Five Times Reactivation of COVID-19 in a Patient with Thymoma

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Abstract

**Background:** The possibility of recurrence in COVID-19 is very rare and hence mostly underdiagnosed. In the face of pandemic, this can lead to circulation of the virus like a hidden iceberg. Better understanding about this topic can improve our knowledge of the COVID-19 pathogenesis and ways to control the transmission.

**Case presentation:** A 41 year old male with no known comorbidities was admitted five times during a period of 7 months each time after being detected RTPCR positive for SARS-CoV-2 and more symptomatic than previously. He had no contact with other COVID-19 patients and was asymptomatic in between admissions. Despite this, he did not develop antibodies against SARS-CoV-2. Later on, he was diagnosed with thymoma on biopsy of the anterior mediastinal mass. Patient’s condition deteriorated on last hospitalization and he died, despite the treatment. Here we present an interesting report on multiple times recurrent COVID-19 infection, probably a case of reactivation and different plausible explanations on the role of thymoma.

**Conclusion:** Acknowledging the potential of SARS-CoV-2 to cause recurrence is very important during the pandemic as a part of the long term transmission mitigation. The case report shows that previous infection does not guarantee complete immunity from COVID-19, especially in immuno-compromised patients. Hence, despite the status of prior infection, vulnerable individuals who recovered from COVID-19 should be under surveillance.

Introduction

The rapid spread of coronavirus disease 2019 (COVID-19) was declared as a pandemic by the World Health Organisation on March 2020. As various measures have been taken successfully to combat the epidemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a growing number of fully recovered patients have been discharged from hospitals. However, some of them have relapsed. Recurrent COVID-19 infection is a new entity and is underdiagnosed. Despite the improvement of our

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knowledge about this virus, it is still a challenging and controversial matter, whether all patients with SARS-CoV-2 infection will reactivate the illness and which risk factors predict eventual recurrence. A recent cohort study observed 27% incidence of COVID-19 reactivation during a median follow-up of 29 days. Better knowledge on this topic is important to understand the immune responses to the virus and contain disease transmission.

Case Report

A 41 year old male, active smoker and policeman by occupation, from Dausa, Rajasthan was admitted in district hospital on day 7 of symptom onset. He presented with complaints of loss of smell and taste for one week and detected COVID-19 positive for first time by reverse transcription polymerase chain reaction (RT-PCR) assay of oropharyngeal swab. Patient did not report any underlying medical condition or immunosuppression. After improvement on symptomatic treatment, he was discharged with twice negative swab (day 12 and day 15) and remained quarantine for next 10 days.

On day 34, he developed symptoms of dyspnoea, cough and fever and chest x-ray showed bilateral consolidation. He was hospitalized again in COVID Containment Unit (CCU) under SawaiMan Singh (SMS) Medical College and was detected second time positive for SARS-CoV-2 by RT-PCR assay of both oropharyngeal and nasopharyngeal swabs. Patient was treated with favipiravir, hydroxychloroquine and azithromycin. He became asymptomatic and got discharged after negative COVID report on day 54. During the 14 days quarantine period, he remained afebrile.

Computed tomography (CT) chest done in view of persisting mediastinal widening in chest radiographs, showed ill-defined soft tissue density mass lesion measuring approximately 74mm*55mm*78mm in right para-mediastinal location with parenchymal changes suggestive of interstitial lung disease (ILD). 2D-Echocardiography revealed no abnormality. He was planned for biopsy of the mass lesion, but pre-procedural COVID testing came out to be positive on day 78. He was asymptomatic and advised strict quarantine for next 14 days. But, his RT-PCR for COVID19 was persistently positive on days 91 and 100.

Later, patient was referred again to CCU for hospitalization on day 103 with complaints of worsening dyspnoea and fever. He was diagnosed with COVID-19 infection for the third time as his RT-PCR was positive with detection of genes “E” and “RdRp” at Ct values of 17 and 21, respectively. He did not give any history suggestive of contact with COVID-19 cases during quarantine period. His SARS-CoV-2 serology was negative for both IgM and IgG. Based on ICMR guidelines, patient had moderate form of disease (SpO2 <94%) and was treated with oxygen via face-mask upto 40% FiO2, remdesivir, enoxaparin, dexamethasone and symptomatics. He improved on treatment and swab tests came negative for COVID on day 119. He was maintaining oxygen saturation on room air and met the discharge criteria. After discharge, his symptoms gradually improved and disappeared completely during quarantine.

Repeat contrast enhanced CT (CECT) thorax and whole abdomen (Figure 1 a, b) revealed the poorly demarcated anterior mediastinal mass and Nonspecific interstitial pneumonia (NSIP) pattern ILD with no significant abnormality in abdomen. CT Guided biopsy of mass revealed spindle cell thymoma WHO type-A confirmed by positive immunohistochemistry (IHC) markers- p63, PanCK, Vimentin, Bcl2. For staging workup and treatment plan, he underwent whole body PET/CT imaging (Figure 2) which showed negligible FDG avid lobulated anterior mediastinal mass and sequela of COVID pneumonitis.

Surgical resection of mass was planned but during pre-anesthetic evaluation, patient was found to be tachypnoeic and hypoxic and was again tested COVID positive (fourth
time) by RTPCR assay targeting E-gene and RdRp gene on day 165. Patient got readmitted in CCU and managed on oxygen support with FiO2 upto 90% via non re-breather mask. Repeat testing for antibodies against SARS-CoV-2 was again negative for both IgM and IgG. Vero E6 cell culture based SARS-CoV-2 isolation was not done due to financial constraint. His clinical condition improved in few days and got discharged with negative COVID report on day 182. He was again referred for resection of the tumour.

After an asymptomatic quarantine period of 15 days with no close contact with other COVID patients, he was tested COVID RT-PCR positive for fifth time on day 197. He was brought to hospital with central cyanosis, severe respiratory distress and altered sensorium. He was admitted in COVID ICU and intubated. Despite the treatment, patient went into septic shock, his condition deteriorated and he died 3 days later.

Discussion

SARS-CoV-2, a highly contagious virus, belonging to the family Coronaviridae, is an enveloped, positive-sense single-stranded RNA virus. WHO designated the disease caused by SARS-CoV-2 infection as COVID-19. In December 2019, in Wuhan, China first case of COVID-19 was reported and the virus then rapidly spread to over 200 countries in a short time period.

The main route of transmission is via aerosolised droplets, while other routes such as direct contact, oral–faecal route, mother-to-child transmission, etc. are also possible. Incubation period is approximately 2–14 days. The diagnosis of the disease mainly depends on SARS-CoV-2 RNA detection in nasopharyngeal swab by real-time polymerase chain reaction (RT-PCR), epidemiological history, clinical manifestations and lung imaging. The most common symptoms are fever, cough, anosmia, dyspnoea, fatigue, diarrhoea and myalgia.

The invasion and pathogenesis of SARS-CoV-2 are associated with the host immune response. The virus invade by binding spike glycoprotein (S protein) on the viral envelop to its receptor, angiotensin-converting enzyme 2 (ACE2), on the surface of human cells (eg. alveolar epithelial cells). Innate immunity is the first line of defence against virus infections. Type-I interferons (IFN) are ubiquitously expressed cytokines that contribute to both innate and cellular immunity against viral infections. SARS-CoV-2 tends to inhibit IFN production through multiple mechanism, thereby enhancing its replication capacity. Weakened innate immunity cause delayed stimulation of adaptive immunity, which play an important role in viral clearance via activated CD8+ cytotoxic T cells and antibody-producing B cells. CD4+ helper T cells stimulate B cells to produce specific antibodies.

Recurrent COVID-19 infection is a rarely diagnosed entity. So far little is known about the causes of recurrence of SARS-CoV-2 infection. Few studies concluded that the possibility of recurrence is very low and the causes of repositivization are false positive test or prolonged shedding of dead virus as the true positive detection rate of RTPCR test ranges from 30-60% and the half-life of respiratory epithelial cells being 1-2 months, the non-viable viral RNA fragments can be detected during this period. But in our patient, the possibility of these are low as he was more symptomatic during each hospitalization. Therefore we consider this patient as a case of recurrence.

Recurrent can occur due to reactivation with the same strain or re-infection with a different strain. Reactivation or relapse is caused by activation of the dormant virus persisting in the body. It is a re-detectable positive viral RNA in a recovered patient which occurs within the first 4 weeks of previous infection. Probable explanation is that despite a negative RTPCR test, virus may be present in other organs with abundant ACE2 receptors like kidney, small intestine (ileum), bladder, myocardium, etc. which can reactivate anytime. Reinfection is subsequent COVID-19 infection after recovery from a previous infection. Few studies supporting reinfection by a new strain of virus with a different gene sequence has been reported but the underlying pathogenesis is still under study. Our patient was in strict isolation according to quarantine norms and the possibility of reinfection with a new strain is unlikely. The absence of antibody production even after repeated infection is also in favour of reactivation.

According to Lafaie et al. study, a probable COVID-19 recurrence may have symptoms with repeat positive SARS-CoV-2, clinical and radiological worsening, positive cell culture during the second episode and absence of neutralizing antibody. Though many studies have concluded that the repositivization might be attributed to false-positive laboratory results and prolonged viral shedding, rather than recurrence, the failure of protective antibody formation might be the key reason for the possible recurrence of SARS-CoV-2 infection. But in this particular patient, there is yet another plausible explanation, discussed below.

Thymomas are rare tumours arising from thymic epithelial cells. Function of thymus is maturation, differentiation, positive and negative selection of T cells. Negative selection prevent autoimmunity by eliminating T cells that react with self-MHC or self-peptides. Thymoma causes autoimmunity as the thymocytes escape negative selection and becomes auto-reactive. According to the combined cellular and humoral deregulation theory, these CD8+ T cells initiate an autoimmune cascade and activation of CD4+ T cells which in turn activate B cells to produce autoantibodies. Autoantibodies to IFN-α, IFN-λ, IFN-ω and interleukin-12 (IL-12) are seen in thymomas. Anti-cytokine autoantibodies may be important in the pathogenesis of opportunistic infections in patients with thymic malignancy. Bastard P et al. showed in their study that neutralizing IgG autoantibodies against type-I IFNs, including IFN-ω and IFN-α can lead to life-threatening COVID-19. Presence of neutralizing anti-cytokine autoantibodies against type-I IFNs can affect both innate and adaptive immune responses against viral infections like COVID-19 leading to reactivation of the disease.

Studies have reported that anti-SARS-CoV-2 IgM antibodies were detectable 1-4 days and IgG antibodies after 14 days from symptom onset in most patients. According to WHO, a negative antibody test against SARS-CoV-2 could mean no prior exposure, immunosuppression or samples collected too early (<14 days from symptom onset). The most plausible
explanation for negative antibodies in this patient may an underlying immunosuppression. Thymoma do not directly affect B cells or antibody production, but T-helper cells are needed for priming humoral immunity. Chronic and recurrent viral infections are seen in thymoma patients with hypogammaglobulinemia, defined as Good’s syndrome. A case of SARS-CoV-2 infection has been documented in a patient with Good’s syndrome. Though this possibility was not ruled out in our patient and it may explain the absence of protective antibodies, it is well known that patients with defective cellular responses are more prone to viral infections than defective humoral immunity. Thus, presence of anti-cytokine autoantibodies might be the best and possible explanation for multiple times recurrence in our patient and future researches should focus on it.

Hence, we believe that the cause for fifth time reactivation in this patient may be due to underlying malignancy and immunosuppression, rather than low viral load, sampling error or re-infection. To the best of our knowledge, no case on five time’s recurrent COVID infection as a result of underlying autoimmunity (due to thymoma) is reported in literature till now.

**Conclusion**

Recurrence of COVID-19, whether reactivation or re-infection pose a major public health concern since it could significantly contribute to the spread of virus in the population. Adding to it, the absence of any reliable predictive markers for reactivation, will make SARS-CoV-2 recurrence a persistent and major public health burden. Considering numerous patients infected or previously exposed to the virus, recurrent cases may be the tip of the iceberg in this pandemic. Even though many studies dispose the concept of re-infection in COVID-19, this case report shows that it is not unlikely and should be kept in mind while treating repeatedly positive COVID-19 patients. Such patients can be contagious and should be thoroughly evaluated and followed up, rather than ignoring it as a dead virus detection. More precautions needed while declaring patients recovered and monitoring of vulnerable patients with regular follow-up should be emphasized in public health policies. Underestimation of reactivation can end in catastrophe.

**List of Abbreviations**


**Declarations**

**Ethics approval and consent to participate**- This study was approved by the ethics committee of SMS Medical College, Jaipur and informed consent were waived.

**Consent for publication**: Written informed consent was obtained from the nearest kin of the patient.

**Availability of data and materials**: All data used during the study are available from the corresponding author on reasonable request.

**Authors’ contribution**: MM, SKJ and KSK contributed to data collection. KSK analysed the data and wrote the manuscript. All authors reviewed and approved the manuscript.

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**References**

4. Tang X, Musa SS, Zhao S, He D. Reinfection or Reactivation of Severe Acute Respiratory Syndrome Coronavirus 2: A Systematic Review. Front Public Health 2021; 9663045.