American Journal of Infectious Diseases

Case Reports

Acyclovir May Be Used to Treat Certain Long COVID Patients Regardless of Herpesvirus Reactivation: Case Report

[1]Denise Stewart and [2]Martin Oswald Savage

[1]Department of Life Sciences, Imperial College London, SW7 2AZ, London, United Kingdom
[2]Center for Endocrinology, Institute of William Harvey Research, Barts and the London School of Medicine and Dentistry, Queen Mary, University of London, London, United Kingdom

Article history
Received: 24-01-2024
Revised: 03-02-2024
Accepted: 28-02-2024

Corresponding Author:
Denise Stewart
Department of Life Sciences, Imperial College London, SW7 2AZ, London, United Kingdom
Email: denise.stewart95@alumni.imperial.ac.uk

Abstract: Fundamental causes of long COVID or Post-Acute Sequelae of COVID-19 (PASC) are still under investigation while it remains a significant burden to millions of patients worldwide even after a relatively mild acute Coronavirus Disease 2019 (COVID-19) episode. Treatment and management programs are yet to be developed. The foremost hypotheses for underlying PASC pathophysiology include: The persistence of the virus in certain tissues, hyperinflammation due to COVID-19 immune dysregulation, and microcoagulation. Reactivation of herpesviruses has been regularly observed in certain patients going through COVID-19 and PASC. Such reactivation is thought to facilitate the entry of the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus into cells, enhancing the viral load, severity, and duration of symptoms. An unusual, non-hospitalized, and immunocompetent PASC patient is presented here. This study is a retrospective and descriptive review of the patient's clinical records with his consent. The prescriptions and clinical investigations were performed by his medical staff upon him seeking help voluntarily due to his symptoms. After suffering for about 12 months since his initial infection with SARS-CoV-2 in March 2020, he developed shingles in March 2021. He was prescribed 800 mg Acyclovir 5 times daily for 7 days by his primary care physician. He recovered not only from shingles but also from all of his PASC symptoms shortly after taking Acyclovir and resumed a normal life. Hence, the possible use of a well-known, safe, affordable anti-viral medication, Acyclovir, for long COVID patients is proposed. Full recovery of a long COVID patient after using solely Acyclovir for only 7 days is presented here for the first time. This observation supports the theory of SARS-CoV-2 lingering in various tissues of the body after several months as one of the causative factors for PASC: Since he recovered from all of his PASC symptoms and anti-viral Acyclovir might have acted against the remaining SARS-CoV-2 as well. Although more systematic clinical trials are needed to confirm these results, this finding could potentially transform the treatment options for PASC sufferers, especially with herpesvirus reactivation globally.

Keywords: Long COVID, COVID-19, SARS-CoV-2, Acyclovir, Post-Acute Sequelae (PASC), Anti-Viral Medication, Latent Virus Reactivation, Herpesviruses, Shingles

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection results in Coronavirus Disease 2019 (COVID-19) with upper and lower respiratory, gastrointestinal, and neurological symptoms: From runny nose, cough, brain fog, anosmia to diarrhea and fatigue, such as symptoms listed in Fig. 1. While most patients recover after the acute infection within a few weeks, over 65 million individuals, based on 10% of world-wide documented COVID-19 cases, continue to suffer from symptoms for many months (Davis *et al*., 2023; Stewart, 2023; Su *et al*., 2022). This is recognized as long COVID or Post-Acute Sequelae of COVID-19 (PASC). Persistence of the virus

(or its fragments) in certain tissues, hyperinflammation due to COVID-19 immune dysregulation with or without latent viruses reactivation, autoimmunity, microvascular dysfunction, gut microbiome disturbance, and microcoagulation are among the main hypotheses for underlying PASC pathophysiology (Davis *et al*., 2023; Stewart, 2023; Su *et al*., 2022). Another theory involves SARS-CoV-2 hiding in various tissues, remaining dormant after apparent recovery from COVID-19 to be reactivated due to stress or a weakened immune system akin to latent viruses (Heidary *et al*., 2021). Complications can lead to multisystem disorders, with potential damage to almost every organ and subsequently to new onset of cardiovascular, thrombotic and/or cerebrovascular conditions besides type-2 diabetes, Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS), dysautonomia and postural orthostatic tachycardia syndrome (Davis *et al*., 2023; Stewart, 2023; Su *et al*., 2022).

There are nine different herpesviruses: Herpes Simplex Virus-1 (HSV-1), HSV-2, Varicella-Zoster Virus (VZV), Epstein-Bar Virus (EBV), Cytomegalovirus (CMV), Human Herpesvirus-6 (HHV-6A), HHV-6B, HHV-7, HHV-8 (Carneiro *et al*., 2022; Vojdani *et al*., 2023). Particular clinical manifestations such as fatigue, brain fog of COVID-19 and PASC resemble those associated with herpesvirus infection and reactivation, which can cause mitochondrial fragmentation thereby affecting energy metabolism (Davis *et al*., 2023; Heidary *et al*., 2021; Carneiro *et al*., 2022; Vojdani *et al*., 2023). SARS-CoV-2 viral load was found to be correlated with HSV-1 levels in COVID-19 patients (Carneiro *et al*., 2022). Unsurprisingly, up to four different types of herpesviruses were detected concurrently in COVID-19 patients (Carneiro *et al*., 2022). Furthermore, EBV lytic replication was shown to increase Angiotensin-Converting Enzyme 2 (ACE2) expression, the cellular receptor of SARS-CoV-2, in epithelial cells *in vitro* (Verma *et al*., 2021). Consequently, SARS-CoV-2 infection can become more potent by pseudotyped virus entry while enhancing the severity and duration of COVID-19, thus leading to PASC (Vojdani *et al*., 2023; Verma *et al*., 2021).

Acyclovir is an anti-viral medication, an acyclic nucleoside analog for guanosine, and used to treat herpesvirus infections, primarily against HSV-1, HSV-2, VZV -the cause of shingles and chickenpox (Heidary *et al*., 2021; Majewska and Mlynarczyk-Bonikowska, 2022). It is used successfully to treat acute COVID-19 (Baker, 2021; 2022) and PASC patients with neurological problems (German *et al*., 2023; Beatty, 2023). However, it has not been shown to help the full recovery of a PASC patient from all of his symptoms. An unusual PASC case with reactivation of VZV leading to shingles is presented here. The patient recovered fully from PASC as well as shingles after Acyclovir treatment. Thus, using Acyclovir, with or without other medications for PASC sufferers is proposed. This is the first time full recovery of an immunocompetent PASC patient by using solely Acyclovir for only 7 days reported after ~12 months of PASC suffering. Using anti-viral medications as a potential solution to PASC was recently published (Stewart, 2023): Parts of this patient's data (Patient-Y) was included in the discussion and supplementary material of that article after receiving his consent (Stewart, 2023). The present report focuses exclusively on Patient-Y and highlights the potential Acyclovir use for PASC more explicitly while evaluating herpesviruses' reactivation significance during COVID-19 and PASC in the discussion.

Materials and Methods

Written informed consent for publication of this patient's data was obtained from the patient. Prescriptions and clinical investigations were performed by his doctors upon him seeking help voluntarily due to his symptoms. The findings here are incidental and this study is a retrospective and descriptive review of this patient's clinical records; therefore the protocol was not submitted to an ethics committee. There was no funding for this study. His expenses were covered by the National Health Service (NHS) and/or his private insurance. Over the counter and prescribed medications were paid for by the patient. He had taken the over the counter medication Lemsip (decongestant against cold/flu), vitamin C, and probiotics if needed between March and September 2020 to no avail. His Primary Care Physician (PCP) prescribed 400 mg Metronidazole 3 times daily for 7 days against *Blastocystis hominis* in September 2020 and 800 mg Acyclovir 5 times daily for 7 days against shingles in March 2021. He also used over the counter calamine lotion on blistered areas as part of a routine shingles regimen. Acyclovir was the breakthrough to his recovery from PASC besides shingles. See case presentation, Fig. 1 and Table 1 for further details.

Case Materials

Case Presentation

Patient-Y, a 49-year-old white male, suffered a significant cough, fever, anosmia, and upper and lower respiratory problems in March 2020 (Fig. 1). His respiratory discomfort over the following weeks was milder as compared to his initial experience. He had more gastrointestinal symptoms, particularly nausea, diarrhea, and bloated stomach, in addition to vertigo (Fig. 1). He was referred to the emergency department by his PCP because of significant vertigo and nausea in June 2020 and then to a gastroenterologist in August 2020. He was not hospitalized: Due to a lack of diagnostic tests at the time, based on his symptoms, particularly anosmia, doctors thought he had COVID-19 and then developed PASC.

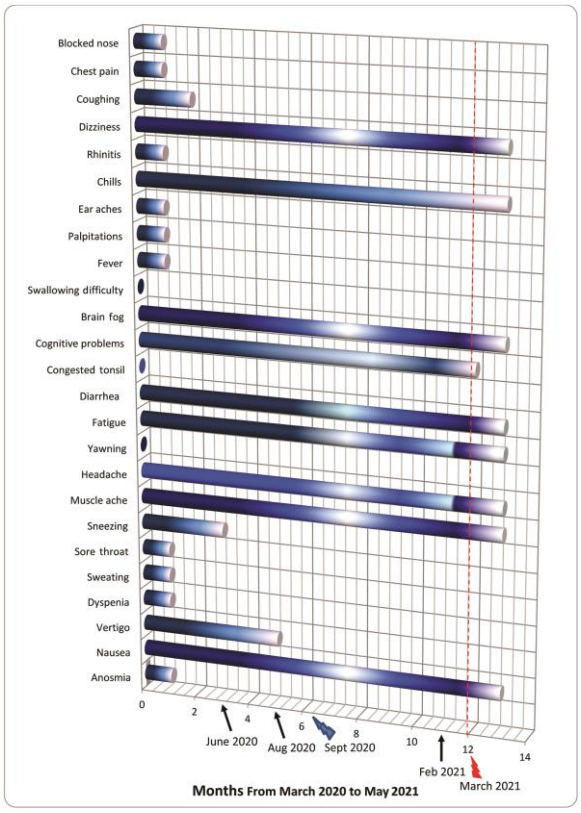

Fig. 1: Patient-Y symptoms and duration

[**Figure 1 Footnotes: Arrows** point to the times Patient-Y contacted medical care. **Blue Lightning bolt** points to the PCP prescribed antibiotic, 400 mg **Metronidazole** 3 times daily for 7 days treatment start time against the parasite, *Blastocystis hominis*, in September 2020, which did not help much. **Red Lightning bolt** points to the PCP prescribed anti-viral medication**,** 800 mg **Acyclovir** 5 times daily for 7 days treatment start time in **March 2021,** which was the breakthrough to his recovery. The intensity of his PASC symptoms was variable with periodic exasperation. They are roughly represented with dark **navy blue** representing the most intense and **white** representing no symptoms: Comparable to a pain scoring system from 0 to 5 with **5** being the most intense as well as more frequent (i.e., **darkest navy,** such as **diarrhea graph bar,** first 4 months); **1** representing very mild besides least frequent (i.e., **very light blue**, such as **sneezing graph bar** at 2nd month) and **0** representing no symptoms (i.e., **white**). **Brain fog graph bar shade** at first 3 months represents **intensity level 4**. **Headache graph bar shade** at first 3 months is equivalent to **intensity level 3**. **Vertigo graph bar shade** in June is equivalent to **intensity level 2.** His recovery is represented by the color gradually **whiten**ing. **Re: Fever:** The bar is a rough demonstration of on/off regular, persistent, variable fever he experienced for ~a month with **dark navy** representing ~40-41°C up to ~10 days in a row on/off and **white** representing normal ~36.5 °C. Shades in between represent the low-grade fever of ~38-39 °C.

The Helicobacter pylori test was negative in February 2021 when he consulted his gastroenterologist due to persisting symptoms. *Blastocystis hominis* (in August 2020) and distal gastritis (via gastroscopy in February 2021) in addition to a small sliding hiatus hernia were discovered during his check-up while he was thought to be going through long COVID. One cannot know how long these were present, however as explained in the main article text, after **Acyclovir** administration due to **shingles**, his symptoms disappeared in a few weeks. He did not have those symptoms prior to the pandemic. This also indicated that gastritis hiatus hernia or *Blastocystis hominis* were not the cause of his long COVID symptoms.

Written informed consent for publication of this patient's data was obtained from the patient. Prescriptions and clinical investigations were performed by his doctors upon him seeking help voluntarily due to his symptoms. The findings here are incidental and this is a retrospective and descriptive review of this patient's clinical records].

Table 1: Clinical characteristics and blood test results of Patient-Y

	Patient-Y				
	Pre-COVID-19 August 2016	Pre-COVID-19 November 2018	During COVID-19 August 2020	Post COVID-19 June/July 2022	Normal range
Age (years)	45	48	49	51	
Sex	Male				
BMI	22	22	22	22	18.5-24.9
Race	White				
Duration of symptoms	~12 months				
Smoking status	Former, none over ~25 years				
Immunocompromised	No				
Glucose	4.6	6.2	4.7		3.0-7.8 mmoL/L
C-Reactive protein (CRP)			<0.5	<1	0.0-10.0 mg/L
Ferritin			161		30-400 µg/L
HbA1c		39	38	40	20-41 mmoL/mol
Vitamin D			115		30-400 µg/L
Cholesterol	5.2		**5.5**	**5.9**	3.3-5.2 mmoL/L
Triglycerides	0.67		0.75	1.33	0.8-2.0 mmoL/L
Low-Density Lipoprotein (LDL)	**3.35**		**3.4**	**3.10**	0.0-3.0 mmoL/L
High-Density Lipoprotein (HDL)	1.55		1.73	2.20	1.1-2.6 mmoL/L

Table 1: Continue

Cholesterol/HDL ratio	3.35		3.2	2.7	0.0-5.0 ratio
Autoimmune profile		Negative	Negative	Negative	
Food allergy tests			Negative		
Calprotectin (for Gastrointestinal inflammation)			Negative		
HIV			Negative		
Hepatitis B (Australia antigen)				Negative	
Hepatitis C (Antibody ELISA, 3rd Generation)				Negative	
Copper (for Wilson's Disease WD)				17.5	10.0-22.0 µmoL/L
Caeruloplasmin (for WD)				0.25	0.15-0.30 g/L
Prolactin		211			86-324 mIU/L
Immunoglobulin G		11.86		12.57	7.0-16.0 g/L
Immunoglobulin A		2.17	2.03	2.12	0.7-4.0 g/L
Immunoglobulin M		1.06		1.05	0.4-2.3 g/L
Hematology					
White Blood Cells (WBC)	$5.5*10^9$	$6.34*10^9$	$5.8*10^9$	$7.92*10^9$	$(4.0\text{-}10.0)*10^9$
Neutrophils	$2.0*10^9$	$3.7*10^9$	$3.88*10^9$	$5.38*10^9$	$(2.0\text{-}7.0)*10^9$
Lymphocytes	$2.6*10^9$	$1.89*10^9$	$1.22*10^9$	$1.44*10^9$	$(1.0\text{-}3.0)*10^9$
Eosinophils	$0.3*10^9$	$0.19*10^9$	$0.12*10^9$	$0.21*10^9$	$(0.02\text{-}0.50)*10^9$
Monocytes	$0.6*10^9$	$0.52*10^9$	$0.54*10^9$	$0.85*10^9$	$(0.2\text{-}1.0)*10^9$
Basophils	$0.0*10^9$	$0.04*10^9$	$0.07*10^9$	$0.04*10^9$	$(0.02\text{-}0.10)*10^9$
Platelets	$169*10^9$	**$142*10^9$**	$160*10^9$	$171*10^9$	$(150\text{-}410)*10^9$
Red Blood Cells (RBC)	$4.77*10^{12}$	$4.51*10^{12}$	$4.45*10^{12}$	$4.74*10^{12}$	$(3.8\text{-}5.5)*10^{12}$
Haemoglobin (Hb)	144	135	144	147	115-170 g/L
Haematocrit (HCT)	0.425	0.408	0.410	0.424	0.37-0.50 L/L
Mean Corpuscular Vl. (MCV)	89.1	90.5	92.2	89.5	83-101 fL
Mean Corpusc Hb. (MCH)	30.2	29.9	32.4	31.0	27-32 pg
Mean Corpusc. Hb conc. (MCHC)	339	331	352	347	315-345 g/L
RBC Distribution Width	13.6	13.4	12.4	13.1	10.9-15.7%
Erythrocyte Sedimentation Rate (ESR)		2	3	2	1-23 mm/h
Liver function					
Bilirubin		8	10.3	9	1.0-21.0 µmoL/L
Total protein		68	75	74	60-80 g/L
Globulin			28	27	18-34 g/L
Albumin		45	47	47	35-50 g/L
Alanine aminotransferase (ALT)		30	24	38	0-55 IU/L
Aspartate aminotransferase (AST)			28	39	5-45 IU/L
Alkaline Phosphatase (ALP)		50	42	73	30-150 IU/L
Thyroid Function					
Free Thyroxine (FT4)	13.3	16.7	14.3	17.9	9.0-22.0 pmoL/L
Thyroid Stimulating Hormone (TSH)	2.04	1.19	1.31	1.43	0.35-4.94 mIU/L
Free Triiodothyronine 3 (T3)				4.3	3.1-6.8 pmoL/L
Cortisol			238		100-540 nmoL/L
Renal profile					
Sodium	141	141	140	137	133-146 mmoL/L
Potassium	4.0	4.2	4.6	4.3	3.5-5.3 mmoL/L
Urea		5.6	4.6	6.7	2.5-7.8 mmoL/L
Creatinine	75	87	89	76	49-104 µmoL/L
Estimated GFR	>90	>85	>79	>90	>60 mL/min/1.73 m^2
Uric Acid			0.32		0.21-0.42 mmoL/L
Bone Profile					
Calcium		2.25	2.32		2.20-2.60 mmoL/L
Adjusted calcium		2.26	2.25		2.20-2.60 mmoL/L
Phosphate		1.17	0.8		0.8-1.5
Magnesium			0.8		0.7-1.0
B12 vitamin profile					
Vitamin B12		329	478	445	187-883
Folic acid		5.3	12.1	8.66	2.3-17.6

[**Table 1 Footnotes:** Values for **Patient-Y** were from August 2016 (Pre-COVID-19), November 2018 (Pre-COVID-19), August 2020 (During COVID-19), and June/July 2022 (Post-COVID-19). If a value is not presented, it means it was not available. Abnormal values are indicated in **bold**. His oxygen levels were 95-98% despite his symptoms since March 2020. **HIV:** Human Immunodeficiency Virus, **GFR:** Glomerular Filtration Rate. **Ig:** Immunoglobulin, **SS:** Sjogren's Syndrome.

Written informed consent for publication of this patient's data was obtained from the patient. Prescriptions and clinical investigations were performed by his doctors upon him seeking help voluntarily due to his symptoms. The findings here are incidental and this is a retrospective and descriptive review of this patient's clinical records.

Autoimmune profile: Anti-nuclear antibodies (ANA), Anti-Neutrophil Cytoplasmic Antibodies (ANCA), Extractable Nuclear Antigen (ENA) screen: Including Anti-U1RNP (ribonuclear protein), Anti-Smith, Anti-Ro (SS-A), Anti-La (SS-B), Anti-Jo 1, Anti-Scl 70, Anti-CENP (Circulating Anti-Centromere antibodies); in addition to protein electrophoresis, paraprotein (for myeloma), liver and gastric parietal cell antibodies (including anti-gastro perietal cell, anti-smooth muscle, anti-mitochondrial, anti-liver/kidney microsomal antibodies), Anti-Thyroperoxidase antibodies.

Food allergy profile: Tissue Transglutaminase antibodies, Anti-Gliadin antibodies (IgG and IgA), IgA Anti-Endomysial antibodies, mixed nut, mixed seafood, wheat, rye, barley, rice, peanut, soybean, chicken, pork, beef, sesame, egg yolk, egg white, cow's milk, cheddar cheese].

His examination in August 2020 determined that he was infected by a parasite, *Blastocystis hominis*. He was never diagnosed with this previously and one cannot know how long this parasite was affecting him. He was treated with 400 mg Metronidazole 3 times daily for 7 days in September 2020 against the parasite and showed some improvement (Fig. 1). Nevertheless, dizziness and some digestive problems came back in a few weeks and were attributed to PASC after eliminating other causes, including celiac disease, food allergies, autoimmune disorders and Human Immunodeficiency Virus (HIV) (Fig. 1, Table 1). At the beginning of March 2021, almost a year after his initial COVID-19, he suffered from shingles, possibly consequential to PASC, identified via itchy and painful blisters on his body (Fig. 2). He was prescribed Acyclovir by his PCP.

Regardless of the cause, upon completing a course of 800 mg Acyclovir 5 times daily for 7 days, Patient-Y felt significantly better. He had also applied over-the-counter calamine lotion on blistered areas as part of a routine shingles regimen. Not only did he recover from shingles, but also all of his PASC symptoms disappeared within a few weeks, after ~12 months of suffering (Fig. 1). He resumed a normal life, including exercises. He was vaccinated at the end of March 2021, then in May 2021 (for the 2nd dose), December 2021 (3rd dose) and December 2022 (4th dose). He had SARS-CoV-2 reinfections in July 2021, December 2021, June 2022, September 2022, and January 2023 after traveling. These were milder compared to the 2020 experience with faster recovery within 5-10 days, except for the June 2022 reinfection lasting ~7 weeks, from which he also recovered fully. Probably, vaccinations provided him with better immunity and he did not develop PASC again.

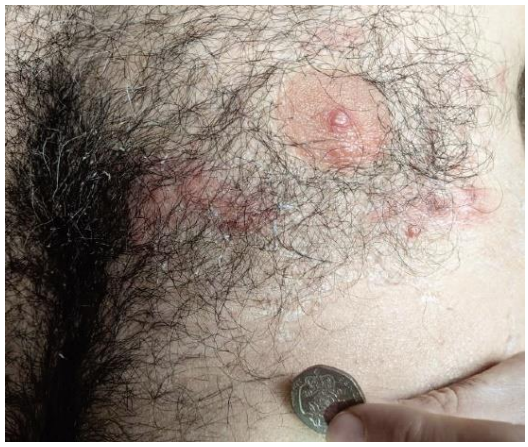

Fig. 2: Patient-Y's skin lesions; He is holding 20 pence (British penny) for scale. His PCP had diagnosed him with shingles based on these itchy and painful lesions: red and white colored blisters were clearly visible. These appeared after ~12 months of initial SARS-CoV-2 infection. Written informed consent for publication of this patient's data was obtained from the patient. Prescriptions and clinical investigations were performed by his doctors upon him seeking help voluntarily due to his symptoms. The findings here are incidental and this is a retrospective and descriptive review of this patient's clinical records

Discussion

Since the cause of PASC is elusive, there are no established treatment methods yet. Patient-Y described here is one of the rare presentations of PASC lasting for ~12 months in a normally healthy and athletic individual, considering PASC is observed in immunocompromised individuals more frequently (Davis *et al*., 2023; Stewart, 2023; Morone *et al*., 2020; Gaebler *et al*., 2021). The immediate recovery of Patient-Y after Acyclovir treatment implies a potential use of existing, available, cost-effective, safe anti-viral medication, for PASC sufferers to help speed up recovery (Stewart, 2023). The findings here are incidental and this study is a retrospective and descriptive review of this patient's clinical records with his consent. The prescriptions and clinical investigations were performed by his medical staff upon him seeking help voluntarily due to his symptoms.

Patient-Y did not have such problems before March 2020 and after recovery since March 2021. Hence, his physicians had concluded he suffered from COVID-19 (primarily due to anosmia) and then PASC, which can be considered sufficient for diagnosis (Davis *et al*., 2023; Stewart, 2023; Morone *et al*., 2020; Yang *et al*., 2020; Parmar *et al*., 2022). He had tested positive for COVID-19 by lateral flow tests for ~3 weeks in a row during his reinfection in June 2022, which lasted for ~7 weeks. Once again, after the initial upper/lower respiratory symptoms,

Patient-Y experienced gastrointestinal problems, besides anosmia and dysgeusia (Stewart, 2023). He recovered fully in ~7 weeks without going into PASC again. This provides further confidence that his symptoms listed in Fig. 1 were attributable to COVID-19 in the absence of diagnostic tests in March 2020 (Stewart, 2023).

Despite causing primarily respiratory infections, SARS-CoV-2 has been found to linger and affect gastrointestinal function in addition to the nervous systems of COVID-19 patients regularly as observed in Patient-Y here (Davis *et al*., 2023; Su *et al*., 2022; Carneiro *et al*., 2022; Vojdani *et al*., 2023; Morone *et al*., 2020; Wu *et al*., 2020; Natarajan *et al*., 2022). This could be due to individual genetic and/or immunologic predisposition: For example, examination of symptom-associated immunological signatures uncovered immunity polarization into four groups with diverging acute severity and PASC, demonstrating the heterogeneity of PASC pathophysiology (Su *et al*., 2022). PASC patients showing gastrointestinal problems were discovered to contain newly expanded cytotoxic $CD8^+$ and $CD4^+$ T-cell populations as well as bystander activation of CMV-specific T-cells (Su *et al*., 2022).

Acyclovir is mono-phosphorylated to be activated by virus-specific thymidine kinase that is only found in virus-infected cells, which makes it harmless for the rest of the body and well-tolerated (Stewart, 2023; Heidary *et al*., 2021; Majewska and Mlynarczyk-Bonikowska, 2022). It is phosphorylated further into tri-phosphate form by other host kinases, which is then incorporated into viral DNA, inhibiting viral DNA-polymerase, viral DNA chain elongation, and replication (Stewart, 2023; Heidary *et al*., 2021; Majewska and Mlynarczyk-Bonikowska, 2022). Acyclovir analogs were found to be effective against coronaviruses SARS-CoV-1, Human Coronavirus-NL63 (HCoV-NL63), Middle East Respiratory Syndrome Coronavirus (MERS-CoV) *in vitro* (Stewart, 2023; Peters *et al*., 2015). Acyclovir was effective for acute cases of COVID-19 with and without herpesvirus reactivation in clinical settings (Baker, 2021; 2022).

Acyclovir treatment for PASC patients was suggested recently by others, particularly for neurological symptoms (German *et al*., 2023; Beatty, 2023). Nevertheless, almost all of the patients studied had pre-existing conditions and were treated with Acyclovir for months (German *et al*., 2023; Beatty, 2023). This makes it harder to determine whether their patients were exclusively affected by PASC and cured by Acyclovir or by natural disease resolution. Whereas Patient-Y presented here did not have any co-morbidities and was treated solely with Acyclovir for only 7 days. Moreover, his recovery happened within a few weeks after the treatment (Fig. 1). This also reflected that *Blastocystis hominis* was not the cause of his symptoms since March 2020. He had taken Metronidazole against *Blastocystis hominis* in September 2020, which had made some difference to his digestive problems but several of his symptoms had returned as presented in Fig. 1. There was a ~1 month gap between the patient taking Acyclovir and his 1st dose of vaccination. Consequently, his significant recovery was attributed to Acyclovir. This was not a placebo effect since he had taken the over-the-counter medication Lemsip (decongestant against cold/flu), Vitamin C, and probiotics if needed between March and September 2020 to no avail.

Recent studies showed significant correlations across COVID-19, PASC, and reactivation of herpesviruses, including HSV-1, VZV, EBV, CMV, and HHV-6 (Heidary *et al*., 2021; Carneiro *et al*., 2022; Vojdani *et al*., 2023; Gold *et al*., 2021; Bhavsar *et al*., 2022). This is credited to COVID-19-induced lymphopenia with significantly reduced total lymphocytes, $CD4^+$ T-cells, $CD8^+$ T-cells, B cells, and natural killer cells as compared to healthy controls although distress associated with COVID-19 has not been overruled for such reactivation (Stewart, 2023; Heidary *et al*., 2021; Carneiro *et al*., 2022; Vojdani *et al*., 2023; Gold *et al*., 2021; Wang *et al*., 2020). A strong correlation between the neurological symptoms of severe COVID-19 patients and HHV-6 reactivation was observed (Carneiro *et al*., 2022). The same group also detected elevated levels of HSV-1 in patients with high SARS-CoV-2 viral load besides CMV and HHV-8 in a significant percentage of patients (Carneiro *et al*., 2022).

Limitation of this study includes the unavailability of testing for COVID-19 at the beginning of the pandemic when Patient-Y's symptoms began in March 2020, besides sequencing to differentiate between persistence of SARS-CoV-2 *versus* other latent viruses in addition to VZV. Patient-Y had primarily gastrointestinal problems and showed some neurological symptoms, including dizziness and brain fog, which can also be attributable to other herpesvirus reactivations, particularly EBV, CMV, HHV-6, and HHV-7 (Carneiro *et al*., 2022; Vojdani *et al*., 2023; Verma *et al*., 2021; Gold *et al*., 2021). The rash he experienced appeared after about one year of these symptoms, which led to the shingles diagnosis and Acyclovir treatment.

One cannot know whether other herpesviruses were reactivated in his system before this. Fatigue and neurological symptoms are predominantly associated with EBV reactivation. Nonetheless, Acyclovir is known not to be a cure against EBV despite reducing oropharyngeal EBV shedding while the medication is taken. Upon treatment cessation, the salivary EBV titer returns within a few weeks (Andersson *et al*., 1985). Acyclovir analogs ganciclovir and Valganciclovir are more effective against EBV (Vojdani *et al*., 2023; Majewska and Mlynarczyk-Bonikowska, 2022; Meng *et al*., 2010). Similarly, HHV-6, HHV-7, and HHV-8 infections are better treated with anti-virals Foscarnet, Ganciclovir, and/or Cidofovir and CMV with

Valganciclovir rather than Acyclovir (Majewska and Mlynarczyk-Bonikowska, 2022).

Taken together, it is highly unlikely that Patient-Y's symptoms were due to EBV, HHV-6, and/or CMV reactivation primarily although herpesvirus reactivations synergistically might have been contributing to the degree and severity of his symptoms (Carneiro *et al*., 2022; Vojdani *et al*., 2023; Verma *et al*., 2021). There is a strong possibility that he was suffering from persisting SARS-CoV-2 in various parts of his body, particularly in gastrointestinal and neuronal cells as observed by others (Davis *et al*. (2023); Stewart (2023); Su *et al*. (2022); Morone *et al*. (2020); Gaebler *et al*. (2021)). Therefore, Acyclovir might have been effective against persisting SARS-CoV-2 mostly, regarding his full recovery shortly after taking Acyclovir. His full blood counts, including inflammatory markers, ferritin, Erythrocyte Sedimentation Rate (ESR), C-Reactive Protein (CRP), calprotectin (for gastrointestinal inflammation) levels, copper and caeruloplasmin levels (for inflammatory Wilson's disease) (Table 1) were within normal range, indicating lack of hyper-inflammation. His electrolytes, kidney, liver function, allergy, and autoimmune screen tests were also normal pre-pandemic, during, and post-pandemic, ruling out allergies and other causes for his symptoms, including *Helicobacter pylori* and HIV (Table 1).

The Acyclovir mechanism of action in coronaviruses, whose genome consists of single-stranded RNA (rather than DNA, which Acyclovir targets principally as mentioned earlier), is unclear. It is thought to inhibit: 1-RNA dependent RNA polymerase (RdRp) of coronaviruses with a similar mechanism to DNA viruses (Stewart, 2023; Heidary *et al*., 2021; Beatty, 2023); 2-expression of viral genes (Li and Yang, 2020); 3-viral proteases (Stewart, 2023; Heidary *et al*., 2021); and/or 4-IL-12 binding to its receptor by changing the surface thereby reducing hyper-inflammation (Stewart, 2023; Heidary *et al*., 2021; German *et al*., 2023; Farasati Far *et al*., 2023). Certain enzymes in host cells -as in the case of other nucleoside analogs such as Sofosbuvir and Ganciclovir and/or enzymes of coronaviruses might have been activating Acyclovir in COVID-19 patients (Stewart, 2023): For example, although human CMVs do not express thymidine kinase, another virally encoded protein kinase (UL97) phosphorylated Acyclovir, making it effective against CMVs to a degree (Talarico *et al*., 1999). Similarly, while EBVs encode thymidine kinase, another virus-encoded serine-threonine kinase was responsible for phosphorylating Acyclovir (Meng *et al*., 2010).

In summary, PASC can affect multiple organs in a heterogeneous manner via yet unclear mechanisms, which makes it hard to treat (Davis *et al*., 2023; Stewart, 2023; Su *et al*., 2022). Genetic/immunologic predisposition and initial SARS-CoV-2 viral load might play a role in its heterogeneity from inflammation to viral persistence in different patients (Davis *et al*., 2023; Stewart, 2023; Su *et al*., 2022). Certainly, SARS-CoV-2 immune dysregulation triggering latent virus reactivations necessitates monitoring the influence of these viruses for PASC besides COVID-19 patients (Heidary *et al*., 2021; Carneiro *et al*., 2022; Vojdani *et al*., 2023; Verma *et al*., 2021). Recent target trial emulation indicated that one of the current COVID-19 treatment anti-viral medications, Nirmatrelvir-Ritonavir (Paxlovid), was limited in its effectiveness against PASC: Showing association only with a reduced combined risk for venous thromboembolism and pulmonary embolism (Ioannou *et al*., 2023). Another report using Nirmatrelvir on four PASC cases also indicated questionable affectivity (Peluso *et al*., 2022). Hence, further treatment options for PASC are urgently needed.

Conclusion

Observations for the patient reported here suggested that 800 mg Acyclovir 5 times daily for 7 days could be a good candidate anti-viral medication to treat PASC if not by itself but in combination with other medications, depending on patients' symptoms, such as currently approved anti-viral medications used against COVID-19, i.e., Paxlovid, Sotrovimab, Remdesivir, Molnupiravir and/or additional herpesvirus targeting medications like Ganciclovir, Valanciclovir or anti-inflammatory Ellagitannins, which inhibit HSV replication and work synergistically with Acyclovir (Majewska and Mlynarczyk-Bonikowska, 2022). For instance, Patient-Y's wife had also suffered PASC for ~14 months mainly with upper/lower respiratory symptoms and she recovered after taking Nitazoxanide (Stewart, 2023). She did not have any signs of herpesvirus reactivation despite her chickenpox history. It would be interesting to test whether Acyclovir could have helped a patient like her considering the $CD4^+$ and $CD8^+$ T cells differences across PASC patients mentioned above (Su *et al*., 2022), or is Acyclovir mostly effective for patients like Patient-Y, suffering from gastrointestinal problems with/without herpesvirus reactivation. Analyzing parameters before and after Acyclovir treatment in future studies could help identify the Acyclovir mechanism of action in such patients in addition to PASC pathophysiology, leading to better PASC treatment plans. Naturally, larger, randomized, systematic clinical trials with PASC patients are awaited to confirm these and we suggest that this report could be an inspiration for them.

Acknowledgment

The prescriptions and clinical investigations were performed by the patient's medical staff upon him seeking help voluntarily due to his symptoms. We are grateful to the medical staff of the patient besides

National Health Services (NHS) for the care of this patient during his COVID-19 problems. This is a retrospective and descriptive review of the patient's clinical records; therefore, the protocol was not submitted to an ethics committee.

Funding Information

There was no funding for this study. The patient's expenses were covered by the National Health Service (NHS) and/or his private insurance. Over-the-counter and prescribed medications were paid for by the patient.

Author's Contributions

Denise Stewart: Conception and design; visualization; data curation; analysis and interpretation; validation; written original draft; written critical review for intellectual content; editing and final approval.

Martin Oswald Savage: Analysis and interpretation; validation; written critical review for intellectual content; editing and final approval.

Ethics

The patient's medical staff had prescribed all his medications.

Consent for Publication

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy by Denise Stewart. Consent was also given in writing to access, collect, and document the data in accordance with the journal's patient consent policy.

Additional Ethical Aspects

Written informed consent for publication of the patient's data was obtained from the patient. The prescriptions and clinical investigations were performed by his medical staff upon him seeking help voluntarily due to his symptoms. This is a retrospective and descriptive review of the patient's clinical records; therefore the protocol was not submitted to an ethics committee.

Highlights

- Long COVID continues to affect many people globally and there are no well-established treatment methods yet
- Repurposing existing anti-viral medications against PASC that could revolutionize treatment in clinical settings globally
- Particular importance of Acyclovir with or without other standard care treatments depending on patients' symptoms to treat PASC
- Importance of patient-specific personalized treatment and initial viral load for COVID-19 and PASC
- This is the first report of full recovery of a long COVID patient after using solely Acyclovir and for only 7 days
- This finding supports the theory of lingering SARS-CoV-2 in the body
- This observation could potentially help transform the treatment for long-term COVID-19 globally

References

Andersson, J., Skoldenberg, B. I. R. G. I. T., Ernberg, I. N. G. E. M. A. R., Britton, S., Henle, W., & Andersson, U. (1985). Acyclovir treatment in primary *Epstein-Barr virus* infection. *A Double Blind Placebo Controlled Study Scand. J Inf. Dis., Supplement*, *47*, 107-115. https://doi.org/10.3109/inf.1985.17.suppl-47.01

Baker, V. S. (2021). Acyclovir for SARS-CoV-2: An ClinicalPractice old drug with a new purpose. *Clin. Pract*, *18*, 1584-1592. ISSN: 2044-9038.

Baker, V. S. (2022). Acyclovir for SARS-COV-2: An old drug with a new therapeutic purpose-an observational study. *Int J Clin Case Rep Rev*, *10*, 1-7. https://doi.org/10.31579/2690-4861/199

Beatty, R. M. (2023). Long COVID-19 symptoms remedied by anti-viral treatment in neurosurgical patients. *American Journal of Infectious Diseases*, *19*(3), 39-44. https://doi.org/10.3844/ajidsp.2023.39.44

Bhavsar, A., Lonnet, G., Wang, C., Chatzikonstantinidou, K., Parikh, R., Brabant, Y., ... & Aris, E. (2022, May). Increased risk of herpes zoster in adults≥ 50 years old diagnosed with COVID-19 in the United States. *In Open Forum Infectious Diseases*, (Vol. *9*, No. 5, p. ofac118). US: Oxford University Press. https://doi.org/10.1093/ofid/ofac118

Carneiro, V. C. D. S., Alves-Leon, S. V., Sarmento, D. J. D. S., Coelho, W. L. D. C. N. P., Moreira, O. D. C., Salvio, A. L., ... & de Paula, V. S. (2022). Herpesvirus and neurological manifestations in patients with severe coronavirus disease. *Virology Journal*, *19*(1), 1-9. https://doi.org/10.1186/s12985-022-01828-9

Davis, H. E., McCorkell, L., Vogel, J. M., & Topol, E. J. (2023). Long COVID: Major findings, mechanisms and recommendations. *Nature Reviews Microbiology*, *21*(3), 133-146. https://doi.org/10.1038/s41579-022-00846-2

Farasati Far, B., Bokov, D., Widjaja, G., Setia Budi, H., Kamal Abdelbasset, W., Javanshir, S., ... & Dey, S. K. (2023). Metronidazole, acyclovir and tetrahydrobiopterin may be promising to treat COVID-19 patients, through interaction with interleukin-12. *Journal of Biomolecular Structure and Dynamics*, *41*(10), 4253-4271. https://doi.org/10.1080/07391102.2022.2064917

Gaebler, C., Wang, Z., Lorenzi, J. C., Muecksch, F., Finkin, S., Tokuyama, M., ... & Nussenzweig, M. C. (2021). Evolution of antibody immunity to SARS-CoV-2. *Nature*, *591*(7851), 639-644. https://doi.org/10.1038/s41586-021-03207-w

German, E. R., Jairath, M. K., & Caston, J. (2023). Treatment of Long-Haul COVID Patients with Off-Label Acyclovir. *Cureus*, *15*(4). https://doi.org/10.7759/cureus.37926

Gold, J. E., Okyay, R. A., Licht, W. E., & Hurley, D. J. (2021). Investigation of long COVID prevalence and its relationship to Epstein-Barr virus reactivation. *Pathogens*, *10*(6), 763. https://doi.org/10.3390/pathogens10060763

Heidary, F., Madani, S., Gharebaghi, R., & Asadi-Amoli, F. (2021). Acyclovir as a potential add-on therapy in COVID-19 treatment regimens. *Heidary F, Madani S, Gharebaghi R, Asadi-amoli F. Acyclovir as a Potential Adjuvant Therapy in COVID-19 Treatment Regimens. Pharm Sci*. https://doi.org/10.34172/PS.2021.38

Ioannou, G. N., Berry, K., Rajeevan, N., Li, Y., Mutalik, P., Yan, L., ... & Bajema, K. L. (2023). Effectiveness of Nirmatrelvir Ritonavir Against the Development of Post COVID-19 Conditions Among US Veterans: A Target Trial Emulation. *Annals of Internal Medicine*, *176*(11), 1486-1497. https://doi.org/10.7326/M23-1394

Li, Z., & Yang, L. (2020). Underlying mechanisms and candidate drugs for COVID-19 based on the connectivity map database. *Frontiers in Genetics*, *11*, 558557. https://doi.org/10.3389/fgene.2020.558557

Majewska, A., & Mlynarczyk-Bonikowska, B. (2022). 40 years after the registration of acyclovir: Do we need new anti-herpetic drugs?. *International Journal of Molecular Sciences*, *23*(7), 3431. https://doi.org/10.3390/ijms23073431

Meng, Q., Hagemeier, S. R., Fingeroth, J. D., Gershburg, E., Pagano, J. S., & Kenney, S. C. (2010). The Epstein-Barr Virus (EBV)-encoded protein kinase, EBV-PK, but not the Thymidine Kinase (EBV-TK), is required for ganciclovir and acyclovir inhibition of lytic viral production. *Journal of Virology*, *84*(9), 4534-4542. https://doi.org/10.1128/JVI.02487-09

Morone, G., Palomba, A., Iosa, M., Caporaso, T., De Angelis, D., Venturiero, V., ... & Paolucci, S. (2020). Incidence and persistence of viral shedding in COVID-19 post-acute patients with negativized pharyngeal swab: A systematic review. *Frontiers in Medicine*, *7*, 562. https://doi.org/10.3389/fmed.2020.00562

Natarajan, A., Zlitni, S., Brooks, E. F., Vance, S. E., Dahlen, A., Hedlin, H., ... & Bhatt, A. S. (2022). Gastrointestinal symptoms and fecal shedding of SARS-CoV-2 RNA suggest prolonged gastrointestinal infection. *Med*, *3*(6), 371-387. https://doi.org/10.1016/j.medj.2022.04.001

Parmar, H., Montovano, M., Banada, P., Pentakota, S. R., Shiau, S., Ma, Z., ... & Xie, Y. L. (2022). RT-PCR negative COVID-19. *BMC Infectious Diseases*, *2*(1), 1-10. https://doi.org/10.1186/s12879-022-07095-x

Peluso, M. J., Anglin, K., Durstenfeld, M. S., Martin, J. N., Kelly, J. D., Hsue, P. Y., ... & Deeks, S. G. (2022). Effect of oral nirmatrelvir on long COVID symptoms: 4 cases and rationale for systematic studies. *Pathogens and Immunity*, *7*(1), 95. https://doi.org/10.20411/pai.v7i1.518

Peters, H. L., Jochmans, D., de Wilde, A. H., Posthuma, C. C., Snijder, E. J., Neyts, J., & Seley-Radtke, K. L. (2015). Design, synthesis and evaluation of a series of acyclic fleximer nucleoside analogues with anti-coronavirus activity. *Bioorganic and Medicinal Chemistry Letters*, *25*(15), 2923-2926. https://doi.org/10.1016/j.bmcl.2015.05.039

Stewart, D. D. (2023). Can Nitazoxanide and/or other anti-viral medications be a solution to long COVID? Case report with a brief literature review. *Clinical Case Reports*, *11*(11). https://doi.org/10.1002/ccr3.8162

Su, Y., Yuan, D., Chen, D. G., Ng, R. H., Wang, K., Choi, J., ... & Heath, J. R. (2022). Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell*, *185*(5), 881-895. https://doi.org/10.1016/j.cell.2022.01.014

Talarico, C. L., Burnette, T. C., Miller, W. H., Smith, S. L., Davis, M. G., Stanat, S. C., ... & Biron, K. K. (1999). Acyclovir is phosphorylated by the human cytomegalovirus UL97 protein. *Antimicrobial Agents and Chemotherapy*, *43*(8), 1941-1946. https://doi.org/10.1128/aac.43.8.1941

Verma, D., Church, T. M., & Swaminathan, S. (2021). Epstein-Barr virus lytic replication induces ACE2 expression and enhances SARS-CoV-2 Pseudotyped virus entry in epithelial cells. *Journal of Virology*, *95*(13), 10-1128. https://doi.org/10.1128/JVI.00192-21

Vojdani, A., Vojdani, E., Saidara, E., & Maes, M. (2023). Persistent SARS-CoV-2 Infection, EBV, HHV-6 and other factors may contribute to inflammation and autoimmunity in long COVID. *Viruses*, *15*(2), 400. https://doi.org/10.3390/v15020400

Wang, F., Nie, J., Wang, H., Zhao, Q., Xiong, Y., Deng, L., ... & Zhang, Y. (2020). Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. *The Journal of Infectious Diseases*, *221*(11), 1762-1769. https://doi.org/10.1093/infdis/jiaa150

Wu, Y., Guo, C., Tang, L., Hong, Z., Zhou, J., Dong, X., ... & Huang, X. (2020). Prolonged presence of SARS-CoV-2 viral RNA in faecal samples. *The Lancet Gastroenterology and Hepatology*, *5*(5), 434-435. https://doi.org/10.1016/S2468-1253(20)30083-2

Yang, Y., Yang, M., Yuan, J., Wang, F., Wang, Z., Li, J., ... & Liu, Y. (2020). Laboratory diagnosis and monitoring the viral shedding of SARS-CoV-2 infection. *The Innovation*, *1*(3). https://doi.org/10.1016/j.xinn.2020.100061

List of Abbreviations

PASC	**:**	Post-Acute Sequelae of COVID-19
SARS-CoV-2	**:**	Severe Acute Respiratory Syndrome Coronavirus 2
COVID-19	**:**	Coronavirus Disease 2019
HSV	**:**	Herpes Simplex Virus
VZV	**:**	Varicella-Zoster Virus
EBV	**:**	Epstein-Bar Virus
CMV	**:**	Cytomegalovirus
HHV	**:**	Human Herpesvirus
HIV	**:**	Human Immunodeficiency Virus
IL	**:**	Interleukin
CD	**:**	Cluster of Differentiation
PCP	**:**	Primary Care Physician