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REINFECTION AFTER SARS-COV2 INFECTION: A LOOMING CONCERN

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ABSTRACT

Many unanswered questions remain about COVID-19 infection caused by SARS-CoV-2 coronavirus. One such looming concern is the possibility of reinfection of recovered cases. We conducted a literature review on various aspects of this possibility, including the case presentations of relapsed/re-infected patients, the immune response of production of neutralizing antibodies, immunity in response to coronavirus during SARS-CoV2 and MERS, possibility of false-positive results of real-time polymerase chain reaction. We concluded that further studies are required to establish whether relapse or reinfection is possible firmly. However, these possibilities point towards the needs of change in the protocol of isolation, quarantine, and discharge. It also undermines the role of the upcoming vaccine in disease prevention and treatment.

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1 Introduction

The first human case of COVID-19 was seen in Wuhan, China, in December 2019. The isolation of the genome has identified it as severe acute respiratory syndrome coronavirus 2 (SARS CoV-2) (Dhama et al., 2020). The World Health Organization declared the outbreak a Public Health Emergency of International Concern on Jan 30, 2020, and a pandemic on Mar 11 (WHO, 2020a; WHO, 2020b). As of October 20 2020, more than 40 million cases of COVID-19 have been reported from more than 217 countries across the world, resulting in more than 1,124,480 deaths.

The risk of reinfection is a significant threat to people worldwide. Along with this threat, there are other concerns which arise in the background of this possibility. Firstly, whether these cases are for real, reinfection or relapse or false-negative results, each of these has different implications. If it is reinfection, is there any protective immunity to COVID-19in the very beginning? If not, convalescent plasma role is doubtful in the treatment of patients. If this is genuinely relapse of prior infection, will prospective vaccine succeed in providing long-term protective immunity to patients? Moreover, when the repeat cases are due to false-negative results, are the criteria used sufficiently to discharge patients and let them be out of isolation. Are we effectively terminating that chain of infection thus or not?

2 Current Status of COVID-19 reinfection

A hospital in Italy has reported two cases of possible reinfection aged 81 and 85 years old with new symptoms such as malaise and muscle pain approximately 2-5 days after a negative nasopharyngeal swab tested via a quantitative reverse transcriptase-polymerase chain reaction. Both patients had mild symptoms in the second wave and recovered spontaneously (Marco & Fiorpaolo, 2020).Wuhan has observed some cases of repeat fever and positive nucleic acid tests after discharge which was supposed to be due to reinfection (Zhou et al.,2020).

Another single centered cohort study has shown 69 (16.7%) out of a cohort of 414 patients to retest positive for COVID-19. 13 patients out of these also had two readmissions, and three patients had three readmissions (Huang et al., 2020). The median time from negative to positive test was 19 days with a range of 6-52 days. This study also suggests that there may be a correlation between transmissibility and retest positivity.

Thevarajan et al. published a case report of a 47-year-old woman who travelled from Wuhan to Australia and after that presented with coronavirus (Thevarajan et al., 2020). They studied the immune response of the patient with the timeline of clinical and laboratory symptoms. This patient did not have severe symptoms and had a complete clinical recovery by day 13 of the symptomatic disease. The patient had a robust immune response comprising of antibody-secreting cells, activated CD4 and CD8 cells and SARS-CoV-2 Ig-M and Ig-G antibodies (WHO, 2020a).This immune response can prevail upon disease recovery as well as possible protection from future infections.

There have also been reports of patients tested positive again after negative in China (Feng & Cheng, 2020). 111 people have been tested positive for the new coronavirus again, after they were tested negative and released from quarantine revealed by the Korea Centers for Disease Control and Prevention (KCDC, 2020).

In another study that investigated 11 cases of repeat symptoms, 4 were healthcare workers with a risk of re-exposure, and seven comorbid patients had repeat CT signs and required re-hospitalization. Three patients died during the second episode. Out of these 7, D21 serology showed 5 to be positive, one weakly positive and three negatives (Gousseff et al., 2020). Now, although the first group of health workers seems to be re-infected, the second group of patients appears to relapse due to inadequate immunological response and comorbid conditions

2.1 Role of RT- PCR in reinfection cases

Real-time polymerase chain reaction (RT-PCR) is the most widely used test for COVID-19. In a study done to estimate the false results of RT-PCR, it was seen that 48/384 (12.5%) patients were found to convert from negative to positive in the first two tests (Alvarez-Moreno & Rodriguez-Morales, 2020). This can be an estimate of the false-negative report. In the initially confirmed cases which converted to negative after the treatment, one patient was found to be positive again after two consecutive negative results. The study showed that the results are quite variable (Li et al., 2020). This can be attributed to insufficient viral material in the specimen, restrictions on sample transportation, or laboratory error during sampling (XI et al., 2020). There are other reported cases of false-negative reverse transcriptase-polymerase chain reaction. A case report in China has shown a 54-year-old man with negative PCR throat swab correlating with clinical recovery and then again, a positive test a few days later in isolation (Zhang et al., 2020). Another study showed that 15/70 patients with previous confirmed SARS-CoV-2 were later found to be positive after two consecutive negative results. These results were suspected to be found due toa high false-negative rate of viral test and prolonged nucleic acid conversion time (Xiao et al., 2020). There also is a possibility that a positive result can come from dead viruses or fragments of viral genomes. The proportion was 9.1% (5/55) in another study (Yuan et al., 2020).

2.2 Immune response to SARS-Cov-2 viral infection

A recent study showing the seroconversion of SARS-CoV-2 suggests that neutralizing antibodies from around the end of week

2 of symptoms (Woefel et al., 2020). Moreover, there is active virus shedding in earlier stages of the disease which decreases in later stages, thus, diminishing the infectivity. Another study of the immune response of SARS-CoV-2 evaluating the neutralizing antibodies showed that they are found at their peak levels on 10-15 days after the onset of symptoms and remain in a plateau phase after that. However, there is a variable immune response amongst individuals infected and recovered with a significant finding that in almost 30% of individuals, there are extremely low titers of neutralizing antibodies (Wu et al., 2020). This pool may be thus susceptible to reinfection. Current studies of SARS- CoV- 2 show cross-reactivity only with SARS- CoV and not with any other previously known coronaviruses (Guo et al., 2020). This study also shows that the median response of neutralizing antibodies is found around five days for IgM and 14 days for IgG.

2.3 Risk factor for COVID-19 reinfection

To understand this risk of relapse or reinfection Bao et al. (2020) performed experimentation on Rhesus macaques' monkeys. They challenged these monkeys with SARS- CoV-2 intratracheally and observed the infection progression via symptoms such as weight loss and rectal temperature and checked the viral loads in respiratory and anal swabs. Specific antibody against SARS-CoV-2 was also found to be elevated at day 14, 21 and 28. When the monkeys reached a stage similar to clinical discharge criteria, some of them were re-challenged with repeat dose with the same strain to find the possibility of reinfection. There was seen a transient elevation of body temperature, but there were not any X-ray abnormalities or pathological or immunological findings corresponding to repeat infection. Thus, they concluded that adequate antibody response in primary infection protected these monkeys from subsequent infection with the same strain (Bao et al., 2020).

Another study regarding the immunological response in ferrets suggested that primary infection is followed by the innate immune response which is interferon-mediated and lead to an inflammatory reaction from SARS-CoV2 infection and in the later stages lead to neutralizing antibodies formation. If reinfection is there, there is no IFN response; only the neutralizing antibody response occurs, which may be protective (Cameron et al., 2012).There are uses of mathematical models to predict the reinfection as well. Alexander Victor Okheusein a method using Susceptible-Exposed-Infectious-Removed-Undetectable-Susceptible (SEIRUS) Model, tried to project the probability of reinfection in patients who are recovered from COVID-19. This model concluded that there are no chances of reinfection in patients who are already recovered (Okheuse, 2020).

There are various factors which interplay to increase the risk of reinfection. The most important being the virus should undergo steady mutation rate to escape the pre-existing immunity. The case fatality rate from COVID-19 varies from 0.3% to 15.6% amongst countries depending upon susceptible population and testing methods with a median of less than 5%. If a disease has low CFR, it tends to produce mutant genomes while transmission and thus can escape previous immunity (Biswas et al., 2020).

3 Lessons learnt from the past

Lessons from the previous infections of corona virus-like SARS-CoV, which occurred in 2003 suggest that there is a robust immune response against coronavirus rendering protection to individuals from reinfection (WHO, 2020a). Another study which followed the recovered patients from SARS-CoV for six years demonstrated that the protective Antibody and memory B cells disappear from the plasma of patients in due course of time which makes them susceptible to reinfection (Tang et al., 2011). Also, the data shows that the previous antibody response peaked around four months and declined after that. Other studies which followed up the patients of Middle East respiratory syndrome CoV (MERS-CoV) showed that the protective neutralizing antibodies in patients with severe infection were found even after 13 months of disease (Al-Abdallat et al., 2014). In contrast, for patients with mild or asymptomatic disease, the neutralizing antibodies were found to be produced at a low rate and were short-lived (Drosten et al, 2014). However, to what extent these results can be used to predict the immune response to SARS-CoV-2 is questionable.

Conclusion

SARS-CoV-2 is a new disease and has many unanswered questions as of now. Whether it is capable of causing reinfection in previously cured patients is still one of the questions. We will need more detailed studies to rule out the possibility of reinfection. Meanwhile, we should keep the false-negative results in mind and thus, modify the guidelines of discharge and isolation. The recovered patients should be considered susceptible to infection and use the relevant precautions until proven otherwise.

Abbreviations:

COVID-19: coronavirus disease 2019,

SARS-CoV-2: Severe acute respiratory syndrome coronavirus-2,

MERS: Middle East respiratory syndrome.

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Conflict of Interest

Authors' declares no conflict of interest

Authors' Contribution

All authors have contributed equally.

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