

Correspondence on 'Onset of rheumatoid arthritis after COVID-19: coincidence or connected?'

We read with great interest the letter by Derksen *et al* on 'Onset of rheumatoid arthritis (RA) after COVID-19: coincidence or connected?' in which they have conducted serology studies on 61 patients, 5 weeks after COVID-19 infection and found no increase in the incidence of anti-citrullinated cyclic peptide (anti-CCP) antibodies.¹ Also, they found that the clinical and autoantibody characteristics of three patients from another cohort with seroconversion were similar to the regular patients with RA. Based on this, they have proposed that RA after COVID-19 may be a coincidence rather than connected.

Triggering of autoimmunity by severe COVID-19 infection has been proposed² and shown by demonstration of various autoantibodies, mainly antinuclear antibodies, antineutrophil cytoplasmic antibodies and antiphospholipid antibodies (APLA), in the sera of such patients.^{3,4} Autoimmune diseases like lupus, Kawasaki disease, systemic vasculitis, APLA syndrome and reactive arthritis have been reported post COVID-19.³ Multiple arthritic manifestations of COVID-19 infection have been reported including a few cases of reactive arthritis^{5,6} and a few of seropositive RA.^{1,7,8} However, information on arthritis-related antibodies like rheumatoid factor (RF) and anti-CCP antibody are sparse.

In this correspondence, we describe a case of a 56-year-old woman who developed seropositive RA after COVID-19 infection. She is a known hypertensive since 3 years, well controlled on 5 mg of amlodipine. She was admitted at the hospital with fever, cough and dyspnoea in July, 2020. She had no prior history of smoking or joint pains. She was hypoxic and required oxygen support. Her reverse transcription- polymerase chain reaction (RT-PCR) for SARS-CoV-2 was positive and she was treated with ceftriaxone, azithromycin and discharged after a week. Two weeks after discharge, she started developing bilateral wrist joint pain and swelling followed by involvement of bilateral knees associated with morning stiffness lasting for about an hour. She was evaluated and had raised C reactive protein and erythrocyte

sedimentation rate. Her RF and anti-CCP antibodies were negative in August 2020. She was treated with short courses of steroids with intermittent relief and hydroxychloroquine for possible post-COVID reactive arthritis.

However, her symptoms persisted and she presented to us in March 2021 with pain in bilateral wrist and knee joints. This time, laboratory evaluation revealed RF titres of 131 IU/mL (normal range <10 IU/mL) and anti-CCP titres of 35 U/mL (normal <20 U/mL). Power Doppler ultrasound showed increased vascularity, synovial proliferation with erosions in bilateral wrist joints. She received intra-articular injections in both wrists with prompt relief in pain and was started on Methotrexate 15 mg/week for RA.

To the best of our knowledge, this is the sixth case of seropositive RA after a COVID-19 infection (table 1). All these patients have previously documented negative serology. This case is unique because the patient had a negative serology at the onset of arthritis, which turned positive on subsequent testing for persistent symptoms. It probably suggests an ongoing autoimmune process even after the acute infection, which triggered the autoimmunity, has subsided.

Derksen *et al* studied autoantibody characteristics of five Dutch patients who suffered from moderate to severe COVID-19 infection and presented with polyarthritis. They found anti-CCP antibodies in three of them.¹ Two other cases of seropositive RA after COVID-19 infection also had significant pulmonary involvement,^{7,8} as did our case. The serum of one out of 29 severely ill COVID-19 patients revealed anti-CCP antibodies but information on joint pain was lacking.⁴

Local airway inflammation and neutrophil extracellular trap (NET) formation has been hypothesised to drive anti-CCP production in the lungs of first degree relatives of patients with RA.⁹ NET derived proteases can cause the release of peptidylarginine deiminases (PADs) which citrullinate self proteins and are known to be pathogenic in RA. Presence of NETs have been demonstrated in COVID-19 infected postmortem lung tissue and in sera of COVID-19 patients.^{10,11} NETs and PADs have been proposed as potential therapeutic targets for COVID-19.¹² Further, viruses have been hypothesised to drive aberrant innate and acquired immune response with increased production of cytokines leading to autoinflammatory and autoimmune diseases, mainly via molecular mimicry and hyperstimulation of

Table 1 Clinical characteristics of previously seronegative patients who presented with arthritis and tested seropositive after COVID-19 infection

	Patient 1 ⁷	Patient 2 ⁸	Patient 3 ¹	Patient 4 ¹	Patient 5 ¹	Present patient
Age	60 years	67 years	67 years	49 years	65 years	56 years
Sex	Female	Male	Male	Male	Male	Female
Smoking	Not mentioned	No	No	No	Yes	Non-smoker
Hospitalisation during COVID	Not mentioned	Yes	Yes	Not during acute phase	No	Yes
Chest CT findings	Ground glassing	Not mentioned	Not mentioned	Not mentioned	Not mentioned	Ground glassing
Time between COVID and arthritis	25 days	37 days	Already present	42 days	3 days	14 days
Joints affected	Metacarpophalangeal and interphalangeal joints	Knees and hands	Both extremities	Both extremities	Upper extremities	Knees and wrists
RF	23 RU/mL	411 IU/mL	Positive- value not mentioned	Positive- value not mentioned	Negative	131 IU/mL
Anti-CCP	76 RU/mL	19.2 U/mL	Positive-value not mentioned	Positive- value not mentioned	Positive- value not mentioned	35 U/mL
Treatment	Methotrexate	Methotrexate, Methylprednisolone	Not mentioned	Not mentioned	Not mentioned	Methotrexate, Intra-articular steroid injection

CCP, citrullinated cyclic peptide; RF, rheumatoid factor.



the immune system.^{3 13} Also, it is noteworthy that the cytokines involved in severe COVID-19 and RA are common.

Hence, we believe that moderate to severe lung involvement may be a risk factor for anti-CCP antibody generation, and thereby RA, and it is probably too early to conclude that this occurrence is only by chance.

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