


Utility of Ct values in differentiating COVID-19 reinfection versus prolonged viral shedding in an immunocompromised patient

Katherine Julian ,¹ Neal Shah,² Rashmi Banjade,³ Dhirisha Bhatt⁴

¹Penn State College of Medicine, Hershey, Pennsylvania, USA

²Department of Internal Medicine, Division of Hematology/Oncology, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

³Department of Internal Medicine, Division of Infectious Disease, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

⁴Department of Internal Medicine, Penn State Health Milton S. Hershey Medical Center, Hershey, Pennsylvania, USA

Correspondence to

Katherine Julian;
kjulian1@pennstatehealth.psu.edu

Accepted 28 June 2021

SUMMARY

We describe the case of a 26-year-old man who presented to an outside hospital with concerns of blurred vision. He subsequently tested positive for COVID-19 and his lab work suggested acute leukaemia. The patient was admitted to our hospital and completed a course of remdesivir. He eventually tested negative for COVID-19 before initiating chemotherapy. Two days after starting chemotherapy, he developed a neutropenic fever and tested positive for COVID-19. Through this case, we aim to bring attention to patients who recurrently test positive with COVID-19 PCR testing, thereby causing a dilemma of differentiating between reinfections and prolonged shedding of the virus, as well as understand and use cycle threshold values to discern these aetiologies.

BACKGROUND

Acute lymphoblastic leukaemia (ALL) is a neoplastic disease that arises from the lymphoid cell line and is characterised by proliferation of blast cells in the bone marrow.¹ The accumulation of these blast cells interferes with normal haematopoiesis and immune response. Because this disease impairs lymphoid cell maturation, it can be further classified into B-cell or T-cell lineage forms of ALL. The patient described in this case was diagnosed with Philadelphia chromosome (Ph+) B-cell ALL, which is associated with expression of the oncogene BCR-ABL. This form of ALL comprises approximately 25% of adult cases of ALL.²

ALL is primarily a disease of children and young adults <20 years old, and there were approximately 6150 new cases of ALL diagnosed in 2020.³ ALL is a more rare form of cancer and accounted for approximately 0.3% of all new cancer cases diagnosed in 2020.¹ Although the presentation may be variable, ALL typically presents with fatigue, fever, easy bruising, unexplained weight loss, night sweats, lymphadenopathy and bone pain. Impairment of normal haematopoiesis, in addition to chemotherapy, results in immunosuppression of patients with ALL. With the ongoing COVID-19 pandemic, certain groups of individuals, such as patients with cancer, have been deemed high risk for morbidity of the virus.⁴ Therefore, it is important to explore and highlight the outcomes of immunocompromised patients in the context of COVID-19 infection and reinfection. This case in particular outlines the unique experience of a young patient with ALL who could have been potentially reinfected with COVID-19 after initiating chemotherapy.

CASE PRESENTATION

A previously healthy 26-year-old man presented to an out of state emergency department with new onset of blurred vision and was incidentally found to be COVID-19 positive on 8 October 2020. Vital signs on admission were temperature 37.7°C, blood pressure (BP) 134/72 mm Hg, heart rate (HR) 89 beats/min, respiration rate (RR) 18 breaths/min and SpO₂ 99% on room air. Initial workup showed a white blood cell count of 358×10⁹/L (normal 4.4–10.5×10⁹/L) with 34% blasts and concomitant anaemia and thrombocytopenia. A few days later, the patient presented to our hospital on 14 October 2020 and underwent a bone marrow biopsy, confirming a diagnosis of Philadelphia chromosome (+) B-cell ALL. He also retested positive for COVID-19 via nasopharyngeal swab on 14 October 2020 and chest CT scan demonstrated COVID-19 changes ([figure 1](#)). The patient was started on a 5-day course of remdesivir on 17 October 2020 and tested positive for COVID-19 antibodies following the completion of this 5-day treatment.

Following the remdesivir treatment, the patient tested negative for COVID-19 via nasopharyngeal swab twice on 2 November 2020 and 3 November 2020 and was cleared to initiate hyper-CVAD chemotherapy on 4 November 2020. The patient completed his induction cycle 1 course A of hyper-CVAD on 7 November 2020 and was discharged home. Two days later, on 9 November 2020, he reported fevers up to 104°F, feeling flushed and was found to have a positive COVID-19 PCR test on 11 November 2020. His vitals were temperature 38.8°C, BP 141/78 mm Hg, HR 141 beats/min, RR 21 breaths/min and SpO₂ 100% on room air. Workup for specific sources of infection was negative, including a urinalysis, blood and urine cultures and imaging studies. Chest X-ray did not show any new evidence of ground glass opacities and a repeat CT scan of the thorax ([figure 2](#)) showed no new or worsening parenchymal infiltrates when compared with his prior CT scan of the thorax. Due to his severe immunocompromised status in light of recent chemotherapy, he was admitted to the hospital and started on empiric antibiotics (cefepime and vancomycin followed by prophylactic ciprofloxacin), while concurrently being continued on home medications for prophylaxis of invasive and opportunistic infections with posaconazole, trimethoprim-sulfamethoxazole and acyclovir. A cycle threshold (Ct) value for COVID-19 PCR on 11 November 2020 was noted to be 37 ([table 1](#)). At



© BMJ Publishing Group Limited 2021. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Julian K, Shah N, Banjade R, et al. *BMJ Case Rep* 2021;**14**:e243692. doi:10.1136/bcr-2021-243692

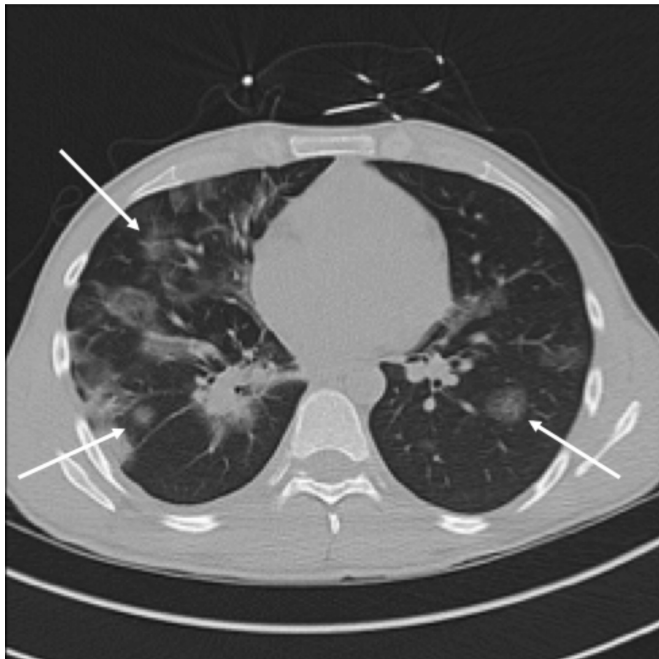


Figure 1 Initial chest CT scan demonstrating moderately severe changes associated with COVID-19 (14 October 2020). Axial CT scan demonstrating diffuse scattered peripheral ground glass opacities (arrows).

this time, labs revealed elevated ferritin at 611.9 ng/mL (normal 30–400 ng/mL), C reactive protein at 5.32 mg/dL (normal <0.50 mg/dL) and erythrocyte sedimentation rate at 24 mm/hour (normal 0–15 mm/hour). Unfortunately, follow-up labs for these inflammatory markers were not trended. Although this patient was severely immunocompromised, he neither manifested any respiratory symptoms nor demonstrated hypoxia, and there were no imaging changes that could be attributed to

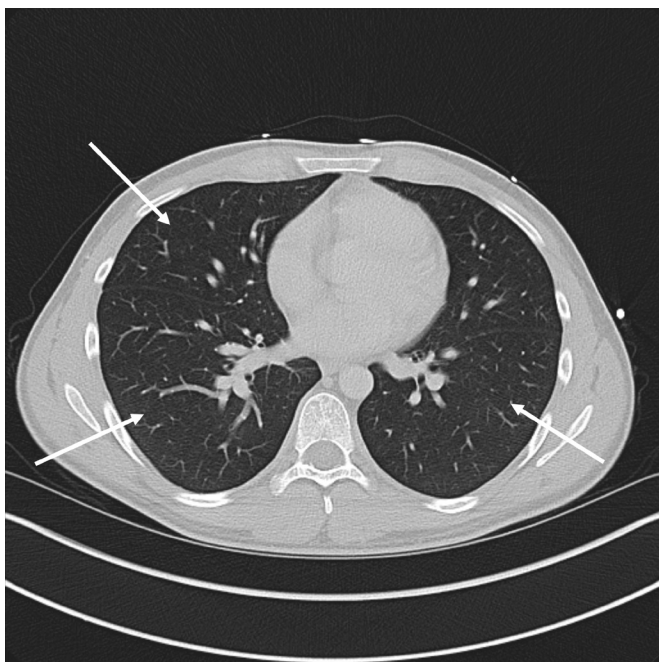


Figure 2 Follow-up chest CT scan (12 November 2020) demonstrating complete resolution of diffuse scattered peripheral ground glass opacities seen in figure 1 (arrows).

Table 1 Known Ct values with positive COVID-19 PCR tests

Date of positive COVID-19 test	Ct
14 October 2020	16.2,18.5
29 October 2020	29, 30
11 November 2020	37

Ct, cycle threshold.

worsening or reinfection with COVID-19 infection. The patient, having completed COVID-19 treatment with remdesivir, had shown a positive COVID-19 antibody response and had also undergone two negative COVID-19 tests a week prior to this repeat positive COVID-19 test. Hence, after an interdisciplinary discussion, it was concluded that this was more likely prolonged viral shedding as opposed to a reinfection or a reactivation of the virus, which occurred within a week of previous COVID-19 treatment.

The patient improved clinically following his antibiotic course for his neutropenic fevers and tested negative for COVID-19 on 25 November 2020. Since then, the patient has undergone his usual chemotherapy outpatient infusions with serial negative COVID-19 testings.

INVESTIGATIONS

Multiplex COVID-19 PCR with Cepheid kit was used to determine if the patient yielded a positive or negative test. However, this test is qualitative and does not provide a quantifiable measurement of the virus. Another important lab value used in this case is the Ct value, which measures the number of cycles of amplification using PCR required for the virus to be detected crossing a predetermined threshold.⁵ A higher Ct value is proportional to a lower viral load. The Ct value therefore provides a relative measure of viral quantity and is used clinically when compared with other known values see trends over time.

DIFFERENTIAL DIAGNOSIS

We considered several diagnoses for this patient's neutropenic fever. In addition to a reinfection with COVID-19, we considered opportunistic infections such as pneumocystis pneumonia, an invasive fungal infection, varicella-zoster virus visceral dissemination and a bacterial infection. At the time of admission for fever, the patient was either previously receiving or immediately started on sulfamethoxazole–trimethoprim, posaconazole, acyclovir and broad-spectrum antibiotics, respectively. Negative blood cultures ruled out a bacterial infection and in-house COVID-19 PCR tested positive concerning for a reinfection due to patient's recent immunocompromised status.

TREATMENT

This patient's management consisted of several pharmacological agents to treat his leukaemia, COVID-19 infection and neutropenic fever of initially unknown origin. This patient was started on the chemotherapy regimen hyper-CVAD, which consists of cyclophosphamide, vincristine, doxorubicin, dexamethasone and alternating methotrexate and cytarabine. This regimen was selected due to the patient's age and health status prior to starting chemotherapy. In addition to chemotherapy, a tyrosine kinase inhibitor was also selected due to potential CNS penetration for CNS prophylaxis and low side effect profile. This patient was also started on remdesivir after his initial positive COVID-19 test due to existing data supporting the antiviral shortening time to recovery.⁶ At the time of his readmission following induction chemotherapy for febrile neutropenia, he was only treated with

vancomycin and cefepime as broad-spectrum empiric therapy for potential bacterial infection.

OUTCOME AND FOLLOW-UP

Since testing negative on 25 November 2020, the patient has not reported any additional neutropenic fevers and has tolerated his hyper-CVAD regimen well. He continues to test negative for COVID-19 before the onset of each inpatient chemotherapy cycle, and most recently he tested negative on 18 December 2020 prior to hospital admission.

DISCUSSION

Within the past year, the COVID-19 pandemic has challenged and overwhelmed the US healthcare system. The initial uncertainty and rapidly changing knowledge surrounding SARS-CoV-2 has left many healthcare providers unsure of how to best care for their patients. This is especially true for higher risk patients, including patients with cancer who are immunocompromised. There are currently limited data that providers can reference when treating patients with cancer in the context of COVID-19. Here, we outlined the case of a young man with ALL who received positive COVID-19 tests at two separate time points with multiple negative COVID-19 tests in between.

A retrospective study performed in Wuhan, China, studied eight patients who were readmitted to the hospital for positive COVID-19 test again after previously being discharged from the hospital following two negative COVID-19 tests. On the second admission, patients were asymptomatic and all had SARS-CoV-2 IgG antibodies. Two patients remained in the hospital for at least 90 days because they were unable to test negative for COVID-19 by PCR three consecutive times.⁷ There can be multiple reasons why a COVID-19 'recovered' patient would test positive within a short period of time following serial negative tests. These include false negative testing due to sampling error, storage errors or reinfection with a new mutant/variant of COVID-19. It could also be attributed to a positive test from viral shedding from 'dead' viral gene fragments without active replication.⁸ Therefore, it is important to use additional lab values, such as Ct, and clinical judgement when evaluating patients. Certain patient populations, such as those receiving glucocorticoid therapies, patient with comorbidities such as diabetes, hypertension, chronic obstructive pulmonary disease or immunosuppressive treatment modalities, may also be 'prone' to more prolonged viral shedding which can delay viral clearance.⁸

The use of Ct values to determine reinfection has been described in prior cases reports. One such report from Brazil describes a 26-year-old man with an initial positive COVID-19 test (Ct value of 31.5). This patient eventually tested negative for COVID-19 and then was diagnosed to be reinfected with a positive COVID-19 test (Ct value of 19.9) 1 month after the negative test. The patient eventually recovered but continued yielding higher Ct values (32.8, 36.6) 2 weeks following the reinfection.⁹ There are case reports suggestive of a reactivation of COVID-19 in immunosuppressed and elderly patients as well. A recently published case report discusses a 69-year-old woman in Japan with previously diagnosed adult T cell leukemia-lymphoma who developed COVID-19 while receiving M-CHOP chemotherapy. The patient was then treated with favipiravir, responded well and did not develop COVID-19 pneumonia.¹⁰ Similar to our case, this patient received an antiviral medication for COVID-19 and had a positive clinical outcome. Another case report details a 62-year-old woman in China with previously diagnosed ALL who developed COVID-19 approximately 2 weeks after

receiving chemotherapy. This patient deteriorated clinically and passed away from cardiogenic shock approximately 1 month after the onset of her symptoms.¹¹ It is important to note that many factors influence a patient's clinical outcome. A study from Ye *et al* reported a 9% proportion of cases with reactivation in patients with COVID-19 after discharge depending of various risk factors.¹²

While it is important to highlight our case and similar patient cases, clinical trajectory is unique to the individual patient. An additional confirmed COVID-19 reinfection has been described in an 89-year-old immunocompromised patient with Waldenström macroglobulinemia. This patient was on B-cell depleting therapy and tested negative for the formation of COVID-19 antibodies after reinfection. She unfortunately passed away shortly after reinfection.¹³

In the context of the COVID-19 pandemic, it is important to highlight the cases of immunocompromised individuals who have contracted COVID-19 and often require serial retesting due to need for further treatments, including chemotherapy, radiation or surgeries. Reinfection with COVID-19 in oncohaematological patients is not only asymptomatic but would also be more likely to cause fevers, CT features of interstitial pneumonia and a variety of respiratory symptoms and are often sicker than with the primary infection.^{14 15} It is imperative to keep in mind that reinfection is not the only possible outcome of a positive COVID-19 on retesting and we must always individually reassess the possibility of prolonged viral shedding as well.

Learning points

It is difficult to distinguish the terms reinfection, reactivation and prolonged viral shedding in the setting of a relatively unknown disease. However, it is essential to differentiate between these in order to:

- ▶ Prevent unnecessary treatment with antiviral medications or immunomodulators.
- ▶ Safely determine duration of isolation of patients in COVID-19 or non-COVID-19 units or on home discharge.
- ▶ Assess the need for postponing versus earlier initiation/resumption of chemotherapy in patients with acute leukaemia.
- ▶ Determine if using cycle threshold values would aid the process of differentiating between active infection and reinfection and prolonged viral shedding.
- ▶ Ensure we take the entirety of a clinical picture to determine course of treatment in all patients.

Contributors KJ: manuscript writing and editing. NS and RB: patient care and manuscript review. DB: patient care, manuscript writing and manuscript editing.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ's website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iD

Katherine Julian <http://orcid.org/0000-0003-3427-9997>

REFERENCES

- 1 American Cancer Society. What is acute lymphocytic leukemia (all)? acute lymphocytic leukemia (all). Available: <https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/what-is-all.html> [Accessed 15 Jan 2021].
- 2 Liu-Dumlao T, Kantarjian H, Thomas DA, *et al*. Philadelphia-positive acute lymphoblastic leukemia: current treatment options. *Curr Oncol Rep* 2012;14:387–94.
- 3 SEER. Acute Lymphocytic Leukemia - Cancer Stat Facts. Available: <https://seer.cancer.gov/statfacts/html/aly1.html> [Accessed 9 Jan 2021].
- 4 Beigel JH, Tomashek KM, Dodd LE, *et al*. Remdesivir for the Treatment of Covid-19 - Final Report. *N Engl J Med* 2020;383:1813–26.
- 5 An overview of cycle threshold values and their role in SARS-CoV-2 real-time PCR test interpretation. Available: <https://www.publichealthontario.ca/-/media/documents/ncov/main/2020/09/cycle-threshold-values-sars-cov2-pcr.pdf?la=en>
- 6 Certain medical conditions and risk for severe COVID-19 illness. centers for disease control and prevention. Available: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html> [Accessed 9 Jan 2021].
- 7 Penn state. Available: <https://www.ncbi.nlm.nih.gov.ezaccess.libraries.psu.edu/pmc/articles/PMC7272974/>
- 8 Kang H, Wang Y, Tong Z, *et al*. Retest positive for SARS-CoV-2 RNA of "recovered" patients with COVID-19: Persistence, sampling issues, or re-infection? *J Med Virol* 2020;92:2263–5.
- 9 Alonso FOM, Sabino BD, Guimarães MAAM, *et al*. Recurrence of SARS-CoV-2 infection with a more severe case after mild COVID-19, reversion of RT-qPCR for positive and late antibody response: case report. *J Med Virol* 2021;93:655–6.
- 10 Hosoba R, Makita S, Shiotsuka M, *et al*. COVID-19 pneumonia in a patient with adult T-cell leukemia-lymphoma. *J Clin Exp Hematop* 2020;60:174–8.
- 11 Wu Y, Lin H, Xie Q, *et al*. COVID-19 in a patient with pre-existing acute lymphoblastic leukaemia. *Br J Haematol* 2020;190.
- 12 Ye G, Pan Z, Pan Y, *et al*. Clinical characteristics of severe acute respiratory syndrome coronavirus 2 reactivation. *J Infect* 2020;80:e14–17.
- 13 Mulder M, van der Vegt D, Oude Munnink BB. Reinfection of SARS-CoV-2 in an immunocompromised patient: a case report. *Clin Infect Dis* 2020;ciaa1538.
- 14 Luciani M, Bentivegna E, Spuntarelli V, *et al*. Recurrent COVID-19 pneumonia in the course of chemotherapy: consequence of a weakened immune system? *J Med Virol* 2021;93:1882–4.
- 15 Kapoor R, Nair RK, Nayan N, *et al*. Reinfection or reactivation of Coronavirus-19 in patients with hematologic malignancies: case report series. *SN Compr Clin Med* 2021;3:670–4.

Copyright 2021 BMJ Publishing Group. All rights reserved. For permission to reuse any of this content visit <https://www.bmj.com/company/products-services/rights-and-licensing/permissions/>
BMJ Case Report Fellows may re-use this article for personal use and teaching without any further permission.

Become a Fellow of BMJ Case Reports today and you can:

- ▶ Submit as many cases as you like
- ▶ Enjoy fast sympathetic peer review and rapid publication of accepted articles
- ▶ Access all the published articles
- ▶ Re-use any of the published material for personal use and teaching without further permission

Customer Service

If you have any further queries about your subscription, please contact our customer services team on +44 (0) 207111 1105 or via email at support@bmj.com.

Visit casereports.bmj.com for more articles like this and to become a Fellow