

Symptomatic relapse and long-term sequelae of COVID-19 in a previously healthy 30-year-old man

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SUMMARY

Much has been reported on the clinical course of severe COVID-19, but less is known about the natural history and sequelae of mildly symptomatic cases and the prospects of reinfection or recurrence of symptoms. We report a case of a patient with mildly symptomatic PCR-confirmed COVID-19 who, after being symptom-free for 2 weeks, redeveloped symptoms and was found to be PCR-positive again >4 weeks from original testing. Surprisingly, IgG and IgM antibody testing was negative 2 months after reinfection. Although no negative testing was performed between the two symptomatic bouts, this case raises the possibility of reinfection after controlling the virus and highlights the long period with which a patient can shed virus and experience symptoms after initial infection. Characterising variations in clinical symptoms and length of viral shedding after improvement is essential for informing recommendations on patients safely resuming contact with others.

BACKGROUND

In November 2019, unexplained severe respiratory illnesses began appearing in the Wuhan region of China. These illnesses would later be found to represent an emerging disease, COVID-19, which is caused by a novel COVID-19, SARS-CoV-2. As of 3 November 2020, there have been 47 328 401 cases throughout the world.¹ Commonly reported symptoms include dyspnoea, chest pain, fever, dry cough and anosmia, but its clinical course varies widely.² In its most severe form, this respiratory infection progresses to a cytokine storm involving acute respiratory distress syndrome, multi-organ system failure and eventual death, which is most common in the elderly and those with comorbidities.³ In the milder form of this disease, patients may be asymptomatic or have mild viral symptoms. Over the past several months, much has been learnt about acute infection with this novel virus thanks to the robust research efforts of the scientific and medical communities, but key questions remain. One unanswered question that is critical to ongoing containment efforts and vaccine development is whether patients can be reinfected after initially controlling the virus. Another key question is related to the various sequelae following SARS-CoV-2 infection. It is becoming more clear that SARS-CoV-2 exposure can lead to asymptomatic SARS-CoV-2 infection, acute COVID-19 followed by remission, long haul COVID-19, multi-system inflammatory syndrome in children and adults, or acute COVID-19 with subsequent relapse of COVID-19.^{4 5} Herein, we report a previously healthy 30-year-old man who experienced a debilitating, testing-confirmed SARS-CoV-2 infection,

fully recovered and then represented with debilitating symptoms and a repeat positive SARS-CoV-2 test over the span of a 6-week period with long term symptoms and sequelae.

CASE PRESENTATION

A previously healthy 30-year-old man with no significant medical history developed substernal chest pain 2 days after an international flight on 15 March 2020. He experienced this burning localised chest pain for 2 days before developing night sweats and a fever to 100.1°F. On 19 March 2020, he was tested for SARS-CoV-2 via nasopharyngeal swab, which was positive for viral nucleic acid. At this time, his wife also had chest pain and went on to develop nausea and vomiting along with his 3-year-old son who also had gastrointestinal symptoms, but they were never tested for COVID-19. The patient had no prior medical comorbidities and took no medications. He is a life-long non-smoker and consumes 1–2 drinks of alcohol per month. See [figure 1](#) for a detailed clinical course.

Over the following 2 weeks under self-quarantined, he continued to have chest pain with progressive fatigue but remained out of the hospital, managing his symptoms with rest and acetaminophen. He reported feeling exhausted after walking up a flight of stairs, which was far from his baseline as an active 30-year-old former college football player. Nine days after his positive test and 13 days after his presumed exposure, he developed anosmia as did his wife. Two days after his anosmia began, his symptoms improved to the point that he was able to participate in normal household activities, beginning on 29 March 2020. He was cleared from self-quarantine by the health department on 31 March 2020, exactly 2 weeks after his positive test, but continued to quarantine with his family until 9 April 2020.

For the following 18 days, the patient reported a full return to his baseline level of health with no dyspnoea or chest pain. He had complete return of normal taste and smell. He was not retested for SARS-CoV-2 viral nucleic acid during this period. He continued to adhere to strict social-distancing and mask-wearing guidelines when he returned to community walks and in-person grocery shopping, but he denied any exposures to COVID-19 patients.

Thirty-two days after his presumed exposure and 30 days after his initial symptoms, he began developing chest discomfort again on 17 April 2020. After 2 days of persistent symptoms, he presented to the emergency department (ED) once more where he was found to be positive for SARS-CoV-2 again, exactly 31 days after his first positive test. A chest X-ray was done at this time which showed no signs of active disease in the



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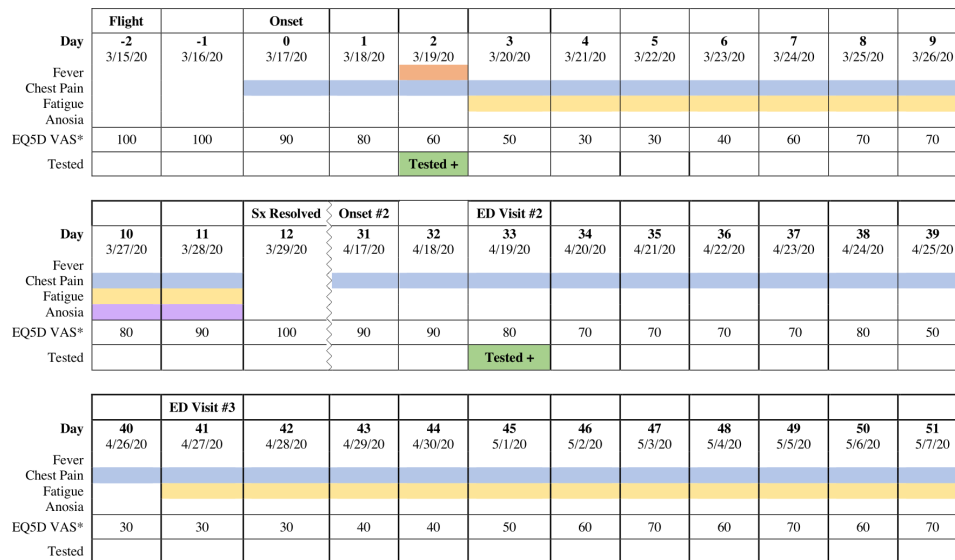


Figure 1 Complete timeline of clinical course, symptomatology and positive COVID-19 testing by RT-PCR. A EuroQol-5D Visual Analogue Scale (VAS) Symptom Scale was administered retrospectively on 7 May 2020 to determine the perceived severity of symptoms throughout his disease course. The number is a quantitative estimate for how good or bad one’s health is on that day. It is scaled from 0 to 100, with 0 being the worst health one can imagine and 100 being the best health one can imagine. ED, emergency department.

lungs. He was given a 5-day course of azithromycin and instructed to quarantine until his symptoms resolved.

For the next 7 days, he continued to have diffuse chest discomfort with dyspnoea and fatigue for which he represented to the ED on 26 April 20. Vital signs were within normal limits. His labs showed a mild leucocytosis (white cell count (WBC) $10.62 \times 10^9/L$), elevated neutrophil count ($8.93 K/\mu L$, neutrophil count percentage 84.0%), mildly depressed lymphocyte count ($1.26 K/\mu L$ (11.9% of WBC)), haemoglobin approaching the upper limits of normal (160 g/L) with mildly low red cell distribution width (10.8%), platelet count near the lower limit of normal ($181 \times 10^9/L$), as well as normal electrolytes, liver function tests, renal function tests, D-dimer ($<0.27 \mu g/mL$), troponin-T ($<0.010 \text{ zzNG/ML}$) and BNP NT-Pro (18 pg/mL). His EKG was normal and a chest X-ray showed no acute abnormalities, including no evidence of pulmonary oedema. He also had a chest CT PE protocol which showed some subsegmental atelectasis but was negative for pulmonary embolus. He was again discharged to home and told to continue quarantining until he felt well for 72 consecutive hours. His symptoms persisted for another 8 days but began improving again 17 days after they began, 50 days after his initial exposure. We are not aware of any individuals who were infected by this patient during his first or second bout of symptoms.

In summary, this patient experienced two bouts of COVID-19 symptoms with positive SARS-CoV-2 testing results at the beginning of both bouts. The patient experienced worsening overall health as assessed by the EQ5D Visual Analogue Scale Symptom Scale during both of these bouts with complete resolution of all functioning in between (figure 2).

OUTCOME AND FOLLOW-UP

At the time of publication, the patient continues to report burning chest pain, dyspnoea, and fatigue and feels he has not returned to his baseline state of health 8 months following initial infection. He was recently diagnosed with intercostal neuralgia for which he is receiving nerve blocks. The patient had IgG and IgM testing performed in June 2020, which found no IgG or IgM antibodies.

DISCUSSION

Prolonged viral shedding is a key characteristic of SARS-CoV-2 that has been well documented in the literature.³⁻⁷ This feature along with an extended period of asymptomatic transmission, makes this virus particularly challenging to control. Most patients are most infectious for approximately 10 days after initial infection.⁸ However, viral shedding has been reported months after infection, with case reports that describe positive tests up to 60 days after symptoms first appeared and 36 days after resolution.⁷ That said, the threshold between non-infectious viral shedding and transmission is unclear. Most of the data on viral shedding comes from hospitalised patients with moderate to severe infection. In fact, delayed viral clearance was more commonly seen in patients with more severe illness at the time of admission as well as those individuals with other poor prognostic indicators including old age, delay of admission after illness onset and invasive mechanical ventilation.⁶ The data on viral shedding in patients with mild disease are sparse, but there have been reports of shedding for over a month in mildly symptomatic patients,⁹ though the risk of infection from this shedding is considered to be low.¹⁰

In this case of COVID-19, a young patient with no comorbidities and an overall mild symptom burden displayed a course that can either be considered to be infection-resolution-re-infection, prolonged viral shedding as he tested positive for the virus 2 days and 33 days after symptom onset, or long haul COVID-19. This case is particularly notable, because this patient developed recurrence of his presenting symptoms 18 days after they had initially resolved, his symptoms have continued for months, and he demonstrated no IgG or IgM antibodies 2 months following a positive SARS-CoV-2 result. His symptomatic relapse is atypical and has not been reported in mild forms of SARS-CoV-2 infection. It is possible that a second exposure to SARS-CoV-2 infection may be responsible for his new symptoms, but the patient was self-isolating for much of his asymptomatic period, practiced social distancing, and had no known exposures at this time. There could also have been a secondary infection with a different virus while he continued to shed SARS-CoV-2, but this is unlikely given his prolonged recurrent symptom course and otherwise negative work-up.

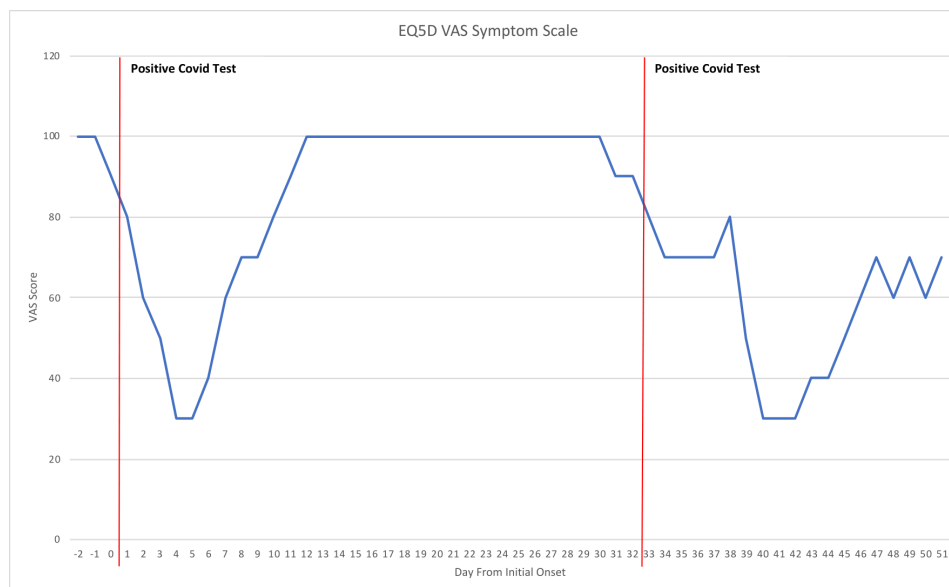


Figure 2 Symptom severity over illness course as assessed by EuroQol-5D Visual Analogue Scale (EQ5D VAS) Symptom Scale. This line graph depicts the results of a retrospectively administered EQ5D VAS Symptom Scale on the patient's perceived overall health as described in figure 1. The blue line represents the score reported by the patient on each day of his clinical course. The red vertical lines are used to identify the days on which the patient's COVID-19 testing was positive.

It has been reported in many severe forms of this disease that patients have a two spiked clinical course with initial worsening, improvement, and then decline in their clinical status once more. This is thought to be due to the strong immunological response that is found in severe COVID-19 cases and not due to viral load itself.¹¹ It is also known that SARS-CoV-2 can cause a prolonged period of symptoms, referred to as long haul COVID-19, with some patients not returning to their baseline months after mild infection. Yet, this is the first case reporting a patient with an overall mild course who had a full symptomatic recovery, followed by an abrupt return of symptoms and then prolonged period of symptoms.¹² Most importantly, clearance of the virus during the asymptomatic period cannot be ruled out based on the data available; SARS-CoV-2 testing was not performed during that time.¹³ Therefore, reinfection or a two-spiked clinical course must be considered as plausible explanations for the reappearance of his symptoms and repeat positive test.

Furthermore, the patient continues to be symptomatic months after the resurgence of his symptoms. On top of the persistent dyspnoea and fatigue, he also developed intercostal neuralgia, which has been occasionally reported to occur following SARS-CoV-2 infection.¹⁴ This patient likely falls within the category of patients recently labelled as 'long-haulers' who continue to have symptoms despite clearance of the virus. Little is known about this cohort but it is thought to be an immune mediated process that causes the

prolongation of symptoms, which usually include fatigue, chest pain, or dyspnoea.⁵ This patient's lack of IgM or IgG antibodies to SARS-CoV-2 when tested 2 months after infection is hard to interpret given the low sensitivity and specificity of serological testing but could provide insights into a cause for the recurrence or the long hauler symptoms.¹⁵ The lack of immunoglobulins may represent an intrinsic dysfunction in antibody-mediated immunity, which could allow reinfection or lead to long-term sequelae. Alternatively, this could highlight a more general phenomenon of poor long-term immunity following SARS-CoV-2 infection.

Patient's perspective

I have been in constant communication with the authors throughout the process of their writing of this case. I want this story to be shared with the world so as to raise awareness for the different kinds of clinical courses that COVID-19 can have, especially for people who have mild symptoms, things can last for a really long time. I want my experience to help educate others on the importance of self-isolation and social distancing even if they don't feel sick. I also want to help figuring this thing out, why am I feeling sick for so long? We need to get this done.

Learning points

- ▶ Prolonged viral shedding for up to 6 weeks is an important feature of COVID-19 that is not limited to hospitalised patients with severe symptoms and can be seen in otherwise healthy young patients with COVID-19 infection.
- ▶ Although the possibility of reinfection can be considered in the setting of repeat positive testing weeks after recovery, a negative test between the bouts of symptoms and genetic testing of the viral strains is needed to confirm a true reinfection. In most cases, persistent viral shedding throughout the course of the initial bout, remission and subsequent bout is most likely.
- ▶ Our ability to generate immunity after infection with COVID-19 remains largely unknown and further research is warranted to better understand the risk of reinfection.
- ▶ Large community-based observational trials are needed to better characterise the clinical course of infections outside of the hospital setting to investigate the incidence of symptomatic relapse and long-hauler COVID-19 symptoms.
- ▶ It is unclear if current recommendations for cessation of self-isolation after a positive COVID-19 diagnostic test apply to all patients with SARS-CoV-2 infection as our case demonstrates the potential for symptomatic relapse and asymptomatic viral shedding for an extended period of time.

This case helps elucidate the potential for patients to continue shedding virus and even become symptomatic once more after their initial recovery from this illness. Knowing that this phenomenon may exist in some patients is important for both clinicians in advising their patients and also for researchers studying reinfection and relapse. Furthermore, it highlights the importance of a confirmed negative test to ensure viral clearance and not simply to use symptomatology as a surrogate, particularly when studying reinfection.

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