# Complete persistent remission of rheumatoid arthritis after COVID-19 infection - A rare case and literature review

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## Abstract

A 55-year-old man was admitted to a hospital in Northeast India with fever, cough and breathlessness and was diagnosed with severe COVID-19 pneumonia. He was a known case of seropositive, erosive rheumatoid arthritis (RA) and was taking disease-modifying anti-rheumatic drugs (DMARDs). The patient was treated with remdesivir, heparin and a short course of corticosteroids for COVID-19 pneumonia. With the improvement of COVID-19 pneumonia, the patient also noticed a marked improvement in his joint symptoms despite not taking any DMARDs for RA. The temporal relationship between the time of disappearance of all signs and symptoms of RA within a few days after COVID-19 pneumonia and maintenance of RA remission for over one year of follow up to date suggests that COVID-19 likely caused the remission of RA. This case highlights the need for larger studies to understand the COVID-19 effects on RA remission and their potential link if any. However, the evidence of worse outcome with COVID-19 in immunosuppression which is common in RA cannot be overlooked.

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## Introduction

Rheumatoid arthritis (RA) is a chronic, autoimmune, inflammatory disease of unknown aetiology characterized by symmetric polyarthritis and extra-articular manifestations. The pathogenic mechanism involves a complex interplay between genetic, environmental and immunogenic factors leading to immune dysregulation. It has been hypothesized that the immune response to *Porphyromonas gingivalis* and Epstein Barr virus may trigger the development of RA. Coronavirus disease (COVID-19) is an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which primarily affects the lungs and, in some cases, leads to an excessive or uncontrolled immune activation and cytokine response in various organ systems. Musculoskeletal manifestations like arthralgia and myalgia can also develop during COVID-19 infection [1]. Our case presents a unique phenomenon of RA remission after COVID-19 infection.

## Case Report

A 55-year-old man was admitted with fever, cough, and shortness of breath during the COVID-19 pandemic in May 2020. The patient had a history of RA, which was diagnosed 4 years earlier in view of bilateral symmetric polyarthritis involving small joints of the hands with erosions, morning stiffness lasting for more than 30 minutes and positive serologic findings with positive rheumatoid

factor (RF) at a concentration of 185 IU/ ml and Anti-Cyclic Citrullinated Peptide Antibody (Anti-CCP) of >340 U/ml. RA was controlled with methotrexate (10 mg/week), hydroxychloroquine (200 mg twice daily), and sulfasalazine (500 mg thrice daily). The patient did not tolerate increasing the oral methotrexate to more than 10mg weekly. Four weeks before his hospital admission with COVID-19 pneumonia, he had a rheumatology assessment which revealed a high disease activity score of (DAS-28) 5.73 (the tender joint count (TJC) was 8, the swollen joint count (SJC) was 5, patient global health 60 mm and erythrocyte sedimentation rate was 46 mm/hour). Due to fear of contracting COVID-19 infection, the patient preferred not to receive any additional immunosuppression.

He presented to the emergency room with worsening shortness of breath with no history of chest pain, orthopnoea, or leg swelling. On examination, the temperature was 37.6°C, the blood pressure 157/74 mm Hg, the heart rate was 124 beats per minute, the respiratory rate was 40 breaths per minute, and the oxygen saturation was 84% on room air. Coarse crackles were heard at bilateral lung bases. A chest radiograph obtained in the emergency department showed bilateral multifocal patchy opacities. Coronal non-enhanced chest CT showed ground-glass opacities, with superimposed septal thickening and adjacent consolidation in bilateral lung parenchyma involving the bilateral middle and lower zone.

The patient tested positive for the SARS-CoV-2 by reverse transcriptase-polymerase chain reaction (RT-PCR) following a nasopharyngeal swab. The patient was admitted to the local hospital, and he was treated with ceftriaxone and azithromycin. There was a rapid decline in oxygen saturation requiring non-invasive ventilatory (NIV) support in the intensive care unit (ICU). His initial blood parameters revealed haemoglobin of 9.4 g/dl (reference range, 13.3-16.2 gm/dl), lymphopenia, elevated C-reactive protein (CRP) of 70.4 mg/dl (reference range, <10), raised ferritin of 586 ng/ml (reference range, 29-248), high Interleukin-6 level of 32.56 pg/ml (reference range, 0-6), with normal renal and liver function tests. The patient continued hydroxychloroquine 200 mg twice daily for his RA, but other DMARDs were withheld. He was commenced on intravenous Dexamethasone 6 mg twice daily for 5 days followed by once daily for 5 more days, remdesivir 200 mg intravenous on day 1 followed by 100 mg once daily for 5 more days, and low molecular weight heparin 40 mg subcutaneous twice daily for 5 days. After 3 days of ICU treatment, the patient was weaned off from NIV support. Repeat SARS-CoV-2 test on day 14 was negative.

With the improvement in pneumonia in 10 days, the patient noticed a marked improvement in his joint symptoms. Therefore, the patient stopped taking all DMARDs and corticosteroids almost a month following COVID-19. During the follow up after 6 months after the hospital discharge, he was in complete remission from RA with no TJC or SJC (Table 1). During his recent rheumatology clinic visit in June 2021, RA remained in complete remission, despite not taking any DMARDs more than a year from stopping all immunosuppressive drugs. Thus, even though the treatment for COVID-19 including steroid and HCQ may have triggered a remission or response in RA, a sustained remission without any DMARDs was the rare finding in our case.

## Literature review

### Search strategy

A thorough literature search was conducted in MEDLINE (*via* PubMed) database to gather all relevant studies to the aims of our review. The Population-intervention-outcome framework was used. After basic keywords including "Rheumatoid arthritis", "COVID-19", "SARS-CoV-2", "remissions" yielded only 16 results, the expanded key search terms including- "SLE", "Rheumatoid arthritis", "Psoriatic arthritis", "sarcoidosis", "autoimmune diseases", "inflammatory diseases", "COVID-19", "SARS-CoV-2", "infection" and "remissions" were used.

The abstracts of any identified literature were screened by hand for relevance following the implementation of the search strategy. The full-text articles of the literature were then independently reviewed by three authors to ensure relevance and mitigate bias. Given that we had to expand on our initial search strategy due to limited findings, the authors carefully selected the additional studies to be discussed in the literature review. Clinical studies, case series and case reports on RA, SLE, osoriatic arthritis, sarcoidosis, inflammatory diseases, other autoimmune diseases in English language were included. Our search yielded 2 case series. In one series, patients on immunosuppressive therapy for immune-medicated inflammatory diseases, there was a higher risk of invasive mechanical ventilation [2]. In another retrospective study over 9 months, 25 patients with RA developed COVID-19 with a higher risk of severity [3].

## Discussion

Our case highlights a unique presentation of RA remission after COVID-19 infection. Improvement or complete remission of autoimmune inflammatory conditions following infections have been reported. The remission of RA following varicella-zoster infection has been reported in the literature [4]. The temporal relationship between the disappearance of all signs and symptoms of RA within a few days after COVID-19 pneumonia or any viral infection raises the suspicion of a link between the two diseases [2]. Remission after COVID-19 infection is limited to arthritis, but many other chronic

**Table 1. Disease activity scores of rheumatoid arthritis pre- and post-COVID-19 infection.**

| Pre COVID-19 (April 2020) | 4 weeks after COVID-19 (June 2020) | 7 months after COVID-19 (December 2020) | 13 months after COVID-19 (June 2021) |
|---|---|---|---|
| TJC 8 | TJC 1 | TJC 0 | TJC 0 |
| SJC 5 | SJC 1 | SJC 0 | SJC 0 |
| PGA 60 | PGA 10 | PGA 0 | PGA 0 |
| CRP 56 | CRP 3.4 | CRP 1 | CRP 1.2 |
| ESR 46 | ESR 34 | ESR 23 | ESR 16 |
| DAS 28 CRP 5.4 | DAS 28 CRP 2.4 | DAS 28 CRP 1.2 | DAS 28 CRP 1.2 |
| DAS 28 ESR 5.7 | DAS 28 ESR 3.4 | DAS 28 ESR 2.1 | DAS 28 ESR 1.9 |

TJC, tender joint count; SJC, swollen joint count; PGA, patient global assessment; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; DAS, disease activity score.

conditions also demonstrated significant improvement. Studies have reported complete remission of follicular and Hodgkin lymphoma after COVID-19 infection [5]. In these cases, the patient's PET-CT scan showed a significant decrease in the lymphoma size after recovering from the infection. Interestingly, it shows that this viral infection influences tumour biology and inflammatory response in a certain way that is yet to be explored. Notably, in these cases, the virus might have caused an initial "flare phenomenon" similar to that seen in patients receiving immunotherapy and eventually leading to an "abscopal effect" [5].

There are reported cases of RA disease flares and reactive arthritis following COVID-19 infection [6-10]. However, this is the first reported case of remission of RA after infection with COVID-19 pneumonia in an adult.

Clinical remission of RA may be an expression of the suppressed autoimmune process following the COVID-19, possibly involving regulatory T cells (Treg) [1]. Treg cells are usually produced in the thymus of our body and induced to suppress immune-mediated inflammation in the periphery. They are primarily heterogeneous and can suppress various classes of T cells (TH1, TH2, TH17). Another possibility is that elevated cytokine IL-9 suppresses the inflammation and thereby prevents chronicity of arthritis. The possible hypothesis for the resolution of arthritis is based on the induction of type 2 innate lymphoid cells (ILC2s) by IL-9, which in turn induces activation of Treg with the help of an expression of GITR/GITRL and ICOS/ICOSL [11]. Furthermore, SARS-CoV-2 consists of a complex transcriptome and has similar molecular proteins as that of humans. This forms the basis of developing autoimmunity and rheumatic manifestations.

Additionally, coronaviruses consist of single-stranded RNA, and the genome of SARS-CoV-2 has 30,000 nucleotides. The complex nature of the transcriptome is mainly attributed to the wide range of recombination activities and discontinuous transcription, which expands the ability to influence the human immune system. Moreover, due to the presence of a variety of protein sequences, a rich source of epitopes is available to influence the immunity response [12]. It is suggested that SARS-CoV-2 infection leads to an immune response that has anti-tumour potential. This may involve a cross-reactivity of tumour antigens with pathogen-specific T cells. Additionally, activation of the natural killer cells may occur due to the release of inflammatory cytokines during infection [5].

The role of induced and pre-existing autoantibodies in RA and their clinical outcome in people affected with COVID-19 is unclear [13]. RA is a complex disease with fluctuating disease activity over time. A state of sustained remission will ideally mean the absence of disease activity and halt any further damage to joints [14]. In the present case, the patient remained in complete remission without the need for any disease-modifying drugs and absence of any joint pain or swellings. However, it must also be remembered that presence of comorbidities and treatment with immunosuppressive medications definitely has an increased risk of COVID-19 [15].

This is the first case highlighting remission of rheumatoid arthritis after COVID-19 infection; however, we cannot extrapolate firm conclusions from this case study. It is plausible that the patient's RA went into remission by chance, but remission of other autoimmune conditions following infections raises the suspicion of a potential association that infection might have caused the RA remission. A limitation of this case that it is an isolated case which needs large-scale studies structured documentation of the outcome of all RA patients who developed COVID-19 to generate conclusive evidence regarding possible physiology. Images of the joints for the patient are not available.

## Conclusion

To conclude, we report the probable first case of remission of RA following COVID-19 infection. Our report merits consideration to inform wider rheumatologists as there is a potential possibility that this may occur in similar autoimmune, inflammatory diseases after infections such as COVID- 19. The pathophysiology attributed to causing the remission of an inflammatory process in patients with RA post-infection needs further evaluation. This may pave the way for understanding pathophysiological links and the development of potential newer targets for the treatment of RA. However, the evidence of worse outcome with COVID-19 in immunosuppression which is common in RA cannot be overlooked.

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