Prolonged COVID-19 Pneumonitis and Severe Lung Injury in a Patient with a History of Diffuse Large B-cell Lymphoma after CAR-T Therapy: Highlighting the Role of Corticosteroids

Mark Ehioghae, MSc; Harini Shah, BS; Anu Taylor, MD; Brian Buggy, MD; Gabriel Mikhael, MD

ABSTRACT

Introduction: COVID-19 can have severe consequences for immunocompromised individuals, including those with hematological malignancies. Prolonged infections causing pneumonia and lung injury are rare in patients with diffuse large B-cell lymphoma (DLBCL) treated with chimeric antigen receptor T-cell (CAR-T).

Case Presentation: A 43-year-old male with a history of DLBCL, in remission for 2 years after CAR-T therapy, developed a persistent COVID infection, as confirmed via positive polymerase chain reaction. This slowly progressed to symptomatic hypoxemic pneumonitis and biopsy-proven diffuse alveolar damage, which responded to corticosteroid treatment.

Discussion: COVID-19 poses increased risks to patients with a history of hematologic malignancies and can lead to severe respiratory distress and mortality. Studies have shown prolonged pneumonitis may require corticosteroids for improvement. However, data on appropriate regimen for managing prolonged COVID-19 pneumonitis are lacking.

Conclusions: This case highlights challenges of the treatment of COVID-19 infections in immunocompromised individuals with hematological malignancies. Corticosteroid treatment shows benefits, but dosing and duration should be based on individual patient response. Extended monitoring, individualized treatment plans, and research are crucial for optimizing outcomes in this vulnerable population.

INTRODUCTION

As of May 2023, the United States has witnessed the significant impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in terms of 98 million COVID-19 cases and 1 128 903 deaths.[1] While most COVID-19 infections have been mild, immunocompromised individuals with hematological malignancies are at a higher risk of developing severe disease and experiencing increased mortality, even following a mild infection.[2] Immunocompromised patients have been observed to have persistent and prolonged COVID-19 infections, leading to secondary organizing pneumonia or severe lung injury, including the presence of hyaline membranes consistent with diffuse alveolar damage.[3,4] However, such manifestations are seen rarely in patients who are 2 years removed from treatment of diffuse large B-cell lymphoma (DLBCL) with chimeric antigen receptor T-cell (CAR-T) therapy.

In this report, we present a case of a patient who exhibited persistent COVID-19 positivity for 2.5 months, presenting as organizing pneumonia, despite being 2 years post-CAR-T treatment for DLBCL. Notably, clinical improvement was achieved only after the initiation of high-dose systemic corticosteroids.

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Author Affiliations: Medical College of Wisconsin, Milwaukee, Wisconsin (Ehioghae, Shah, Taylor); Advocate Aurora St. Luke's Medical Center, Milwaukee, Wisconsin (Buggy, Mikhael).

Corresponding Author: Mark Ehioghae, MSc, 1349 S 84th Milwaukee, WI 53214; phone 414.737.1721; email O_ehioghae@hotmail.com; ORCID ID 0000-0002-8579-2953

CASE PRESENTATION

A 43-year-old male with a history of mediastinal DLBCL in remission for 2 years after CAR-T therapy presented with cough, myalgia, and headache on day 1. Chest x-ray and computed tomography (CT) of the chest were normal (Figure 1). A qualitative antigen test for the presence of SARS- CoV-2 (Abbott BinaxNOW) was positive. He was given symptomatic treatment. Prior COVID vaccinations were with Moderna mRNA-1273 vaccine 13, 12, 11, and 6 months prior to presentation.

The patient had persistent cough, malaise, and mild exertional dyspnea. He then developed a severe diffuse headache and presented to hospital again on day 21 of his illness. CT of the head suggested mild cerebral edema, which was confirmed on magnetic resonance imaging, with the addition of diffuse dural thickening. Cerebrospinal fluid analysis was completely normal with a nega-

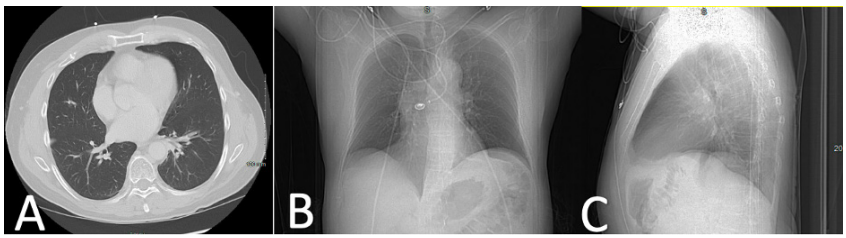
tive viral encephalitis panel and negative cytology. Peripheral blood analysis showed total white blood cell count was 2.4 K/mcl with an absolute neutrophil count of 2.2 K/mcl and a total lymphocyte count of 0.5 K/mcl. COVID-19 polymerase chain reaction (PCR) (Cepheid Xpert N-2 platform) was positive with a cycle threshold of 36.3. He was treated symptomatically without remdesivir or steroids, but symptoms persisted with continued fever, chills, nonproductive cough, and increasing dyspnea. However, his headache resolved by day 35.

Respiratory symptoms worsened, and on day 51, chest x-ray revealed bilateral ground glass opacities. Pulse oximetry on room air at rest was 93%. He was treated with empiric azithromycin and ceftriaxone. Blood cultures, urinary antigens for *Legionella pneumophila* and *Streptococcus pneumoniae*, and a multiplex viral respiratory panel were negative. COVID PCR remained positive at a cycle threshold of 34.5. Total lymphocyte count remained at 0.6 K/mcl. IgG was 406 mg/dl (reference range 700-1600), IgA was 38 (reference range 70-400), and IgM was 37 (reference range 40-250). He refused treatment with remdesivir and was given prednisone 40 mg daily (approximately ½ mg/kg/day) with a 3-week taper with no clinical improvement.

Two weeks later on day 65, he presented to the hospital again with worsening infiltrates on both chest x-ray and chest CT (Figure 2), now with resting hypoxemia of 83%. This improved to 96% on 4 liters/minute of supplemental oxygen. COVID cycle threshold was unchanged at 34.6. Bronchoscopy was performed, and all infectious diagnostic studies on lavage fluid (bacterial, fungal, mycobacterial, viral) were negative except for a barely detectable *Aspergillus galactomannan* antigen on 1 of 2 bronchoalveolar lavage specimens (index value of 0.60 with threshold of <0.50, ARUP Labs). He was given posaconazole while awaiting 16s ribosomal DNA analysis for bacteria and mycobacteria with 28s ribosomal DNA for fungi (University of Washington), all of which were ultimately negative. Transbronchial biopsy revealed diffuse alveolar damage with hyaline membrane formation (Figure 3).

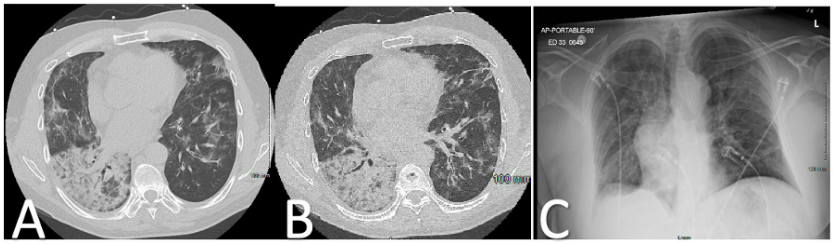
Intravenous methylprednisolone at 1 mg/lg/day for 5 days was administered with rapid clinical improvement. He was placed on a prolonged (2 month) prednisone taper starting at 0.75 mg/kg/day with sustained clinical resolution of his symptoms and clearance of the infiltrates on chest x-ray.

Figure 1. Computed Tomography (CT) and Chest X-ray of the Patient on Day 1



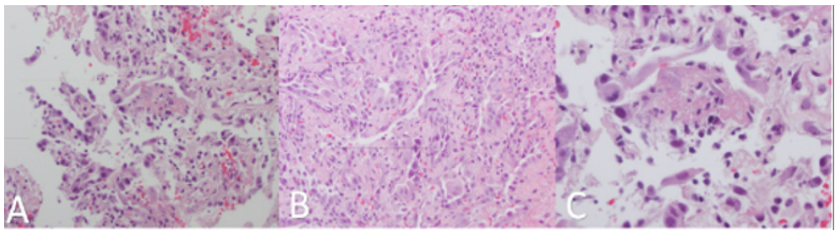
A: Axial chest CT.
B and C: Anterior/posterior and lateral chest x-ray.

Figure 2. Computed Tomography (CT) and Chest X-ray of Patient on Day 65



A and B: Axial chest CT of bilateral ground glass opacities.
C: Anterior/posterior chest x-ray of interstitial infiltrates

Figure 3. Biopsy Images



A and B: Biopsy of intact alveolar membranes within alveolar spaces.
C: Biopsy of organizing phase of hyaline membranization.

DISCUSSION

In immunocompetent individuals, a mild COVID-19 infection typically resolves within 4 weeks.[3] However, patients with malignancies who contract COVID-19 often experience severe respiratory distress and higher mortality rates.[2,3]

Similar cases have been described by Golbets et al,[5] where a patient with a history of DLBCL and receiving maintenance rituximab showed improvement after introducing corticosteroids to treat secondary organizing pneumonitis associated with COVID-19. Siafarikas et al[6] presented 2 cases of patients who deteriorated rapidly with organizing pneumonia after acute COVID-19 infec-

tion, with clinical improvement seen after corticosteroid (methylprednisolone at 1 mg/kg/day) intervention. Dayco et al[7] described a patient in remission from DLBCL after chemotherapy who contracted COVID-19, developed pulmonary fibrosis, and showed improvement following high-dose corticosteroid treatment starting with prednisone 40 mg for 1 week, subsequently decreasing by 5 mg every 7 days.

In contrast, Hensley et al[8] presented a patient with prolonged COVID-19 positivity who did not receive early high-dose corticosteroid treatment. The patient, an immunocompromised individual on CAR-T therapy, received standard COVID-19 interventions but ultimately died from respiratory failure. The timing, dosage, and severity of COVID-19 are crucial factors influencing the outcomes of corticosteroid treatment, which has been associated with decreased all-cause mortality in hospitalized COVID-19 patients.[9,10] However, no standardized protocol currently exists for managing patients with prolonged COVID-19 pneumonitis and pulmonary manifestations. We believe that our patient's initial lack of response to prednisone was based on insufficient dosing of steroids, and his prompt response to higher dosing supports this conclusion.

It is important to note that in our case, the patient had not undergone CAR-T therapy for nearly 2 years. Studies have shown that patients who have undergone CAR-T therapy may experience neutropenia beyond 3 months[11] and cytopenia lasting 15 to 21 months post-therapy.[12] Despite our patient's total leukocyte count being within normal limits, lymphocyte counts remained consistently below the reference range, potentially impairing effective clearance of the COVID-19 virus and resulting in persistent positivity.[13,14] Hill et al[15] reported that viral infections are the most common pathogens within 28 days after CAR-T infusion, with fungal infections such as aspergillus increasing after 90 days. However, as demonstrated in our patient's case, these infection risks may extend far beyond the expected timeframe—as seen in our case for up to 2 years—which emphasizes the importance of extended monitoring.

CONCLUSIONS

This case report underscores the enduring challenges posed by severe COVID-19 in individuals, persisting up to 2 years following CAR-T therapy for hematological malignancies. The occurrence of prolonged viral activity in these patients accentuates the potential role of sustained lymphopenia, indicating the need for prolonged vigilance and monitoring. Notably, the positive response to high-dose steroids demonstrated in this case suggests a viable therapeutic avenue for managing severe COVID-19 complications in immunocompromised individuals with a CAR-T therapy history. However, the absence of a standardized protocol highlights the complexity of prolonged COVID-19 pneumonitis in this unique population, emphasizing the urgent necessity for further research. The imperative for ongoing investigation is clear, as elucidating the timing, dosage, and overall efficacy of interventions is paramount to refining treatment strategies and ultimately improving outcomes in this specific and vulnerable patient cohort.

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