Case Report of Breakthrough Long COVID and the Use of Nirmatrelvir-Ritonavir

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Abstract

Post-Acute Sequelae of SARS-CoV-2 (PASC), or long COVID, is a major public health problem. Encouraging data suggest that vaccination can reduce the risk of PASC. We report a cautionary case of breakthrough PASC and its resolution following a course of the novel combination antiviral nirmatrelvir-ritonavir.

Full Text

Post-Acute Sequelae of SARS-CoV-2 (PASC), or long COVID, is a major public health problem with paucity of clinical guidelines [1]. The definition of PASC is evolving and it currently encompasses a heterogeneous spectrum of individuals who develop persistent symptoms that last for many weeks or longer after the initial COVID-19 infection [2]. The pathobiology of PASC is not understood and there is no effective therapy at this time. There is limited but encouraging data to suggest that vaccination can reduce the risk of PASC [3], but it is not clear in whom and how PASC presents after breakthrough infections. Here, we present one of the first reports of breakthrough PASC and its resolution following a course of the novel combination antiviral nirmatrelvir-ritonavir (Paxlovid).

Case Report

A previously healthy 47 year-old woman was evaluated at our post-COVID clinic for 7 months of PASC symptoms. She developed acute COVID-19 infection in the summer of 2021 and had received two doses of the BNT162b2 (Pfizer-BioNTech) vaccine 6 months prior to the onset of her infection. Her acute symptoms included cough, sore throat, altered smell and taste, headache, fever, chills, body aches, chest pressure, and fatigue, which were managed with home care. COVID-19 infection was confirmed by PCR test. Most acute symptoms resolved after 48 hours, but over the next several months she continued to suffer 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. She also experienced headaches and hair loss, both of which self-resolved.

Workup included normal complete blood count, complete metabolic panel, thyroid function tests, troponin I, NT-proBNP, D-Dimer, EKG, chest X-ray, and echocardiogram. Trials of different management strategies were generally ineffective, but she did have some gradual improvement with time until plateau at about 5 months post-infection. 6-months post-infection, the patient was potentially exposed to COVID-19 again and developed new symptoms of headache, congestion, sore throat, low grade fever, sweats, and malaise. She tested negative for COVID-19 by antigen test but was started on a 5-day course of nirmatrelvir (300mg)-ritonavir (100mg) twice daily on day 3 of her acute symptoms by her primary care provider, given considerations of a potential false negative and her prior breakthrough infection history. Her acute flu-like symptoms had already begun to self-improve by day 3, but she noticed rapid improvement of her pre-existing PASC symptoms after taking the antivirals. At 7-months post-initial

infection, her PASC symptoms had resolved, and she reported being back to her normal, pre-COVID health status and function including working fulltime and exercising rigorously.

Discussion

This case is a cautionary tale that demonstrates PASC can still occur in vaccinated individuals who develop breakthrough COVID-19 infection. The symptomatology, prolonged duration, and functional debilitation experienced by this patient are similar to that seen in many unvaccinated individuals with PASC [4]. We suspect that her initial infection was likely the Delta variant of SARS-CoV-2 based on time frame, but we do not have confirmatory data in this case. To our knowledge, the only other published case report of PASC from breakthrough COVID-19 infection is of a healthcare worker in Brazil who was re-infected with the Gamma variant after 2-dose vaccination with adsorbed (inactivated) SARS-CoV-2 vaccine (CoronaVac-Sinovac/Butantan) [5]. Studies are needed to clarify whether specific variants manifest PASC differently and how that is modified by vaccination status.

Another interesting feature of this case is the timing of the patient's rapid PASC symptom resolution following administration of nirmatrelvir-ritonavir for possible re-infection during the Omicron variant surge period at end of 2021 and start of 2022. It is unclear whether the patient had COVID-19 re-infection with false-negative testing or she acquired a different viral infection that caused similar symptoms and how that may have impacted her chronic PASC symptoms. The temporal relationship of the antiviral therapy administration and PASC symptom resolution is correlative and based a single case, but this observation is important to consider in the context of previously proposed hypotheses about the pathobiology of PASC, which include SARS-CoV-2 viral persistence and reactivation of other latent viruses [6]. An increasing number of studies have shown the presence and persistence of SARS-CoV-2 RNA in various tissues in some patients [7–10]. Further studies are needed to determine whether these signify active replicating virus and whether they 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 [6, 11, 12]. 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 date, there are no published studies addressing this question.

This case report highlights the need to remain vigilant about PASC in vaccinated populations and underscores the need for rigorous mechanistic studies and well-designed clinical trials to better understand the pathobiology of PASC and develop effective therapies for the millions of people around the world impacted by this condition.

Declarations

Patient Consent: The patient consented to participate and publish their clinical data and images.

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CONFLICTS OF INTEREST: All authors report no conflicts of interest.

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