



Reinfection or Reactivation of Coronavirus-19 in Patients with Hematologic Malignancies: Case Report Series

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Accepted: 27 January 2021 / Published online: 10 February 2021

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Abstract

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been relentless. We are into the 10th month of the pandemic, and we are still getting surprised every day. Although neutralizing antibodies are generated in response to coronavirus disease-19 (COVID-19), these antibodies do not appear to confer lifelong immunity, as lately there have been reports from various parts of the world of reinfection with the virus, starting from Hong Kong, Belgium, and the USA. The Indian Council of Medical Research (ICMR) has been on-record claiming three cases of reinfection in India. Herein, we report three patients of hematologic malignancy who most probably had reinfection with SARS-CoV-2, after complete documented recovery from first infection. All three patients were immunocompromised owing to their primary hematologic malignancy coupled with ongoing therapy, and the second infection was documented to be severe in all the three cases from the first episode.

Keywords COVID-19 · Reinfection · Reactivation · Severe COVID-19 · Hematologic malignancy

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has ravaged the world with its relentless stride. We are into the 10th month of the pandemic, and yet, every day, we hear of new challenges. Our knowledge from viral neutralizing antibody formation tells us that neutralizing antibodies are generated in response to coronavirus disease-19 (COVID-19) [1]. And while there was talk of, and some nations even apparently even had a plan to exploit, the so-called herd immunity, lately there have been reports from various parts of the world of

reinfection with the virus. To et al. [2] were the first to report reinfection with SARS-CoV-2 from Hong Kong, and now we have reports from Belgium [3] and the continental USA [4] that suggest the possibility of reinfection exists. There have been reports of possible reinfection with SARS-CoV-2 in patients with malignancies as well. Bentivegna et al. [5] reported a case of a 69-year-old diabetic lady with recently diagnosed urinary tract neoplasm who has evidence of two positive reports of anti-SARS-CoV-2 IgM along with RTPCR positivity, with four negative RTPCR reports and one negative anti-SARS-CoV-2 IgM between the two, and Luciani et al. [6] report a case of recurrent COVID-19 pneumonia in a patient with newly diagnosed classic Hodgkin's lymphoma with mixed cellularity. The Indian Council of Medical Research (ICMR) has been on-record claiming three cases of reinfection in India (<https://www.livemint.com/news/india/few-covid-19-reinfection-cases-identified-two-in-mumbai-one-in-ahmedabad-govt-11602588308358.html>). Herein, we report three patients of hematologic malignancy who most probably had reinfection with SARS-CoV-2, after complete documented recovery from first infection.

This article is part of the Topical Collection on *Covid-19*

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Patient 1

Thirty nine-year-old male is a known case of high-risk multiple myeloma on treatment with proteasome inhibitor

(bortezomib), immunomodulatory drug (pomalidomide), and weekly steroid (dexamethasone). He was initially was found to have COVID-19 on routine screening by RT-PCR done on nasal and nasopharyngeal swab in June 2020. He remained asymptomatic and remained in institutional quarantine for 02 weeks. He was discharged after repeat RT-PCR done on nasal, and nasopharyngeal swab was negative. Post discharge, his treatment for pre-existing myeloma was continued on day care basis and was given anti-CD38 monoclonal antibody, Daratumomab. Approximately 03 months after having tested negative for COVID-19, he developed high grade fever, chills, and rapidly worsening shortness of breath. Chest radiograph was suggestive of bilateral viral pneumonia. The presence of infection with SARS-CoV-2 was confirmed by RT-PCR done on nasal and nasopharyngeal swab. In view of severe COVID-19, he was managed with high flow oxygen (HFO), followed by non-invasive ventilation (NIV), Inj Remdesivir, convalescent plasma, and intravenous immunoglobulin (IVIG). He made a complete recovery from the second bout of infection as well. Figure 1 depicts a timeline of the patient’s illnesses. The cycle threshold (CT) values of the various RT-PCRs done on the patient are depicted in Fig. 2 and Table 1.

Patient 2

Twenty six-year-old male is a known case of Philadelphia chromosome positive acute lymphoblastic leukemia (ALL) on dasatinib and chemotherapy. He was found to be COVID-19 positive during evaluation for fever and cough in June 2020. He deteriorated clinically, and was managed as a case of severe COVID-19 pneumonia with Inj Remdesivir and NIV support. He was discharged on day 20 of illness, after

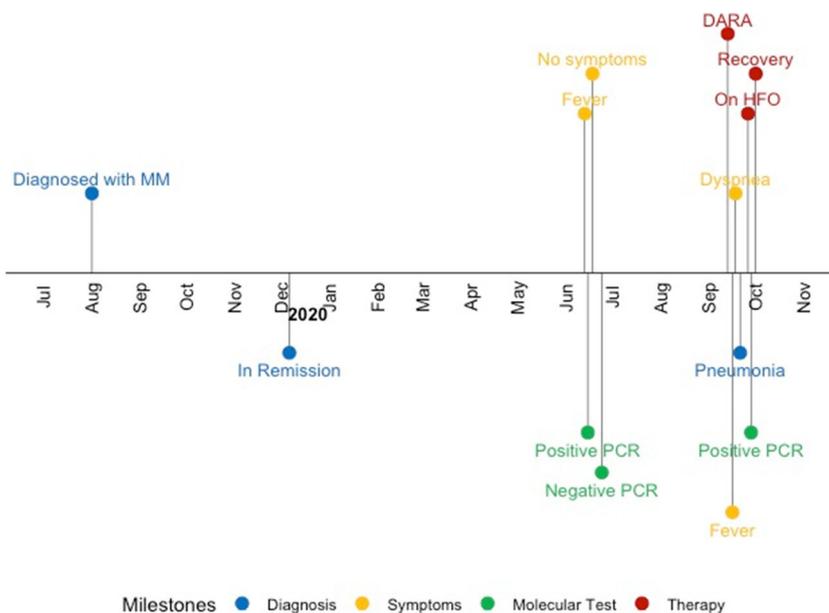
RT-PCR for SARS-CoV-2 done on nasal and nasopharyngeal swab was negative. He was continued on tyrosine kinase inhibitor (TKI) and oral chemotherapy. In October 2020, he developed submandibular lymphadenopathy, headache, vomiting, and high grade fever. His peripheral blood picture and the fine needle aspiration cytology (FNAC) of the submandibular lymph node were suggestive of relapse of ALL. RT-PCR done on nasal and nasopharyngeal swab again confirmed the presence of SARS-CoV-2. He was subsequently managed as severe COVID-19 pneumonia and made a complete recovery the second time around as well. Figure 3 depicts a timeline of the patient’s illnesses.

Patient 3

Thirty three-year-old case male, a known case of T cell ALL, was detected to be positive for COVID-19 in August 2020 which was done as part of screening prior to starting chemotherapy. He remained symptom-free throughout institutional isolation and was discharged after RT-PCR done on nasal and nasopharyngeal swab was negative. He was started on intensive chemotherapy which included high-dose steroids, anthracycline, vincristine, and pegylated L-asparaginase. He developed fever in October 2020 and was confirmed to be infected by SARS-CoV-2 by an RT-PCR done on nasal and nasopharyngeal swab. He was managed as a case of moderate COVID-19 with HFO, and subsequently recovered from the second bout of illness in early November 2020. Figure 4 depicts a timeline of the patient’s illnesses.

Salient features of these patients have been summarized in Table 2 below:

Fig. 1 Timeline of the two SARS-CoV-2 infections in Patient-1



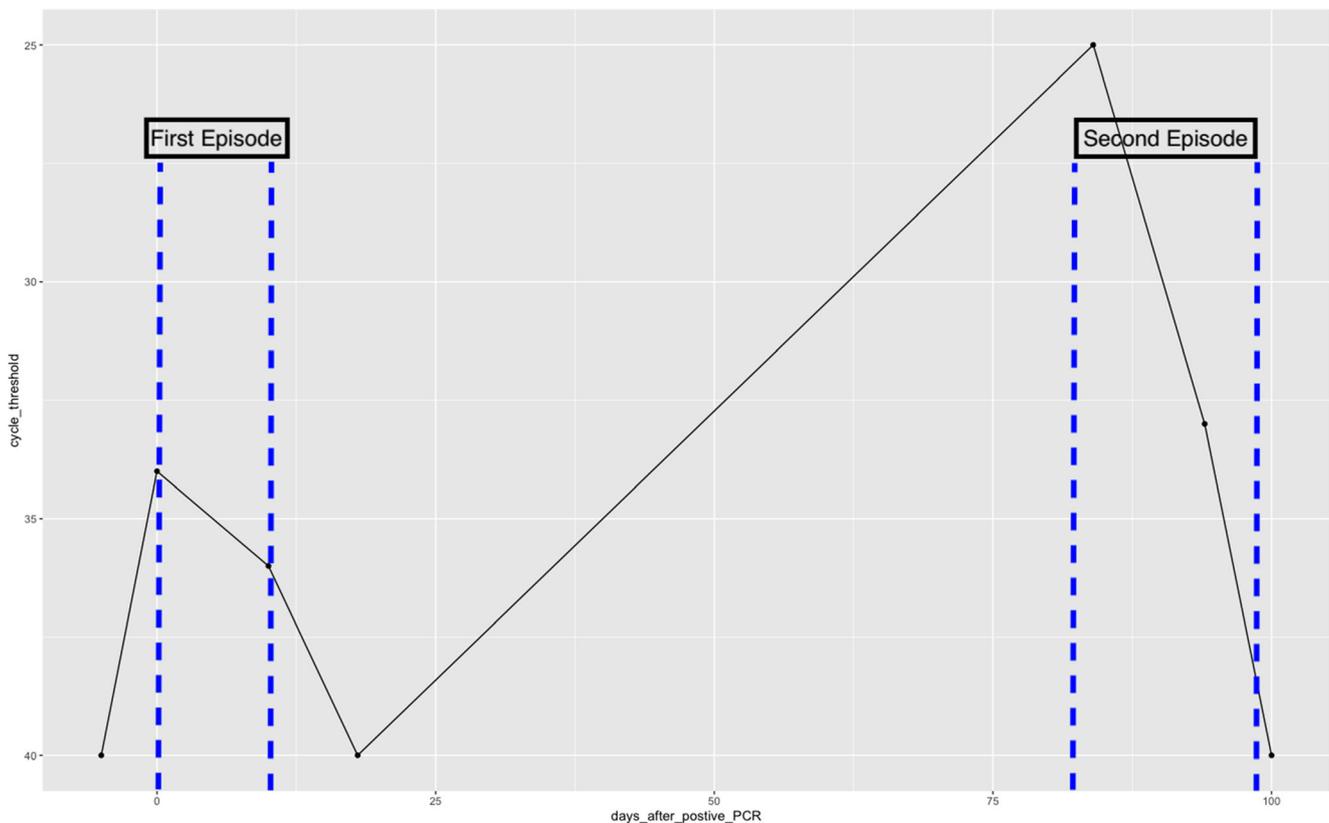


Fig. 2 The cycle threshold (CT) values of the various RT-PCR tests done on Patient-1

Discussion

COVID-19 keeps on posing new challenges and creating controversies for health care providers. One of the controversy is reinfection; is it a reality or just a myth [7]. Reinfection also raises many questions about the way forward in tackling this scourge—and will go a long way in attempting to make the right public health policy. Cancers are one of the vulnerable groups where COVID-19 can be severe and lead to fatality [8]. All our three patients are high-risk immunosuppressed patients suffering from established hematologic malignancy on chemotherapy, who were documented to have achieved RT-PCR negativity after a bout of infection. The three patients

subsequently became positive for the virus after 84 days, 91 days, and 60 days of returning a negative RTPCR report, respectively. In two of these three patients, the second infection was severe as per risk stratification [9], which raises a possibility of “antibody-dependent enhancement” classically seen in severe dengue infection [10]. Or is the absence of protective antibodies in our patients, consequent to their immunosuppressed state, the reason behind acquiring a second bout of the infection? It also begs the question of whether the antibodies protect the individual from infection, or disease, or neither and whether quantifying antibody levels in recovered patients is a good idea to evolve answers to these questions in the future.

Even as dynamic PCR results have raised a possibility of oscillating positive/negative reports in COVID-19 patients [9], all three of our patients were symptomatic, more so the second time around, which raise a serious concern that reinfection is no longer a myth in COVID-19 especially in immunosuppressed population. Another possibility to be considered is reactivation of dormant virus which is commonly seen in immunosuppressed with viruses like cytomegalovirus (CMV), herpes group, and Epstein Barr virus (EBV). This issue of viral reactivation or reinfection with a different strain can be resolved by sequencing of viral genome during the suspected reactivation, which could not be done for our patients.

Table 1 The cycle threshold (CT) values of the various RT-PCRs done on the patient

Serial no.	Cycle threshold (CT) value	Days after positive RT-PCR
1	40	– 5
2	34	0
3	36	10
4	40	18
5	25	84
6	33	94
7	40	100

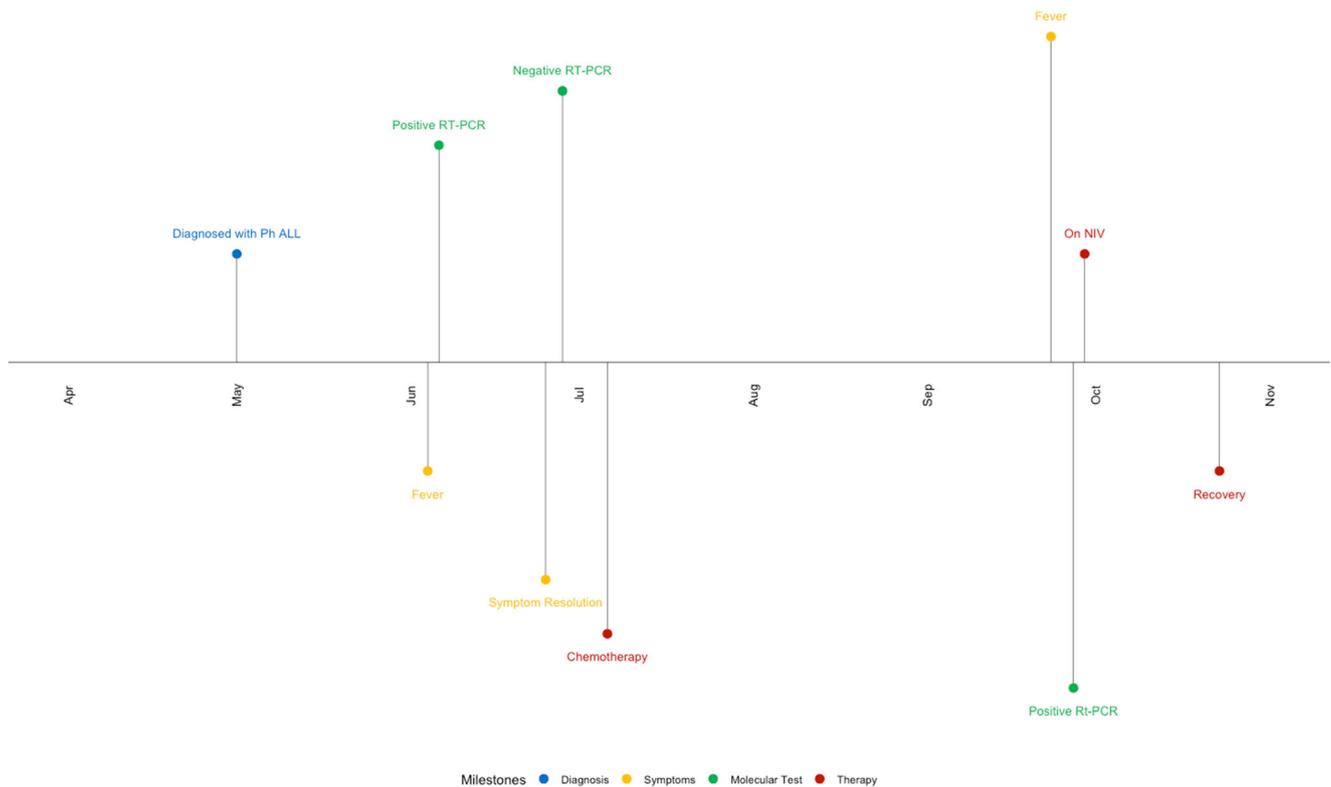


Fig. 3 Timeline of the two SARS-CoV-2 infections in Patient-2

Question arises, whether these patients, and others who have to undergo chemotherapy and live with its possible consequence of immunosuppression, are better off delaying the same during the pandemic to avoid risk of reinfection? Or, is an active surveillance of all patients on chemotherapy, the way forward? Most patients of aggressive hematologic malignancies will relapse and develop a refractory disease if there are

breaks in chemotherapy protocol; hence, it is recommended to continue with chemotherapy in these patients. Patients with indolent hematologic malignancies, and in patients with known risk factors of severe COVID-19 infection like advanced age, multiple co-morbidities can be started on less intense chemotherapy protocols. In addition, all patients on chemotherapy should be on active surveillance by a

Fig. 4 Timeline of the two SARS-CoV-2 infections in Patient-3

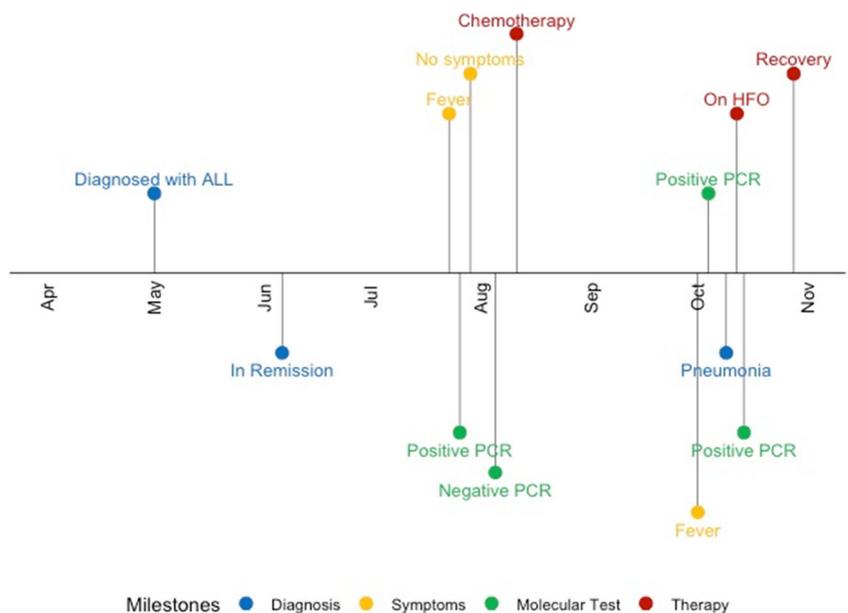


Table 2 Salient features of these patients

Patient no.	Age	Diagnosis	First infection with SARS-CoV-2			Second infection with SARS-CoV-2		Days to second RT-PCR positivity
			Date of RT-PCR positivity	Category of COVID-19	Date of PCR negativity	Date of RT-PCR positivity	Category of COVID-19	
1	39	MM	29 June 20	Mild	08 July 20	30 September 20	Severe	84
2	27	ALL	15 June 20	Severe	07 July 20	06 October 20	Severe	91
3	33	ALL	30 July 20	Mild	09 August 20	08 October 20	Moderate	60

MM multiple myeloma, *ALL* acute lymphoblastic leukemia, *RT-PCR* real-time polymerase chain reaction

combination of nasopharyngeal or oropharyngeal RT-PCR testing for the presence of SARS-CoV-2 infection along with surveillance antibody screen at the start of each chemotherapy cycle. To conclude, there is an urgent need to systematically study all reported cases of reinfection, particularly in immunosuppressed patients.

Author contributions All the listed authors have made substantial contributions to the conception and the design of the study and the acquisition, analysis, or interpretation of sections of data for the work. All the listed authors have been involved in drafting the paper and revising it critically for important intellectual content, and all were involved in the final approval of the version to be published. All the authors agree to be held accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Data availability All relevant data and material is available with the corresponding author.

Code availability Not applicable.

Declarations

Ethics Approval Ethics approval was waived off, in view of the ongoing pandemic and relevance of the study in mitigating the same. However, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent to Participate All the participants in the study were included after provision of informed written consent.

Consent for Publication Not applicable.

Conflict of Interest The authors declare that they have no conflict of interest.

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