Case Report

Unexpected Positive Effects of Rituximab and Corticosteroids on COVID-19 in a Patient Suffering from Granulomatosis with Polyangiitis

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Abstract

The COVID-19 pandemic has raised concerns among physicians and patients with autoimmune disorders about how this viral infection affects the patients receiving immunosuppressive drugs. There are speculations about a higher incidence and severity of COVID-19 in patients receiving a variety of immunosuppressant drugs. However, we reported the rapid recovery from COVID-19 in a 67-year-old male with granulomatosis with polyangiitis who did not experience severe symptoms of the COVID-19 as expected, despite having a history of serious lung involvement due to the autoimmune disease. He received conventional medications to treat COVID-19, though he had been receiving rituximab and corticosteroids before the onset of COVID-19 symptoms. Prevention of the cytokine storm caused by SARS-CoV-2 infection owing to taking the immunosuppressive drugs (rituximab and corticosteroids) could be a reason for these unexpected observations. Therefore, this case showed that taking immunosuppressive drugs is unlikely to be directly related to the increased severity of COVID-19.

Keywords: *COVID-19, cytokine storm, granulomatosis with polyangiitis, immunosuppressive drugs, rituximab*

Introduction

Granulomatosis with polyangiitis (GPA) is a chronic systemic disease related to antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis that typically affects the respiratory tracts (from sinuses to lungs) and kidneys. This inflammatory disorder that was formerly known as Wegener's granulomatosis is the result of granuloma formation and inflammation of the small blood vessels (vasculitis). This autoimmune disease is potentially dangerous and injuries caused by GPA on vital organs, such as the lungs and kidneys, can be fatal.[1,2]

Currently, a combination of corticosteroids and biologic disease-modifying antirheumatic drugs (DMARDs), such as rituximab, is used to treat the disease.[1] Rituximab is a chimeric monoclonal antibody against CD20 located on the surface of B cells, which destroys B cells through binding to CD20 antigens.[3] Since this medication kills both normal and dysfunctional B cells, the number of functional B cells will also reduce during the therapy with rituximab, leading to a decrease in the body's defense and pathogen attacks.[4] In addition, corticosteroids widely used to reduce inflammation in the treatment of autoimmune diseases, including GPA, are considered as immunosuppressive drugs that decrease the ability of the immune system to fight different infections in patients.[5]

The recent outbreak of COVID-19 originated from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)[6] has sparked a flurry of speculation about a higher incidence and severity of COVID-19 in the patients receiving a variety of immunosuppressant drugs.[7] For example, patients with GPA who are being treated with immunosuppressive drugs such as rituximab and corticosteroids may be in more serious conditions if they become infected with this virus. Despite all the concerns about the increased risk of COVID-19 in patients taking immunosuppressive drugs, we have observed the mild symptoms of COVID-19 and rapid recovery from this disease in a patient with GPA who has been receiving immunosuppressant drugs,

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including rituximab and prednisolone, since August 2019. Therefore, the main reason for this report is to show the efficacy of immunosuppressive drugs in reducing the risk and severity of COVID-19 in a patient with an autoimmune disorder.

Case Report

The patient is a 67-year-old male with lung lesions, who has been diagnosed with GPA since August 2019. A written informed consent was obtained from the patient. He presented early clinical symptoms including a mild fever (37.5°C), cough, and bloody sputum (hemoptysis). Following a computed tomography (CT) scan, a big pulmonary mass was observed in the right lung [Figure 1]. The patient also had high values of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP). Moreover, the negative results of tuberculosis (TB), interferon gamma release assay (IGRA), and acid-fast Bacillus tests and the positive results for the PR3-ANCA (cANCA) test (more than three times the normal value) led to the rejection of TB and the diagnosis of GPA. Therefore, as the induction therapy, the patient was immediately treated with 500 mg/day of rituximab (total cumulative dose = 2 g) and methylprednisolone 500 mg pulse (1 g/day) for 3 days. Moreover, the patient also took other medications including prednisolone (1.25 mg/day), cotrimoxazole 400/80 mg (400/80 mg/12 h), and iron–folic acid 1 mg (1 mg/day). After disappearing the early symptoms (remission phase), the patient was scheduled to receive rituximab (500 mg) every 6 months for six consecutive periods. The patient also suffered from cardiovascular disease before being diagnosed with GPA and used carvedilol 6.25 mg (6.25 mg/day), losartan 25 mg (1 tablet/day), and atorvastatin 20 mg (1 tablet/day) to treat it.

Treatment with prednisolone (1.25 mg/day) continued until on April 4, 2020 when the patient visited the doctor for only brief symptoms of shortness of breath. According to the chest X-ray results [Figure 2], increasing the amounts of cANCA (145 U/mL), and CRP (58.9 mg/L), he was diagnosed with a pulmonary abscess due to GPA. Therefore, the dose of prednisolone increased up to 15 mg/day, and he was also prescribed hydroxychloroquine sulfate 200 mg (200 mg/day) and azithromycin 250 mg (500 mg [2 tablets] on the 1st day and 250 mg/day from the 2nd day to the 5th day), which quickly improved his clinical conditions.

Two weeks later (April 20, 2020) that coincided with an increase in the prevalence of COVID-19, the patient went to a hospital with symptoms including body aches, a nonproductive cough, shortness of breath, sore throat, loss of appetite, nausea and vomiting, fatigue, and severe weakness. A reverse transcription (RT)-polymerase chain reaction (PCR) test and lung CT scan [Figure 3] were performed to check the possibility of COVID-19. The RT-PCR test was positive for COVID-19, and the result of the CT scan showed the signs of bilateral multiple ground-glass opacity that were indistinguishable from the recurrence of GPA. The patient was immediately hospitalized, and his vital signs including O_2Sat (87%), PR, (89) temperature (36.8°C), and blood pressure (BP) (137/98 mm Hg) were recorded. He was treated with hydroxychloroquine sulfate 200 mg (200 mg/6 h), azithromycin 500 mg (500 mg/8 h), prednisolone 5 mg TDS (5 mg/8 h), and cotrimoxazole 400/80 mg BD (400/80 mg/12 h), while he was receiving folic acid 1 mg (1 tablet/day), chlorphenamine 4 mg (1 tablet/day), carvedilol 6.25 mg (6.25 mg/day), losartan 25 mg (25 mg/day), atorvastatin 20 mg (20 mg/day). During his hospitalization, the COVID-19 symptoms were mild. A week later of the hospitalization, with the disappearance of the initial symptoms, a negative result of RT-PCR and appropriate vital signs including O_2Sat (92%), PR (79), temperature (36.5°C), and BP (100/6 mm Hg), the patient was allowed to leave the hospital and undergo the home quarantine. All treatments for COVID-19 were applied before the second period of rituximab infusions.

Discussion

Following the outbreak of COVID-19, the use of immunosuppressive drugs is expected to increase the severity of this viral infection in patients with autoimmune

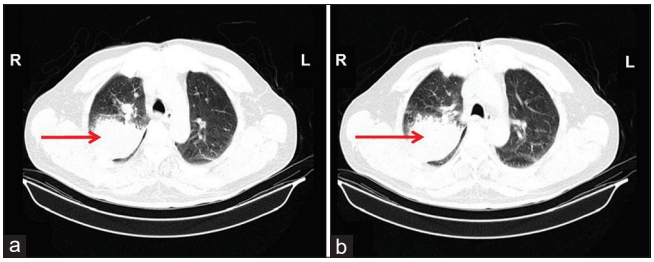

Figure 1: The results of computed tomography scan of the lung with granulomatosis with polyangiitis (a and b). There is a big pulmonary mass in the right lung indicated by arrows

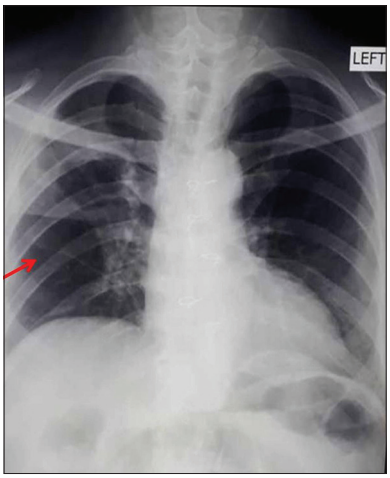

Figure 2: The radiograph of the lung with granulomatosis with polyangiitis. Arrow shows a big pulmonary cavity in the right lung

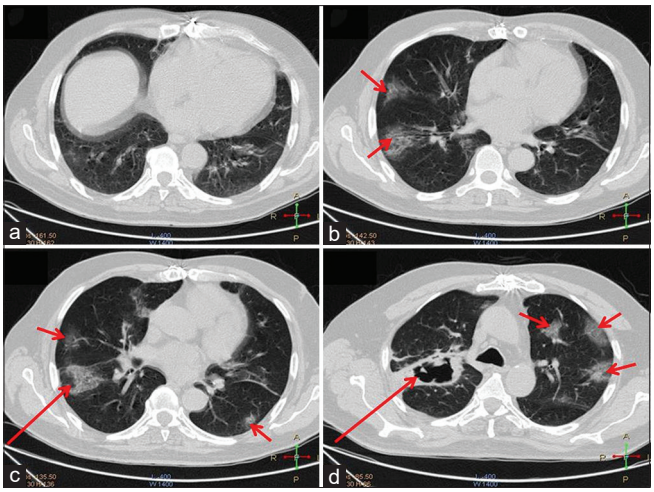

Figure 3: Computed tomography scan of the lung with COVID-19 (a-d). There are multiple scattered patchy ground-glass opacities in both lungs (short arrows), mostly with peripheral distribution, which are highly suggestive for COVID-19 pneumonia. There is also a cavity lesion (long arrows) in upper zone of right lung adjacent to major fissure, suggesting for concomitant infective or noninfective processes

diseases. However, our report indicated mild symptoms of COVID-19 and rapid recovery in a 67-year-old patient with GPA who has been under treatment with rituximab and corticosteroids since August 2019. Moreover, he already had a cardiovascular disease, which according to recent studies, COVID-19 will be more dangerous and complicated in patients with cardiovascular problems.[8] Similarly, there is a report of recovery from COVID-19 in a 52-year-old woman with GPA who received immunosuppressive drugs during COVID-19 treatment.[9] Recovery from COVID-19 was also observed in patients with chronic arthritis who temporarily stopped taking bDMARD or tsDMARD as soon as COVID-19 diagnosis.[7]

The mild symptoms of the COVID-19 and rapid recovery from this disease in our patient with extensive pulmonary involvement due to GPA are probably related to the functions of rituximab and glucocorticoids, including prednisolone, in modulating cytokine storm. The cytokine storm is the result of the excessive and uncontrolled release of pro-inflammatory cytokines including interleukin 1 (IL1), IL6, IL8, IL12, IL18 tumor necrosis factor alpha (TNFα), and interferon gamma.[10] Previous studies have shown that the cytokine storm in patients with COVID-19 can be a reason for the rapid progression of the disease, multiple organ failure, and mortality. Therefore, the control of cytokine storm is currently an effective strategy in the treatment and rescue of patients with COVID-19.[11]

The production of cytokine by B-cells can play a significant role in autoimmune disease development.[12] Moreover, pulmonary infections originated from bacteria, fungi, and viruses such as SARS-CoV-2 are one of the factors that promote cytokine storm, leading to systemic sepsis. The balance between pro-inflammatory cytokines and their receptors or inhibitors determines the intensity of lung inflammation.[10]

Due to the destruction of B-cells, rituximab can directly or indirectly inhibit the production of cytokines, especially pro-inflammatory cytokines.[12-14] For example, in patients with rheumatoid arthritis, a significant decrease in the serum concentrations of IL-2, IL-6, and IL-7 in response to rituximab therapy indicated the positive effects of rituximab on the regulation of pro-inflammatory cytokine level.[15]

Corticosteroids also play a significant role in reducing pro-inflammatory cytokines through the downregulation of inflammatory genes.[16] There is a report of a dramatic reduction in plasma cytokines such as TNFα, IL6, and IL-1ß in patients with acute respiratory syndrome treated with corticosteroids.[17] A decrease in IL12 production in patients with severe sepsis was observed after treatment with a low-dose steroid.[18] Moreover, corticosteroid therapy reduced the concentration of serum IL-2, IL-6, IL-8, and IL-10 in children with Kawasaki disease.[19]

In contrast, immunosuppressive therapies may improve immune system responses to acute respiratory syndrome through an increase in the level of anti-inflammatory cytokines such as IL-10.[12] For example, the IL-10 level increased in response to rituximab treatment.[14] In addition, corticosteroids induce the expression of several anti-inflammatory genes including IL-10, annexin 1, secretory leucocyte protease inhibitor (SLPI), and the inhibitor of nuclear factor-kappa B (kB) (IkB-a).[16]

Conclusion

Our case report indicates that having an autoimmune disorder and taking immunosuppressive drugs do not necessarily increase the severity of COVID-19, despite the ability of these drugs to lower the level of immunity. Moreover, these drugs may also be useful in preventing the cytokine storm caused by SARS-CoV-2 infection. Therefore, according to this case, immunosuppressive drugs, including rituximab and corticosteroids, probably do not have a direct positive correlation with the increased severity of COVID-19.

Ethics approval

This study was carried out based on the ethical principles of the declaration of Helsinki, and all study procedures were approved by the Isfahan University of Medical Science Ethics Committee (Code No. IR.MUI.MED.REC. 1399. 199).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts

will be made to conceal identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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