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Case Report

Persistent COVID-19 Pneumonia and Failure to Develop Anti-SARS-CoV-2 Antibodies During Rituximab Maintenance Therapy for Follicular Lymphoma

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Clinical Practice Points

- Patients undergoing recent rituximab therapy are likely to fail to develop anti-severe acute respiratory syndrome coronavirus 2 antibodies, which may lead to severe and prolonged COVID-19 infections.
- Rituximab therapy should be avoided whenever possible during the COVID-19 pandemic.

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Introduction

The global COVID-19 pandemic has been reported to inflict higher death rates in patients with hematologic malignancies compared with the general population.[1] Proposed theoretical mechanisms include lymphopenia, which is often seen in this patient group, and suppressed immune function owing to the hematologic malignancy itself or because of treatment. We report the first case of persistent COVID-19 pneumonia that was still ongoing at 2 months after onset in a patient with follicular lymphoma (FL) undergoing rituximab maintenance therapy. The patient failed to develop anti-severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) immunoglobulin (Ig)G and IgM antibodies, which was most probably the result of prior rituximab therapy, and thus provoked this unusual chronic state of COVID-19 pneumonia.

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Case Report

A 61-year-old woman was admitted to our hospital in April 2020 owing to COVID-19 pneumonia diagnosed by 2 sequential positive real-time polymerase chain reaction (RT-PCR) results from nasopharyngeal swabs performed on different days. Four other family members were simultaneously diagnosed with COVID-19. In September 2018, she was diagnosed with concurrent uterine cancer and FL involving the small intestine, multiple lymph nodes, and bone marrow. Serum IgG, IgA, and IgM were 504 mg/dL, 31 mg/dL, and 39 mg/dL, respectively. She underwent ovariohysterectomy and resection of the small intestine FL lesion, followed by G-CHOP (obinutuzumab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) therapy. However, after the second course of CHOP and fourth administration of obinutuzumab, chemotherapy was withheld owing to a sustained decrease of platelet counts around 60×10^9/L, which was thought to be a side effect of obinutuzumab. Platelet counts gradually rose, but approximately 6 months were required for the platelet count to return to baseline. Because of the long-term treatment interruption, a positron emission tomography scan was carried out in August 2019 and showed complete metabolic response. Six courses of CHOP were originally planned, but because of the long-term interruption and because she was in complete metabolic response, CHOP therapy was discontinued, and rituximab maintenance therapy was initiated from September 2019. Three bimonthly administrations of rituximab maintenance therapy had been carried out before the patient developed COVID-19 pneumonia.

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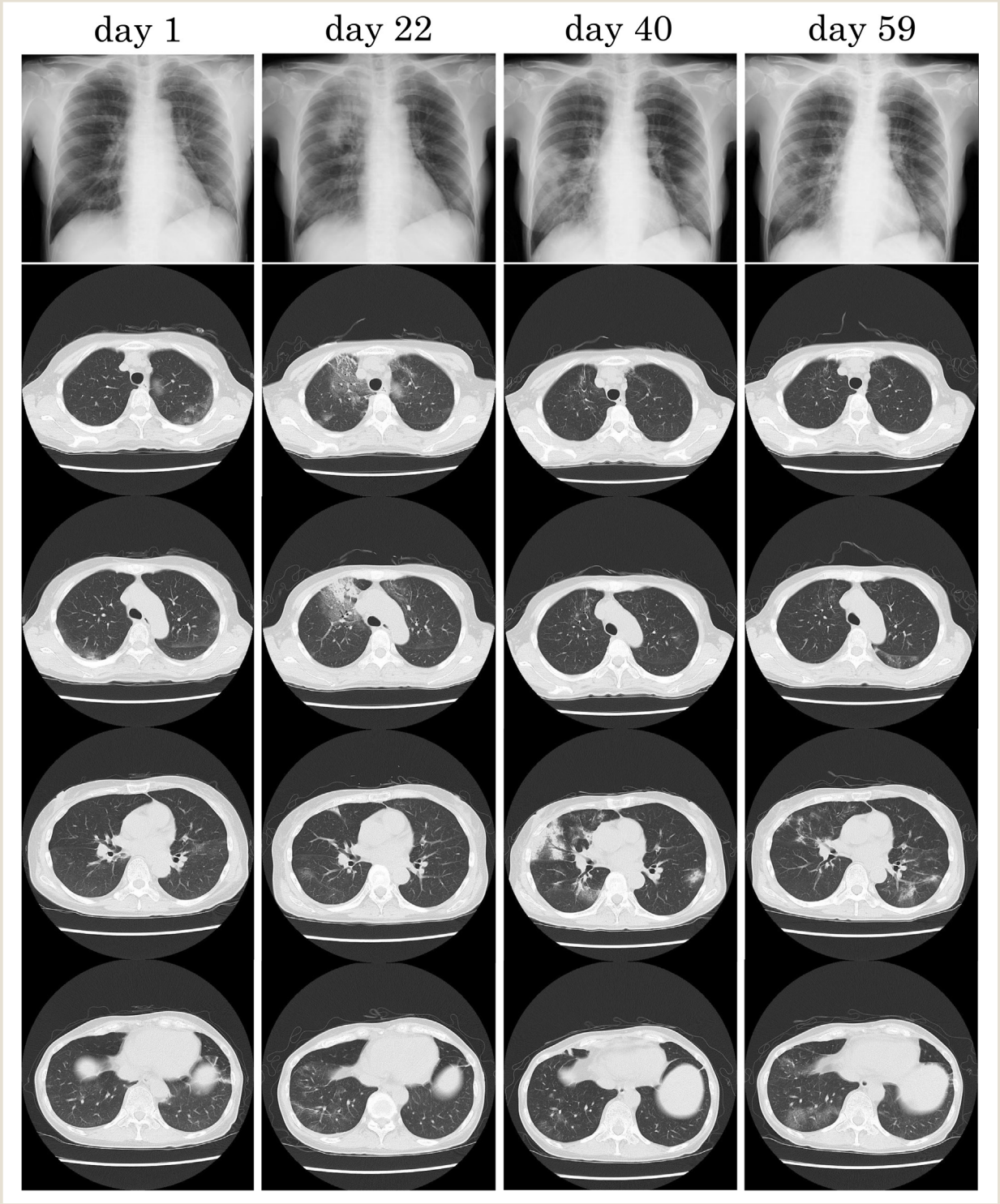
Upon admission for COVID-19 pneumonia, the patient presented with fever, cough, and multiple bilateral ground glass opacities on computed tomography scans. Serum IgG, IgA, and IgM were suppressed at 225 mg/dL, 14 mg/dL, and 30 mg/dL, respectively. After admission, repetitive Ig replacement therapy was carried out, and IgG levels were maintained at approximately 500 mg/dL. COVID-19 pneumonia was treated according to the protocols of a clinical trial from day 1 of hospitalization, and

Figure 1 **Transition of COVID-19 Pneumonia Lung Lesions in the Presented Case. Chest X-Rays and Computed Tomography Scans Show Constantly Migrating COVID-19 Lung Lesions. Days are Shown as the Number of Days After Hospitalization**



disappearance of the pneumonia was confirmed by chest radiographs on day 16 along with a C-reactive protein (CRP) peak-out after topping at 6.0 mg/dL on day 17, and fever receded on day 19. However, a new lung lesion suddenly appeared in the right upper lung region around day 22, and the lesion migrated to the right middle lung region on day 28. Fever, cough, and CRP elevation also recurred around day 34. On day 40, another new lesion developed in the middle region of the left lung. Because of the atypical disease course with waxing and waning disease and constant migration of lung lesions, other causes of pneumonia were explored, but serologic testing for tuberculosis, cytomegalovirus, and fungi were all negative. Follow-up nasopharyngeal SARS-CoV-2 RT-PCR tests done on day 15, 16, 22, 23, 35, and 36 were all negative, but bronchoscopy was performed on day 46, and SARS-CoV-2 RT-PCR done on bronchoalveolar lavage (BAL) tested positive. Transbronchial lung biopsy revealed no significant findings. Elecsys Anti-SARS-CoV-2 immunoassay (Roche Diagnostics GmbH, Mannheim, Germany) done on serum samples of day 3, 11, 17, 23, 31, 47, and 50 all failed to detect anti-SARS-CoV-2 IgG and IgM antibodies. Fever and cough receded again on day 51, and CRP levels also declined. However, a computed tomography scan performed on day 59 revealed new lesions in the right lower lung region. Failure to develop anti-SARS-CoV-2 antibodies owing to prior obinutuzumab and rituximab therapy were thought to be the cause of persistent COVID-19 pneumonia, and the patient is still under careful surveillance. The transitions of lung lesions during the disease course are shown in Figure 1.

Discussion

Anti-CD20 monoclonal antibodies including obinutuzumab and rituximab not only deplete malignant B-lymphocytes but also their normal counterparts, and therefore impair humoral immunity. In fact, patients with prior rituximab treatment are known to be poor responders to various types of vaccinations including influenza viruses, *Haemophilus influenzae*, and *Streptococcus pneumoniae*.[2,3] Despite the long-term exposure to the virus, our case also failed to develop anti-SARS-CoV-2 antibodies. Rituximab has also been reported to provoke other serious viral conditions such as hepatitis B reactivation and progressive multifocal leukoencephalopathy caused by the JC virus.[4] Not only viral infections, but infections in general were found to be increased in patients with FL undergoing rituximab maintenance therapy in the PRIMA study, and the association of increased infections and rituximab therapy is a well-established concept.[5]

The presented case initially tested positive for nasopharyngeal SARS-CoV-2 RNA on 2 occasions at disease onset, but tested negative on 6 follow-up nasopharyngeal swabs despite the persisting symptoms and lung lesions. Later on, on day 46, the patient finally tested positive for SARS-CoV-2 RNA on BAL specimen. The sensitivity of RT-PCR done on BAL has been reported to be the highest at 93%, follow by sputum at 72%, nasal swab at 63%, and pharyngeal swab at 32%.[6] In patients with a high clinical suspicion of COVID-19 who test negative on nasopharyngeal swabs, additional testing on BAL specimens may be a rational approach.

It has been reported that patients with COVID-19 with hematologic malignancies show prolonged persistence of SARS-CoV-2 RNA in respiratory samples,[1] but this case demonstrates that actual clinical manifestations can also persist. Above all, anti-SARS-CoV-2 IgG and IgM antibodies are likely to be absent throughout the disease course in patients with prior anti-CD20 therapy as seen in this case, and provides one explanation for the worse prognosis of patients with COVID-19 with hematologic malignancies. The European Society for Medical Oncology currently recommends avoidance of anti-CD20 antibody-based maintenance therapy for FL during the COVID-19 pandemic, and the clinical course of the presented case strongly supports this recommendation. Other than B-cell malignancies, rituximab is currently used in a wide range of other disorders, including rheumatoid arthritis, granulomatosis with polyangiitis, microscopic polyangiitis, and pemphigus vulgaris, and awareness of its increased risk for use during the COVID-19 pandemic is necessary across the entire medical community.

Conclusion

Patients undergoing recent rituximab therapy are likely to fail to develop anti-SARS-CoV-2 antibodies, which may lead to severe and prolonged COVID-19 infections. Rituximab therapy should be avoided whenever possible during the COVID-19 pandemic.

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Disclosure

The authors have stated that they have no conflicts of interest.

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