CASE REPORT

Coronavirus Disease-19 and Reinfections: A Review of Cases

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ABSTRACT

Since first surfacing in Wuhan, China, in December 2019, the novel coronavirus disease-2019 (COVID-19) has led to a global pandemic with confirmed cases and death bells tolling in the millions with new cases still emerging daily. Despite sharing genetic similarities to the severe acute respiratory syndrome (SARS) virus, the specific viral proteins found on the novel SARS coronavirus 2 and its structure seems to make this strain much more elusive and destructive. Based on peer-reviewed cases, there seems to be an increase in patient reinfection, but due to current testing and treatment limitations, it is yet to be determined if the new trend of reinfection is due to a persistent COVID-19 infection that involves a latent period, a recurrent infection due to the same strain of COVID-19, or a mutated strain of COVID-19. The purpose of this study is to discuss the recent reports of the development of reinfection in previously confirmed COVID-19 cases in an attempt to gain a further understanding of the mechanisms of virulence, the effects on the human immune system, and how current testing and treatment modalities are faring. While the virus seems to have a penchant for patients with existing comorbidities, newer data indicate that everyone may be susceptible to possible infection and that not all patients will present with typical respiratory symptoms, making it imperative to examine established cases of reinfection in an attempt to further help with developing drugs for treatment, vaccines, and protocols for prevention.

Key words: Coronavirus, coronavirus disease-2019, severe acute respiratory syndrome-coronavirus-2, reinfection

INTRODUCTION

Coronaviruses, which circulate among animals, are enveloped viruses with a positive sense, single-stranded RNA, having a nucleocapsid of helical symmetry.[1,2] The club-shaped protrusions on the outer surface of the virus give a crown or "solar corona".[3] It originates from the family of coronaviridae and is in the order *Nidovirales* and realm *Riboviria*. The novel severe acute respiratory syndrome coronavirus (SARS-CoV-2), first observed in Wuhan, China, in December 2019, is seen to have 70% similarity to the SARS and is spherical with four glycoproteins: S, E, M, and N.[4] The pathogen is from the RNA beta coronavirus genus, sharing a similarity in terms of the genome to a bat coronavirus.[1,3,4]

As of October 2020, the novel coronavirus disease-2019 (COVID-19) has led to a global pandemic with over 42,055,863 confirmed cases and 1,141,567 deaths spanning 218 countries.[5] Infections occur once the virus enters the host cell, through the angiotensin-converting enzyme 2 (ACE-2), an entry receptor located predominantly in the

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respiratory tract,[6] and uses the transmembrane serine protease 2 (TMPRSS2) for S protein activation.[7] The fusion of cell membranes allows the SARS-CoV genome to be released into the cytoplasm of the host cell, where replication occurs through RNA-dependent RNA polymerase. Through exocytosis, the newly synthesized virions are released[8] to further replicate in respiratory epithelial cells.[9] The transmission of the virus occurs through either the nasal or oral mucosa through air droplets and contact routes from symptomatic and asymptomatic patients[10] which is dependent on proximity between individuals. The incubation period is roughly 4–6 days and patients are seen to show symptoms at 14 days following infection.[11] It is still uncertain at what point a patient is no longer contagious, given that the viral load can increase up to 37 days from the initial acute infection.[12,13]

In comparison to the 40 million cases worldwide, reinfections appear to be rather rare occurrences.[14] Despite this statistic, crucial information can still be gathered from the cases as different patterns of reinfection have emerged which provides substantial evidence that SARS-CoV-2 continues to be actively present among humans even after initial incidence in an individual. Examining reinfections provide a rich area for evolving research on protective correlates for drug, vaccine development, and precautionary measures. An analysis of reinfections allow questions to arise about the virulence of the viral strain, its impact on the immune system, and the subsequent immunity that develops in humans.

This paper aims to present and explore a review of COVID-19 confirmed reinfections and brings further insight into the mechanism of the virus with regard to the persistence of the virus shedding and/or reinfection.

CASE REPORTS

Case One

An 89-year-old female with a history of Waldenström's macroglobulinemia presented to the emergency department (ED) with severe cough and fever. Laboratory results showed a lymphocyte count of 0.4 × 10^9/L and a positive SARS-CoV-2 quantitative reverse transcription polymerase chain reaction (RT-qPCR) from the patient's nasopharyngeal swab. The patient was discharged from the hospital after 5 days with residual fatigue. Within 59 days after the initial COVID-19 infection, the patient experienced dyspnea, fever, and cough. On readmission, the patient's vitals showed a respiratory rate of 40 breaths per minute and an oxygen saturation rate was 90%, with a positive SARS-CoV-2 RT-qPCR on a nasopharyngeal swab. The patient's serum was tested for SARS-CoV-2 antibodies on days 4 and 6, while on readmission, both tests were reported as negative. Her condition deteriorated further on day 8 and within 2 weeks the patient died.[15]

Case Two

A 25-year-old American male from Washoe County, Nevada, tested positive for SARS-CoV-2 while attending a community testing event on April 18, 2020. He presented with symptoms consistent with a viral infection, such as diarrhea, sore throat, headache, cough, and nausea, which had started 3 weeks prior. The patient's symptoms resolved during self-isolation. However, on May 31, 2020, the patient reported to an urgent care facility with complaints of diarrhea, fever, nausea, headache, cough, and dizziness. A negative SAR-CoV-2 test was found. On June 05, 2020, the patient followed up with his primary care physician and was found to be hypoxic with shortness of breath; therefore, instructed to go to the ED where he tested positive for a 2nd time with SARS-CoV-2.[16]

Case Three

An 82-year-old male suffering from hypertension, diabetes, chronic kidney disease, and advanced Parkinson's presented to the ED in early April of 2020, with shortness of breath and fever of 1-week. RT-PCR for SARS-CoV-2 was positive. Vitals showed that the patient was hypoxic, tachypneic, and febrile at 100.4°F. Basilar patchy opacities were seen peripherally on the chest X-ray (CXR). Due to his declining hypoxic state, the patient was intubated and sent to the intensive care unit (ICU) where he remained for 28 days before he was extubated. By early May of 2020 or day 39 of hospitalization, the patient was discharged following two subsequent negative results of RT-PCRs for SAR-CoV-2 to a rehabilitation center. On day 48, since the initial presentation of symptoms, or 10 days post-discharge, the patient was readmitted to the ED because of hypoxia and fever. Vitals recorded a 99.9°F temperature, blood pressure of 70/40 mmHg, respiratory rate of 110 beats per minute, and oxygen saturation of 83% on room air. CXR showed bilateral ground-glass opacities and computed tomography (CT) scan showed unilateral focal consolidations, both indicative of SARS-CoV-2 and bacterial pneumonia. Respiratory cultures grew *Corynebacterium* and RT-PCR for SARS-CoV-2 tested positive. Complications such as delirium, septic shock, and acute renal failure occurred during this course. On hospital days 11 and 12, the patient underwent a repeat RT-PCR for SARS-CoV-2, both of which resulted as negative; therefore, the patient was discharged on hospital day 15 to an inpatient rehabilitation center.[17]

DISCUSSION

As of October 2020, the race to create a viable treatment and/or vaccine for this novel disease continues to evolve. COVID-19 can present with a wide spectrum of symptoms ranging from having no symptoms to having severe respiratory failure.[18] The initial presentation reported by most patients includes but is not limited to, non-specific systemic and/or respiratory symptoms, anorexia, fatigue, shortness of breath, and arthralgia or myalgia.[19] In a study conducted from South Korea, 213 COVID-19 patients were

evaluated, and of those with mild symptoms, 40% had a cough and 39.5% had hyposmia.[20] There are even symptoms of COVID-19 that may not be specifically respiratory. It has been found that gastrointestinal symptoms may precede respiratory symptoms and be the first manifestation of the disease including lack of appetite, diarrhea, and vomiting.[21]

With cases rapidly increasing around the world, the race for accurate and accessible diagnostics is in the spotlight. At present, the preferred method is to use RT-PCR for diagnosis and is an important diagnostic tool in providing accurate RNA detection of SARS-CoV-2. RT-PCR works using gene-specific primers that target various viral protein genes, such as the envelope protein gene or the nucleocapsid protein gene. This is done by the collection of upper respiratory samples from nasopharyngeal and oropharyngeal swabs.[18] Although RT-PCR is the diagnostic gold standard used around the world today, there does seem to be false positives associated with it.[22] Many factors, including the sampling procedure of swabs, the caliber of the sampling tube, and/or the level of quality of the reagent used make it possible for a patient to have two false-negative tests, but still, be positive for the virus.[23] Perhaps, the variables identified above could be the confounding elements in the "reinfection" from the cases detailed above. Once a patient is diagnosed with COVID-19, the antibodies in the blood can be detected as early as the 4th day after symptom onset.[24] These tests detect the immunoglobulin G (IgG) antibodies in the blood. IgG antibodies are associated with "viral neutralizing" and can shed some light on conferred immunity from the disease.[25] It is also recommended that the serology for antibodies be tested 3–4 weeks after a patient has symptoms of COVID-19.[26,27] By doing so, these tests can serve as a confirmatory tool in those with negative tests.

The normal human response to viral infection is to produce CD4+ and CD8+ T cells. It has been noted that in COVID-19, there may be an overactive or under activated response by the immune system.[28] Although it is not known how long immunity is conferred once the infection has resolved, there seem to be sporadic cases of reinfection. The T-cell response can decrease exponentially in those over the age of 65; therefore, the goal in this age group is to boost T-cell response byways of vaccination.[29] This decrease, coupled with an inactive or hyperactive T-cell response, complicated by comorbid conditions, explains reinfection in older age people. Parallels to this idea can be seen in the cases presented above, where one patient was 89 years old (case one) and the other 82 years old (case three), and both with comorbid conditions. Furthermore, it has been identified that several cases of reinfection have occurred globally, though the question remains whether these isolated incidences are due to new COVID-19 infection or simply a persistence of the initial infection.[14-17,30] In the United States, a 25-year-old man had tested positive twice for COVID-19. On further investigation, it was found that the genetic material from his prior and current infection varied greatly, thus indicating that the man had been infected by two different strains.[16,31]

As of October 22, 2020, the Food and Drug Administration (FDA) has approved Veklury (remdesivir), as the only antiviral drug for the treatment of COVID-19 disease.[32] Therapy for the disease focuses mainly on the prevention of complications and the management of the symptoms. The National Institutes of Health recommends that those with COVID-19 disease on high-flow or non-invasive ventilation receive dexamethasone to prevent further complications.[33] Of the other treatments being studied, the use of convalescent plasma also has the potential to be used as a solid therapeutic. In a study of blood collected from 70 COVID-19-positive patients, it was found that the use of convalescent plasma in these patients resulted in higher neutralizing antibody response, resulting in a better recovery time.[34] Other therapeutics that were highlighted earlier on in the pandemic, such as hydroxychloroquine, have been found to not be useful or therapeutic in COVID-19 disease. The FDA revoked the emergency use authorization in mid-June for hydroxychloroquine.[35]

CONCLUSION

SARS-CoV-2 is a virus that has infiltrated multiple countries and caused millions of casualties, even proving to be fatal in some patients who are without proper management of symptoms and prevention of their pre-existing comorbidities/complications. In this article, confirmed COVID-19 reinfections bring further insight into the mechanism of the virus with regard to the persistence of virus shedding and/or reinfection. It is yet to be determined if the new trend of reinfection is due to a persistent COVID-19 infection that involves a latent period, a recurrent infection due to the same strain of COVID-19, and/or a mutated strain of COVID-19. There need to be more studies to further investigate how and what increases the likelihood of being reinfected with SARS-CoV-2. Due to the recent misinformation about COVID-19, there also needs to be more public awareness in hopes to reduce transmission and optimize care using facial masks, thorough hand hygiene, and personal space sanitation in all individuals including those that have survived the disease once.

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