



Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.



Correspondence



Reinfection versus failure of viral clearance in a COVID-19 patient with hematologic malignancy

1. Background

COVID-19 continues to be a significant global source of morbidity and mortality, particularly in older and immunocompromised patients [1,2]. Despite the increase in worldwide infection rates, the mortality rate has significantly decreased [3]. This decline could be attributed to multiple reasons, including early hospitalization of at-risk patients, improved access to supportive care, and administration of multiple anti-COVID-19 treatments, such as COVID-19 convalescent plasma (CCP), remdesivir, and dexamethasone [4–6]. However, there continues to be uncertainty whether contracting COVID-19 can impart immunity against reinfection, and, if so, how long the immunity lasts. There have been few reported cases of patients who initially cleared SARS-CoV-2, but then subsequently tested positive at a later date (Table 1).

True re-infection versus disease relapse due to failure of virus clearance remains to be a critical question. This question could be better addressed when screening tests with a higher sensitivity are available and widely employed to further identify continual infection versus true reinfection. Recently, we reported a high rate of false negative SARS-CoV-2 testing with RT-PCR-based assays in patients with hematological malignancies [7]. We also found that testing with clustered regularly interspaced short palindromic repeats (CRISPR) may successfully diagnose these cases [7]. These high sensitivity tests may be especially useful in high-risk populations, including patients with hematologic malignancies who have a weakened adaptive immune system and may not be able to properly respond to an infection.

2. Case presentation

We present a 59-year-old Caucasian male with classical Hodgkin lymphoma, treated initially with Adriamycin, Bleomycin, Vinblastine and Dacarbazine (ABVD), then subsequently treated with Bleomycin, Etoposide, Adriamycin, Cyclophosphamide, Vincristine, Procarbazine, and Prednisone (BEACOPP), and involved-site radiation therapy (ISRT) due to incomplete response and residual disease. The patient was on surveillance for a year when he presented with an enlarging submandibular lymph node, which was biopsied and revealed grade IIIA follicular lymphoma (FL). He was started on bendamustine and obinutuzumab (G-Benda) due to rapidly enlarging lymphadenopathy. On day 14 of cycle 2 of G-Benda, he presented to the Emergency Department with shortness of breath and dry cough for one week. Vital signs revealed tachycardia and oxygen desaturation to 85% on room air. Physical examination revealed moderate respiratory distress and decreased bibasilar breath sounds.

Complete blood count showed leukopenia, lymphopenia, and anemia; comprehensive metabolic panel was unremarkable. Chest X-ray showed vascular congestion while CT angiography of the chest showed

no pulmonary embolism but diffuse, multifocal, peripherally predominant peribronchovascular patchy ground glass and consolidative densities with associated air bronchograms and bronchial wall thickening concerning for COVID-19. Nasopharyngeal swab for SARS-CoV-2 was positive by RT-PCR. The patient was initially treated with oxygen, hydroxychloroquine and azithromycin. His oxygen requirement began increasing for which he received lopinavir/ritonavir. Due to continued lack of improvement, the patient received one unit of CCP, followed by administration of a second unit due to minimal improvement following the first unit. Immunoglobulin G (IgG) level was 195 mg/dL, so he received 0.5 g/kg intravenous immunoglobulin (IVIG).

Remdesivir was initiated under the Emergency Use Authorization due to continual worsening respiratory status. The patient's oxygen requirements finally decreased with improvement in respiratory status, and after a 90-day hospitalization, he was discharged home on 1 L per minute (LPM) oxygen via nasal canula (NC). Repeat COVID-19 PCR testing throughout his entire hospitalization remained positive, including at the time of discharge. He was retested after discharge for COVID-19 twice, with the first returning positive and the second negative, 16 and 20 weeks from the initial diagnosis, respectively. Chemotherapy was not restarted after discharge due to poor performance status.

Two months later (more than five months following initial presentation), the patient returned to the ED with chills, worsening shortness of breath, and a productive cough. On admission, he was febrile, tachycardic, hypotensive, and hypoxic requiring 3 LPM oxygen via NC. He tested negative for COVID-19 by guideline-directed PCR on presentation. His chest X-ray showed a right lower lobe consolidation not seen on previous imaging. CT scan showed slight improvement in ground glass opacities, no pulmonary embolism, and an increased right lung consolidation. Antibiotics were administered for a presumed bacterial pneumonia. His IgG level was 252 mg/dL, and he thus received a dose of IVIG.

The patient continued to be febrile, so a bronchoscopy with bronchoalveolar lavage was completed, which revealed normal flora and was negative for bacterial, fungal and viral infections. This lavage was not tested for COVID-19 given that three repeat nasopharyngeal tests during this time came back negative. Despite repeat negative tests, clinical suspicion for COVID-19-related organizing pneumonia remained high, but unfortunately, CRISPR was not available to us at that time. Therefore, the patient was treated with 1 g of methylprednisolone daily for 3 days then prednisone 60 mg daily for an 8-week course. The patient's hypoxia continued to worsen and eventually required high-flow NC. His steroid dose was increased to a pulsed regimen, and the patient received 1 g of intravenous methylprednisolone for three days with improvement in symptoms and decrease in oxygen requirement. Repeat RT-PCR test while patient was still symptomatic and oxygen-dependent returned

<https://doi.org/10.1016/j.leukres.2021.106514>

Received 1 January 2021

Available online 20 January 2021

0145-2126/© 2021 Elsevier Ltd. All rights reserved.

Table 1

Literature review of reported cases of COVID-19 reinfection after testing negatively at least for once. None reported a hematologic malignancy expect Mulder et al [8]. RT-qPCR: Real Time-quantitative polymerase chain reaction.

Report identifier	Age (years)	Origin of report	Days from first negative test to retesting positive	Testing method	Comorbidities	Outcome
Mulder et al [8]	89	The Netherlands	60	RT-qPCR	Waldenström macroglobulinemia	Died
Duggan et al [9]	82	USA	16	RT-qPCR	Parkinson's disease, insulin-dependent diabetes, chronic kidney disease, and hypertension	Survived
Goldman et al [10]	69	USA	100	RT-qPCR	Severe emphysema and hypertension	Survived
Nachmias et al [11]	20	Israel	36	RT-qPCR	None	Survived
Prado-Vivar et al [12]	46	Ecuador	49	RT-qPCR	None	Survived
Selvaraj et al [13]	70	USA	7	RT-qPCR	Obesity, asthma, obstructive sleep apnea, and hypertension	Survived
To et al [14]	33	Japan	95	RT-qPCR	None	Survived
Torres et al [15]	36	Brazil	9	RT-qPCR	None	Survived
Tillett et al [16]	25	USA	9	RT-qPCR	None	Survived
AlFehaidi et al [17]	46	Qatar	70	RT-qPCR	None	Survived

positive for SARS-CoV-2, roughly at six weeks from the second presentation. The patient remained stable on 2–3 LPM oxygen via NC and began working with physical and occupational therapy for transfer to inpatient rehabilitation.

Overall, across both presentations, the patient had thirteen positive COVID-19 RT-PCR-based tests, followed by four negative tests, then nine positive tests (supplemental Table 1). The patient's white blood count (WBC), absolute lymphocyte and neutrophil counts, as well as IgG levels checked during the various points of his disease course, are also documented (supplemental Table 1). The values show severe persistent lymphopenia, out of proportion to the degrees of leukopenia and neutropenia. Despite multiple IVIG doses, the patient continued to be hypogammaglobulinemic, which is expected in the setting of severe lymphopenia.

3. Discussion and conclusions

Here we present a case of a patient with a hematologic malignancy and COVID-19, who initially tested positive with RT-PCR for SARS-CoV-2, recovered and tested negative, then relapsed and tested positive using the same technique. The patient had thirteen positive COVID-19 PCR-based tests, followed by four negative tests, before retesting positive nine times (Supplemental Table 1). With more than five months between the two presentations, this case illustrates possibility of reinfection versus reactivation of COVID-19, in an immunocompromised host.

While not definitively clear, reinfection seems more likely due to clinical improvement after initial infection, time between the two presentations (more than five months), and RT-PCR conversion to negative that was concomitant with clinical improvement. This is further evidenced by multiple negative tests between the positive tests, including a negative test as an outpatient before his second hospitalization.

As we have previously reported, the failure to detect SARS-CoV-2 initially at the second presentation could be due to high rate of false negative testing in patients with hematological malignancies, reflecting then need for more sensitive testing, like CRISPR, in this patient population [7].

Although reinfection appears more likely, reactivation of prior infection due to incomplete viral clearance is also possible in the setting on impaired immune system. The patient might not have cleared the virus completely but reduced it to a low level that resulted in clinical improvement. When the virus reactivated, the patient became symptomatic while still testing negative with RT-PCR, then tested positive when a viral load crossed the test threshold. Higher sensitivity testing, such as CRISPR, may play a critical role in identifying patients who are not able to clear the virus and capture early infection/reactivation during the window period in which RT-PCR is failing. The possibility of a reactivation/relapse of COVID-19 illustrates the ability of the virus to survive for a long period of time in an immunocompromised host.

The Centers for Disease Control and Prevention proposed a

methodical approach to investigate reinfection, advising that the best evidence for reinfection is a proof of differing viral clades coupled with other evidence of actual infection. Unfortunately, our patient's samples were not available for sequencing at the time.

A large contributor to this patient's clinical course is his weakened immune system. The patient had received lymphodepleting chemotherapy leading to a weakened humoral response to COVID-19. We have shown that that patients with COVID-19 and hematological malignancies who have received a lymphodepleting chemotherapy within a month from COVID-19 diagnosis have significantly worse outcomes compared to their counterpart without a history of a lymphodepleting chemotherapy [7]. Indeed, our patient was on a lymphodepleting chemo-regimen when he was first diagnosed with COVID-19 and suffered a significant morbidity due to two severe COVID-19 diseases.

Author contributions

MI, AV, AN, KP, and RC contributed substantially to original draft writing while HS, FS, AL and NS contributed significantly to reviewing and editing.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Declaration of Competing Interest

The authors report no declarations of interest.

Acknowledgements

We thank the patient for the permission to write-up this case report.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.leukres.2021.106514>.

References

- [1] M. Fung, J.M. Babik, COVID-19 in immunocompromised hosts: what we know so far, *Clin. Infect. Dis.* (2020).
- [2] F. Perrotta, G. Corbi, G. Mazzeo, M. Boccia, L. Aronne, V. D'Agnano, et al., COVID-19 and the elderly: insights into pathogenesis and clinical decision-making, *Aging Clin. Exp. Res.* 32 (8) (2020) 1599–1608.
- [3] J.M. Dennis, A.P. McGovern, S.J. Vollmer, B.A. Mateen, Improving Survival of critical care patients with coronavirus disease 2019 in England: a national cohort study, March to June 2020, *Crit. Care Med.* (2021), 9000; Online First.

- [4] J.H. Beigel, K.M. Tomashek, L.E. Dodd, A.K. Mehta, B.S. Zingman, A.C. Kalil, et al., Remdesivir for the treatment of Covid-19 - preliminary report, *N. Engl. J. Med.* (2020).
- [5] Dexamethasone in hospitalized patients with Covid-19 — preliminary report, *N. Engl. J. Med.* (2020).
- [6] M. Ibrahim, P. Pal, A. Niu, K. Zwezdaryk, E. Tatje, L. Ko, et al., COVID-19 convalescent plasma decreased oxygen requirement and hospital stay in COVID-19 hospitalized patients including those with hematological malignancies: a report of 16 patients, *Blood*. 136 (Supplement 1) (2020) 40–41.
- [7] M. Alex Niu, Bo Ning, Francisco Socola, Hana Safah, Tim Reynolds, Moayed Ibrahim, M.D. Firas Safa, Tina Alfonso, Alfred Luk, David M. Mushatt, Hu Tony, Nakhle S. Saba, COVID-19 in patients with hematological malignancies: high false negative rate with high mortality, *Blood* (2020).
- [8] M. Mulder, D.S.J.M. van der Vegt, B.B. Oude Munnink, C.H. GeurtsvanKessel, J. van de Bovenkamp, R.S. Sikkema, et al., Reinfection of severe acute respiratory syndrome coronavirus 2 in an immunocompromised patient: a case report, *Clin. Infect. Dis.* (2020).
- [9] N.M. Duggan, S.M. Ludy, B.C. Shannon, A.T. Reisner, S.R. Wilcox, Is novel coronavirus 2019 reinfection possible? Interpreting dynamic SARS-CoV-2 test results through a case report, *Am. J. Emerg. Med.* (2020).
- [10] J.D. Goldman, K. Wang, K. Roltgen, S.C.A. Nielsen, J.C. Roach, S.N. Naccache, et al., Reinfection With SARS-CoV-2 and Failure of Humoral Immunity: a Case Report, *medRxiv*, 2020, 2020.09.22.20192443.
- [11] V. Nachmias, R. Fusman, S. Mann, G. Koren, The first case of documented Covid-19 reinfection in Israel, *IDCases*. 22 (2020) e00970.
- [12] Ba B.-W. Prado-Vivar, Monica and Guadalupe, Juan Jose and Marquez, Sully and Gutierrez, Bernardo and Rojas-Silva, Patricio and Grunauer, Michelle and Trueba, Gabriel and Barragan, Veronica and Cardenas, Paul, COVID-19 Re-Infection by a Phylogenetically Distinct SARS-CoV-2 Variant, First Confirmed Event in South America, *SSRN*, 2020.
- [13] V. Selvaraj, K. Herman, K. Dapaah-Afiriye, Severe, Symptomatic Reinfection in a Patient with COVID-19, *R I Med. J.* 103 (10) (2020) 24–26, 2013.
- [14] K.K.-W. To, I.F.-N. Hung, J.D. Ip, A.W.-H. Chu, W.-M. Chan, A.R. Tam, et al., Coronavirus disease 2019 (COVID-19) Re-infection by a phylogenetically distinct severe acute respiratory syndrome coronavirus 2 strain confirmed by whole genome sequencing, *Clin. Infect. Dis.* (2020).
- [15] Torres DdA, Ribeiro LdCB, Riello APdFL, D.D.G. Horovitz, L.F.R. Pinto, J. Croda, Reinfection of COVID-19 after 3 months with a distinct and more aggressive clinical presentation: case report, *J. Med. Virol.* (2020) n/a(n/a).
- [16] R.L. Tillett, J.R. Sevinsky, P.D. Hartley, H. Kerwin, N. Crawford, A. Gorzalski, et al., Genomic evidence for reinfection with SARS-CoV-2: a case study, *Lancet Infect. Dis.* (2020).
- [17] A. AlFehaidi, S.A. Ahmad, E. Hamed, SARS-CoV-2 re-infection: a case report from Qatar, *J. Infect.* (2020).

Moayed Ibrahim¹

Section of Hematology and Medical Oncology, Deming Department of Medicine, Tulane University, New Orleans, LA, USA

Andrew Vogel

Deming Department of Medicine, Tulane University, New Orleans, LA, USA

Alex Niu

Section of Hematology and Medical Oncology, Deming Department of Medicine, Tulane University, New Orleans, LA, USA

Ketaki Panse, Rebecca Chen

Deming Department of Medicine, Tulane University, New Orleans, LA, USA

Hana Safah, Francisco Socola

Section of Hematology and Medical Oncology, Deming Department of Medicine, Tulane University, New Orleans, LA, USA

Alfred Luk

Section of Infectious Diseases, Deming Department of Medicine, Tulane University, New Orleans, LA, USA

Nakhle S. Saba*

Section of Hematology and Medical Oncology, Deming Department of Medicine, Tulane University, New Orleans, LA, USA

* Corresponding author at: Tulane University School of Medicine, Section of Hematology and Medical Oncology, Deming Department of Medicine, 1430 Tulane Ave., SL-78, New Orleans, LA, 70112-2699, USA
E-mail address: nsaba@tulane.edu (N.S. Saba).

¹ Co-first author.