







Contentious Issue in Recurrent COVID-19 Infection: Reactivation or Reinfection

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Coronavirus disease 2019 (COVID-19) has spread over 200 countries in the form of a pandemic. The few favorable features include the mild nature of infection in most patients and the role of social distancing and personal protective equipment in preventing the spread [1]. However, the natural history of infection, symptoms, recovery, and cure still remain unclear. In addition, recovery and subsequent protective immunity are the areas of active focus, presence and duration of which is an important question to answer. Although a study claimed that COVID-19 infection gives rise to a long-lasting and robust T-cell-mediated immunity for asymptomatic/mild disease [2], another study has shown varied timing of antibody-mediated response with decrease in immunoglobulin M levels in 3 weeks of infection and persisting immunoglobulin M response [3].

We report a case series of 5 patients who were admitted with COVID-19 infection (microbiological diagnosis) and then discharged/shifted to the non-COVID-19 area after becoming asymptomatic or testing negative for the virus (based on real-time polymerase chain reaction [PCR]) on 2 occasions. All the 5 patients eventually developed acute symptoms of febrile illness and turned out to be COVID-19 positive again. This is probably the first series of such cases reported from India till date. The details of the 5 patients are summarized in Table 1. They belonged to diverse age groups (within the range of 18–78 years), and 2 had comorbidities (coronary artery disease and post-tubercular obstructive airway disease). Moreover, 1 patient died, and another recovered after requiring intensive care unit (ICU) admission and oxygen support. It is noteworthy that 1 patient (patient 5) had an initial mild infection and subsequently developed a severe infection, requiring ICU admission.

Furthermore, 3 patients turned COVID-19 positive again within 7 days; this can possibly be explained by the reactivation of the virus rather than reinfection, as postulated by the Korea Centers for Disease Control and Prevention [4]. This immediate reactivation may suggest that the patient did not develop adequate protective antibodies, which may be because the patients received immunosuppressive/immunomodulatory therapy (steroids or hydroxychloroquine), and the advanced age of 2 patients may have made their immune response less robust. Another possibility is that sampling and testing may have been faulty or not sufficiently sensitive when the virus was dormant. In addition, the technique of sampling (when the tests were negative) can have an impact on the adequacy of the sample and may lead to a false-negative result. It has also been speculated that the persistent positivity in the PCR may be owing to the viral particle ribonucleic acid being detected by the tests, implying that although the test is positive, the virus has been eliminated and the patient is deemed noninfective [5]. The absence of routine viral cultures limits our ability to assess this hypothesis in this case series.

However, the patient who had developed acute febrile illness with PCR-positive result for COVID-19 after 40 days of original illness puts a question mark on the duration of immunity that humans mount. During the first admission, he had been declared PCR-negative on the basis of 2 consecutive nasopharyngeal swabs. Other possible mechanisms include mutations in the virus, making the immunity ineffective, or patients who had already recovered from the disease being reinfected by a different strain circulating in the community. In 1 patient, although the initial infection was mild, the subsequent infection led to severe manifestations. A similar phenomenon has been observed in other viral infections, such as dengue; the initial infection by 1 serotype leads to a mild infection, and a subsequent infection by a different serotype leads to severe manifestations [6].

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Table 1. The 5 cases of COVID-19 reinfection/resurgence and their clinical profile

Age/sex	Comorbidity	First infection	Initial symptoms	Treatment given	Reinfection/resurgence	Time gap (days)	Symptoms	Radiology	Treatment
1 18/F	Treated PTB 5 years back	May 26, 2020-June 10, 2020 COVID-19 positive on May 26, 2020 and 2 PCR-negative on June 08, 2020 and June 10, 2020	Fever and cough for 5 days	HCQ, azithromycin	June 15, 2020–June 24, 2020 COVID-19 positive on June 17, 2020	5	High-grade fever, cough, and dyspnea for 2 days	Right lung consolidation suggestive of pneumonia	Meropenem, enoxaparin, oxygen
2 78/M	Coronary artery disease	April 24, 2020–May 7, 2020 COVID-19 positive on April 25, 2020 and 2 PCR-negative on May 05, 2020 and May 06, 2020	Fever and cough for 2 days	HCQ	June 20, 2020–June 30, 2020 COVID-19 positive on June 21, 2020	43	Fever cough and dyspnea for 1 day	Normal chest X-ray	PCM
3 42/M	None	May 04, 2020–May 12, 2020 COVID-19 positive on May 08, 2020 and negative on May 11, 2020 and May 12, 2020	Fever, cough, and dyspnea for 4 days	HCQ, azithromycin, dexamethasone	May 16, 2020–Death. COVID-19 positive on May 16, 2020	4	High-grade fever and worsened dyspnea	Left lung consolidation	Meropenem
4 25/F	None	May 29, 2020–June 12, 2020 COVID-19 positive on May 31, 2020 and negative on June 11, 2020 and June 12, 2020	Asymptomatic healthcare worker	None	June 18, 2020–till Date (June 22, 2020) COVID-19 positive on June 20, 2020	6	Fever and cough for 2 days	Normal	PCM
5 64/M	None	May 18, 2020–June 02, 2020 COVID-19 positive on May 22, 2020 and negative on June 01, 2020 and June 02, 2020	Fever and cough for 2 days	HCQ	June 19, 2020–till date (June 22, 2020) COVID-19 positive on June 20, 2020	17	Fever, cough and dyspnea for 3 days	Right lung consolidation	Dexamethasone, oxygen, enoxaparin, antibiotics

F: female; M: male; PTB: pulmonary tuberculosis; PCR: polymerase chain reaction; HCQ: hydroxychloroquine; PCM: paracetamol; COVID-19: coronavirus disease 2019

Table 2. Review of literature of COVID-19 reinfection

Study and year	Number of patients	Symptoms at first admission	Treatment given	Discharge policy	Time gap between first and reinfection/resurgence	Symptoms at second admission	Treatment given	Outcome
Xing et al. [7]	2	Case 1 fever, chills, and fatigue Case 2 headache and pharyngalgia	Case 1 standard care Case 2 standard care	1) Afebrile for 3 days 2) Alleviation of respiratory symptoms 3) Radiological improvement on CT 4) 2 consecutive negative RT-PCR for SARS-CoV-2, 24 h apart	Case 1 January 28, 2020-February 15, 2020 (17 days) Case 2 January 21, 2020-February 19, 2020 (18 days)	Case 1 asymptomatic (found positive in surveillance) Case 2 asymptomatic (found positive in surveillance)	Case 1 N/A Case 2 N/A	Case 1 alive Case 2 alive
Lan et al. [8]	4	3 cases: fever, cough, or both 1 case: asymptomatic	Antiviral treatment (oseltamivir, 75 mg, BD)	1) Afebrile for 3 days 2) Alleviation of respiratory symptoms 3) Radiological improvement on CT 4) 2 consecutive negative PCR for SARS-CoV-2, 24 h apart	5-13 days	Asymptomatic (found positive in surveillance)	N/A observation	Alive
Yuan et al. [9]	25	Fever and cough	1) Ritonavir/ lopinavir, 500 mg, 24 h 2) IFN- γ , 50 μ g, BD 3) Herbal medication	1) Afebrile for 3 days 2) Alleviation of respiratory symptoms 3) Radiological improvement on CT 4) 2 consecutive negative PCR for SARS-CoV-2, 24 h apart	7.32 \pm 3.86 days	Mild cough (32%) asymptomatic (68%)	Chinese herbal formula of lung cleansing and detoxifying decoction	Alive
Chen et al. [10]	1	Fever, sore throat, cough, and chest tightness	1) Oseltamivir 2) Arbidol 3) Lopinavir/ ritonavir 4) Moxifloxacin	1) Afebrile for 3 days 2) Alleviation of respiratory symptoms 3) Radiological improvement on CT 4) 2 consecutive negative PCR for SARS-CoV-2, 24 h apart	8 days	Asymptomatic	N/A observation	Alive
Wang et al. [11]	8	N/A	According to Chinese national health commission of China. New coronavirus pneumonia prevention and control program (6 th edition)	1) Afebrile for 3 days 2) Alleviation of respiratory symptoms 3) Radiological improvement on CT 4) 2 consecutive negative RT-PCR for SARS-CoV-2, 24 h apart	Post-discharge resurgence First week: 4 positive, remaining 4 not tested Second week: 3 new positives, 4 converted negative, and 1 not tested Third and fourth weeks: 7 negative, 1 positive	Symptoms post-discharge First week: 1 patient had cough, 1 had fever, 6 asymptomatic Second week: 1 patient had cough, 1 had fever, 6 asymptomatic Third and fourth week: 1 patient had cough, 7 asymptomatic	Supportive and symptomatic treatment	Alive
Yang et al. [12]	1	Fever, malaise, and fatigue	1) Steroids (methylprednisolone) 2) Ganciclovir 3) Arbidol 4) Moxifloxacin 5) Traditional Chinese medicine	1) Afebrile for 3 days 2) Alleviation of respiratory symptoms 3) Radiological improvement on CT 4) 2 consecutive negative RT-PCR for SARS-CoV-2, 24 h apart	Patient remained positive from February 03, 2020-April 02, 2020. (further status unknown)*	Postadmission, patient became asymptomatic after 1 week and continued to be asymptomatic during the course of stay	1) Interferon nebulization 2) Thymalfasin 3) Chloroquine diphosphate	Alive till April 2, 2020 further status unknown*

*shifted to another hospital, contact lost. RT-PCR: reverse transcriptase-polymerase chain reaction; N/A: not applicable; BD: twice daily; COVID-19: coronavirus disease 2019; IFN- γ : interferon- γ ; CT: computed tomography; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

The previously reported cases and case series with COVID-19 reinfection are summarized in Table 2. These reports and this article support the following conclusions. These cases raise doubts over acquired immunity to COVID-19, its persistence, the mutability of the virus, and the dilemma of defining cure. Viral cultures need to be made available for the subsequent positive samples to assess the infectivity of such patients. Serosurveillance studies would help to determine the protective degree and duration of protection after an infection. In addition, the factors that promote and extend the efficacy of these protective antibodies need to be studied to develop effective vaccines in future.

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