

Case Report
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Case Report on Reinfection Case of COVID-19

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ABSTRACT

Background: The degree of protective immunity conferred by infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is currently unknown. As such, the possibility of reinfection with SARS-CoV-2 is not well understood. We describe an investigation of two instances of SARS-CoV-2 infection in the same individual.

Methods: A 24-year-old man who was a resident of Harjah Governorate in the KSA, Region of Aseer presented to health authorities on two occasions with symptoms of viral infection, once at a community testing event in June, 2020, and a second time to the hospital in the September, 2020. Nasopharyngeal swabs were obtained from the patient at each presentation and Two Times during follow-up. Nucleic acid amplification testing was done to confirm SARS-CoV-2 infection. We did next-generation sequencing of SARS-CoV-2 extracted from nasopharyngeal swabs. Sequence data were assessed by two different bioinformatics methodologies. A short tandem repeat marker was used for fragment analysis to confirm that samples from both infections came from the same individual.

Findings: The patient had two positive tests for SARS-CoV-2, the first on June 24, 2020, and the second on September 19, 2020, separated by one negative test done during follow-up in July, 2020. Genomic analysis of SARS-CoV-2 showed genetically significant differences between each variant associated with each instance of infection. The second infection was symptomatically more severe than the first.

Interpretation: Genetic discordance of the two SARS-CoV-2 specimens was greater than could be accounted for by short-term in vivo evolution. These findings suggest that the patient was infected by SARS-CoV-2 on two separate occasions by a genetically distinct virus. Thus, previous exposure to SARS-CoV-2 might not guarantee total immunity in all cases. All individuals, whether previously diagnosed with COVID-19 or not, should take identical precautions to avoid infection with SARS-CoV-2. The implications of reinfections could be relevant for vaccine development and application.

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Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) leads to a detectable immune response, but the susceptibility of previously infected individuals to reinfection with SARS-CoV-2 is not well understood. SARS-CoV-2 infection results in generation of neutralising antibodies in patients. However, the degree to which this immune response indicates a protective immunity to subsequent infection with SARS-CoV-2 has not yet been elucidated. In studies of immunity to other coronaviruses, loss of immunity can occur within 1–3 years. Cases of primary illness due to infection followed by a discrete secondary infection or illness with the same biological agent can best be ascertained as distinct infection events by genetic analysis of the agents associated with each illness event. Reports of secondary infection events with SARS-CoV-2 have been published from Hong Kong, the Netherlands and Belgium, and Ecuador. We present a case report of an individual who had two distinct COVID-19 illnesses from genetically distinct SARS-CoV-2 agents.

Methods
Case history

We present a case report of a 24-year-old male patient who was a resident of Harjah Governorate in the KSA Region of Aseer.

The patient presented to a community testing event held by the AL-harjah General Hospital ER department on June 24, 2020. He had symptoms consistent with viral infection (sore throat, cough, headache, loss of smell and taste, Fatigue). The patient had no history of clinically significant underlying conditions, and no indications of compromised immunity were identified. During isolation, the patient's symptoms resolved (reported on July 4, 2020) and he continued to feel well until September 19, 2020. On September 19, 2020, the patient sought care at Tatman clinic with self-reported fever, headache, dizziness, sore throat, cough, nausea, and diarrhoea, loss of smell and taste, at which time chest radiography was done and he was discharged home. 3 days later (September 22, 2020), the patient presented to a Tatman Clinic doctor and was found to be hypoxic with shortness of breath. He was instructed to go to the emergency department after provision of oxygen.

Results

The first nasopharyngeal swab, obtained at the community screening event on June 24, 2020, was positive for SARS-CoV-2 on real-time RT-PCR testing. One subsequent nucleic acid amplification test obtained after resolution of symptoms were negative for SARS-CoV-2 RNA. The patient's symptoms

returned on September 19, 2020, and he was admitted to hospital on September 22, 2020, at which time a second nasopharyngeal swab was obtained and was positive for SARS-CoV-2 infection by real-time RT-PCR testing. The patient required ongoing oxygen support in hospital and reported symptoms that included myalgia, cough, and shortness of breath. On September 19, 2020, the patient was tested for IgG and IgM against SARS-CoV-2 and positive results were obtained.

Discussion

Our case report presents details of the first individual in Region of Aseer in the KSA to have symptomatic reinfection with SARS-CoV-2. Our patient showed increased symptom severity in their second infection. The mechanisms that could account for a more severe secondary infection can only be speculated. First, a very high dose of virus might have led to the second instance of infection and induced more severe disease. Second, it is possible that reinfection was caused by a version of the virus that was more virulent, or more virulent in this patient's context. Third, a mechanism of antibody-dependent enhancement might be the cause, a means by which specific Fc-bearing immune cells become infected with virus by binding to specific antibodies. This mechanism has been seen previously with the betacoronavirus causing severe acute respiratory syndrome. In that case, the patient recovered and was discharged from hospital.

The individual associated with these two SARS-CoV-2 infections had no immunological disorders that would imply facilitation of reinfection. They were not taking any immunosuppressive drugs. The individual was negative for HIV by antibody and RNA testing (data not shown) and had no obvious cell count abnormalities. The secondary positive case (reinfection) occurred simultaneously to a positive case in a cohabitant (parent), who also provided a specimen on September 19, 2020, that was positive by nucleic acid amplification testing (transcription-mediated amplification). Sequencing is underway on the co-habitant specimen to ascertain its potential role in reinfection. However, the positive specimen from the co-habitant was obtained and tested in the Hologic Aptima format, which did not align with the procedures established at our sequencing laboratory. Nevertheless, the co-habitant positive case provides a possible source for secondary exposure and reinfection of our patient.

It is possible that we have reported a case of continuous infection entailing deactivation and reactivation. However, for such a hypothesis to be true, a mutational rate of SARS-CoV-2 would be required that has not yet been recorded. If such an amount of base change did occur in that timeframe, the remarkable nature of specimens A and B would shift from a case of possible reinfection to one of high-rate evolution within an infected individual. Another alternative explanation for the observed differences in specimens A and B would be that of co-infection. In a co-infection hypothesis, the patient would have been infected with viruses of both genotypes at the time of sample collection. Such a hypothesis would then further require that the specimen B type virus be present, yet undetected in June, 2020, and then conversely, specimen A type virions become depleted before the September, 2020, sample collection date. Specimens A and B were both in clade 20C, which was the predominant major clade seen in Aseer Regional Laboratory at the time samples were obtained. Our survey of viruses in Aseer Regional Laboratory identified samples resembling each of the case genotypes. Although evidence exists that SARS-CoV-2 quasispecies exist at low and fluctuating frequencies in infected samples, whereby low-frequency (eg, 1%) SNVs could be seen in various samples from the same patient,

this possible situation would not itself account for the genotype switch observed between the first infection and reinfection.

Our findings have implications for the role of vaccination in response to COVID-19. If we have truly reported a case of reinfection, initial exposure to SARS-CoV-2 might not result in a level of immunity that is 100% protective for all individuals. With respect to vaccination, this understanding is established, with influenza regularly showing the challenges of effective vaccine design. A major limitation of our case study is that we were unable to undertake any assessment of the immune response to the first episode of SARS-CoV-2 infection. We also could not assess fully the effectiveness of the immune responses (eg, neutralizing antibody titers) during the second episode, when the individual was antibody-positive for total antibody assay to the SARS-CoV-2 nucleocapsid protein. If our patient is a case of natural viral evolution *in vivo* (although highly unlikely in view of the requirement of four reversions to reference genotypes) then the implications of these data are that SARS-CoV-2 can adapt with enough genetic dexterity to avoid a natural immune response in a manner to re-establish detectable levels of infection in an individual. If our patient is a case of reinfection, it is crucial to note that the frequency of such an occurrence is not defined by one case study: this event could be rare. The absence of comprehensive genomic sequencing of positive cases in the KSA and worldwide limits the advances in public health surveillance needed to find these cases. Certainly, limitations in screening and testing availability for SARS-CoV-2 exacerbate the poor surveillance efforts being undertaken not only to diagnose COVID-19 but also to obtain actionable genetic tracking of this agent.

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