

Case Report
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Recurrent SARS-CoV-2 Infection: Case Reports and Review of the Literature

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ABSTRACT

We describe a 37-year-old woman who became infected with SARS-CoV-2. Over time, 4 other members in her family unit became infected, with 3/5 developing 2-3 separate clinical syndromes over two months. It is possible that each person had a single prolonged infection, with the literature reporting RNA detection for as long as 83 days in some cases. Syndromes of relapsing/remitting infection have also been well described. Intermittent negative RNA readings may represent “false negative” results with intermittent levels of viremia that occasionally fall below the limit of detection of the assay. An alternative explanation may be multiple episodes of infection, clearance, and re-infection within the family unit. Preliminary reports in the literature suggest onward transmission after recurrent infection in 3 reported cases. An understanding of the prevalence of cases series such as ours and their pathophysiologic and immunologic significance will improve our knowledge about SARS-CoV-2 infection and strategies to control it.

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Introduction

To date, the generational pandemic of SARS-CoV-2 infection has affected over 160 million people worldwide [1]. The World Health Organization has estimated that the majority of infections are mild or asymptomatic (80% of infections), but some cases are severe enough to require oxygen (15%) or ventilation (5%) [2]. Once recovery occurs, it is generally assumed that most individuals develop protective antibodies and will not become re-infected, nor will they be vectors of onward transmission. However, the natural history of infection may be more variable than currently appreciated, including multiple episodes of clinical disease. Although transmission to uninfected contacts in an institutional setting or in the broader community is the principal mode of disease spread, it may also be that an individual who is in the early stages of recovery can become symptomatic once again after exposure to another person who has recently become infected themselves. We describe a series of cases within a family unit that may illustrate these points and better inform our understanding of the possible dynamics of viral transmission.

Patients

On March 4th, 2020, a 37-year-old woman developed a sore throat and rhinorrhea. She is of Iranian descent. She had not traveled away from the city of Vancouver, Canada, for several months. She did, however, frequent a market specializing in Persian food. At this market, she would have come in frequent and repeated contact with several individuals who would have recently returned from Iran, some of whom were subsequently diagnosed with SARS-CoV-2 infection in March and April. She was unwell but stable until March 11th when she developed persistent headaches, a dry

cough, and a fever measured at 38.5°C at times. By March 17th, she had severe fatigue and lethargy, also reporting anosmia and dysgeusia. She underwent testing for SARS-CoV-2 on March 18th. The result was inconclusive, due to improper processing. On March 19th, she was short of breath and presented to the emergency room for evaluation. A chest X-ray was normal and her oxygen saturation on room air was 98%. A complete blood count was normal. She was sent home with a prescription for oseltamivir 75 mg twice daily for 5 days. As she was not significantly improved by March 23rd, she was given a prescription for azithromycin 500 mg loading dose, then 250 mg/day for 5 days. By March 27th, she was better and only reported minor anosmia and dysgeusia. She continued to improve until April 9th, when she had sudden onset of high fever (40°C), lethargy, and diffuse myalgias. She was not offered SARS-CoV-2 testing. She was told to remain at home and take acetaminophen as required. She slowly improved over the next week (to April 16th) and remained well until April 26th. She was severely unwell once again (with a high fever, myalgias, and lethargy) and presented to a community-based testing center. The SARS-CoV-2 test was positive. She remained unwell until May 8th. She improved slowly thereafter, but with persistent anosmia, dysgeusia and shortness of breath on exertion persisting through mid-June 2020. She period has been well since then.

She shares her home with 5 other individuals.

Her 12-year-old daughter was well until April 2nd when she developed a fever (38.5°C) with myalgias, abdominal cramps, and watery diarrhea. She was not offered a SARS-CoV-2 test. She managed her symptoms appropriately and had fully recovered by April 16th. She developed a high-grade fever (39.5°C) and myalgias on April 26th. She presented to a community-based testing center.

The SARS-CoV-2 test was positive. She slowly improved over several days, with persistent headaches being her most prominent symptom. She has been well since May 8th, 2020.

Her 15-year-old niece was well until April 4th when she developed a severe systemic illness, from which she slowly recovered by April 18th. A similar illness developed April 26th. She presented to a community-based testing center. The SARS-CoV-2 test was not performed as the operator could not obtain a satisfactory nasopharyngeal sample. She stayed home and slowly improved over time. She has been well since May 8th, 2020.

Her 39-year-old sister was well until April 16th when she developed severe shortness of breath and a high fever (40°C), severe lethargy, and weakness. She recalled significant anosmia and dysgeusia. She was transported to the emergency room. A SARS-CoV-2 test was positive. She was not felt to warrant admission to hospital. She returned home. By May 6th, she had fully recovered except for mild shortness of breath on exertion persisting through in mid-June 2020, before resolving.

Her 22-year-old nephew was well until April 29th, when he had a low-grade fever (38.0°C), along with some lethargy and myalgias. He presented to a community-based testing center. The SARS-CoV-2 test was positive. He slowly improved over several days and had fully recovered by May 9th, 2020.

Her 53-year-old brother-in-law was able to self-isolate in a separate part of the house from all other occupants from the time of the initial diagnosis of the index case in early March. He has remained well throughout the entire period of observation.

SARS-CoV-2 RNA testing was performed on all 6 members of the family unit on June 4th, 2020. All results were negative.

Discussion

We report on a case of SARS-CoV-2 infection acquired in the community and subsequently transmitted over time to 4/5 other household members. The one individual who did not become clinically infected was able to isolate himself early in the course of disease spread within the household. Starting with the index case, the infection spread to the four other family members serially, in order of frequency and intensity of contact with her. An interesting aspect of this case series is the identification of repeated bouts of symptomatic infection in 3 of the individuals, with 3 distinct episodes (separated by prolonged asymptomatic periods) in the index case, and 2 such episodes in those who most interacted together (her daughter and niece), with single episodes of disease in her sister and nephew.

It is interesting to speculate on the pathophysiology of the observed events. One possible explanation is that each of the 5 infected individuals suffered single episodes of infection after the virus was introduced into the household from the Persian food market. The longest and most severe infection (up to 65 days) was in the index case, as she was likely exposed to multiple infected individuals and received a larger viral inoculum. The periods when she was relatively asymptomatic may correspond to a partial immune response to the virus, leading to control of symptoms but not viral eradication. Over time, the immune response became more efficient and led to a prolonged and maintained recovery. A similar explanation would apply to the two adolescents who experienced repeated symptomatic episodes (34 and 36 days in duration). The other two individuals experienced straightforward single episodes of clinical disease (10 and 20 days in duration)

from which they recovered. Duration of illness may relate to progressively less significant viral exposure in the daughter/niece and sister/nephew pairs.

This explanation fits with our knowledge of the possible duration of viral shedding. In one study of 161 individuals for whom an infection exposure was identified, the median duration of viral shedding was 20 days, interquartile range (IQR) 16-28 days [3]. Similarly, among 113 patients hospitalized with COVID-19, the median duration of viral shedding was 17 days, IQR 13-22 days. [4]. Single cases of shedding for 48 [5], 51 [6], 60 [7], and 83 [8] days have been documented. In a detailed study of 33 individuals, 16 had positive RNA detection beyond 22 days, including one for at least 59 days [9]. Slower clearance was associated with less rapid development of anti-SARS-CoV-2 antibodies. Finally, in one retrospective study comparing persistently RNA positive individuals with eventual viral clearance beyond (n = 19) or within (n = 18) a week of observation, slower clearance was associated with T and B cell lymphopenia [10]. Thus, what we are observing in this family unit may simply be an illustration of the broad spectrum of clinical disease, with differences in disease duration linked to host-related (perhaps immunologic) considerations, in addition to the intensity of initial viral exposure. The prolonged clinical symptomatology observed in the index case and her sister are increasingly described in the lay press [11].

We are left to consider remitting-relapsing infection in 3 of the individuals in this family unit. There is now increasing evidence for this clinical presentation. One 8-year-old boy was positive for SARS-CoV-2 on February 6th, 2020, and negative 10-11 days later. He became symptomatic again on February 29th, with a positive RNA test on March 5th. A single individual developed a severe respiratory illness associated with a positive SARS-CoV-2 test. He had recovered by week 2 and tested RNA negative at both weeks 2 and 4. After two additional weeks (6 weeks after the initial test and illness), he became unwell again and tested positive. In another study of 55 individuals who were initially infected, 5 developed a positive test 4-17 days after a negative test result, 4/5 with recurrent symptoms [12-14]. In another case, a critically ill individual admitted to hospital January 26th, 2020 had recovered by February 3rd. He was readmitted on February 21st with recurrent symptoms and a positive test result. Three other cases have been reported with two separate hospitalizations weeks apart. Finally, in the case of an 81-year-old woman, recurrent clinical disease several weeks after initial hospital admission led to readmission and a fatal outcome [15-17]. Thus, the occurrence of multiple clinical episodes separated by asymptomatic periods that may last for weeks have been previously described and are consistent with the observations we report in this family unit.

If we are to argue for a single infectious event in each of the 5 affected individuals, we are left to explain the significance of alternating positive and negative RNA results over time. This is a fairly common phenomenon. Recurrence of viral shedding after documentation of a negative test result has been frequently observed. In the largest series reported to date, 81/1067 (7.6%) individuals were found to have a positive test after a documented negative result [18]. Interestingly, this appeared to be linked to elevated lymphocyte counts and elevated IL-6 levels, indicating a possible effect of the host response on this phenomenon. In another study including 267 individuals, 30 (11.2%) had a positive test result within 14 days of a negative one, the only correlate of this observation being severity of the initial disease [19]. The highest prevalence of this phenomenon comes from a series of 70 individuals among whom 15 (21.4%) had a positive test, one

case as long as 45 days after initial symptomatic presentation [20]. In one 44-year-old male, a positive test was documented as long as 70 days after the initial illness was diagnosed, over 40 days after an initial negative result [21]. All of these observations notwithstanding, the clinical and biological significance of the intervening negative results must be considered. Some have argued that in many cases, some negative results may represent cases of “false negative” test results in between multiple positive results that are slow to clear, and persistent viral shedding that, on occasion, is below the limit of detection of the test [22]. If this holds, the conclusion that 5 separate single infections occurred in this family unit remains plausible.

Another explanation that must be considered is that the index case had an initial infection which she transmitted to her daughter and niece. She recovered completely, only to be re-infected by her now infected daughter and niece. As these three individuals recovered, they were all re-infected (for the 2nd or 3rd time, depending on the individual in question) by the symptomatic 39-year-old woman (sister of the index case). Eventually, as all 5 individuals had become infected and were recovering, no further viral transmission occurred.

Currently, there has been no documentation of recoverable, infectious virus isolated after viral RNA clearance that would indicate a re-infection [23]. A total of 6 monkeys re-challenged with the same SARS-CoV-2 virus during the recovery phase did not have evidence of virologic re-infection [24]. In another report, among 38 individuals with recurrent symptoms and a positive test result, 21 close home contacts were studied [25]. They interacted closely with the 38 patients discharged from hospital and none became infected. Finally, in a report from the Korean Centers for Disease Control and Prevention, of 790 contacts of 285 individuals with a recurrent positive test, 3 became infected, although other possible exposures were not definitively ruled out [26].

One possible criticism of our report is the lack of serial SARS-CoV-2 testing for each clinical event. This relates to different criteria for an offer of testing over time. Until sometime in April, testing was only offered to health care providers, those at risk of hospitalization, and select others. It is likely that each episode of clinical illness is related to SARS-CoV-2 due to the diagnosis being ultimately confirmed in 4 cases and each individual clinical illness being consistent with SARS-CoV-2 infection. In particular, the initial illness in the index case had a clear epidemiologic link with community-based infection. Further, anosmia and dysgeusia were prominent features of the initial presentation, symptoms now felt to be strongly associated with SARS-CoV-2 infection.

The cases we present, whatever their explanation, serve to improve our knowledge about clinical SARS-CoV-2 disease and may suggest important avenues for research. If each individual had a single infectious episode, this expands our understanding of the spectrum of disease. Beyond the linear progression of symptoms towards resolution or deterioration (that may require admission to hospital and carry a risk of mortality), we may have identified a third possibility: remitting-relapsing infection (up to 3 clinical episodes in this case series) with eventual resolution. The correlates of this presentation and the frequency of its occurrence merit further study.

A more intriguing possibility is that of re-infection soon after an initial infection having occurred and been cleared. This may relate to an ineffective immune response that would allow this to occur, or an immune response that is not yet fully developed, allowing for the possibility of re-infection if a repeat exposure takes place

prematurely. In this case, serial samples over the period of March to May in the relevant family members are not readily available. However, convalescent samples are available in all subjects. These will be studied to determine if the quality and quantity of the immune response varies from one individual to the other, and whether certain immunologic phenotypes are more effective at inhibiting viral replication. Data such as these may also inform vaccine research, in comparing the immune response elicited by different therapeutic interventions.

In conclusion, we describe a group of 5 family members with SARS-CoV-2 infection, three of whom had multiple separate clinical episodes of disease. A deeper understanding of the frequency of such occurrences and their pathophysiologic and immunologic significance will serve to improve our knowledge about this novel coronavirus and may also provide insights about strategies to control it.

Declarations of Interest

None.

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