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CASE SERIES

Resilience and Beyond the Acute Phase Challenges: Case Series on Prolonged COVID-19 Infection in Immunocompromised Individuals

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Background: COVID-19 infection is associated with an increased risk of severe illness and adverse outcomes in individuals with immunocompromising conditions. Immunocompromised patients may have difficulty with viral clearance, which can lead to persistent infection and potential relapses in viral replication.

Case Presentation: Herein, we present four cases of persistent COVID-19 pneumonia in immunocompromised patients, including those with diffuse large B-cell lymphoma, polyarteritis nodosa, and end-stage renal disease post-kidney transplant. Three patients had previously received rituximab. Notably, all patients in this cohort demonstrated positive anti-receptor binding-domain immunoglobulin G (IgG) and negative anti-nucleocapsid IgG values.

Conclusion: Persistent COVID-19 infection should be considered in the differential diagnosis of immunocompromised patients who exhibit ongoing symptoms or lack of improvement in chest X-ray findings following initial COVID-19 treatment. Early recognition, beyond the diagnosis of post-COVID organizing pneumonia, may significantly improve clinical outcomes with timely and appropriate treatment.

Keywords: COVID-19 pneumonia, persistent COVID-19, immunocompromised patients, SAR-CoV-2

Introduction

COVID-19 infection has been associated with an increased risk of hospitalization and mortality in individuals with immunocompromising conditions.[1–3] T cell-depleting drugs and B cell-depleting therapies have been linked to more severe COVID-19 illness.[4] Additionally, these patients may experience relapses in viral replication, delayed viral clearance, and persistent infection.[5,6]

We report four cases of persistent COVID-19 pneumonia in immunocompromised patients: two with diffuse large B-cell lymphoma (DLBCL), one with polyarteritis nodosa (PAN), and one with end-stage renal disease (ESRD) post-kidney transplant (KT). Three patients had received rituximab therapy. Notably, all patients within the cohort demonstrated positive anti-receptor binding-domain immunoglobulin G (Anti-RBD IgG) and negative anti-nucleocapsid immunoglobulin G (Anti-N IgG) results.

Case Presentation

Case Report: Patient No. 1

A 36-year-old woman with a 10-year history of PAN complicated by cryoglobulinemia presented in May 2023 with a two-week history of fever, shortness of breath, and cough. She had been on rituximab for the past six years, with the last dose administered six months prior, along with methotrexate (7.5 mg/week) and azathioprine (50 mg/day). She had

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a documented prior SARS-CoV-2 infection in May 2022. The patient had received the final dose of mRNA-1273 COVID-19 vaccine 15 months before this period (Supplementary Table 1).

On presentation, she had a high fever and an oxygen saturation (SpO2) of 94%. Both nasopharyngeal swab (NPS) antigen test kit (ATK) and polymerase chain reaction (PCR) were positive for SARS-CoV-2 with a cycle threshold (Ct) of 18. There was no significant travel history or known household exposure to COVID-19 during this period. She received a 10-day course of remdesivir, methylprednisolone (250 mg), tapering to dexamethasone over 30 days, and two weeks of baricitinib, showing significant improvement post-treatment (Figure 1A–C).

Despite this, she experienced persistent symptoms and chest X-ray (CXR) abnormalities for five months, diagnosed as post-COVID organizing pneumonia (OP). Initial dexamethasone (8 mg/day) was ineffective. In July 2023, her CXR showed increased opacities, prompting a 5-day course of dexamethasone (10 mg/day). However, adding tofacitinib and reducing corticosteroids did not change her symptoms and CXR findings (Figure 1D–F). A transbronchial biopsy revealed mild chronic inflammation without evidence of other infections. Active Livedo reticularis from August to October 2023 led two doses of rituximab, with slight improvement in her CXR. She received two additional 400 mg doses in October and November 2023, but intermittent cough and bilateral reticular opacities persisted.

Worsening dyspnea resulted in hospital admission in November-December 2023. Bronchoalveolar lavage (BAL) revealed SARS-CoV-2 via RT-PCR with a Ct of 25.5. Her serum anti-RBD IgG was 2091.8 AU/mL, while anti-N IgG remained negative. An extended 21-day course of remdesivir led to significant improvement in both CXR and symptoms, with RT-PCR becoming undetectable by December 14, 2023 (Figure 1H).

Case Report: Patient No. 2

A 69-year-old female with stage IV DLBCL underwent eight cycles of R-Hyper-CVAD and intrathecal methotrexate (IT-MTX), followed by rituximab and IT-MTX every three months until September 2022.

She was admitted on December 2, 2022, with fever, cough, and dyspnea, and tested positive for SARS-CoV-2 by NPS-PCR (Ct 34.1). Imaging revealed multifocal ground-glass opacities (GGO) and consolidation (Figure 2A), leading to a diagnosis of COVID-19-induced OP. She was treated with dexamethasone (20 mg/day for four days), resulting in

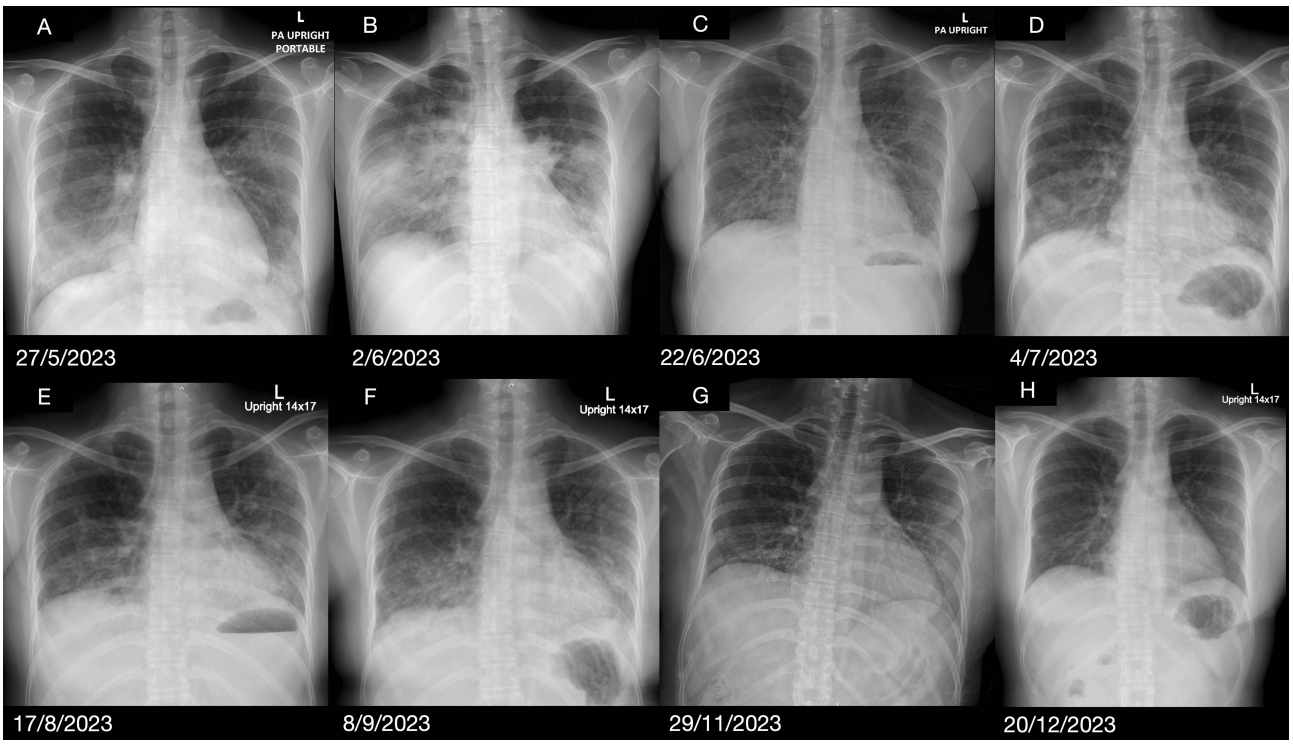

Figure 1 (**A-H**) Demonstrating chest radiograph of patient No.1.

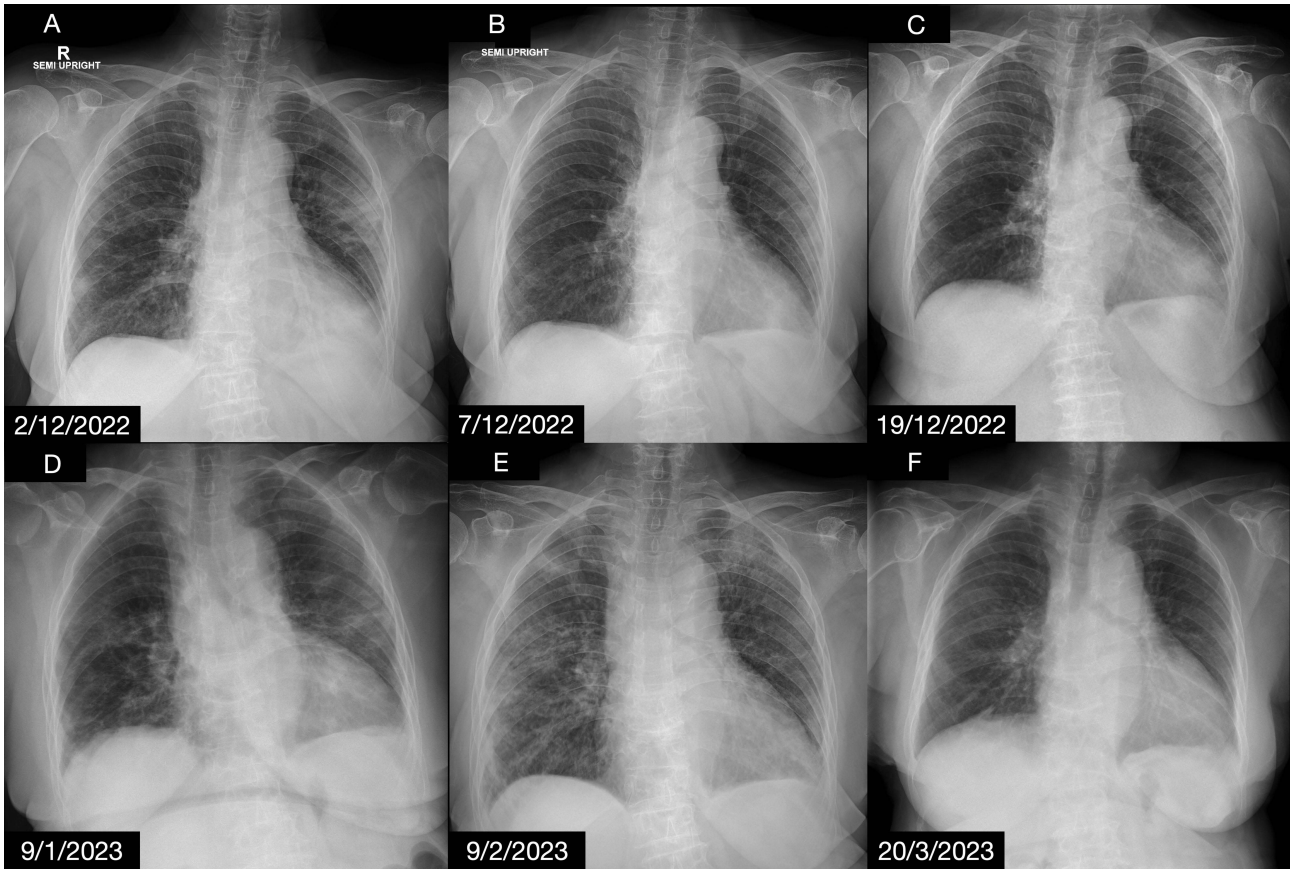

Figure 2 (**A-F**) Demonstrating chest radiograph of patient No.2.

clinical improvement and CXR stabilization (Figure 2B). However, tapering prednisolone (from 40 mg to 15 mg/day over 60 days) led to worsening hypoxemia and dyspnea. Follow-up CXR on December 19, 2022, and January 9, 2023, showed increased infiltrates (Figure 2C and D).

On February 9, 2023, she was readmitted with fever and cough, SpO2 of 85%, and increasing bilateral opacities (Figure 2E). A CT scan revealed dispersedly multifocal GGO and consolidation. A transbronchial biopsy was performed, but following the bronchoscopy, she developed acute respiratory failure, requiring mechanical ventilation. BAL-PCR confirmed COVID-19 (Ct 21.29), with no evidence of additional infection. Her anti-RBD IgG was elevated at 16,830 AU/mL, while anti-N IgG was negative. After a five-day course of remdesivir, her symptoms improved, allowing for extubation. Subsequent CXRs showed reduced infiltration (Figure 2F).

Case Report: Patient No. 3

A 57-year-old male with stage IV DLBCL was treated with rituximab, mini-ESHAP (etoposide, methylprednisolone, cisplatin, and cytarabine), and venetoclax in December 2022. He was first hospitalized on January 3, 2023, with fever and tested positive via NPS-ATK, though CXR showed no infiltration (Supplementary Figure 1A). He received a five-day course of remdesivir and tixagevimab/cilgavimab. Chemotherapy with mini-ESHAP and venetoclax resumed on January 27, 2023.

Two weeks later, he developed a fever again, and a CT scan revealed multifocal subpleural GGO (Supplementary Figure 1Bi, 1Bii, 1Biii). NPS-PCR was positive for SARS-CoV-2 (Ct 30). He was treated with a 10-day course of remdesivir. Anti-RBD IgG was markedly elevated (>40,000 AU/mL), while anti-N IgG was negative. Following treatment, his fever resolved, and a follow-up CT scan on March 15, 2023, showed resolution of the opacities (Supplementary Figure 1Ci, 1Cii).

Case Report: Patient No. 4

A 69-year-old male with diabetic end-stage renal disease (ESRD) post-KT in 2010 was maintained on tacrolimus (1 mg/day), mycophenolate (1440 mg/day), and prednisolone (5 mg/day). Over the past year, his diabetes was uncontrolled, with HbA1c levels ranging from 7.18% to 8.73%, despite daily treatment with 18 units of insulin degludec and liraglutide, dapagliflozin/metformin (10/1000 mg), pioglitazone (30 mg), and gliclazide MR (60 mg). His most recent HbA1c before this event, was 8.1%.

On June 4, 2023, he presented with cough and dyspnea and tested positive for COVID-19 by NPS-ATK. CXR revealed patchy bilateral infiltrates (Supplementary Figure 2A). Initial treatment with favipiravir was later switched to remdesivir, leading to symptomatic and radiologic improvement (Supplementary Figure 2B-C). His glucose levels spiked to 340–484 mg/dL during a 72-hour course of systemic corticosteroids, for which he received intravenous (IV) insulin.

On September 4, 2023, he developed a five-day fever and cough. His SpO2 was 95%, and NPS-PCR was positive (Ct 34.02). CXR and CT scan revealed bilateral GGO (Supplementary Figure 2Di, 2Dii). Anti-RBD IgG was positive (4900 AU/mL), while the anti-N IgG was negative. A 10-day course of remdesivir resolved the fever, and a follow-up CT showed opacities resolved (Supplementary Figure 2E).

Discussion

We reported persistent COVID-19 pneumonia in immunocompromised patients, especially those on rituximab, who exhibited prolonged symptoms, imaging abnormalities, and sustained NPS-PCR positivity. This phenomenon is well-documented with Furie et al, reporting NPS-PCR positivity lasting between seven days and thirteen months, and symptomatic or radiological abnormalities up to seven months, consistent with our findings (Supplementary Table 1).[7] These findings underscore the crucial role of impaired humoral immunity in viral persistence, particularly in patients with B-cell malignancies or those receiving anti-CD 20 monoclonal antibodies.[7–9] Notably, patients on immunosuppressive regimens like tacrolimus and mycophenolate, as observed in one of our cases (post-KT), exhibited similar prolonged viral shedding despite the absence of anti-CD20 therapy, suggesting an impaired B-cell response.[10]

Metabolic syndrome, particularly uncontrolled diabetes (HbA1c >7%) and hypertension, is recognized risk factor for severe COVID-19 outcomes.[11] In one case (Patient No. 4), the patient, with an HbA1c of 8.1%, required IV insulin for hyperglycemia. Sardu et al found that hyperglycemia is associated with severe disease progression, breakthrough infections despite mRNA-BNT162b2 vaccination.[11–13] Elevated levels of pro-inflammatory cytokines, notably IL-6 and TNF-α, reduce virus-neutralizing antibody capacity and diminish the efficacy of Tocilizumab.[11,14] Moreover, lowering blood glucose within the first 24 hours of hospitalization, as in our case, correlates with improved survival, and insulin infusion in hyperglycemic patients has been linked to better outcomes and reduced severe disease incidence.[15]

What's new: Our study reveals a novel discrepancy between anti-RBD IgG and anti-N IgG in case of persistent COVID-19 pneumonia. All patients exhibited elevated anti-RBD IgG levels (16 to over 40,000 AU/mL), while anti-N IgG remained negative. Two factors likely explain this: Chang et al found that most COVID-19-recovered kidney transplant recipients were anti-N IgG negative, with only 28% showing positivity,[16] likely due to their compromised immune status. Additionally, anti-N IgG levels typically decline after 100 days post-infection which may account for the negative results in our cohort based on the timing of sample collection. The role of anti-N IgG in antiviral immunity in immunocompromised individuals remains uncertain and requires further investigation. These cases highlight the importance of considering persistent viral infection in patients with prolonged symptoms, rather than attributing their condition solely to post-COVID organizing pneumonia.

Immunocompromised patients with severe COVID-19 outcomes are at higher risk of developing long COVID. The prevalence of SARS-CoV2-RNA in post-COVID-19 conditions ranges from 5% to 59%, although definitions vary across studies.[17,18] Notarte et al identified a potential link between autoantibodies and post-COVID symptoms, suggesting ongoing inflammation.[19] In our cases, ongoing viral infection likely contributes to long COVID development, with symptoms such as fatigue, respiratory difficulties, and cognitive dysfunction persisting due to persistent infection.

Treatment guidelines for persistent infection remain unclear.[20] Prolonged antiviral courses or combination therapy with high-titer convalescent plasma may be considered.[21] Hettle et al reported a similar case where a 21-day course of

remdesivir proved effective.[22] The limitation of our case reports is the absence of phylogenetic analysis, which prevent differentiation between persistence and reinfection. Nonetheless, Choudhary et al noted that persistent COVID-19 infections are predominately seen in immunosuppressed patients.[23]

Conclusion

Persistent COVID-19 infection should be considered a differential diagnosis in immunocompromised patients who continue to show symptomatic or exhibit no improvement in chest X-ray following COVID-19 treatment.

Abbreviations

Anti-N IgG, anti-nucleocapsid immunoglobulin G; Anti-RBD IgG, anti-receptor binding-domain immunoglobulin G; ATK, antigen test kit; BAL, bronchoalveolar lavage; Ct, cycle threshold; CXR, chest X-ray; DLBCL, diffuse large B-cell lymphoma; ESHAP, etoposide, methylprednisolone, cisplatin, and cytarabine; ESRD, end-stage renal disease; GGO, ground glass opacity; KT, kidney transplant; NPS, nasopharyngeal swab; OP, organizing pneumonia; PAN, polyarteritis nodosa; PCR, polymerase chain reaction; SpO2, oxygen saturation.

Ethical Approval

All patients have provided written informed consent to have the case details and any accompanying images published. The case series was approved by the Ethics Committee on Human Experimentation of Ramathibodi Hospital, Faculty of Medicine, Mahidol University, Bangkok (MURA2024/203).

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Disclosure

The authors declare that they have no competing interests.

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