant rejection (6). Given the fact that rituximab is a commonly used medication for the highly active forms of MS, it is important to consider the possible risk of PJP in these patients.

In the current study, we presented a case of COVID-19 infection, who was complicated with PJP, following treatment with rituximab for RRMS.

Case presentation

A 27-year-old male patient with MS for the past 12 years has been referred to our center with complaints of cough, dyspnea, body pain, and fever, in April 2022. The patient was admitted to the hospital due to cough with sputum, myalgia, fever, sweating, and frequent outpatient treatment (the last appointment was about a week before hospitalization) due to the exacerbation of previous myalgia, and the initiation of cough, fever, and dyspnea. In June 2021, he was also hospitalized in another center for 5 days with fever, cough, and

dyspnea due to COVID-19 infection, and treated with remdesivir and glucocorticoid. Eventually, he was this discharged, 24 hours after the termination of his fever.

He had also a previously-diagnosed RRMS for the past 12 years, which resulted in neurological symptoms such as blurred vision, headaches and paresthesia in the lower limbs. Due to the uncontrollable MS, intravenous (IV) injections of rituximab (1gr per 6 month) was applied. The last injection was in February 2022. He was also taking prednisolone (5mg daily) for maintenance therapy and other medications such as salmeterol plus fluticasone inhaler, montelukast, NAC, and aspirin.

On physical exam, his temperature was 38 °C; blood pressure, 125/80 mmHg; respiratory rate, 17 breaths per min; pulse rate, 88 beats per min; and oxygen saturation, 94% (without any oxygen therapy). His fever was during day, but the sweating was preferably overnight. He also had a dyspnea that made him unable to walk (FCIII). The patient's cough contained yellow sputum, and the body pain was responsive to analgesic. He had symmetric chest wall movements and no crackles or wheezing was detected. However, we could find rhonchi. There was no evidence of organomegaly, tenderness, or rebound tenderness in the examination of abdomen and it was not distended. In the neurological examination, no abnormal findings were detected. His laboratory data on admission showed an increased LDH (2061 U/L) along with increased levels of hepatic biomarkers (Table 1). Moreover, the levels of CRP, ESR, and PCT were higher than normal range. Transthoracic echocardiography (TTE) revealed an increased pulmonary artery pressure (30 mmHg).

First, we were highly suspicious of infections; thus, we began empiric treatment with ceftriaxone. However, due to persistent fever, the suspicion of nosocomial infections, the progression of pulmonary lesions, and reduced oxygen saturation, we began treatment with piperacillin + tazobactam, vancomycin, and levofloxacin. Nevertheless, patient's fever did not stop after the aforementioned empiric treatment and his conditions got worse. Therefore, we were highly suspicious of opportunistic infections such as Cytomegalovirus, tuberculosis (TB), pulmonary aspergillosis, and Pneumocystis jirovecii.

We also considered the probability of infection in other sites. Thus, echocardiography and abdominal and pelvic ultrasonography were performed and revealed to be normal. Accordingly, bronchoalveolar lavage (BAL) fluid was obtained through bronchoscopy and was assessed for infections. In the case of TB, both BAL smear and RT-PCR were negative. Aspergillosis was also excluded due to a negative level of galactomannan in the BAL. However, RT-PCR demonstrated that COVID-19 infection was still remained (cycle threshold of 27). Further, the cytological assessment of BAL fluid showed no evidence of malignancy. Pneumomediastinum and pneumothorax were also excluded on the CT scan images. In figure 1, the patient's CT scan findings were demonstrated, on admission day, right before bronchoscopy, discharge day, and 3 months later.

On the 12^{th} day, his conditions worsened and he was admitted to the intensive care unit, due reduced oxygen saturation (SpO_2 = 88%), and treatment was switched to linezolid and imipenem. At this time, the result of BAL fluid, tested for Pneumocystis jirovecii by RT-PCR, turned out to be positive. Therefore, we started trimethoprim-sulfamethoxazole (treatment of choice for PCP) and dexamethasone. Following the treatment, his conditions improved and the levels of PCT and CRP decreased. He was discharged in May 2022.

Discussion

Respiratory viral infections can put patients in the risk of secondary infections, especially by bacterial and fungal organisms (7). In a previous study, about 30% of SARS-CoV-2 infected cases were at the risk of developing secondary pneumonia without a known reason (8). In fact, SARS-CoV-2 infection can interfere with the immune system and its balance; therefore, it may result in an increased risk of fungal infections such as invasive candidiasis, pulmonary aspergillosis, and Pneumocystis jirovecii (9). Given the fact that Pneumocystis pneumonia (PCP) and COVID-19 may have similar and common clinical features such as profound hypoxemia and bilateral multifocal infiltrates, coinfection with PJP could be missed, especially in those with life-threatening forms of COVID-19 infection. Hence, it seems wise to apply additional diagnostic workup for PJP in severe COVID-19 patients, especially in the presence of clinical features that support coinfection, like cystic formations on chest CT scan and an increased level of lactate dehydrogenase, even if there were no risk factors for PJP (10).

It seems that immunosuppression plays an important role in the association of COVID-19 and PCP. Although impaired immune balance may be useful in the context of COVID-19 severity, due to the reduced immune respond and inflammation, which are related to the severity of manifestations, it is also a chief risk factor for the occurrence of PCP (11). In that case, preexisting immunodeficiency (e.g. HIV- or drug-induced) could increase the risk of COVID-19 and PJP coinfection. Importantly, it might be observed in those who are not included in the known risk groups, which could be a result of severe COVID-19-induced lymphopenia or immunosuppressive therapy (12).

PJP has two morphological forms in its life cycle, including cystic and trophic forms. It is an infection usually identified in patient with impaired T cell immunity, particularly $CD4^{+}$lymphopenia. Unfortunately, severe COVID-19 infection is associated with severely diminished levels of $CD4^{+}$ cells (9), which makes these patients highly susceptible to PJP. Moreover, COVID-19 infection could result in conditions like acute respiratory distress syndrome, which requires immunosuppressive therapies (e.g. corticosteroids), a familiar risk factor for developing PCP (9).

Conclusion

SARS-CoV-2 infection can interfere with the immune system and its balance; therefore, it may result in an increased risk of fungal infections such as invasive candidiasis, pulmonary aspergillosis, and PJP. In the current study, we presented a case of COVID-19 infection, who was complicated with PJP, following treatment with rituximab for RRMS. We hope this article helps clinicians consider causes other than COVID-19, especially opportunistic infections such as PJP, in patients with respiratory symptoms and fever.

Author contributions

MSHZ and HM : treating the patient, collecting the medical history, helped with manuscript writing and revision. **RM** : report of CT scan images and helped with manuscript writing.**MGA** : collecting the medical history and helped with manuscript writing and revision. **ATP** : collecting the medical history, writing the main part of the paper, and revising the content of manuscript.

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Data availability statement

The Data supporting the findings of this study are available upon request from the corresponding author and with permission from Babol University of Medical Sciences, Babol, Iran.

Conflict of interest disclosure

The authors declare no conflict of interest.

Ethics statement

For publication of this article, we obtained written informed consent from the patient to release any potentially identifiable data.

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Figure 1: a) on admission day CT scan, there were multilobal bilateral patchy consolidations, ground glass opacities and interlobular septal thickening, with peripheral and peri-bronchovascular distribution. "Crazy paving" is the dominant feature at right upper lobe; b) CT scan right before bronchoscopy showed increased consolidations, ground glass opacities and crazy paving in the same manner at multiple lung segments; c and d) on discharge day CT scan, there were decreased consolidations and change to ground glass opacities and crazy paving appearance at the same involved segments. There was also evidence of "reverse halo" in several segments and progression to fibrotic changes predominantly at lung bases, as parenchymal and sub pleural bands; e) CT scan image, 3 months after discharge.