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LETTER TO THE EDITOR

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Autoimmune rheumatic disease after SARS-CoV-2 vaccination

To the Editor,

COVID-19, caused by SARS-CoV-2, has become one of the greatest global public health concerns of the century. Numerous studies have documented the presence of various autoantibodies in patients with COVID-19, including antinuclear antibody (ANA), anti-Ro antibody, rheumatoid factor (RF), and antibodies against cytokines.[1–3] Moreover, COVID-19 can lead to a cytokine storm, which may induce the formation of autoantibodies causing autoimmune rheumatic diseases (ARDs).[1,4,5] One study reported that 165 of 1101 (14.9%) patients developed ARDs flares after SARS-CoV-2 vaccination.[6] Therefore, vaccination for SARS-CoV-2 may be related to autoimmunity. However, the incidence of ARDs following SARS-CoV-2 vaccination is unknown. Herein, we describe four retrospectively identified patients who developed ARDs after SARS-CoV-2 vaccination (Table 1). None of these four patients had a past history of ARDs. Written informed consent was obtained.

1 | CASE 1

A previously healthy woman in her sixties developed swelling and pain in both wrists, elbows, knees, and the right ankle 10 days following the second dose of ChAdOx1-S (AstraZeneca). Laboratory testing revealed the following: erythrocyte sedimentation rate (ESR), 76 mm/h; C-reactive protein (CRP), 8.5 mg/dl (<0.3 mg/dl); RF, 378 IU/ml (<15 IU/ml); and anti-cyclic citrullinated peptide antibody, 669 U/ml (<10 U/ml). She was diagnosed with seropositive rheumatoid arthritis. The disease activity was well controlled with low-dose glucocorticoid (tapered 9 months after diagnosis), methotrexate, sulfasalazine, and hydroxychloroquine.

2 | CASE 2

A previously healthy man in his thirties developed severe hip pain 4 days and neck stiffness and jaw pain 10 days after the first dose of mRNA-1273 (Moderna). Twenty-five days after vaccination, he developed swelling and pain in the right ankle and presented to the hospital. Laboratory testing revealed the following: ESR, 75 mm/h; and CRP, 10.0 mg/dl (<0.3 mg/dl). We diagnosed this patient with palindromic rheumatism. Symptomatic improvement was achieved with prednisolone 10 mg and naproxen 500 mg administered BID for 2 weeks. Subsequently, naproxen was administered to control mild arthralgia. He received the second dose of mRNA-1273, 4 months after the first, and developed pain in the temporomandibular joint 1 month after the second dose. The symptoms improved following prednisolone administration. The patient was followed-up for approximately 6 months. He was advised to visit the hospital in case of symptom exacerbation but has not been seen for 3 months.

3 | CASE 3

A previously healthy woman in her twenties was hospitalized with headache and fever (38.5°C) 10 days after the first dose of mRNA-1273 (Moderna). Laboratory testing revealed the following: ESR, 120 mm/h; and CRP, 4.3 mg/dl (<0.30 mg/dl). cerebrospinal fluid analysis found no pathogens; she was diagnosed with aseptic meningitis. She had an intermittent fever for 20 days, hair loss, and necrotizing cervical lymphadenitis. Laboratory analysis revealed the following: ANA, 1:1280); anti-Ro antibody >240 U/ml (<7 U/ml); anti-La antibody >320 U/ml (<7 U/ml); and positive direct Coombs test. Symptomatic improvement was achieved with prednisolone 15 mg and naproxen 500 mg BID. Chilblain lupus developed on the fingertips during steroid tapering. She was diagnosed with systemic lupus erythematosus.This patient had low disease activity and was followed up for approximately 7 months. She was treated with hydroxychloroquine 300 mg OD, prednisolone 2.5 mg OD, and naproxen 500 mg BID.

4 | CASE 4

A woman in her sixties with a history of dyslipidemia, osteoporosis, and cataract developed general body ache 3 days after the first dose of ChAdOx1-S (AstraZeneca) and visited the hospital upon symptom exacerbation 12 days later. She complained of difficulty in lifting both shoulders for 1 month due to pain. Morning stiffness appeared in both shoulders. Laboratory testing revealed the following: ESR, 98 mm/h; CRP, 3.0 mg/dl (<0.3 mg/dl); ANA, 1:160; and anti-dsDNA antibody, 18 IU/ml (<10 IU/ml). Shoulder pain and stiffness improved after administration of prednisolone 5 mg BID for 2 weeks. However, it recurred after discontinuation, and glucocorticoid was re-administered. She was diagnosed with polymyalgia rheumatica. She was treated with prednisolone 5 mg daily and methotrexate 15 mg weekly, and followed up for approximately 10 months.

The SARS-CoV-2 spike protein and nonstructural protein 3 possess the largest number of immunogenic peptides among the

TABLE 1 Clinical characteristics of patients with autoimmune inflammatory rheumatic disease after SARS-CoV-2 vaccination

	Age	Sex	Vaccine type	Time (days) after vaccination	Clinical manifestations	ESR (mm/h)	CRP (mg/dl)	Significant laboratory findings	Prognosis
Case 1	60s	F	ChAdOx1-S AstraZeneca (second dose)	10 days	Inflammatory polyarthritis (seropositive RA)	76	8.5	ANA−, RF 378 IU/ml, anti-CCP Ab 669 U/ml	Improved after low-dose GC, MTX, SSZ, and HCQ
Case 2	30s	M	mRNA-1273 Moderna (first dose)	4 days	Migratory inflammatory arthritis (Palindromic rheumatism)	75	10.0	ANA−, RF−, anti-CCP Ab−	Improved after short-term GC and NSAIDs
Case 3	20s	F	mRNA-1273 Moderna (first dose)	10 days	Aseptic meningitis, necrotizing lymphadenitis, hair loss, chilblain lupus (SLE[a])	120	4.3	ANA 1:1280, anti-Ro Ab > 240 U/ml, anti-La Ab > 320 U/ml, direct coombs test+	Improved after medium-dose GC, HCQ, and NSAIDs
Case 4	60s	F	ChAdOx1-S AstraZeneca (first dose)	3 days	Bilateral shoulder stiffness and pain (PMR)	98	3.0	ANA 1:160, anti-dsDNA Ab 18 IU/ml, RF−, anti-CCP Ab−	Improved after low-dose GC and MTX

Abbreviations: Ab, antibody; ANA, antinuclear antibody; CCP, cyclic citrullinated peptide; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; GC, glucocorticoid; HCQ, hydroxychloroquine; MTX, methotrexate; NSAIDs, nonsteroidal anti-inflammatory drugs; PMR, polymyalgia rheumatica; RA, rheumatoid arthritis; RF, rheumatoid factor; SLE, systemic lupus erythematosus; SLICC, Systemic Lupus International Collaborating Clinics; SpA, spondyloarthritis; SSZ, sulfasalazine; +, positive; −, negative.

[a]We diagnosed this patient with SLE based on the SLICC criteria.

SARS-CoV-2 proteins.[7] A recent study using selective mapping showed similarities and homology between the spike, nucleoprotein, and numerous other SARS-CoV-2 proteins with the human tissue antigens mitochondria M2, F-actin, and TPO.[8] The Pfizer, Moderna, and AstraZeneca SARS-CoV-2 vaccines focus on the spike protein. Owing to this mechanism of action, SARS-CoV-2 vaccination may be followed by various rheumatic conditions and trigger the onset of underlying ARDs.[9] Although a causal relationship between SARS-CoV-2 vaccination and autoimmune rheumatic manifestations cannot be established easily, it is necessary to consider that symptoms occurring after SARS-CoV-2 vaccination may become chronic and indicate ARDs.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the letter or revising it critically for important intellectual content and approved the final manuscript to be submitted, and agreed to be accountable for all aspects of the work. Byeongzu Ghang, Sunjoo Kim, and Jinseok Kim designed the study and wrote the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The present study protocol was approved by the Institutional Review Board of Jeju National University Hospital.

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REFERENCES

1. Chang SE, Feng A, Meng W, et al. New-onset IgG autoantibodies in hospitalized patients with COVID-19. *Nat Commun*. 2021;12:5417.
2. Wang EY, Mao T, Klein J, et al. Diverse functional autoantibodies in patients with COVID-19. *Nature*. 2021;595:283-288.
3. Knight JS, Caricchio R, Casanova JL, et al. The intersection of COVID-19 and autoimmunity. *J Clin Invest*. 2021;131:e154886.
4. Derksen VFAM, van der Woude D, Derksen V, et al. Onset of rheumatoid arthritis after COVID-19: coincidence or connected? *Ann Rheum Dis*. 2021;80:1096-1098.
5. Hsu TY, D'Silva KM, Patel NJ, Fu X, Wallace ZS, Sparks JA. Incident systemic rheumatic disease following COVID-19. *Lancet Rheumatol*. 2021;3:e402-e404.
6. Barbhaiya M, Levine JM, Bykerk VP, Jannat-Khah D, Mandl LA. Systemic rheumatic disease flares after SARS-CoV-2 vaccination among rheumatology outpatients in New York City. *Ann Rheum Dis*. 2021;80:1352-1354.
7. Lyons-Weiler J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. *J Transl Autoimmun*. 2020;3:100051.
8. Vojdani A, Vojdani E, Kharrazian D. Reaction of human monoclonal antibodies to SARS-CoV-2 proteins with tissue antigens: implications for autoimmune diseases. *Front Immunol*. 2020;11:617089.
9. Singh R, Kaur U, Singh A, Chakrabarti SS. Refractory hypereosinophilia associated with newly diagnosed rheumatoid arthritis following inactivated BBV152 COVID-19 vaccine. *J Med Virol*. 2022;94:3482-3487.