D J Med Sci 2021;7(3):288-292
doi: 10.5606/fng.btd.2021.30

Case Report

A case of COVID-19 pneumonia in an immunosuppressed patient with late-onset of respiratory symptoms

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ABSTRACT

The current coronavirus disease 2019 (COVID-19) pandemic has resulted in significant morbidity and mortality all around the world. In immunocompromised patients, the clinical features and outcomes of the disease are not well defined. This case report presented a confirmed case of COVID-19 pneumonia in an immunosuppressed patient with an unexpectedly late onset of respiratory symptoms.

Keywords: COVID-19, immunosuppression, SARS-CoV-2.

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-caused novel coronavirus disease 2019 (COVID-19) pandemic has resulted in significant morbidity and mortality throughout the world.[1] Given the uncertainty of COVID-19's early symptoms and the small and localized imaging findings, it's difficult to predict how the disease will progress and whether mild symptoms will progress to serious forms later on.[2] According to studies, mild to moderate disease symptoms can last for 8 to 13 days after the onset of the disease.[3,4] However, in some patients, shortness of breath may develop in the second week of the disease, which may be accompanied by hypoxemia.[5,6] The clinical characteristics and outcomes of COVID-19 in immunocompromised patients, who are thought to be at a higher risk of severe disease but may also have reduced damaging inflammatory responses, are unclear.[7] In this case report, we presented an immunosuppressed COVID-19 pneumonia case with an unusually late onset of respiratory symptoms and a long-term positive SARS-CoV-2 reverse transcription-polymerase chain reaction (RT-qPCR) test. We aimed to contribute to the literature on clinical worsening in immunosuppressed patients long after the onset of the disease.

CASE REPORT

A 27-year-old female patient was admitted for three days with fever, cough, chest pain, wheezing, and loss of appetite. She had a history of renal transplantation two years ago due to chronic renal failure secondary to vesicoureteral reflux. The patient was taking several medications for this reason, including everolimus, prednisolone, and mycophenolate mofetil. Furthermore, she had previously received rituximab treatment and radiotherapy for post-transplant lymphoproliferative disease six months prior. The patient was diagnosed with COVID-19, which only presented as anosmia, 29 days prior to the current application, and the SARS-CoV-2 RT-PCR result obtained at that time was positive, and she received favipiravir treatment for five days, with the anosmia

Received: March 25, 2021
Accepted: May 04, 2021
Published online: January 28, 2022

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Cite this article as:
Güçlü Kayta SF, Alkan Çeviker S, Önder T, Akça A, Yüksel C, Vurucu S, et al. A case of COVID-19 pneumonia in an immunosuppressed patient with late-onset of respiratory symptoms. D J Med Sci 2021;7(3):288-292.

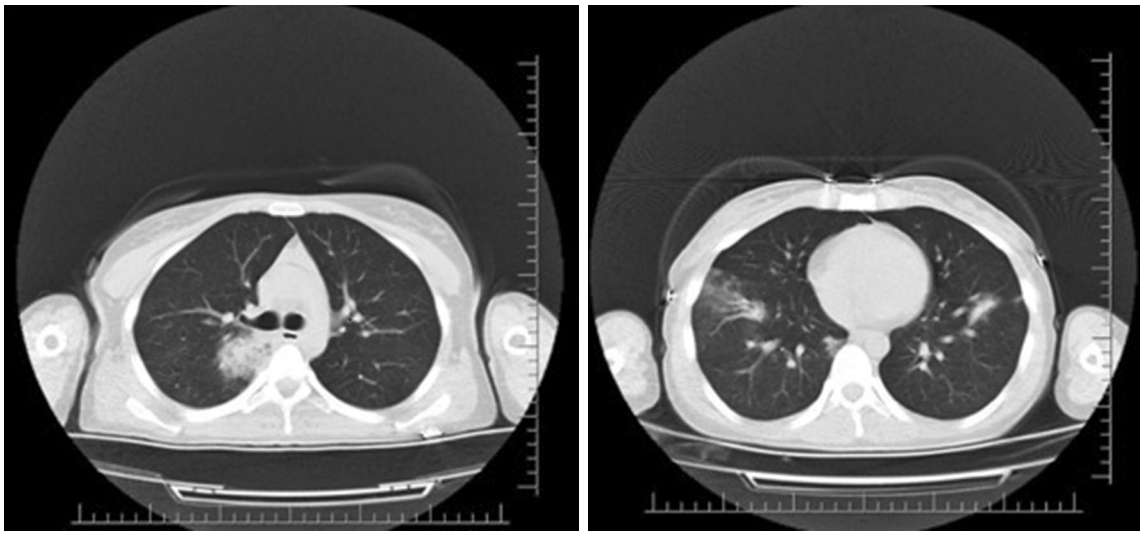

Figure 1. Thorax computed tomography images.

complaint persisting, though it had decreased. At the time of admission, the patient's blood pressure was 126/75 mmHg, heart rate was 130/minute, respiratory rate was 27/minute, and SpO_2 was 98% on room air. Auscultation revealed diffuse rhonchi in the bilateral lungs and rales at the right lung base during the respiratory examination. Examinations of the neurological, abdominal, cardiac, and locomotor systems were all normal. The following laboratory results were determined: leukocyte count: 2,970/mm^3, lymphocyte count: 440/mm^3, platelet count: 129,000/mm^3, hemoglobin level: 12.8 g/dL, erythrocyte sedimentation rate (ESR): 41 mm/h, C-reactive protein (CRP) levels: 4.1 mg/dL (normal value: <1 mg/L), creatinine levels: 1.65 mg/dL, and estimated glomerular filtration rate (eGFR): 42 mL/min. The results of the liver function tests and the coagulation profile tests were both normal. In the patient's sputum culture, no bacterial or fungal growth was found. In both lung parenchyma, a focal area of ground-glass opacity and a consolidated region with localized diffusely predominantly peripheral

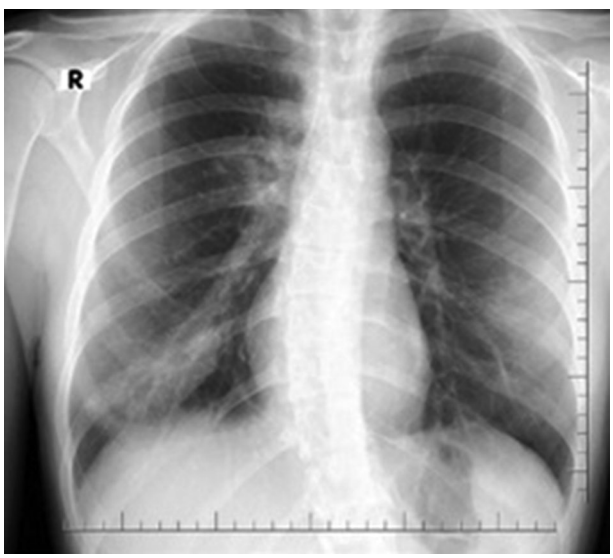

Figure 2. Chest radiograph taken on the 4th day of follow-up.

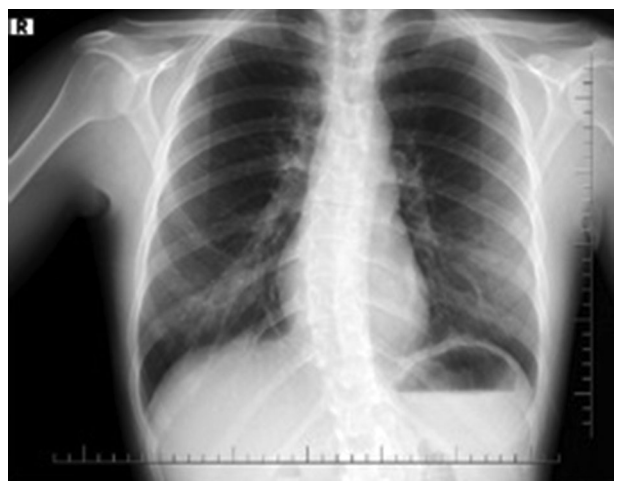

Figure 3. Chest radiograph taken on the 7th day of follow-up.

involvement were seen on computed tomography (CT) imaging of the thorax (Figure 1). The symptoms were evaluated primarily in favor of COVID-19 pneumonia. The patient was placed in an isolation ward. The test for SARS-CoV-2 was positive using RT-PCR from a combined throat and nasal swab sampling. The patient was started on oral favipiravir 2×1,600 mg after loading, 2×600 mg maintenance dose, subcutaneous enoxaparin 1×4,000 IU, and intravenous ceftriaxone 1×2 g treatments. The patient's immunosuppressive treatments, mycophenolate mofetil, and prednisolone were discontinued. Everolimus treatment was maintained at the same dose. On the fourth (Figure 2) and seventh (Figure 3) days of the follow-up, control chest radiographs were taken. The patient's respiratory symptoms improved on the seventh day. Control chest radiographs revealed regression in pre-existing infiltrative areas. The patient's treatment was completed in 10 days, and she was discharged. A written informed consent was obtained from the patient.

DISCUSSION

The SARS-CoV-2 is a betacoronavirus with an envelope surface consisting of a lipid bilayer derived from the host membrane that belongs to the subgenus Sarbecovirus and the subfamily Orthocoronavirinae. Its genome encodes spike (S) glycoproteins, small envelope (E) protein, membrane protein (M), and nucleocapsid (N) protein, as well as accessory proteins that interfere with the host's immune response.[8] SARS-CoV-2 binds to its host cellular receptor, angiotensin-converting enzyme 2 (ACE2). In ACE2-expressing cells, it causes organ damage, particularly in the lungs. The active replication and release of the virus in lung cells induce nonspecific symptoms such as fever, myalgia, headache, and respiratory symptoms.[9] The virus has been shown in an experimental hamster model to cause temporary damage to cells in the olfactory epithelium, resulting in olfactory dysfunction, which may explain the temporary loss of smell and taste common in COVID-19.[10] Interleukin (IL)-1, IL2, IL-4, IL-7, IL-10, IL-12, IL-13, IL-17, macrophage colony-stimulating factor (M-CSF), monocyte chemoattractant protein-1 (MCP-1), hepatocyte growth factor (HGF), cytokines such as IFN-γ and TNF-α were found to be high in the pathogenesis of the disease. This indicates that the lung injury is a result of secondary to a cytokine storm caused by the inflammatory response.[11]

Given the pandemic's sudden onset and rapid spread, little is known about SARS-CoV-2 infection and its association with specific diseases, especially in immunosuppressed patients. Considering the pathogenesis of COVID-19, there are two possible hypotheses regarding the effect of immunosuppression on the disease's progression. One of them is that the patients' current immunosuppressive condition can prevent the cytokine storm that occurs as a result of an uncontrolled immune response and thus contribute positively to the disease's progression. On the other hand, due to the increased risk of infection, insufficient immune response, and failure to suppress viral replication and virus propagation, this situation may present as a poor prognostic factor.[11] In our case, in addition to the use of multiple immunosuppressive drug regimens due to renal transplantation, there is also a type of hematological malignancy known as transplantation-associated lymphoproliferative disease. The presence of two different immunosuppression mechanisms, as well as the use of multiple drugs related to their current diseases and treatment history, made predicting the course of the disease and managing the disease extremely difficult.

Cancer patients, particularly those with lung cancer and hematological malignancies, appear to be at a higher risk for severe COVID-19 disease and mortality, with an increased risk of adverse outcomes from this viral infection due to immunosuppression caused by cancer-related factors and treatment effects.[7,12] According to Aries et al.,[12] the most important factor associated with the severity of the disease and mortality in patients with hematological malignancies was age, and another factor was the presence of comorbidities. High blood pressure, diabetes, cardiovascular disease, and cerebrovascular disease are the most common and significant comorbidities.[12-14] The young age of the patient and the absence of primary comorbidities such as hypertension, diabetes mellitus, and cardiovascular disease may explain why the condition did not progress to severe

disease and the rapid clinical response to treatment in the follow-up of our case.

The most common symptoms at the onset and course of the disease were fever, cough, and shortness of breath.[9] Likewise, the most common presenting symptoms in patients with hematological malignancies and solid-organ transplant recipients are similar.[12,15] Shortness of breath may develop in some patients, usually in the second week of illness, and may be accompanied by hypoxemia.[5,6] According to Pongpirul et al.,[16] the median (interquartile range (IQR)) period between the onset of the disease and the detection of pneumonia was 7.0 (5.0-9.0) days. Although none of these symptoms were present at the time of our case's first admission, that is, at the beginning of the disease, complaints of fever, cough, and shortness of breath, which indicate pneumonia, appeared approximately 26 days later. The symptoms mentioned may also occur as a result of pneumonia caused by other factors, particularly bacteria. However, the patient's persistence of SARS-CoV-2 RT-PCR test positivity, the absence of growth in her sputum culture, and the absence of a specific appearance for other pneumonia agents in radiological imaging, on the contrary, the presence of specific imaging findings for COVID-19 suggested the patient's late presentation of the COVID-19.

According to the Ministry of Health's current guidelines, our patient's antiviral treatment was arranged as a maintenance treatment after the favipiravir loading dose, and the duration of treatment was determined to be 10 days due to the prolongation of the symptoms.[17] Furthermore, experience with respiratory viruses in transplant recipients demonstrates greater susceptibility, faster progression to pneumonia, greater disease severity, and prolonged spread of potentially infectious virus compared to normal hosts. These hosts are also more likely to develop bacterial or fungal superinfection.[18] Therefore, in our case, in addition to the standard antiviral treatment of favipiravir, we empirically added antibiotherapy with ceftriaxone due to the high risk of developing bacterial superinfection.

Although treatment for COVID-19 among solid organ transplantation (SOT) recipients varies significantly by study, reduced immunosuppression still is the mainstay of therapy. According to a review by Fung and Babik,[7] in studies from 14 different centers, most patients (up to 90%) had antimetabolite therapy discontinued, and to a lesser extent, calcineurin inhibitor was discontinued or reduced (up to 70%). As described in these studies, the majority of COVID-19 cases among SOT recipients are managed with immunosuppression reduction. This approach risks immune reconfiguration and rejection, but it may improve viral clearance.[18,19] Due to our patient's worsening respiratory symptoms and condition, we discontinued the anti-metabolite mycophenolate mofetil treatment and continued the everolimus, which has synergistic immunosuppressive activity with calcineurin inhibitors (CNIs), allowing CNI-reduction.

Despite significant heterogeneity among studies, many studies have shown an increase in disease severity and mortality among SOT recipients with COVID-19 and patients with hematological malignancies.[7,12]

In conclusion, given the pandemic's sudden onset and rapid spread, little is known about SARS-CoV-2 infection and its link to certain diseases, especially in immunosuppressed patients. The optimal management of these patients, including changes in immunosuppressive regimens and targeted antiviral therapy, is unknown. Comprehensive studies are required to determine the effects of the current status of immunosuppression on the course of symptoms, the severity of the disease, and the optimal treatment.

Declaration of conflicting interests

The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding

The authors received no financial support for the research and/or authorship of this article.

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