

Recurrence of disease in a patient with Covid-19: Re-activation or re-infection?

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ABSTRACT

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was expected to induce a monophasic disease with subsequent immunity. However, case reports have since emerged which have found patients with either re-infection or re-activation of the virus. We describe a 44-year-old man with severe Covid-19-induced pneumonia who had recurrence of the disease after testing Covid-19-negative on three consecutive reverse transcriptase-polymerase chain reaction (RT-PCR) tests. Our patient underlines that caution should be exercised while planning for discharge of a patient irrespective of his previous negative test, especially in vulnerable patients and those who had moderate-to-severe disease requiring the use of immunosuppressive therapy. The fact that such patients could experience a re-activation or re-infection, requires monitoring and vigilance in the management of the pandemic at individual and collective levels.

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INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or Covid-19 is third in the line of a coronavirus outbreak that has emerged among the human population in the past two decades. The other two being the SARS-CoV outbreak in 2002–03 and the Middle East respiratory syndrome coronavirus (MERS-CoV) outbreak in 2012–13. SARS-CoV-2 belongs to the beta-coronavirus 2b lineage and shares around 80% identity sequencing with the original SARS epidemic virus.¹ As with other coronaviruses, SARS-CoV-2 was expected to induce a monophasic disease with subsequent immunity and be an immunizing non-relapsing disease.² Few case reports around the world have since reported patients with either re-infection or re-activation of the virus. We describe a patient with Covid-19 pneumonia, who had recurrence of disease after being Covid-negative by reverse transcriptase-polymerase chain reaction (RT-PCR) on three occasions.

THE CASE

On 7 June 2020, a 44-year-old man presented to our hospital with a history of fever, dry cough and shortness of breath for 3–4 days. Physical examination revealed tachypnoea with oxygen

saturation (SpO₂) of 88% on ambient air. He was put on oxygen at 6 L/minute using a venturi mask (VM), after which the SpO₂ increased to 94%. The patient did not have any comorbid conditions such as diabetes, hypertension, cardiovascular disease, HIV or any chronic lung, liver or kidney disease. There was no history of tuberculosis or having taken immunosuppressive therapy in the past. With a suspicion of Covid-19, he was admitted to the severe acute respiratory illness (SARI) ward. The chest X-ray showed bilateral peripheral-based multiple opacities with predominant lower lobe involvement (Fig. 1a). A nasopharyngeal and throat swab was positive by RT-PCR for SARS-CoV-2 and the patient was diagnosed as having Covid-19-induced pneumonia. Based on the WHO criteria, the patient had a severe form of the disease due to the presence of respiratory distress with a respiratory rate of 30/minute and radiological signs of pneumonia and SpO₂ <90%.³ Laboratory investigations on admission showed leucocytosis of 20 000/cmm and C-reactive protein of 100 mg/L. D-dimer was not elevated (60 ng/ml). His renal and liver function tests were within normal limits. Urine routine and culture, blood cultures and sputum examination were unremarkable. Arterial blood gas analysis on ambient air revealed a pO₂ of 30 mmHg and pCO₂ of 35 mmHg. He was treated with O₂ at different volumes (up to 60% FiO₂ via VM), injectable antibiotics, hydroxychloroquine (400 mg b.i.d. on day 1, and 200 mg b.i.d. afterwards), enoxaparin 60 mg subcutaneously b.i.d. and injection methylprednisolone (40 mg b.i.d.).

He was shifted to the Covid-19 intensive care unit (ICU) and managed with mechanical ventilation. Gradually, the patient became afebrile; his respiratory symptoms improved and was weaned off the ventilator. The chest X-ray also improved with reduced parenchymal opacities (Fig. 1b). The two nasopharyngeal and throat swabs collected on 5 and 7 July were both negative for SARS-CoV-2 infection by RT-PCR. As per the hospital policy, after the resolution of fever and respiratory symptoms and two consecutive negative RT-PCR reports, 48 hours apart, he was shifted to the general ward and later discharged in a stable condition on 10 July 2020 with complete resolution of his symptoms. A high-resolution CT chest revealed nodular fibrocalcific opacities, interlobular septal thickening and mosaic attenuation of both lungs suggestive of sequelae of Covid-19 pneumonia (Fig. 2). Later, a third RT-PCR at his follow-up visit on 15 July 2020 was also negative.

However, on 20 July 2020, he visited the emergency department again with fever (101 °F spikes) and dry cough of 2 days' duration. He was re-admitted to the SARI ward. Physical examination revealed normal vital signs and SpO₂ of 97% on ambient air. The chest X-ray did not reveal any fresh opacity (Fig. 1c). However, SARS-CoV-2 RT-PCR on 20 July was positive. Routine laboratory investigations, including urine culture, blood culture and sputum examination, were unremarkable. HIV, hepatitis B surface antigen and hepatitis C virus antibody, and Mantoux test were negative. He was started on injectable antibiotics, hydroxychloroquine (400 mg b.i.d. on day 1, and 200 mg b.i.d. afterwards) and injection enoxaparin 60 mg subcutaneously once daily. The patient improved and was discharged after 10 days of onset of symptoms in a stable condition with advice of home quarantine for a further period of 14 days. The RT-PCR done at discharge was negative for Covid-19.

DISCUSSION

Our knowledge, so far, regarding immunity after Covid-19

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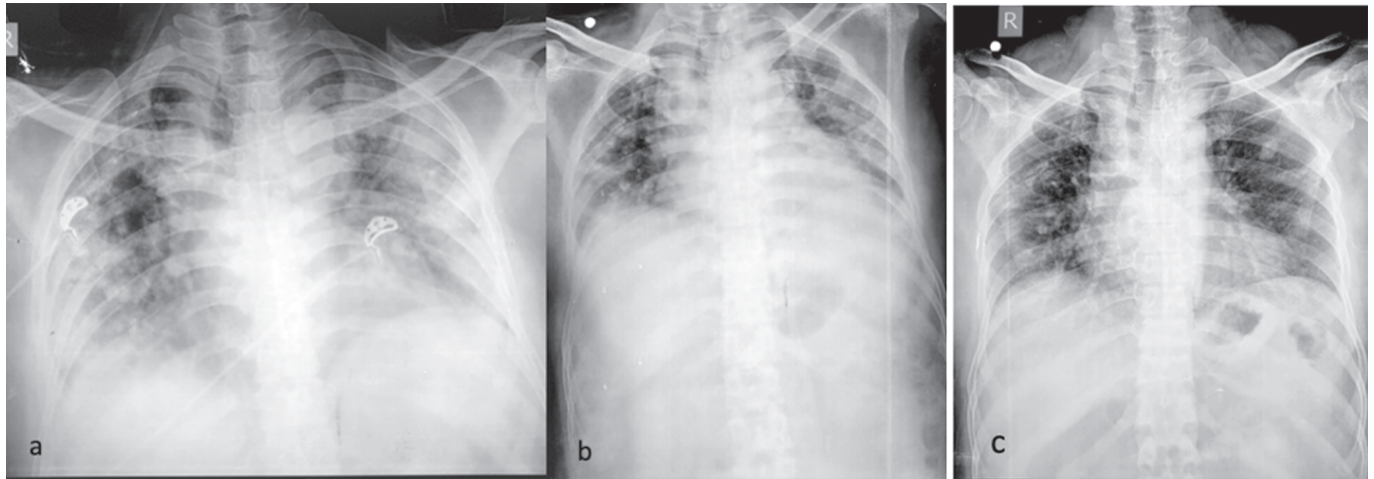


FIG 1. (a) Bilateral peripheral-based multiple opacities with predominant lower lobe involvement; (b) improved chest X-ray just before discharge; (c) no new opacities at the time of re-admission with clinical and virological recurrence of Covid-19

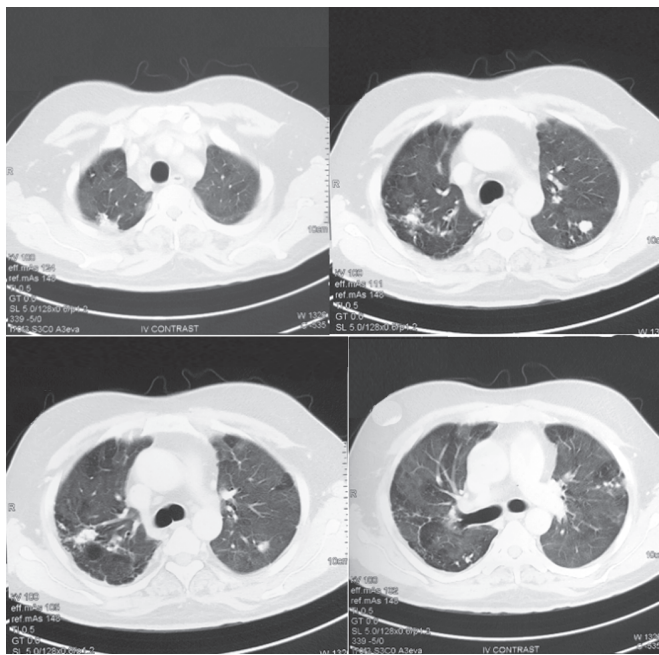


FIG 2. High-resolution computed tomography and contrast-enhanced computed tomography chest done after first discharge showing nodular fibrocalcific opacities, interlobular septal thickening and mosaic attenuation of bilateral lungs suggestive of novel corona virus-induced pneumonia sequelae

infection is limited. Most institutional discharge policies consider two consecutive negative reports for SARS-CoV-2 tests from respiratory tract specimens at least 48 hours apart. However, our patient tested positive on 7 June 2020, became symptomatic and positive on RT-PCR again on 20 July after three consecutive negative results on 5, 7 and 15 July 2020. The time to negativity during the first admission was longer than what is commonly observed in most patients, but prolonged positivity in few patients has been mentioned in the literature. The patient had severe Covid-19 and was managed in an ICU setting on mechanical ventilation, which might have delayed testing and contributed to the seemingly longer duration of time to negativity.

Furthermore, the patient received steroids, which are known to delay viral clearance.

The two separate symptomatic Covid-19 episodes in our patient, associated with viral RNA detection, raise two pathophysiological hypotheses underlying these episodes: viral re-infection or viral re-activation.

Following infection with Covid-19, IgM and IgG antibodies develop and are detectable within days to weeks of symptom onset in most infected individuals. However, antibody detection and higher titres have not always been found to correlate with clinical improvement in Covid-19.⁴⁻⁶ Although information is increasing about the viral load and seroconversion of the virus, what appears to be certain is that the viral burden typically peaks early in illness and then declines as antibodies develop and their titres rise over the subsequent 2–3 weeks.^{5,6} The durability of these neutralizing antibodies (primarily IgG) against SARS-CoV-2 is yet to be defined although persistence up to 40 days from symptom onset has been described.⁴ Re-infection by other viruses of the family has been debatable. SARS has not re-emerged since 2004 and MERS cases remain sporadic. The possible causes for re-infection include both short-lived protective immunity obtained post-infection and possible re-exposure to a genetically distinct form of the same virus. Re-infection in our case, although possible, appears less likely as he was confined to home-quarantine post-discharge and none of his family members tested positive.

With recurrence of symptoms and a positive RT-PCR testing after clinical and virological remission, re-activation of SARS-CoV-2 is the other possibility. Ye *et al.* have reported an incidence of 9% re-activation in Covid-19 patients after discharge from the hospital.⁷ Risk factors of re-activation would probably include weakened host immune status and virological features. Immunosuppressive factors such as the use of corticosteroids and other immunosuppressive agents could contribute to impaired viral clearance in the first place. In a study, it has been shown that the duration of viral RNA detection in throat swabs and faecal samples in the glucocorticoid treatment group was longer than that in the non-glucocorticoid treatment group.⁸ This could perhaps result in the persistence of the virus in the gastrointestinal tract or the entrapment of the viral nucleic acid in the host lung due to extensive fibrosis leading to its subsequent

re-activation. The hosts immune status may also play a role. A suppressed immune system may lead to suboptimal control of the SARS-CoV-2 infection, resulting in re-activation and a second episode of viral replication.

It is also possible that our patient represents a persistent Covid-19 illness. It may represent prolonged sporadic viral RNA shedding below the limit of assay detection. The viral load during the discharge of the patient would be suboptimal and due to the fluctuant nature of the viral load, it may have been detected as positive at a later date.

Another possibility is of a false-positive RT-PCR during the second admission. However, the clinical recurrence in the form of fever and dry cough, after three consecutive negative RT-PCRs over a period of more than 2 weeks, with no evidence of any alternate diagnosis, goes against this possibility. All the RT-PCRs were conducted by the same laboratory using the same methodology in our institution, which has a quality assurance. The chance of false-positivity appears very low.

Data to effectively differentiate these possibilities are lacking, highlighting an area of uncertainty. Routine collection of such data, specifically viral burden and viral culture from a larger sample of patients under standard protocols, is needed.

Though there was no suggestion on history and clinical examination, the possibility of primary immunodeficiency could not be completely ruled out. We could not conduct genome studies for viral strains as these are not available in our institute. Another limitation of our study was that we could not do Covid-19 antibody titres due to non-availability of the test at our institute at the time.

The possibility of re-activation of Covid-19 poses a major public health concern and should be kept in mind while

discharging patients as it could contribute to the spread of the virus in the community. Quarantine of 14 days post-discharge should apply to at least the hospitalized Covid-19 patients who had suffered from moderate-to-severe disease and in whom immunosuppressive therapies had to be used, irrespective of their previous negative tests. Further investigations would better define the most appropriate strategy for quarantine in these patients.

Conflicts of interest. None declared

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Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attraction of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his or her education and training and highlight the achievements as well as disappointments. A photograph should accompany the obituary.

—Editor