Dual antiviral therapy for persistent COVID-19 and associated organizing pneumonia in an immunocompromised host

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RUNNING TITLE

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ABSTRACT

The management of patients with prolonged viral shedding and COVID-19 symptoms remains unclear. Combining antivirals, as practiced in other infections, is theoretically advantageous. We present a case of persistent, symptomatic SARS-CoV2 infection and associated organizing pneumonia that was successfully treated with an extended course of combination antiviral therapy.

KEY WORDS

SARS-CoV2

COVID-19

Immune compromise

INTRODUCTION

Prolonged viral shedding has been widely described in immunocompromised hosts with SARS-CoV2 infection [1-3]. This can lead to the emergence of drug-resistant variants, increased infectivity, and prolonged COVID-19 symptoms. However, the management of patients afflicted by prolonged shedding beyond the initial first weeks of infection is unclear. Several antivirals against COVID-19 , including remdesivir, nirmatrelvir/ritonavir, and molnupiravir are now available. Current COVID-19 treatment guidelines recommend the use of a single agent within the first week of symptoms. The choice of antiviral is dictated by the patient's inpatient vs. outpatient status. Several case reports describe repeated or extended courses of remdesivir in immunocompromised patients with persistent COVID-19 with variable success [3-5]. We present a case of persistent, symptomatic SARS-CoV2 infection and associated organizing pneumonia (OP) in a patient with chronic lymphocytic leukemia (CLL) that was successfully treated with an extended course of combination antiviral therapy.

CASE REPORT

In early February 2022, a 64-year-old man with asthma and CLL who previously received 3 doses of the Pfizer COVID-19 mRNA vaccine developed cough and dyspnea and tested positive for SARS-CoV2 infection on a home antigen test. CLL was followed expectantly until January 2022, when he started venetoclax and obintutuzumab (humanized anti-CD20 monoclonal antibody) for progression of disease. COVID-19 was treated with a 5-day course of nirmatrelvir/ritonavir from February 5th to 10th. Several weeks later, he developed progressive dyspnea and fever to 38.8°C that did not improve with outpatient antibiotics and required a hospitalization. CT chest revealed bilateral diffuse patchy ground-glass opacities (Figure 1A) and treatment with broad-spectrum antibiotics was started. Bronchoalveolar lavage fluid (BALF) cultures were negative for bacteriaor fungus. Repeat SARS-CoV2 PCR performed on March 14 was positive prompting initiation of dexamethasone and a 10-day course of remdesivir. While mildly improved, his cough and dyspnea persisted and in late March, he received prednisone 60mg daily with prolonged taper for suspected OP. Despite the COVID directed therapy his SARS-CoV2 PCR remained positive on the 22nd of March. In mid-April, after his prednisone decreased to 30mg daily, the patient reported worsening cough, dyspnea on exertion without hypoxemia, and recurrent fever. His prednisone dose increased to 60mg, and he received another course of antibiotics. He did not improve and was hospitalized a week later. A new CT chest showed persistent, multifocal reticular and ground glass opacities with some areas of improvement (Figure 1B). SARS-CoV2 PCR remained positive. BALF cultures, stains, and molecular tests were negative for bacteria, fungi, non-SARS-CoV-2 viruses, and acid-fast bacilli. Cytology was also negative. His prednisone was increased to 80mg with a slow taper for the possibility of worsening OP. His dyspnea and cough partially improved but worsened once his prednisone was reduced to 60mg daily. Throughout this time, he continued to have severe dyspnea interfering with activities of daily living (ADLs) and ability to work. In May, his cough, dyspnea, fever, and body aches persisted, and a repeated PCR on May 1 was positive at a cycle threshold of 22, possibly

consistent with a high SARS-CoV-2 load. Note that cycle thresholds can vary among specimens and in this manuscript are being used as a general estimated of the magnitude of viral shedding. He received an infusion of bebtelovimab on May 6 for persistent SARS-COV2 infection. This led to brief symptomatic improvement but in June, after his prednisone decreased to 65mg daily, his symptoms worsened and he was hospitalized. Repeat CT chest revealed unchanged multifocal ground glass opacities (Figure 1C) and BALF for bacterial, fungal, or other viral pathogens was unrevealing except for positive BALF SARS-CoV2 PCR at a cycle threshold of 25. Transbronchial biopsy revealed normal bronchial tissue and alveolated lung parenchyma with focal changes consistent with OP. Prednisone was maintained at 60mg and we initiated combination therapy with remdesivir and nirmatrelvir/ritonavir (under an Investigational New Drug that was approved by the Food and Drug Administration). By the third treatment day, his fever resolved, and he experienced marked improvement in body aches, cough, and dyspnea, which he had not experienced since his initial COVID infection. In order to monitor for adverse events the patient had regular lab monitoring and was seen daily by the infectious disease consulting team while in the hospital. He was also screened for any new symptoms including but not limited to worsening fatigue, new pain, nausea, vomiting, or diarrhea. The patient was discharged after 9 days of combination antiviral treatment and prednisone taper and had a negative COVID-19 nasopharyngeal PCR at the time of hospital discharge. Combination antiviral therapy was continued to complete 20 days without adverse effect. At each follow-up visit, the patient had lab monitoring including complete blood counts, liver enzymes, and bilirubin which were all within normal limits. Upon completion of 20 days of remdesivir and nirmatrelvir/ritonavir the patient felt well and remained negative for SARS CoV2 PCR.. At two month follow up after this most recent hospitalization, he had tolerated prednisone taper to 10 mg daily and his dyspnea and cough had completely resolved. His repeat CT chest showed significant improvement in ground glass opacities (Figure 1D) and eventually, he completed full wean off prednisone. His SARS-CoV-2 PCR remained negative at two months post discontinuation of antivirals.

DISCUSSION

To our knowledge this is the first report of successful treatment of persistent SARS-CoV2 infection and organizing pneumonia in an immunocompromised patient using an extended course of remdesivir in combination with an extended course of nirmatrelvir/ritonavir.

The management of immunocompromised patients with persistent symptomatic COVID-19 infection remains unclear. Convalescent plasma, monoclonal antibody, and multiple courses of remdesivir as well as extended courses of remdesivir have been described with variable success [1-5]. During the 4-month period of COVID-19 symptoms, our patient received repeated courses of remdesivir, as well as a single course of nirmatrelvir/ritonavir and of bebtelovimab. Besides limited and transient improvement, his symptoms persisted, and his PCR remained positive with a cycle threshold consistently below 30 on the Abbot Alinity, Hologic Panther, and Genexpert platforms. When admitted in June 2022, his presentation with fever, body aches, dry cough, and dyspnea was consistent with ongoing COVID-19 which was not cured by repeated courses of treatment with a single antiviral for 5-10 days. At this point, we postulated that combining two antivirals that inhibit SARS-CoV-2's RNA-dependent RNA polymerase (remdesivir) and protease (nirmatrelvir) may be beneficial for their potential additive effect, following the recent publication by Schultz et al of an in vitro additive effect of nirmatrelvir/ritonavir and remdesivir or molnupiravir [6-8]. Combination therapy would also reduce the opportunity of the virus to evade treatment by mutations providing resistance to one of the medications [9-10]. Extended courses were reported for remdesivir but not for nirmatrelvir/ritonavir. We postulated that a long course of therapy could prevent the rebound of viral shedding and symptoms, well described after standard courses of nirmatrelvir/ritonavir, possibly due to insufficient drug exposure [9-10].

Our patient's radiographic and pathologic findings were consistent with organizing pneumonia. While there are no standard treatments for COVID-related organizing pneumonia, Myall et al recently proposed a course of prednisone daily at 0.5mg/kg tapered over 3 weeks [11]. Others have proposed

daily doses of 0.75-1.25mg/kg for 4 weeks followed by taper over 3-6 months [12] but relapses often occur when the dose is lowered below 20mg /day. Our patient's symptoms and radiographic findings mildly improved, but never fully resolved with steroids, even with doses as high as 80mg/day of prednisone. All symptoms fully resolved with combination antivirals despite tapering of prednisone, suggesting that persistent SARS-CoV-2 infection can lead to radiographic and pathologic findings consistent with organizing pneumonia.

This patient's history of CLL was likely a major contributor to his severity of disease. Given the impaired T-cell response and hypogammaglobulinemia associated with this diagnosis, our patient may have been more prone to both initial as well as persistent infection. With these considerations in mind this particular regimen may be worth considering in similarly immunocompromised populations.

A possible limitation of this presentation is the lack of genotyping of the virus. Thus, it is possible that this patient's course reflects reinfection rather than persistent infection. However, the persistence of his symptoms over the entire period since the initial diagnosis is clinically consistent with one continuum of disease.

In summary, we present a case of persistent viral shedding and COVID-19 symptoms, as well as radiographic and pathologic findings consistent with OP, over a 4-month period in an immunocompromised patient that was successfully treated with prolonged combination of remdesivir and nirmatrelvir/ritonavir. Additional data is required from clinical trials to support our approach. Until such data becomes available, clinicians should consider combination antivirals in clinical settings like the one we describe.

NOTES

Consent: Verbal consent was obtained from the patient prior to drafting this manuscript and again at his follow-up visit.

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Conflict of Interest: RK reports consulting fees paid to author from Azurity Pharmaceuticals, participation on a Data Safety Monitoring Board or Advisory Board for Theratechnologies, paid to author, and stock or stock options from Azurity Pharmaceuticals. YG reports consulting fees from Appili Therapeutics, Inc. (prior to becoming an employee) and from Pfizer, Sanofi, Seres Therapeutics (unrelated to COVID-19); honoraria for speaking from Pfizer, Merck, Paratek, Shionogi, AbbVie, Sanofi. CA reports patents planned, issued or pending for NASAL EPITHELIUM GENE EXPRESSION SIGNATURE AND CLASSIFIER FOR THE PREDICTION OF LUNG CANCER. All other authors: No reported conflicts of interest.

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Figure 1 Legends: Series of Chest CT images of the patient throughout his course from initial admission to outpatient follow-up.

1A: March/2022 first admission

1B: April/2022 second admission

1C: June/2022 third admission prior to antiviral therapy, new areas of ground-glass opacities with some resolution of ground-glass opacities in some of the previously affected areas

1D: August/2022 outpatient follow up with minimal symptoms and completion of prednisone taper with largely resolved ground-glass opacities

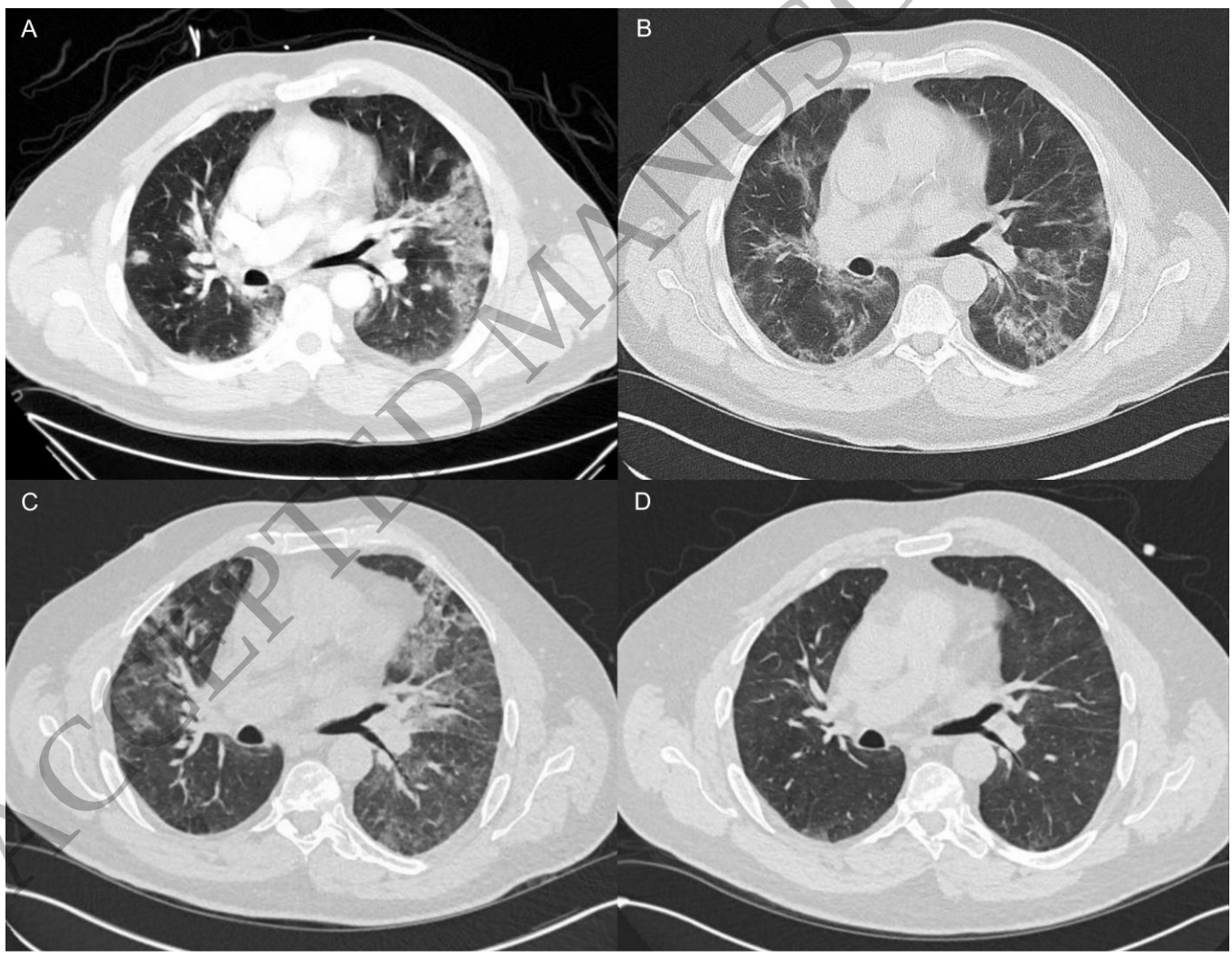

Figure 1
178x137 mm (x DPI)