

Migratory Pulmonary Infiltrates in a B-Cell-Depleted COVID-19 Patient

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Background: Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is still rampant around the world. Immunocompromised patients are prone to have long-term infection with coronavirus disease 2019 (COVID-19). However, it is difficult to decide on an appropriate treatment for persistent SARS-CoV-2 infection.

Case Presentation: We present a case of prolonged SARS-CoV-2 infection in a patient who had undergone B-cell depletion therapy. Chest computed tomography (CT) revealed notable migratory pulmonary infiltrates, and bronchoalveolar lavage fluid was positive for SARS-CoV-2 (day-120). The patient responded well to the combination treatment of antiviral medication, convalescent plasma, and corticosteroid.

Conclusion: When chest CT shows migratory pulmonary infiltrates in patients with recent COVID-19, it is necessary to be alert to the possibility of persistent SARS-CoV-2 infection, especially in B-cell-depleted immunocompromised patients. Once the diagnosis is confirmed, repeated antiviral therapy and intravenous convalescent plasma should be considered.

Keywords: SARS-CoV-2, migratory pulmonary infiltrates, B-cell depletion, antiviral therapy, convalescent plasma

Background

Coronavirus disease 2019 (COVID-19) results from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, leading to the ongoing worldwide pandemic. The most common computed tomography (CT) findings of COVID-19 pneumonia are peripheral ground-glass opacities (GGOs) and consolidation in severe cases, which might progressively evolve toward an organizing pneumonia pattern.¹⁻³

Immunocompromised or immunodeficient patients are at high risk for viral and other opportunistic infections.^{4,5} B-cell-related humoral immunity plays a vital role in defending against virus infection and clearing viruses. Previous reports have suggested that patients with B-cell immunodeficiency caused by underlying diseases or drug therapy may develop prolonged and persistent SARS-CoV-2 infection.^{6,7} Obinutuzumab is an anti-CD-20 monoclonal antibody that mainly affects B cells. Consequently, patients receiving obinutuzumab have a reduced ability to elicit antibody responses after SARS-CoV-2 infection, enabling prolonged, active viral replication once infected.⁸

Here, we describe a B-cell-depleted COVID-19 patient after obinutuzumab therapy. His serial chest CT revealed rapidly changing migratory pulmonary infiltrates. To our knowledge, precious few cases⁹⁻¹¹ have been reported concerning migratory pulmonary infiltrates in rituximab-treated patients with SARS-CoV-2 infection, and this is the first reported case of prolonged COVID-19 with notable migratory pulmonary infiltrates in a patient with previous obinutuzumab therapy.

Case Presentation

On December 15, 2022, a 42-year-old male who had been treated with obinutuzumab on November 18, 2022, for primary immune thrombocytopenia developed a fever. His nasopharyngeal SARS-CoV-2 antigen test was positive. He had received three doses of COVID-19 vaccine (recombinant SARS-CoV-2 S-protein receptor-binding domain vaccine, ZF2001, China) in 2021. The body temperature became normal two days later and his nasopharyngeal SARS-CoV-2 antigen test turned negative.

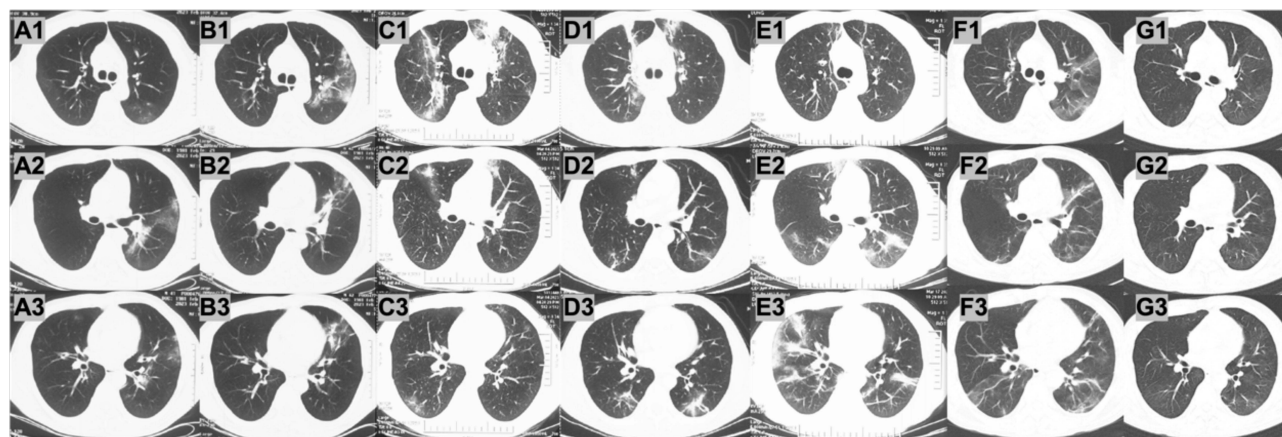


Figure 1 Chest CT (day-64, in **(A)**) revealed bilateral GGOs, predominantly in the left lower lobe. CT scans taken on day-70, day-79, day-85, day-92, and day-120 after COVID-19 onset (in **B–F** respectively) showed rapidly changing migratory pulmonary infiltrates consistent with organizing pneumonia. In **(G)** the CT scan showed the resolution of the pulmonary infiltrates on day-141. Supplementary note: A1, B1, C1, D1, E1, F1, and G1 are the chest CT at the bifurcation level of the trachea. A2, B2, C2, D2, E2, F2, and G2 are the chest CT at the level of right middle bronchus and left main bronchus. A3, B3, C3, D3, E3, F3, and G3 are the chest CT at the level of right middle bronchus.

He developed cough and white sputum in January 2023. Chest CT performed on day-64 post-infection revealed multiple GGOs in both lungs, predominantly in the left lower lobe (**Figure 1A**). Follow-up CT (day-70) revealed that the original GGOs in the left lower lobe resolved, and multiple GGOs emerged in the left upper lobe (**Figure 1B**). On day-76, the patient was admitted to a local hospital. On physical examination, his body temperature was 38.6°C; blood pressure, 121/80 mmHg; pulse, 83 beats/min; respiratory rate, 19 breaths/min, and pulse oxygen saturation, 99% on room air. Laboratory tests showed a moderately elevated erythrocyte sedimentation rate (ESR) (42 mm/h), as well as a reduced lymphocyte count (400/ μ L). Other routine blood tests were within normal range. The nasopharyngeal swab was negative for the SARS-CoV-2 antigen. Moxifloxacin (day-76) and high-dose methylprednisolone (up to 80mg daily, day-81) were administered successively without obvious clinical remission. During this period, chest CT showed rapidly changing migratory pulmonary infiltrates (**Figure 1C–F**).

On day-120, he was transferred to our hospital because of the persistent fever and undiagnosed pulmonary infiltrates. Laboratory analysis showed an average lymphocyte count (1500/ μ L), while the peripheral blood B-cell count was zero. Blood eosinophil count, C-reaction protein (CRP), ESR, and rheumatoid factor were all within normal ranges. Antineutrophil cytoplasmic antibodies and antinuclear antibodies were negative. Blood and sputum cultures for bacteria and fungi were negative. No SARS-CoV-2 specific antibodies were detected in the serum. The nasopharyngeal SARS-CoV-2 antigen test was negative. However, the nasopharyngeal swab was positive for SARS-CoV-2 RNA (Cycle threshold, Ct value of 38.67), and bronchoalveolar lavage fluid (BALF) testing was also positive (Ct value of 31.72). The differential cell counts of BALF revealed remarkably lymphocytic inflammation (lymphocyte percentage 57.5%). Considering the possibility of secondary organizing pneumonia associated with prolonged SARS-CoV-2 infection, the patient received antiviral therapy (nirmatrelvir/ritonavir), infusion of convalescent plasma and oral methylprednisolone (up to 48 mg daily), resulting in rapid improvement of clinical symptoms. Chest CT (day-141) revealed significant dissipation of previous GGOs, and no new infiltrates were detected (**Figure 1G**).

Discussion and Conclusions

Here, we reported a case of prolonged SARS-CoV-2 infection with migratory pulmonary infiltrates in a patient who had undergone B-cell depletion therapy. Serial CT scans revealed migratory opacities consistent with a pattern of organizing pneumonia (OP). In addition to OP, migratory pulmonary infiltrates are commonly seen in eosinophilic lung diseases (eg, chronic eosinophilic pneumonia, eosinophilic granulomatosis with polyangiitis, and drug-induced hypersensitivity syndrome), parasitic infestations, and alveolar hemorrhage. For our patient, eosinophilic lung diseases were excluded according to normal eosinophil counts in both BALF and serum. Pulmonary parasitosis and alveolar hemorrhage were excluded due to negative

epidemiological history and non-bloody BALF. Organizing pneumonia is classified into cryptogenic OP (COP) and secondary OP (SOP). Secondary OP can be caused by various viral infections, including adenovirus, cytomegalovirus, herpes, human immunodeficiency virus, influenza, and Middle East respiratory syndrome coronavirus, perhaps via immune system stimulation by viral antigens.¹² Given the prior findings^{9–11} that the duration of active SARS-CoV-2 replication was prolonged and migratory pulmonary infiltrates on imaging in patients previously treated with anti-CD20 monoclonal antibodies, such as rituximab, and that radiological features of OP were commonly seen in COVID-19 patients, we assumed that our patient developed SOP to SARS-CoV-2 infection after 120 days of onset.

For the management of SOP, it is essential to treat the cause of disease. Nirmatrelvir/ritonavir is an oral antiviral drug consisted of nirmatrelvir, a novel SARS-CoV-2 primary protease inhibitor targeting 3CLpro of SARS-CoV-2, plus ritonavir (for its action as an inhibitor of cytochrome P450 3A4 to decrease nirmatrelvir metabolism and increase its serum levels).¹³ A standard course of nirmatrelvir/ritonavir treatment is associated with a markedly reduced risk of progression to severe COVID-19 or mortality.^{13,14} But nirmatrelvir/ritonavir alone will not clear the virus. Whether a standard course of nirmatrelvir/ritonavir treatment is sufficient for patients with persistent viral infection needs further study. Given that nirmatrelvir/ritonavir can only suppress viral duplication, SARS-CoV-2 specific antibodies are necessary to achieve viral clearance. The convalescent plasma contains protective antibodies produced by COVID-19 patients, which could reduce the incidence of hospitalization and death when a sufficient dose is given to patients with a recent onset of symptoms and to those who do not have a sufficient antibody response to SARS-CoV-2 infection.¹⁵ Patients with B-cell-depletion may not be able to produce antibodies effectively, leading to the persistent replication of the virus. Combining antiviral therapy with COVID-19 convalescent plasma or COVID-19 immunoglobulin may be beneficial to virus clearance and disease improvement in these immunosuppressed patients. This approach has succeeded in treating our patient, and also partly demonstrates the prolonged low titer virus replication in his lungs. In patients hospitalized with COVID-19, dexamethasone resulted in lower 28-day mortality among those receiving either invasive mechanical ventilation or oxygen alone at randomization.¹⁶ However, there is no consensus on the dosage and course of corticosteroid use for patients with OP-like changes on chest CT. Further research is needed on the strategy of corticosteroid therapy in B-cell-depleted COVID-19 patients with SOP.

In conclusion, we describe a prolonged clinical course in an immunocompromised patient with B-cell depletion who developed migratory pulmonary infiltrates after infection with SARS-CoV-2 and improved after antiviral therapy, convalescent plasma, and corticosteroid therapy. Notably, COVID-19 should be included in the differential diagnosis of migratory pulmonary infiltrates, especially in patients with B-cell depletion, due to the incompetent humoral immunity and disability of protective antibodies production. Combined antiviral therapy and convalescent plasma therapy may be an effective strategy for prolonged SARS-CoV-2 infection in patients with B-cell-depletion, however, further studies are needed to confirm it. The rational use of corticosteroids, including initiation timing, optimal dosage, and duration, in such patients needs further investigation.

Abbreviations

BALF, bronchoalveolar lavage fluid; COVID-19, coronavirus disease 2019; CRP, C-reaction protein; COP, cryptogenic organizing pneumonia; CT, chest computed tomography; Ct, cycle threshold; ESR, erythrocyte sedimentation rate; GGOs, ground-glass opacities; OP, organizing pneumonia; SOP, secondary organizing pneumonia; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Ethics and Consent

The patient provided informed consent to publish their case details and any accompanying images. In our institution, ethical approval is waived for case reports.

Acknowledgments

We would like to express our sincere gratitude and deep appreciation to Dr. Juhong Shi for her guidance and recommendations in this case report.

Funding

National High Level Hospital Clinical Research Funding (2022-PUMCH-A-010).

Disclosure

The authors report no conflicts of interest in this work.

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