

[CASE REPORT]

Successful Use of Certolizumab Pegol for Refractory Psoriatic Arthritis Triggered by COVID-19 Infection

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Abstract:

Recently, the coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2, has spread worldwide. Although nearly all patients incur mild-to-moderate disease from this viral infection, some develop severe manifestations with a poor prognosis. COVID-19 can also induce autoimmune disease; several cases of arthritis following COVID-19 have been documented in the literature, such as reactive arthritis and chronic arthritis. We herein report a case of psoriatic arthritis triggered by COVID-19. Although the arthritis had been refractory to glucocorticoids and methotrexate, certolizumab pegol subsequently led to remission.

Key words: certolizumab pegol, COVID-19, psoriatic arthritis, severe acute respiratory syndrome coronavirus 2

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Introduction

The COVID-19 pandemic is a global pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Symptoms of COVID-19 are variable, including a fever, cough, dyspnea, fatigue, and loss of smell and taste (1). Although almost all patients develop mild-to-moderate symptoms, some develop severe symptoms, leading to respiratory failure, shock, and multi-organ dysfunction (1).

COVID-19 can also induce autoimmune phenomena, such as macrophage activation syndrome, Kawasaki-like disease, hemolytic anemia, antiphospholipid antibody syndrome, Guillan-Barre syndrome, and arthritis (2-6).

We herein report a case of psoriatic arthritis (PsA) triggered by COVID-19. This patient was unresponsive to therapy with glucocorticoids and methotrexate (MTX), but adding certolizumab pegol (CZP) led to remission.

Case Report

A 42-year-old woman was referred to our hospital for complaints of arthralgia. She had been treated for diabetes

for the past two years but was otherwise deemed stable in terms of glycemic control. The patient had also had skin lesions on her hands over the past two years and was being treated with topical medication with no appreciable response to therapy. She did not have any other skin lesions, including on her scalp or nails. The patient had no history of arthritis or back pain, no personal history of irritable bowel disease, and no family history of psoriasis.

Twelve weeks prior to consulting with our department, she was referred to another institution for a sudden fever without cough or dyspnea. Blood tests showed a leukocyte count of $2,890 \times 10^3/L$, lymphocyte count of $1,210 \times 10^3/L$, hemoglobin level of 15.3 g/dL, platelet count of $194 \times 10^3/L$, lactate dehydrogenase (LDH) level of 208 U/L, C-reactive protein (CRP) level of 2.82 mg/dL, and creatinine level of 0.49 mg/dL. Computed tomography (CT) revealed ground-glass opacities in both lungs (Fig. 1). She was diagnosed with COVID-19 upon targeted polymerase chain reaction testing. She was admitted to the hospital but did not require oxygen supplementation. She underwent subsequent lysis of the fever despite no intensive treatment and was discharged from the hospital within six days.

Four weeks following discharge, she started experiencing joint pain. She was treated with celecoxib 400 mg/day for 4

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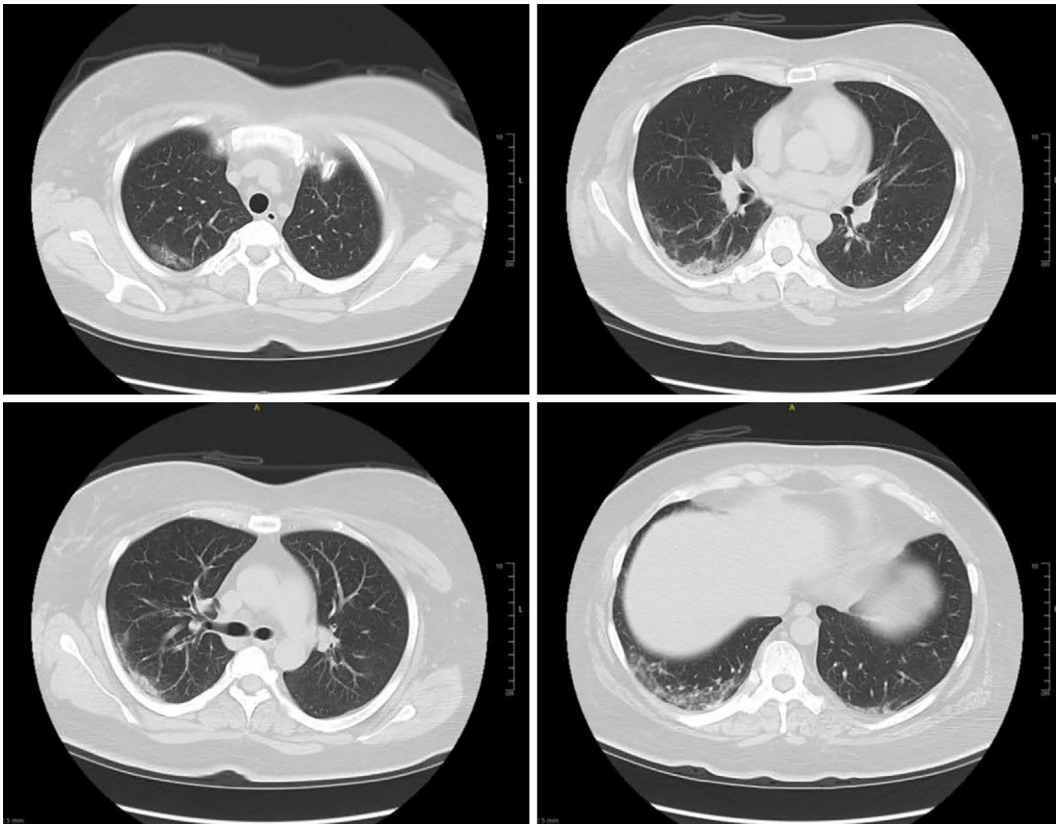


Figure 1. Chest CT findings upon presentation at the hospital for COVID-19. Chest CT findings showed ground-glass opacity in both lungs upon admission due to COVID-19. CT: computed tomography

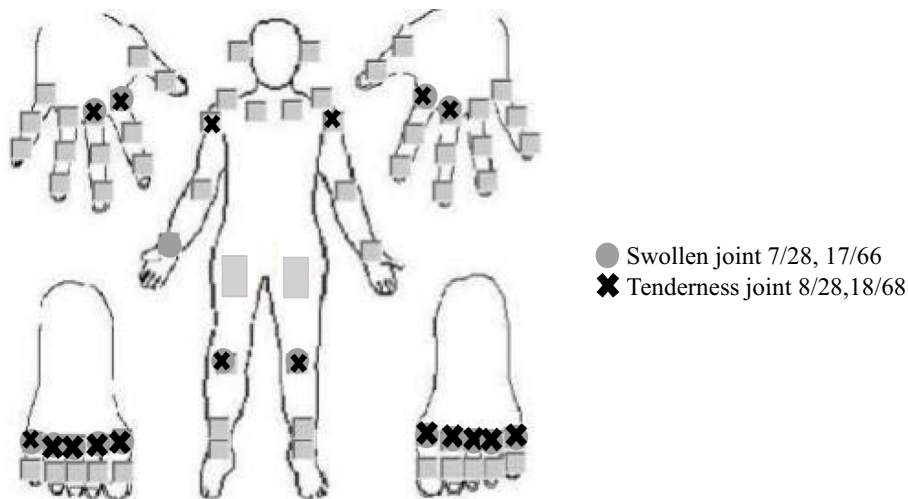


Figure 2. Joint findings. Joint findings showed polyarthritis.

weeks, which did not diminish her pain symptoms. Later, she was referred to our hospital for a six-week history of joint pain. Her temperature was 36.5°C, blood pressure was 109/73 mmHg, and pulse rate was 77 beats per minute. Her blood oxygen saturation upon pulse oximetry was 99% on room air. She had polyarthritis, with swelling in 8/28 joints and tenderness in 7/28 joints (Fig. 2). Her Disease Activity Score (DAS) 28-CRP, DAS28-ESR, Simplified Disease Activity Index (SDAI), and Clinical Disease Activity Index

(CDAI) scores were 6.2, 6.87, 38.4, and 32.0, respectively. The patient did not have pain in the back or in any part of the axial skeleton.

Upon a physical examination, she had erythema with scales on her left hand (Fig. 3). The patient did not have scalp or nail lesions. Subsequent blood tests showed a leukocyte count of $7,170 \times 10^3/L$, a lymphocyte count of $1,936 \times 10^3/L$, a hemoglobin level of 13.3 g/dL, a platelet count of $517 \times 10^3/L$, an LDH level of 116 U/L, a CRP level of 6.40

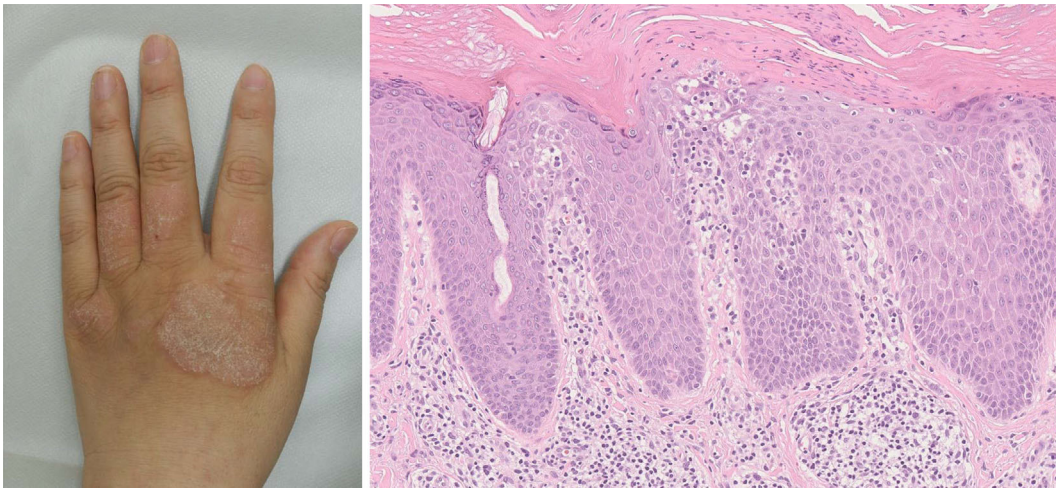


Figure 3. Skin lesions and pathological findings. Skin lesions showed erythema with scales on her left hand; pathological findings showed regular elongation of the rete ridge, inflammatory cell infiltration of the epidermis and dermis, spongiosis of the dermis, and hypogranulosis.

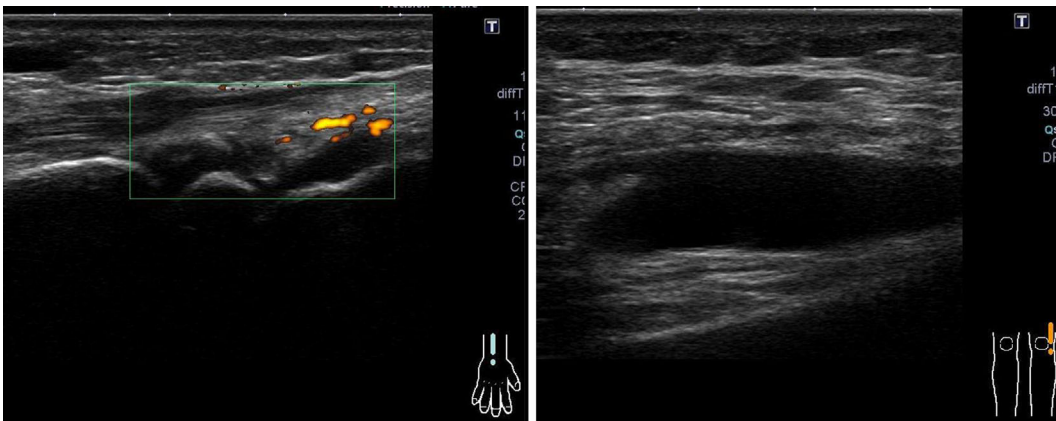


Figure 4. Ultrasound test findings for left hand and left knee. Ultrasonography showed her left hand with gray scale 2 with a power Doppler 1 signal of the left radial carpal joint and left knee with effusions.

mg/dL, an erythrocyte sedimentation rate (ESR) of 87 mm/h, and a matrix metalloproteinase-3 (MMP-3) level of 209.1 ng/mL. Tests for syphilis, ASO, *Mycoplasma*, *Chlamydia pneumoniae*, *C. trachomatis*, T-SPOT.TB test, polymerase chain reaction test for human parvovirus B19, antinuclear antibody, rheumatoid factor, anticyclic citrullinated peptide antibody (ACPA), anti-SS-A/Ro antibody, anti-SS-B/La antibody, anti-DNA antibody, anti-RNP antibody, anti-Smith antibody, anti-aminoacyl-tRNA synthetase antibody, and human leukocyte antigen (HLA)-B27 findings were negative. Arthrocentesis of her left knee revealed a leukocyte count of $2,670 \times 10^3/L$ without monosodium urate or calcium pyrophosphate crystals. The culture of the synovial fluid was negative.

Radiography of her hands, feet, and knees showed no erosive changes or enthesophytes. Whole-body CT showed no characteristic lesions. Her skin biopsy showed regular elongation of the rete ridge, inflammatory cell infiltrates of the epidermis and dermis, spongiosis of the dermis, and hy-

pogranulosis (Fig. 3); these lesions were consistent with psoriasis. Musculoskeletal ultrasonography showed gray scale 2 with a power Doppler 1 signal of the left radial carpal joint and effusion involving the left knee (Fig. 4). The clinical course is shown in Fig. 5.

Based on these findings, she was diagnosed with PsA and treated accordingly with prednisolone (PSL) 30 mg per day for severe arthritis. Despite resolution of skin lesions, her arthritis did not improve. Subsequently, MTX was initiated. Neither PSL nor MTX led to remission of joint pain. Therefore, CZP 400 mg every 2 weeks was initiated in combination with MTX and PSL at 11 weeks after referral to our hospital. She received CZP with the following dosing schedule: 400 mg at 0, 2, and 4 weeks, followed by 200 mg every other week. Upon initiation of CZP, her DAS28-CRP, DAS28-ESR, SDAI, and CDAI values improved to 3.81, 4.67, 14.13, and 13.6, respectively; her arthritis remarkably improved, thus allowing incremental dose reduction of PSL prior to complete discontinuation. Twelve weeks after initiat-

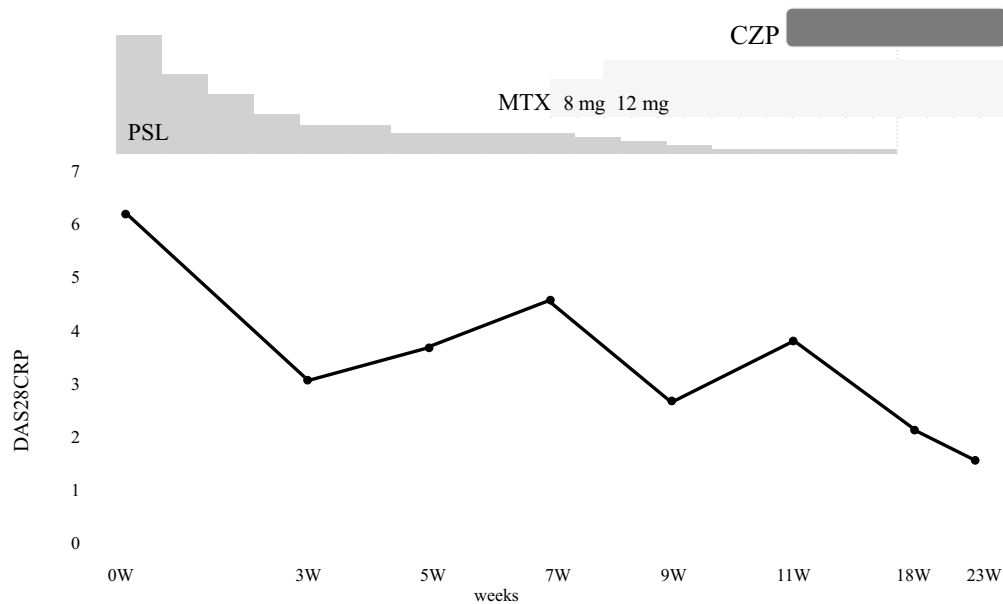


Figure 5. Progress chart documenting the course of treatment for psoriatic arthritis. CRP: C-reactive protein, CZP: certolizumab pegol, DAS: Disease Activity Score, MTX: methotrexate, PSL: prednisolone

ing CZP, her DAS28-CRP, DAS28-ESR, SDAI, and CDAI were 1.56, 2.17, 1.78, and 1.6, respectively. Clinical remission was thus achieved.

Discussion

To our knowledge, this is the only documented case of PsA triggered by COVID-19 (7). COVID-19 can induce autoimmune phenomena, and several investigators have reported arthritis following SARS-CoV-2 infection (7-15). The mechanism underlying the onset of autoimmune disease following COVID-19 remains unclear; however, severe COVID-19 might be associated with a cytokine syndrome (16). Severe COVID-19 patients show increased levels of interleukin (IL)-2, IL-7, granulocyte colony-stimulating factor, interferon- γ inducible protein 10, monocyte chemoattractant protein 1, macrophage inflammatory protein 1- α , and tumor necrosis factor (TNF)- α (16). Patients with fatal outcomes also have elevated ferritin and IL-6 levels, which resemble secondary hemophagocytic lymphohistiocytosis (17). Another report suggested that all patients with severe COVID-19 should be screened for hyperinflammation to identify patients in whom immunosuppression therapy might reduce the risk of mortality (18). Patients with COVID-19 also have higher counts of T helper 17 (Th17) cells than those without it; moreover, the severity of COVID-19 is correlated with IL-17 and Th17-related proinflammatory cytokines (19). IL-17 is the most recognized, multifunctional cytokine family and has proinflammatory effects involving the induction of other cytokines. Among patients with psoriasis, IL-17 is a key cytokine and represents a primary therapeutic target for inhibition (20).

The mechanism underlying the onset of PsA after

COVID-19 in the present case was unclear, but one study reported that oligodeoxynucleotide (ODN)/imiquimod stimulation induced entheselial plasmacytoid dendritic cells (pDCs) related interferon (IFN)- α production via NF- κ B signaling, Toll-like receptor signaling, and JAK/STAT signaling pathways (21). In addition, the Disease Activity Index score for PsA increases following COVID-19 due to the stimulation of Toll-like receptor 7 pathways in patients with PsA (21).

Almost all cases of new-onset arthritis following COVID-19 were clinically similar to reactive arthritis; moreover, joint inflammation commenced following the resolution of COVID-19 symptoms. In such cases, nonsteroidal anti-inflammatory drugs (NSAIDs) and intra-articular corticosteroid injections improved arthritis (8-13). In contrast, some patients had presentations more consistent with chronic arthritis, such as rheumatoid arthritis (RA), spondyloarthritis (SpA), and PsA (7, 15, 22). Some of them required immunosuppressive therapy for the treatment of chronic arthritis (14, 23). In our case, although the patient had psoriasis, seronegative polyarthritis ensued following recovery from COVID-19. Polyarthritis persisted despite NSAIDs and glucocorticoid therapy, thus requiring MTX and CZP. This prompted the hypothesis that COVID-19 might have triggered PsA.

To examine the characteristics of patients who developed PsA after COVID-19, we searched the literature that had been reported until 2021 (Table). Both of the case reports found involved women with no family history of psoriasis. One case was a new onset, our case had been treated for two years, and neither case had scalp or nail lesions. Neither case received intensive COVID-19 treatment, and both recovered within 14 days. The time between the resolution of COVID-19 symptoms and development of arthritis was

Table. Characteristics of Patients with PsA Triggered by COVID-19.

Clinical characteristics	Patient 1	Patient 2
Age (years old)	27	42
Gender	F	F
Comorbidity	-	Diabetes
Family history	-	-
Psoriasis duration (years)	New onset	2
Scalp or nail lesion	-	-
Symptoms of COVID-19	Anosmia, dysgeusia	Fever
Pneumonia in CT findings	-	+
Intensive treatment for COVID-19	-	-
Resolution of COVID-19 symptoms (days)	14	6
Time between resolution of COVID-19 symptoms and developing arthritis (weeks)	1	4
Peripheral arthritis	+	+
Axial involvement	+	-
Enthesitis	NA	-
HLA-B27	Negative	Negative
Rheumatoid factor	-	-
ACPA	-	-
CRP (mg/dL)	NA	6.4
Treatment for PsA	NA	PSL, MTX, CZP
PsA outcome	NA	Improve
Reference	(7)	Our patient

ACPA: anticyclic citrullinated peptide antibody, CRP: C-reactive protein, CT: computed tomography, CZP: certolizumab pegol, F: female, HLA: human leukocyte antigen, MTX: methotrexate, NA: not assessed, PsA: psoriatic arthritis, PSL: prednisolone

within four weeks. Both cases had peripheral arthritis, but axial involvement was only noted in one case. Tests for rheumatoid factor, ACPA, and HLA-B27 were negative.

Experts recommend psoriasis treatment including biologics during COVID-19 pandemic. One study suggested the administration of IL-17 and IL-23 inhibitors rather than TNF inhibitors during the COVID-19 pandemic because IL-17, IL-12/23, and IL-23 inhibitors are associated with a low infection risk compared to TNF inhibitors (24). In contrast, a global registry-based study showed that hospitalization was more frequent in patients using nonbiologic systemic therapy than in those using biologics (25). Furthermore, another report showed that IL-17, IL-12/23, IL-23, and TNF inhibitors were not associated with COVID-19-related death (26). These results showed that biologics in patients with psoriasis did not increase death related to COVID-19. However, there have been no reports demonstrating that biologics are the safest treatment for COVID-19 infection.

The present patient was treated with TNF inhibitors in combination with MTX and glucocorticoids based on European Alliance of Associations for Rheumatology (EULAR) recommendations for PsA (27), which reported that TNF, IL-17, and IL12/23 inhibitors are equally recommended for active PsA, and she achieved clinical remission once CZP was initiated. The best treatment for chronic arthritis after COVID-19 remains unclear. Further studies are thus required to determine the ideal treatment for chronic arthritis after COVID-19.

In conclusion, patients with autoimmune diseases, including chronic arthritis, must be carefully observed following recovery from COVID-19.

Written informed consent for the documentation of this case report was obtained from our patient.

The authors state that they have no Conflict of Interest (COI).

References

- Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* **19**: 141-154, 2020.
- Otsuka R, Seino KI. Macrophage activation syndrome and COVID-19. *Inflamm Regen* **40**: 19, 2020.
- Niazkar HR, Zibae B, Nasimi A, Bahri N. The neurological manifestations of COVID-19: a review article. *Neurol Sci* **41**: 1667-1671, 2020.
- Lechien JR, Hervochon R, Hans S. Post-COVID-19 Kawasaki-like syndrome. *Ear Nose Throat J* 1455613211006011, 2021. Epub ahead of print.
- Cristiano A, Fortunati V, Cherubini F, Bernardini S, Nuccetelli M. Anti-phospholipids antibodies and immune complexes in COVID-19 patients: a putative role in disease course for anti-annexin-V antibodies. *Clin Rheumatol* **40**: 2939-2945, 2021.
- Jacobs J, Eichbaum Q. COVID-19 associated with severe autoimmune hemolytic anemia. *Transfusion* **61**: 635-640, 2021.
- Novelli L, Motta F, Ceribelli A, et al. A case of psoriatic arthritis triggered by SARS-CoV-2 infection. *Rheumatology (Oxford)* **60**: e21-e23, 2021.
- Hønge BL, Hermansen MF, Storgaard M. Reactive arthritis after

- COVID-19. *BMJ Case Rep* **14**: e241375, 2021.
9. Jali I. Reactive Arthritis After COVID-19 Infection. *Cureus* **12**: e11761, 2020.
 10. Saricaoglu EM, Hasanoglu I, Guner R. The first reactive arthritis case associated with COVID-19. *J Med Virol* **93**: 192-193, 2021.
 11. Ono K, Kishimoto M, Shimasaki T, et al. Reactive arthritis after COVID-19 infection. *RMD Open* **6**: e001350, 2020.
 12. Liew IY, Mak TM, Cui L, Vasoo S, Lim XR. A case of reactive arthritis secondary to coronavirus disease 2019 infection. *J Clin Rheumatol* **26**: 233, 2020.
 13. De Stefano L, Rossi S, Montecucco C, Bugatti S. Transient monoarthritis and psoriatic skin lesions following COVID-19. *Ann Rheum Dis* 2020: annrheumdis-2020-218520.
 14. Perrot L, Hemon M, Busnel JM, et al. First flare of ACPA-positive rheumatoid arthritis after SARS-CoV-2 infection. *Lancet Rheumatol* **3**: e6-e8, 2021.
 15. Derksen VFAM, Kissel T, Lamers-Karnebeek FBG, et al. Onset of rheumatoid arthritis after COVID-19: coincidence or connected? *Ann Rheum Dis* 2021: annrheumdis-2021-219859.
 16. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *Lancet* **395**: 1033-1034, 2020.
 17. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* **395**: 497-506, 2020.
 18. Ruan Q, Yang K, Wang W, Jiang L, Song J. Clinical predictors of mortality due to COVID-19 based on an analysis of data of 150 patients from Wuhan, China. *Intensive Care Med* **46**: 846-848, 2020.
 19. Pacha O, Sallman MA, Evans SE. COVID-19: a case for inhibiting IL-17? *Nat Rev Immunol* **20**: 345-346, 2020.
 20. Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. *Clin Rev Allergy Immunol* **55**: 379-390, 2018.
 21. Zhou Q, Vadakekolathu J, Watad A, et al. SARS-CoV-2 infection induces psoriatic arthritis flares and enthesitis resident plasmacytoid dendritic cell Type-1 interferon inhibition by JAK antagonism offer novel spondyloarthritis pathogenesis insights. *Front Immunol* **12**: 635018, 2021.
 22. Alivernini S, Cingolani A, Gessi M, et al. Comparative analysis of synovial inflammation after SARS-CoV-2 infection. *Ann Rheum Dis* 2020: annrheumdis-2020-218315.
 23. Talarico R, Stagnaro C, Ferro F, Carli L, Mosca M. Symmetric peripheral polyarthritis developed during SARS-CoV-2 infection. *Lancet Rheumatol* **2**: e518-e519, 2020.
 24. Ricardo JW, Lipner SR. Considerations for safety in the use of systemic medications for psoriasis and atopic dermatitis during the COVID-19 pandemic. *Dermatol Ther* **33**: e13687, 2020.
 25. Mahil SK, Dand N, Mason KJ, et al.; PsoProtect study group. Factors associated with adverse COVID-19 outcomes in patients with psoriasis-insights from a global registry-based study. *J Allergy Clin Immunol* **147**: 60-71, 2021.
 26. Strangfeld A, Schäfer M, Gianfrancesco MA, et al.; COVID-19 Global Rheumatology Alliance. 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* **80**: 930-942, 2021.
 27. Gossec L, Baraliakos X, Kerschbaumer A, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. *Ann Rheum Dis* **79**: 700-712, 2020.

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