

# Delayed Onset of COVID-19 in an Immunosuppressed Patient

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**Abstract:** We report on a case of delayed presentation of COVID-19 in a postpartum immunosuppressed patient with the confounding variable of cytomegalovirus viremia. This case highlights the importance of maintaining high suspicion for COVID-19 disease even with delayed onset of symptoms, as this diagnosis has important treatment and public health implications.

**Key Words:** SARS-CoV-2, COVID-19, immunosuppression

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In the latter part of December 2019, the novel coronavirus (SARS-CoV-2) broke out in Wuhan, China. It has subsequently continued to spread resulting in millions of cases worldwide. Information on viral shedding, duration of infection with replication competent virus, and length of symptoms informs health policies related to quarantine and precautions set forth by the Centers for Disease Control and Prevention.<sup>1</sup> Immunosuppressed patients are known to have prolonged disease course and prolonged viral shedding with other viruses such as influenza.<sup>2</sup> However, the duration of SARS-CoV-2 shedding among individuals with immunosuppression, clinical presentation, and disease course may differ compared with immunocompetent patients.<sup>3,4</sup> We present a case of a profoundly immunosuppressed patient who was admitted to the hospital with symptoms of coronavirus disease 2019 (COVID-19) approximately 19 days from initial diagnosis and 24 days from exposure.

The patient was a 35-year-old woman who was 13.5 weeks postpartum with recent hospitalization 4 weeks prior, from June 3 to July 1, 2020, for cold autoimmune hemolytic anemia and postpartum hemophagocytic lymphohistiocytosis (HLH), meeting 6 of 8 inclusion criteria with clinically compatible presentation. During that hospitalization, she was treated with high doses of dexamethasone (10 mg for 2 weeks with taper to 5 mg) and etoposide 75 mg for 10 doses. After this hospitalization, although deconditioned, she was back to baseline. She was exposed to SARS-CoV-2 during a family gathering on the fourth of July, subsequent to which 3 family members tested positive, including our patient on July 9, at which time she was undergoing screening during a brief hospitalization related to hyperglycemia secondary to steroids. She then re-presented to the hospital with shortness of breath, cough, sputum production, and hypoxia on July 28, 2020, which was 24 days after initial exposure.

On the day of admission, the patient had a temperature of 37.3°C, heart rate of 116 beats/min, and blood pressure of 168/108 mm Hg. The patient was noted to desaturate to 85% on room air and required 3 L of oxygen by nasal cannula. Laboratory results on admission were notable for acute kidney injury with a creatinine

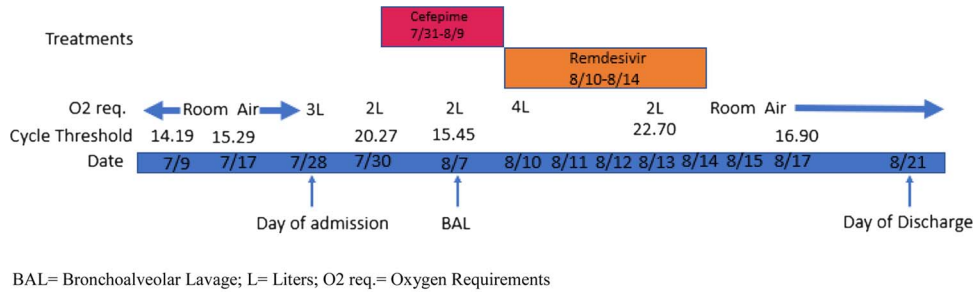
of 0.8 mg/dL (baseline on 0.47 mg/dL), a normal white blood cell count, and normal transaminases. Inflammatory markers were noted to be elevated, with ferritin of 6346.5 ng/mL; however, the patient had chronic elevation in these laboratory results from prior tests. A computed tomography angiogram of the chest was performed, which demonstrated bilateral ground-glass opacities and lower lobe infiltrates. Sputum culture from the day of admission grew pan-susceptible pseudomonas for which the patient completed 9 days of cefepime. During this time, the patient's leukocytosis increased, and her oxygen requirement progressed to 4 L. She began having fevers (temperature >37.5°C) on day 7 of admission. Workup for worsening hypoxia despite targeted antibacterial therapy included the following: sputum for pneumocystis jirovecii pneumonia polymerase chain reaction (PCR), serum fungitell, serum Aspergillus antigen, urine and serum histoplasma antigen testing, blastocystis serology, and serum Epstein-Barr virus PCR, all of which yielded negative results. Serum cytomegalovirus (CMV) PCR was found to be greater than 12,000 copies/mL. Repeat SARS-CoV-2 PCR testing was performed on days 3 and 11 of hospitalization, and the results remained positive. The molecular pathology laboratory was contacted to determine the cycle threshold (CT) of each sample as an indicator of virus titer. The results were as follows: 7/9 CT was 14.19, 7/17 CT was 15.29, 7/30 CT was 20.27, and 8/7 CT was 15.45 (Fig. 1). As the patient's overall clinical status was worsening, a repeat computed tomography scan was performed, which demonstrated progression of bilateral ground-glass opacities to involve all 5 lobes. Because of the unclear clinical significance of the serum CMV PCR testing in the context of worsening clinical status and concern for sustained high SARS-CoV-2 viral burden with a persistently low CT, the decision was made to treat the patient with intravenous remdesivir, which has been granted an emergency use authorization by the Food and Drug Administration for the treatment of COVID-19. In addition, the patient was placed on dexamethasone 12 mg by the hematology/oncology service because of concern that HLH could be again triggered by SARS-CoV-2. The pulmonology service performed a bronchoscopy for bronchoalveolar lavage and lung tissue biopsy on 8/13 to exclude other possible etiologies given her immunocompromised state. Fungal, bacterial, acid-fast bacilli cultures, Epstein-Barr virus PCR, pneumocystis jirovecii pneumonia PCR, shell vial culture for CMV, and aspergillus antigen were all negative. Qualitative CMV PCR testing yielded a positive result. However, pathology from biopsy demonstrated organizing pneumonia and was negative for viral inclusions and immunohistochemical staining was negative as well, making it less likely that the CMV was causing active pulmonary disease. The pulmonology team on consult thought it was less likely to be organizing pneumonia given the development of clinical and radiographic findings while the patient was on steroids. The SARS-CoV-2 PCR testing on bronchoalveolar lavage demonstrated a CT of 22.70, and 4 days later, repeat PCR testing from a nasopharyngeal swab was found to be 16.90. The patient had a decline in oxygen requirement within 13 hours of initiation of remdesivir and was weaned to room air by 104 hours of therapy (Fig. 1). However, at the time of discharge, she still had a persistent sinus tachycardia to the 120s and desaturated with ambulation,

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**FIGURE 1.** Time course demonstrating CT of RT-PCR testing, oxygen requirements, and treatments.

25 days from initial presentation and 44 days from initial positive test. Follow-up CT on September 25, 2021, was greater than 35.

### DISCUSSION

Our case highlights several important points related to COVID-19 including the importance of having a high suspicion for delayed presentation of clinically relevant symptomatic COVID-19 in patients with immunosuppression, the importance of considering alternate etiologies of infection, and the possible benefit of using remdesivir for the treatment of COVID-19 outside of the typical treatment window in cases of delayed symptomatic infection.

In our patient, after extensive testing, we were unable to find any alternative explanation for her respiratory symptoms and significant hypoxemia besides COVID-19. Given her immunocompromised history and serum CMV viremia, we had to rule out tissue invasive CMV disease. However, biopsy from bronchoalveolar lavage was negative for both viral inclusions and immunohistochemical staining, which is the criterion standard for the diagnosis of invasive disease,<sup>5</sup> and shell vial culture did not yield growth of viable CMV from the bronchoalveolar washings. Notably, her CMV qualitative PCR from the bronchoalveolar lavage was positive, but this is not sufficient to demonstrate invasive disease.<sup>6,7</sup> Furthermore, viral shedding can occur from the lungs in the absence of invasive disease, although it may be associated with a higher overall mortality.<sup>8</sup>

After ruling out invasive CMV pneumonitis, with all other test results being negative, in the setting of clinical and radiographic features of COVID-19 with increasing SARS-CoV-2 viral load as indicated by CT, we had high index of suspicion for the contribution of SARS-CoV-2 to her clinical presentation with the concern of protracted symptoms related to her relative immunocompromised state after recent systemic immunosuppressive therapies that were given for management of autoimmune hemolytic anemia and postpartum HLH. Our clinical suspicion for active COVID-19 infection was supported by the high SARS-CoV-2 viral titers corresponding to persistently low CT that indicated high burden of virus-associated nucleic acid. It has been shown that patients with high viral loads are more likely to have active virus.<sup>9</sup> In addition, patients who are immunocompromised are also suspected of having a longer duration of shedding of potentially infectious viral particles, with current recommendations suggesting prolonged isolation up to 20 days among such individuals. Importantly, our patient had a dramatic response to IV remdesivir therapy, rapidly weaning off oxygen to room air while on therapy.

In immunocompetent patients, the time of incubation from exposure to disease onset can be up to 14 days but, on average, is 4 to 5 days.<sup>10</sup> COVID-19 presentation in immunosuppressed patients has varied from more rapid disease progression to more

indolent disease with delayed presentation and mild symptoms.<sup>11</sup> Our patient's delayed presentation and improvement with remdesivir was similar to a patient presented by Helleberg et al<sup>4</sup> with CLL who was treated with chemotherapy 3 months before hospital admission for COVID-19 and who demonstrated a prolonged febrile illness for 60 days and was treated with 2 courses of remdesivir before resolution of symptoms.

The longest duration that viable virus has been able to be cultured from an immunocompetent patient is 18 days<sup>3</sup>; however, this patient was an outlier, as most other studies have shown that patients with mild to moderate disease manifestations are not considered to be infectious after 10 days.<sup>1</sup> It is important to recognize that patients with immunosuppression can present with COVID-19 far outside of the typical 2- to 14-day range, and that these patients may have more prolonged disease courses after their atypical presentation. Such a diagnosis should be entertained, and careful consideration should be given to treat such cases that may seem to be outside the typical window for administration of remdesivir. More research needs to be done to correlate the presence of replication-competent virus and CT in immunocompromised hosts and to provide clinicians with appropriate tools to manage these complex cases. Acknowledging the possibility of delayed presentations and prolonged disease course in immunocompromised patients is critical for appropriate management of disease and to prevent ongoing transmission within the health care setting and in the community.

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