

CASE REPORT

A Case of Long-Term SARS-CoV-2 Infection in a Patient with Follicular Lymphoma

Dan Zhang, Zhuan Zheng

Department of Medical Laboratory, Shaoxing People's Hospital, Shaoxing, P.R. China

SUMMARY

Background: Currently, coronavirus disease 2019 (COVID-19) is still having a substantial impact on medical and health systems around the world. Patients with malignant tumors usually have a low immune status and face more potential risk factors, making them more susceptible to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Once infected, the clinical prognosis of such patients is usually more unfavorable. For patients with hematological tumors, the above observations should be considered more seriously.

Methods: We report a case of long-term severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in a patient with follicular lymphoma. We used reverse transcription real-time PCR to detect SARS-CoV-2 and used the Ct value to measure the relative concentration of the virus.

Results: The patient was infected with SARS-CoV-2 one month after receiving obinutuzumab treatment. After 15 days of hospitalization, the patient was discharged after two consecutive negative SARS-CoV-2 nucleic acid test results. However, 10 days after discharge, the patient was readmitted to the hospital with symptoms such as fever and difficulty breathing; after admission, the result of a nucleic acid test for SARS-CoV-2 was positive. The viral infection persisted for 4 months; the patient developed a persistent high fever, his oxygen saturation continued to decline, and the patient died of respiratory failure.

Conclusions: The humoral immunity of lymphoma patients who receive obinutuzumab combined with chemotherapeutic drugs is severely impaired, potentially making them unable to produce protective antibodies or only able to produce low antibody titers against SARS-CoV-2, resulting in a prolonged clearance time for SARS-CoV-2 that affects patient prognosis and increases the risk of death.

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Correspondence:

Zhuan Zheng
Department of Medical Laboratory
Shaoxing People's Hospital
Shaoxing 312000
P.R. China
Phone: +86 13967500299
Email: zengzuan5032@yeah.net

KEYWORDS

follicular lymphoma, SARS-CoV-2, long-term infection, obinutuzumab

INTRODUCTION

Follicular lymphoma is the most common inactive lymphoma in clinical practice, and commonly used treatment options include anti-CD20 monoclonal antibody immunotherapy with or without chemotherapy [1]. During the coronavirus disease 2019 (COVID-19) pandemic, studies showed that lymphoma patients are susceptible to SARS-CoV-2 infection and are prone to developing severe complications after infection [2]. We treated a patient with follicular lymphoma in whom SARS-

CoV-2 continued to replicate for 4 months after receiving obinutuzumab; the details are described herein.

CASE PRESENTATION

A 65-year-old man was admitted to our hospital on May 25, 2022, due to "swollen lymph nodes in the neck for half a year and dull pain in upper abdomen for 1 month". After the abdominal pain resolved, the patient was transferred to the hematology department in our hospital for further treatment. Bone marrow biopsy showed low proliferation in hematopoietic tissues, and a left axillary lymph node biopsy showed follicular lymphoma. From June to October 2022, the patient received 6 cycles of the G-CHOP regimen (obinutuzumab, cyclophosphamide, doxorubicin, vincristine, and prednisone) chemotherapy, and consolidation chemotherapy with obinutuzumab was given in December 2022. On January 8, 2023, the patient was admitted to the hospital due to "fever, cough, difficulty breathing, and muscle soreness". He underwent a nucleic acid test for SARS-CoV-2 and a plain CT chest scan. The nucleic acid test results were positive: the Ct value for the ORF1ab gene was 28.48, and the Ct value for the N gene was 28.81. Chest CT showed multiple patchy high-density shadows in both lungs, indicating inflammatory lesions. After 15 days of symptomatic treatment, the patient's fever and respiratory symptoms improved, and the patient underwent two COVID-19 nucleic acid tests on January 23 and January 24, 2023; the results were both negative, and the patient was discharged from the hospital. The patient had a fever and returned to the hospital on February 5, 2023. The patient underwent a nucleic acid test for SARS-CoV-2 and a plain CT chest scan. The nucleic acid test results were positive: the Ct value for the ORF1ab gene was 22.35, and the Ct value for the N gene was 22.27. Chest CT showed multiple patchy high-density shadows in both lungs. The patient did not have pneumonia after symptomatic and anti-infective treatment. The condition of the patient did not improve, and the replication status of SARS-CoV-2 (Figure 1), the level of serum IgG antibody (Figure 2), and lymphocyte subsets continued to be monitored. Until June 8, 2023, the patient's high fever persisted, his oxygen saturation decreased, and respiratory failure occurred; his family refused further treatment.

DISCUSSION

Since 2020, SARS-CoV-2 has caused a large-scale epidemic around the world [3]. Based on symptom severity, COVID-19 can be divided into mild, moderate, severe, and critical. Since the development of vaccinations, the fatality rate for patients with COVID-19 has decreased significantly. However, the incidence and mortality of severe and critical pneumonia caused by SARS-CoV-2 in patients with lymphomas is still an is-

sue that needs to be addressed. Lymphoma patients have humoral immune dysfunction; treatment further suppresses the body's autoimmune function, and as a result, the protective effect of SARS-CoV-2 vaccinations in this group is lower than that in the normal population [4-7].

The patient in this case study was infected with SARS-CoV-2 one month after receiving chemotherapy. Fifteen days after admission to the hospital, two consecutive nucleic acid test results for SARS-CoV-2 were negative, and the patient was discharged from the hospital after respiratory symptoms improved. However, 10 days after discharge, the patient returned to the hospital with fever, which lasted for 4 months until the patient's death. SARS-CoV-2 nucleic acid tests result were positive. As shown in Figure 1, the single SARS-CoV-2 nucleic acid test result for this patient on March 19, 2023, may have been a false negative. According to reports in the literature, the sensitivity of alveolar lavage fluid as a sample for the detection of SARS-CoV-2 nucleic acids is high, at 93%, followed by that of sputum specimens at 72%, nasal swab specimens at 63%, and throat swab specimens at 32% [8]. Therefore, for patients with COVID-19 who are highly clinically suspected but have negative nasopharyngeal swab results, alveolar lavage fluid is the specimen of choice. We can also reduce false-negative results in nucleic acid testing through standardized training on specimen collection, the addition of weak positive quality controls, and the addition of SARS-CoV-2 antigen and antibody tests.

Obinutuzumab is a novel humanized anti-CD20 mAb that can remove normal B lymphocytes in tumor patients and cause durable immunosuppression [9,10]. As shown in Figure 2, from January 9 to June 6, 2023, the serum IgG levels in the patient during hospitalization were all lower than the lower limit of the normal reference range, suggesting that the patient had low immunoglobulin levels. The flow cytometry results showed that CD19 was absent; CD19 is the surface marker of B cells, suggesting an absence of B cells in the patient. The SARS-CoV-2 nucleic acid test results indicated that SARS-CoV-2 replicated in this patient for at least 4 months. This may have been due to the inhibition of abnormal B lymphocytes and B lymphocytes with normal immune function, thereby affecting humoral immunity; therefore, the patient could not produce corresponding protective antibodies or the protective antibodies produced were of short duration, leading to a low antibody titer. Therefore, for lymphoma patients with COVID-19, the risks and benefits of each patient should be considered when implementing chemotherapy. Targeted therapy drugs with few adverse reactions should be chosen whenever possible, and drugs that suppress humoral immunity and cellular immunity should be used with caution. In addition, it is very important to improve the self-protection of patients and increase patient knowledge regarding the prevention of COVID-19.

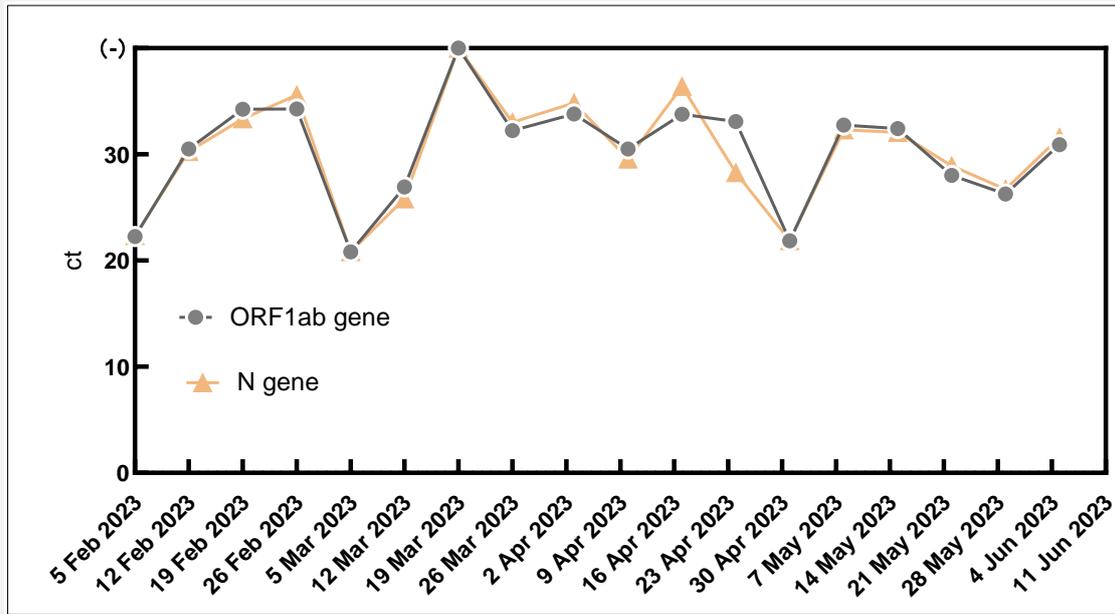


Figure 1. Changes in the Ct value for SARS-CoV-2 (ORF1ab gene and N gene) during hospitalization; a Ct value ≥ 40 was considered a negative result.

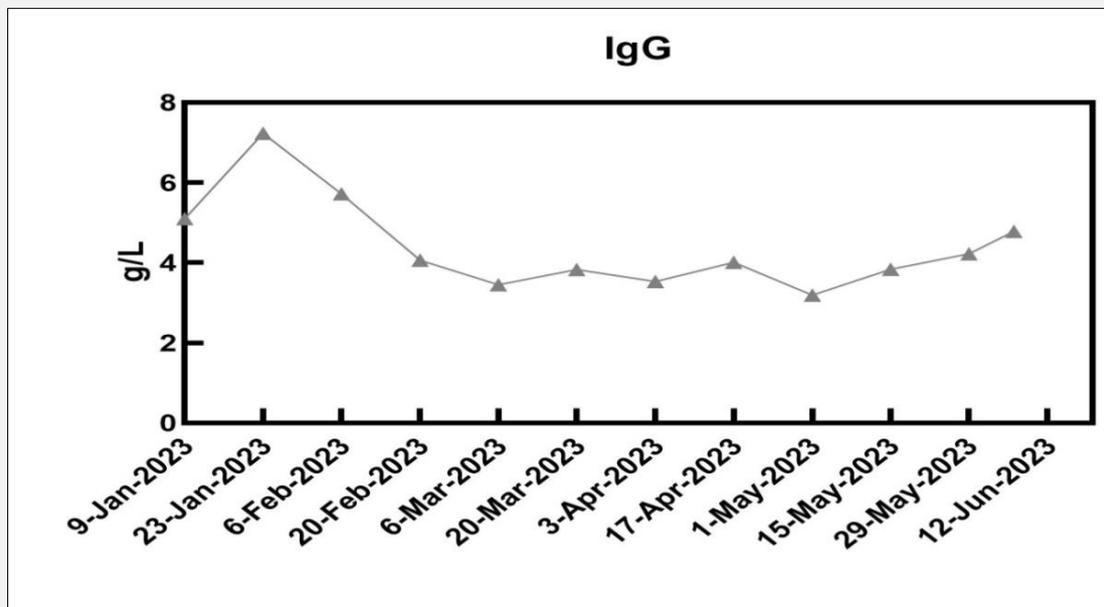


Figure 2. Changes in serum IgG levels during hospitalization (the normal reference value of IgG is 7 - 16 g/L).

CONCLUSION

Obinutuzumab can suppress humoral immunity in patients with lymphoma, and as a result, patients may not be able to produce protective antibodies against SARS-CoV-2. For this high-risk population, medical institutions should take extra protective measures, such as following strict epidemic prevention measures, avoiding gatherings, and requiring patients to wear masks. Medical personnel should also develop an individualized treatment plan based on the specific conditions of each patient to reduce the risk of SARS-CoV-2 infection.

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Declaration of Interest:

All authors declare that they have no competing interests.

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