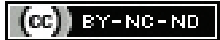


# Joint Manifestations following COVID-19 Infection- A Case Series of Six Patients

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## ABSTRACT

A rare subset of Coronavirus Disease-2019 (COVID-19) positive patients has musculoskeletal manifestations including arthritis, arthralgia, myalgia and non specific bodyaches. Moreover, postviral Reactive Arthritis (ReA) has been reported following COVID-19 infection. This article reports the characteristic joint manifestations of Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) infection in 6 out of 211 consecutive patients with laboratory-confirmed diagnosis of COVID-19 and treated at dedicated hospital. One 49-year-old female patient developed arthritis while having active COVID-19 infection, one 54-year-old male had post COVID-19 ReA, and one 48-year-old female was found to have undifferentiated arthritis. One 58-year-old female patient was initially thought to have ReA the diagnosis was reconsidered later when her symptoms resolved without any disease modifying agents. Two patients 37-year-old male and 63-year-old female, developed arthralgia following COVID-19 infection. Non Steroidal Anti-Inflammatory Drugs (NSAIDs) and steroids were found to be beneficial in the series of patients. The key point to be noted is that not all arthritis or arthralgia following COVID-19 is ReA.

**Keywords:** Coronavirus disease-2019, Postviral arthritis, Severe acute respiratory syndrome-coronavirus-2

## INTRODUCTION

The ongoing pandemic of COVID-19 caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) has affected more than thirty two crore cases across the world till mid-January 2022. Most common symptoms include fever, cough, fatigue, breathing difficulties, and loss of smell and taste [1]. At least a third of the patients remain asymptomatic.

The ReA belongs to a group of diseases called spondyloarthropathies typically causing monoarthritis or oligoarthritis that usually involves the lower limbs (ankles and knees). It is commonly preceded by a gastrointestinal (*Campylobacter*, *Salmonella* and *Shigella*) or urogenital (*Chlamydia*) infection [2,3]. A rare subset of COVID-19 patients has musculoskeletal manifestations including arthritis, arthralgia and non specific bodyache [3]. Moreover, few case reports of postviral ReA have been reported following COVID-19 infection [4-7]. This article compiles a series of six patients with musculoskeletal manifestations following COVID-19 infection.

## CASE SERIES

All the patients reported between September 1, 2020 to December 31, 2020 at a tertiary centre in Kerala, India. Overall, 211 consecutive patients with a history of COVID-19 infection were analysed for musculoskeletal manifestations during active infection and following it. Only those cases confirmed by a positive result to real-time Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) assay for COVID-19 from throat swab specimens were included in the series [8]. All patients with history of rheumatological diseases or joint disorders were excluded. Out of 211, 6 patients had musculoskeletal manifestations. The clinico biochemical parameters of the patients in present study are mentioned in [Table/Fig-1].

### Case 1

A 49-year-old female had oligoarthritis with early morning stiffness involving left knee and left ankle on the second day of admission for COVID-19 infection. Inflammatory markers were high (ESR- 92 mm/hr, CRP-204 mg/dL). Rheumatoid Factor (RF), Anti Cyclic Citrullinated Peptide (anti-CCP) and antinuclear antibody by

Immunofluorescence-ANA (IFA) were negative. X-rays of ankles and knees were normal. A possibility of acute viral arthritis was made. Along with the ongoing Dexamethasone i.v. 6 mg once daily for active COVID-19 infection, colchicine was also added. Steroids were later converted to oral on discharge after he turned seronegative (14<sup>th</sup> day) and tapered and stopped over two weeks. Oral colchicine was continued for a total of three weeks, following which patient became completely asymptomatic, and the drug was stopped.

### Case 2

A 54-year-old male with background history of hypertension developed right knee pain and swelling with early morning stiffness lasting more than 30 minutes, 3 weeks following detection of COVID-19 infection (patient was in isolation at home). Laboratory parameters showed raised Erythrocytes Sedimentation Rate (ESR) (64 mm/hr) and CRP (146 mg/dL). X-rays of knees, RF, Anti CCP and ANA were normal. A provisional diagnosis of post COVID-19 ReA was made. Synovial fluid aspiration and local steroid injection was not attempted, as patient didn't gave consent. Stat dose of i.v. Dexamethasone 4 mg was given and patient was advised to take oral etoricoxib 60 mg twice daily, daily calcium and weekly Vitamin D 60000 units. The symptoms improved significantly on a two week follow-up and was advised to continue etoricoxib 90 mg once daily. On review after four weeks he was asymptomatic and inflammatory markers normalised (ESR 22 mm/hr, CRP- 0.9 mg/dL).

### Case 3

A 58-year-old female presented with mild left knee arthritis with early morning stiffness lasting less than 30 minutes for three days duration, two weeks after recovery from COVID-19. Patient was admitted at the present facility during COVID-19 infection. Knee radiographic examinations were normal. Inflammatory markers were mildly raised (ESR - 32 mm/hr, CRP-12 mg/dL). Possibility of ReA was considered. RF and CCP were normal. Synovial fluid study couldn't be done as patient did not consent. She was given stat oral etoricoxib 60 mg and topical preparations thereafter in view of five year history of type 2 Diabetes Mellitus and high normal creatinine values (0.9 mg/dL).

Parameters	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Gender	Female	Male	Female	Female	Male	Female
Age (years)	49	54	58	48	37	63
Admission for COVID-19 and category	Yes Cat B	No Cat A	Yes Cat B	Yes Cat C	Yes Cat C	Yes Cat A
Co-morbidities	Iron deficiency anaemia	HTN	Type-II DM HTN DLP	HTN	Type-II DM	HTN DLP
Treatment during COVID-19	Dexamethasone i.v. 6 mg ODx5 days- followed by oral steroidsx10 days Tab. Colchicine 0.5 mg BDx3 weeks	Tab. Azithromycinx5 days, Multivitamins	Tab. Favipiravirx5 days Tab. Azithromycinx5 days	Dexamethasone i.v. 4 mg TDS- tapered and stopped in 2 weeks Inj. Remdesivir 100 mg ODx5 days	Dexamethasone i.v. 6 mg i.vx7 days Inj. Remdesivir 100 mg ODx5 days	Tab. Azithromycinx5 days
Latent period from COVID-19 infection to musculoskeletal symptoms	Simultaneously	3 weeks	2 weeks	2 weeks	6 days	3 weeks
Musculoskeletal involvement	Oligoarthritis left knee and ankle	Right knee arthritis	Left knee mild arthritis	Oligoarthritis bilateral knees and elbows	Oligoarthritis bilateral knees and right ankle	Polyarthralgia of small and large joints
Highest ESR (mm/hr)/CRP (mg/dL)	92/204	64/146	32/12	13/4.5	67/2	20/2.2
RF Anti CCP ANA (IFA)	Negative	Negative	Negative	Negative	RF/CCP-Negative ANA-2+ Speckled	Negative
X-rays	Normal	Normal	Normal	Early osteoarthritic changes bilateral knees	Normal	Normal
Other relevant investigations	Nil	Nil	Nil	Nil	CT Chest - Bilateral Upper lobe predominant lung fibrosis with honey combing, traction bronchiectasis and septal thickening	Nil
Treatment	Mentioned above	Dexamethasone i.v. 4 mg stat Etoricoxib 60 mg BDx2 weeks followed by 90 mg ODx4 weeks	Oral etoricoxib 60 mg stat, Topical diclofenac	Oral daily calciumx4 weeks	Tab.Prednisolone 40 mg ODx4 weeks, Tab. Hydroxychloroquine 300 mg OD	Tab.Paracetamol (SOS)
Outcome	Asymptomatic in 3 weeks	Asymptomatic in 6 weeks	Asymptomatic on 2 week review	Asymptomatic on 1 month review	Symptoms better at 1 month review	Asymptomatic in 5 days

**[Table/Fig-1]:** Clinico-biomechanical parameters of patients suffering from musculoskeletal manifestations after COVID-19.

HTN: Hypertension; DM: Diabetes mellitus; DLP: Dyslipidemia

Two weeks later on her review visit, she was completely asymptomatic. As she became completely asymptomatic without any active intervention, the possibility of ReA was considered unlikely at this stage.

#### Case 4

A 48-year-old female presented a week after recovering from COVID-19 infection with arthralgia involving bilateral elbows and knees with generalised bodyache. Laboratory parameters showed normal inflammatory markers (ESR-13 mm/hr, CRP 4.5 mg/dL). X-rays showed early osteoarthritic changes in bilateral knees. She was reassured and was sent home on oral calcium and vitamin supplements. She was asymptomatic on her 1-month revisit.

#### Case 5

A 37-year-old male, known diabetic with nephropathy, developed bilateral knee and right ankle arthritis three months after COVID-19 infection. He had high ESR of 67 mm/hr with normal CRP, normal knee and ankle X-rays. The Computed Tomography (CT) Chest showing bilateral ground glass opacities probably sequela of COVID-19, ANA 2+ speckled pattern with normal complements. The RF (8 IU/mL) and anti CCP (5 U/mL) were normal and coombs test was negative. A provisional diagnosis of undifferentiated arthritis, probably triggered by COVID-19 was made and was initiated on oral prednisolone (0.5 mg/kg/day) and hydroxychloroquine 300 mg. He is assumed to return for his follow-up visit before long and is yet to be reviewed.

#### Case 6

A 63-year-old female, had non specific generalised joint pains involving small and large joints with no objective evidence of arthritis,

two weeks following COVID-19 infection. Her inflammatory markers and X-rays were normal. She was reassured and was asked to review in case of persistent symptoms. She remained asymptomatic on follow-up after a month.

## DISCUSSION

Molecular mimicry is one among the proposed mechanisms of pathogenesis of viral associated arthritis [9]. Examples of molecular mimicry concerning SARS-CoV-2 are reported and this mechanism is hypothetically involved in the pathogenesis of both the acute systemic infection and the postinfective viral related immunological consequences [10-12]. Studies demonstrate that coronaviruses share molecular epitopes with human proteins (e.g., spike glycoprotein S) [13].

Out of 211 patients with history of SARS-CoV-2 infection, six patients developed joint manifestations. Out of six, only one patient developed ReA. One patient had arthritis during active COVID-19 infection. Two developed arthralgia following COVID-19 infection. One was diagnosed with undifferentiated connective tissue disease. Lower limb predominant oligoarticular involvement was observed to be the most common pattern of disease. None of them developed any extra-articular manifestations of ReA.

The most frequent presentation of ReA is oligoarthritis [14]. It can affect any peripheral joint, but the knee is considered to be the most involved. Axial manifestations may go under-recognised [15]. The diagnosis of ReA is established on the association of clinical and microbiological criteria [16]. Since, the emergence of COVID-19, only a few cases of post COVID-19 ReA has been published. Honge BL et al., describes about post COVID-19 reactive monoarthritis

involving right knee in a 53-year-old male [4]. He was hospitalised for 12 days due to COVID-19. Few days following discharge, he developed severe right knee monoarthritis restricting his mobility. Synovial fluid analysis revealed numerous polymorphonuclear cells with sterile cultures with elevated CRP (279 mg/L). His RF, Anti CCP, HLA B-27 was negative. He was treated with NSAIDs (Ibuprofen 400 mg thrice daily) and short course of steroids (prednisolone 25 mg) for 10 days following which he became asymptomatic.

Mukarram IG et al., describes about post COVID-19 ReA involving right knee in a 34-year-old male patient 10 days after testing positive for COVID-19 [5]. The MRI of knees showed mild joint effusion and had elevated levels of CRP and ferritin. Treatment with intra-articular steroids and 10 days with NSAIDs made him asymptomatic.

Ono K et al., reports on a 50-year-old male patient who was admitted for COVID-19 pneumonia and developed bilateral ankle arthritis and right achilles tendinitis [6]. Synovial fluid was inflammatory in nature with no growth of any organism. The RF, Anti CCP, HLA B-27 all were negative. He was diagnosed with ReA; NSAIDs and intra-articular corticosteroid injection resulted in moderate improvement.

A 73-year-old man with diabetes mellitus, hypertension, and coronary heart disease as reported by Saricaoglu EM et al., developed swelling, redness, pain, and tenderness in the left first metatarsophalangeal, proximal and distal interphalangeal joints and right second proximal and distal interphalangeal joints two weeks following onset of symptoms of COVID-19 [7]. The CRP and ferritin were markedly elevated. The RF, Anti CCP and serum uric acid levels were normal. Arthritis symptoms resolved completely with one week NSAIDs.

In the current study group and previous published case reports, post COVID-19 ReA was reported in males. The ReA patient had right knee monoarthritis as in the other two reports [4,5]. Lower limb predominant oligo or monoarthritis involving large joints was the common pattern observed except in Saricaoglu EM et al., case [7]. Inflammatory markers were elevated in all cases like in present case (CRP -146 mg/dL, ESR- 64 mm/hr). Synovial fluid study revealed inflammatory picture with negative culture in the published case reports and the authors couldn't attempt the same due to lack of consent. The RF, Anti CCP and X-rays of affected joints were normal in all the cases as in present case.

The treatment of choice for ReA caused by other pathogens is NSAIDs and glucocorticoids. In present case series, and previously reported cases [4-7], NSAIDs were employed and patients became clinically better although Mukarram IG et al., and Ono K et al., employed intra-articular steroids while Honge BL et al., used oral steroids in addition to NSAIDs [4-6]. As in present case, all patients became asymptomatic or clinically better within one to two weeks following treatment.

The course of ReA varies considerably, probably depending upon the triggering pathogen and the genetic background of the host [17]. The typical disease duration is three to five months. Most patients either remit completely or have little active disease within

6-12 months after presentation, but 15-20% may experience more chronic persistent arthritis [18]. All of our patients improved clinically and biochemical parameters also improved during our follow-up after one month. One of our patients is yet to follow-up. Currently, five out of the six patients described above are asymptomatic and not on any medications now. Considering the current scenario, the prognosis of these patients is expected to be good. This series is limited by the lack of synovial fluid analysis and HLAB27 gene testing as the patients did not consent for the same.

## CONCLUSION(S)

All joint pains following COVID-19 may not be due to ReA. Out of six patients having musculoskeletal manifestations from our 211 post COVID-19 patients, only one had ReA. He was successfully treated with parenteral steroids and oral NSAIDs. As increasing number of COVID-19 related arthritis reports are coming, further study is warranted.

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