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Case Report

The Use of Nirmatrelvir-ritonavir in a Case of Breakthrough Long COVID

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Abstract

Post-acute sequelae of SARS-CoV-2 (PASC) or long COVID is a major public health problem. The underlying mechanism(s) of this disease remains unclear, and there is a lack of effective therapies. We report a case of a 47-year-old patient who experienced breakthrough acute COVID-19 with PASC after two doses of COVID-19 vaccination, and its symptom resolution following a course of the novel combination of antiviral nirmatrelvir-ritonavir. One of several leading hypotheses on the pathogenesis of PASC is a persistent viral reservoir. This case report raises important questions on the potential role of antiviral therapies in long COVID, and the need for further research and clinical trials in this field of study.

Introduction

Post-acute sequelae of SARS-CoV-2 (PASC) or long COVID is a major public health problem with a paucity of clinical guidelines.[1] The definition of PASC is evolving, and this presently encompasses a heterogeneous spectrum of individuals who develop persistent symptoms that last for a number of weeks or longer after the initial COVID-19 infection.[2] Furthermore, the pathobiology of PASC is not understood, and there are no established therapies at this time. Limited but encouraging data suggest that vaccination can reduce the risk of PASC,[3] but it has been shown that PASC can develop after breakthrough infections.[4,5] However, it is not known how novel antivirals that target SARS-CoV-2 might impact the development or course of PASC. The present case report presents a case breakthrough PASC and its resolution following a course of the novel combination antiviral nirmatrelvir-ritonavir (Paxlovid), highlighting the need to test the efficacy of antivirals in long COVID through well-designed clinical trials.

Case report

A previously healthy 47-year-old woman was evaluated at our post-COVID clinic for seven months of PASC symptoms. The patient developed acute COVID-19 infection (confirmed by positive PCR testing, with an unknown genotype and viral load) in the summer of 2021. The patient received and tolerated two doses of the BNT162b2 (Pfizer-BioNTech) vaccine at six months prior to the onset of infection. The acute symptoms included cough, sore throat, altered smell and taste, headache, fever, chills, body aches, chest pressure and fatigue, which were managed with supportive home care, including rest and hydration. Most of the acute symptoms resolved after 48 hours. However, over the next several months, the patient continued to suffer from severe fatigue, cognitive difficulties, post-exertional malaise, insomnia, tachycardia, chest pressure and body aches, resulting in significant functional debilitation and a leave of absence from work. The patient also experienced headaches and hair loss, both of which self-resolved.

The workup included normal complete blood count, complete metabolic panel, thyroid function tests, troponin I, NT-proBNP, D-Dimer, EKG, chest X-ray and echocardiogram. The trials of different management strategies, including lifestyle modifications and various symptom-based medications (*e.g.*, stimulants, sleep aids, *etc.*), were generally ineffective, according to the patient's subjective report. The patient did have some gradual improvement with time, and this plateaued at approximately five months post-infection. At six months post-infection, the patient was potentially exposed to COVID-19 again with multiple positive close contacts, and developed new symptoms of headache, congestion, sore throat, low grade fever, sweats and malaise. Although the patient tested negative for COVID-19 by antigen test, the patient was started on a 5-day course of nirmatrelvir (300 mg)-ritonavir (100 mg) twice daily on day three of the acute symptoms by the patient's primary care provider, considering the potential false negative, the patient's exposures, and the patient's prior breakthrough infection history. The patient's acute flu-like symptoms

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Abbreviations: PASC, post-acute sequelae of SARS-CoV-2.
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began to improve by day three, and the patient also noticed a rapid improvement in pre-existing PASC symptoms after taking the antivirals. At seven months after the initial infection, the patient's PASC symptoms were resolved, and the patient reported being back to normal, with pre-COVID health status and function, including working fulltime and rigorously exercising. During the long-term six-month follow-up period after the use of nirmatrelvir-ritonavir, the patient reported that she was still generally doing well, continuing to work full time and remaining active. After a couple of months of follow-up, the patient developed intermittent, self-limited joint aches and leg cramps, which were not clearly related to the prior PASC.

Discussion

It is presently well-recognized that PASC can still occur in vaccinated individuals who develop breakthrough COVID-19 infection,[6] but it remains unclear whether the clinical presentation of breakthrough PASC differs from that of PASC that develop pre-vaccination. The symptomatology, prolonged duration and functional debilitation experienced by the present patient were similar to the conditions observed from various unvaccinated individuals with PASC.[7] Based on the time frame, it was suspected that the patient's initial infection was likely the Delta variant of SARS-CoV-2, but no confirmatory data is available for the present case. Therefore, studies are needed to clarify whether specific variants manifest PASC differently, and determine how this is modified by the vaccination status.

The notable feature of the present case was the timing of the patient's rapid PASC symptom resolution after the administration of nirmatrelvir-ritonavir for possible re-infection during the Omicron variant surge period at the end of 2021 and the start of 2022. Nirmatrelvir is a peptidomimetic inhibitor of the SARS-CoV-2 main protease that prevents viral replication, and ritonavir acts as a CYP3A4 inhibitor that enhances the bioavailability of nirmatrelvir.[8] The present emergency use authorization for nirmatrelvir-ritonavir is indicated for individuals with mild or moderate acute COVID-19, and high risk of severe infection.[9] However, it remains unclear whether the patient had COVID-19 re-infection with false-negative testing, or whether the patient acquired a different viral infection that caused similar symptoms, and how this may have impacted the chronic PASC symptoms. The temporal relationship of the antiviral therapy administration and PASC symptom resolution was correlative and based a single case. However, other studies have also reported in pre-print a small case series, with the observed association of PASC symptom alleviation and nirmatrelvir-ritonavir in some individuals.[10] There is presently no established effective treatment for PASC, though non-pharmacologic and pharmacologic interventions have been proposed.[11] These clinical observations for nirmatrelvir-ritonavir generate important hypotheses for the further testing of antiviral agents in PASC.

The underlying pathobiological mechanism(s) of PASC remains unknown. However, the leading hypotheses include immune and inflammatory dysregulation, SARS-CoV-2 viral persistence, and the reactivation of other latent viruses.[11–13] An increasing number of studies have revealed the presence and persistence of SARS-CoV-2 RNA in various tissues in some patients,[14–17] and the persistence of the SARS-CoV-2 antigen in circulation.[18–20] Further studies are needed to determine whether these signify active replicating virus, and whether these necessarily cause PASC symptoms. Another hypothesis is that dormant viruses, such as Epstein-Barr virus, may be reactivated in the setting of immune dysregulation resulting from SARS-CoV-2 and are then allowed to drive new symptoms, including in those who were initially asymptomatic during their acute COVID-19 infection.[12,21,22] Thus, the question then that follows from these viral-mediated models of PASC pathogenesis is whether antivirals may have a role in not only acute COVID-19 treatment but also in PASC treatment. To the authors' knowledge, no published clinical trial has addressed this question, at present. However, recent retrospective data suggests that nirmatrelvir-ritonavir use during acute COVID-19 infection for high risk individuals may reduce the risk of PASC.[23]

These findings and other clinical anecdotes highlight the need to consider viral persistence and antiviral therapies, as this field of study urgently pushes forward with rigorous mechanistic studies and well-designed clinical trials.

Clinical perspectives

There are presently no established effective therapies for the treatment of PASC. Future research should prioritize randomized controlled trials and other studies to investigate the potential role of antiviral therapies for PASC.

Conclusions

Breakthrough long COVID after vaccination can lead to significant PASC symptoms. The present case and other reported clinical cases have raised the observed association of PASC symptom improvement and Paxlovid treatment in these individuals. Further research studies, such as randomized controlled trials, are needed to determine whether Paxlovid and other antivirals can be effective therapies for PASC.

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Conflict of interest

All authors report no conflicts of interest.

Author contributions

All authors contributed to the clinical concept and made significant contributions. LG drafted and revised the manuscript; HB, RS, MM and PY reviewed and revised the manuscript.

Ethics statement

A written informed consent was obtained from the patient for the publication of this case report.

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