Annals of Pharmacotherapy
1–3

DOI: 10.1177/10600280221129823
journals.sagepub.com/home/aop
SAGE

Fatal COVID-19 Pneumonia in a Rheumatoid Arthritis Patient Receiving Long-Term Rituximab Therapy

A 58-year-old male received a diagnosis of rheumatoid arthritis (RA) in September 2011, involving shoulders, elbows, hands, knees, ankles, and feet with bony erosions. He had a pulmonary tuberculosis history (Figure 1a) complicated by restrictive pericarditis, successfully managed by antibiotics and pericardiectomy in 1995. Biweekly injection of 40 mg adalimumab, a tumor necrosis factor monoclonal antibody (mAb), was initiated in May 2014 due to refractory responses to prednisolone 10 mg/day and disease-modifying antirheumatic drugs (hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine). After adalimumab therapy, there was a low disease activity (DAS28 < 3.2) with reduced medication regimen to prednisolone 5 mg/day and methotrexate 15 mg/week.[1] Negative results of QuantiFERON test, a whole-blood interferon-γ release assay helpful for tuberculosis diagnosis,[2] were obtained before and after adalimumab therapy. In September 2017, he was admitted with dyspnea and cough for 1 week. Diffuse pulmonary ground-glass infiltrations were found (Figure 1b) with negative microbiological survey. Under the suspicion of drug-induced lung injury (DILI), methotrexate use was terminated with the prescription of high-dose glucocorticoids, leading to resolved pulmonary infiltrations 1 month later (Figure 1c). There was a switch of biologics use due to a worsening activity without methotrexate therapy. Infusion of rituximab, a B-cell depleting mAb, was initiated in July 2018, 1 g every 2 weeks for two doses repeated every 6 months, together with prednisolone 10 mg/day and hydroxychloroquine 400 mg/day. There was a disease remission (DAS28 < 2.6) after rituximab therapy.

The patient received rituximab infusions on June 14 and 30, 2022. Owing to the admission for percutaneous intervention of occluded coronary arteries, nasopharyngeal SARS-CoV-2 polymerase chain reaction test was done with negative results on June 17, 2022. There was no known COVID-19 vaccination history. He visited the Emergency Department with acute onset of dyspnea and cough on July 4, 2022. There were diffuse pulmonary ground-glass infiltrations (Figure 1d) and positive results of SARS-CoV-2 test (cycle threshold 18.8), establishing a diagnosis of COVID-19 pneumonia. Despite the use of mechanical ventilation and antiviral (molnupiravir and remdesivir) and immunomodulating (dexamethasone and tocilizumab) therapy,[3] he succumbed to acute respiratory distress syndrome and multiorgan failure 15 days later.

During the COVID-19 pandemic, owing to associated comorbidities and activity/medication-related immunosuppression, inflammatory rheumatic diseases might form a vulnerable group at increased risk of severe SARS-CoV-2 infection.[4,5] Higher prescribed glucocorticoids dosages (more than 10 mg/day prednisolone-equivalent dose) in such patients have greater odds of COVID-19-related death.[5] Furthermore, B-cell depletion therapy can compromise humoral immune responses with difficulties in the clearance of SARS-CoV-2.[4-6] Notably, rituximab use in systemic lupus erythematosus is associated with increased hospitalization and death outcome as well as poor vaccination efficacy with lower seroconversion rates and antibody levels.[6] Despite the remarkable efficacy, rituximab therapy in our patient might be a COVID-19-associated death risk other than male sex, cardiovascular comorbidity, and glucocorticoids use.

Besides disease activity with lung involvement, acute diffuse pulmonary complications in RA are due to treatment-related adverse drug reaction (ADR) and infection.[7,8] DILI can occur during methotrexate therapy in RA, a reversible condition if under earlier management such as the pneumonitis episode in this case.[8] Indeed, COVID-19 pneumonia should be a differential diagnosis of acute diffuse pulmonary complications in RA patients receiving rituximab therapy.

Note of Authors

Increasing evidences support the association of severe SARS-CoV-2 infection in RA patients receiving rituximab therapy regardless of their vaccination status.[5,9] We reported a possible ADR of rituximab in this patient to the Food and Drug Administration through the National Adverse Drug Reaction Reporting System on August 24, 2022.[10]

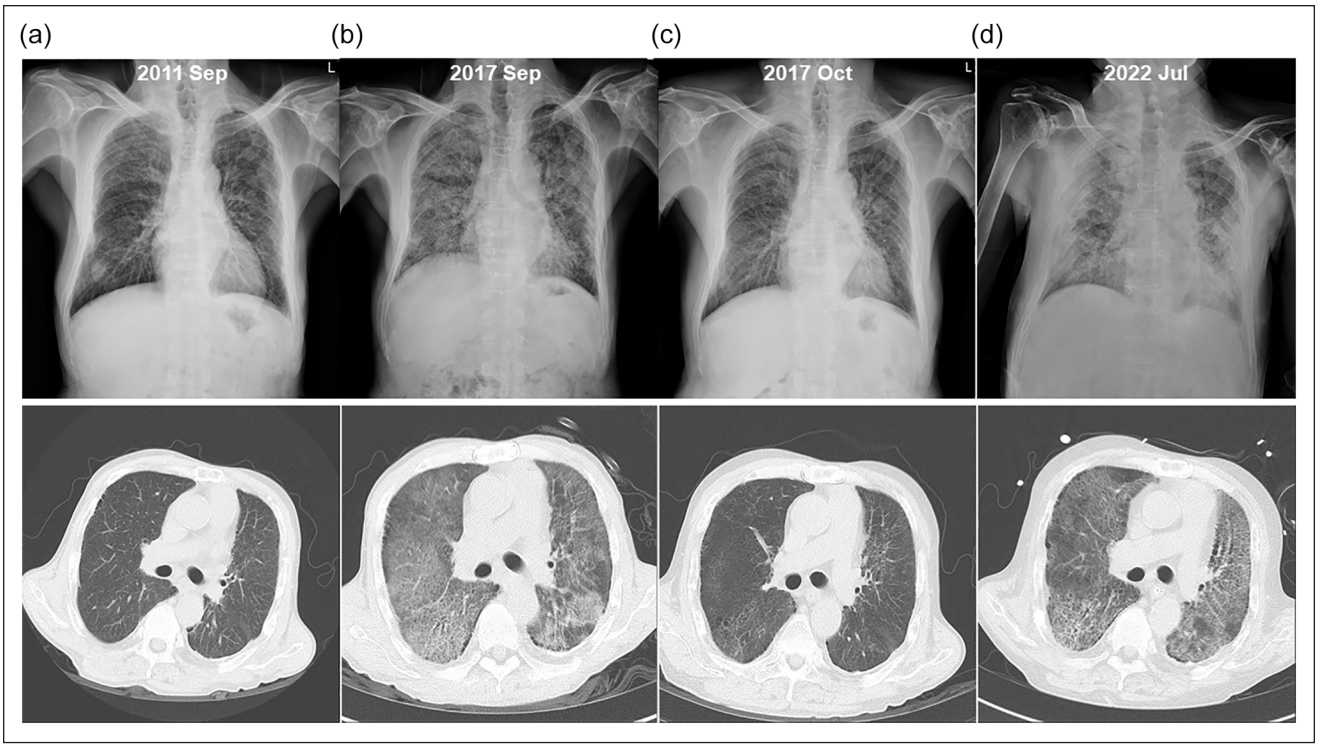

Figure 1. Serial chest images in a rheumatoid arthritis patient under long-term rituximab therapy complicated with fatal COVID-19 pneumonia. (a) Chest X-ray (CXR) with bilateral reticulonodular lesions over upper lobes (old tuberculosis sequelae), bilateral rib fractures and sternum surgical wires (pericardiectomy) in September 2011. (b) Bilateral diffuse ground-glass infiltrations on CXR and chest computed tomography (CT) in September 2017. (c) Resolved diffuse pulmonary infiltrations on CXR and chest CT after discontinuing methotrexate use and initiating high-dose glucocorticoids therapy for 1 month in October 2017. (d) Bilateral diffuse ground-glass infiltrations related to severe acute respiratory syndrome-coronavirus 2 infection on CXR and chest CT after initiating rituximab infusion for 4 years in July 2022.

Chrong-Reen Wang, MD, PhD
Division of Rheumatology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan

Wei-Chieh Lin, MD, PhD
Division of Critical Care Medicine, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan

Acknowledgments

The National Cheng Kung University Hospital Institutional Review Board approved this study (B-ER-105-108) and waived the requirement of informed consent from this deceased case. The authors are indebted to physicians and nurses involved in managing this rheumatoid arthritis (RA) patient at our hospital. This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors. All authors had the access to the data related to this communication and a contribution in its writing.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Chrong-Reen Wang https://orcid.org/0000-0001-9881-7024

References

1. Singh JA, Saag KG, Bridges SL Jr, et al. 2015 American College of Rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res (Hoboken)*. 2016;68:1-25. doi:10.1002/acr.22783.
2. Mazurek GH, Jereb J, Vernon A, et al. Updated guidelines for using Interferon Gamma Release Assays to detect Mycobacterium tuberculosis infection—United States, 2010. *MMWR Recomm Rep*. 2010;59:1-25.
3. *Coronavirus Disease* 2019 *(COVID-19) Treatment Guidelines* [Internet]. Bethesda, MD: National Institutes of Health; 2021-2022.
4. Santos CS, Férnandez XC, Moriano Morales C, et al. Biological agents for rheumatic diseases in the outbreak of COVID-19: friend or foe? *RMD Open*. 2021;7:e001439. doi:10.1136/rmdopen-2020-001439.

5. Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. *Ann Rheum Dis*. 2021;80:930-942. doi:10.1136/annrheumdis-2020-219498.
6. Mehta P, Gasparyan AY, Zimba O, et al. Systemic lupus erythematosus in the light of the COVID-19 pandemic: infection, vaccination, and impact on disease management. *Clin Rheumatol*. 2022;41:2893-2910. doi:10.1007/s10067-022-06227-7.
7. Nakajima R, Sakai F, Mimura T, et al. Acute- or subacute-onset lung complications in treating patients with rheumatoid arthritis. *Can Assoc Radiol J*. 2013;64:200-207. doi:10.1016/j.carj.2011.12.017.
8. Hallowell RW, Horton MR. Interstitial lung disease in patients with rheumatoid arthritis: spontaneous and drug induced. *Drugs*. 2014;74:443-450. doi:10.1007/s40265-014-0190-z.
9. Sparks JA, Wallace ZS, Seet AM, et al. Associations of baseline use of biologic or targeted synthetic DMARDs with COVID-19 severity in rheumatoid arthritis: results from the COVID-19 Global Rheumatology Alliance physician registry. *Ann Rheum Dis*. 2021;80:1137-1146. doi:10.1136/annrheumdis-2021-220418.
10. Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther*. 1981;30:239-245. doi:10.1038/clpt.1981.