



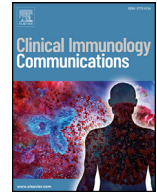
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A case of de novo seronegative inflammatory oligoarthritis associated with COVID-19 infection

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A B S T R A C T

Infection with SARS-CoV-2 (COVID-19) virus is characterized by an acute respiratory viral illness, often accompanied by extrapulmonary manifestations. Musculoskeletal symptoms such as myalgias and arthralgias are observed in 60 – 70% of cases. Inflammatory arthritis associated with SARS-CoV-2 infection has been reported in the literature, however, nearly all such cases describe a post-viral or reactive phenomenon occurring a few weeks following the infection. We report a unique case of de novo arthritis at the onset of a confirmed COVID-19 infection in a 55-year-old woman. Magnetic resonance imaging demonstrated synovial enhancement consistent with synovitis. Her disease was deemed refractory after failing several immunosuppressive agents. Lastly, we compare our patient's clinical presentation with two other similar cases to understand the natural history of this emerging syndrome.

Introduction

SARS-CoV-2 infection is frequently associated with musculoskeletal symptoms, including myalgias and arthralgias, which are prevalent in up to 60–70% of cases. Inflammatory arthritis associated with COVID-19 infection has also been reported in the literature, with nearly all cases describing a post-viral or reactive syndrome, however, de novo arthritis occurring at the onset of COVID-19 infection is not well characterized. Herein, we present a case of new onset inflammatory arthritis, its clinical course in the setting of COVID-19 infection and briefly summarize similar cases described to date.

Case report

A 55-year-old woman presented with pain, swelling and prolonged stiffness in both wrists. Additionally, she reported headaches, shortness of breath and a dry cough. Two days after the symptoms started, a SARS-CoV-2 nucleic acid amplification test (NAAT) of an upper respiratory specimen resulted positive. Previous medical problems included hypertension and obesity. Review of systems was negative for fatigue, fever, weight loss, blood in the stools, psoriatic plaques, or episodes of uveitis. All initial symptoms except for her arthritis resolved within a week. A repeat SARS-CoV-2 NAAT test was negative at Day 10. She was initially managed with non-steroidal anti-inflammatory drugs (NSAIDs) without success. During the next 8 months, her joint symptoms remained unchanged. Thus, she was referred to our rheumatology service.

Upon initial rheumatology visit, the patient's vitals were within normal limits —temperature of 97.8 F, blood pressure of 114/76 mmHg, heart rate with 97 beats per minute, and an oxygen saturation of 96% on ambient air. Her body mass index was 32.8 kg/m². Physical exam revealed decreased range of motion and significant tenderness of both wrists without overt synovitis. The remainder of the musculoskeletal exam was normal. Laboratory tests demonstrated a normal cell blood count, hepatic and renal function. Inflammatory markers revealed a C-reactive protein of 6.1 mg/L (<10 mg/L) and an erythrocyte sedimentation rate of 13 mm/h (<36 mm/h). Serologic testing was remarkable for a negative anti-nuclear antibody screen by immunofluorescence, a negative rheumatoid factor of <8.6 IU/mL (<12.0 IU/mL) by immunoturbidimetric assay and a negative anti-citrullinated peptide antibody IgG <16 U (<20 U) by immunoassay. Infectious workup showed a negative urine NAAT for *Chlamydia trachomatis* and *Neisseria gonorrhoeae*. Additionally, she was negative for Human Immunodeficiency Virus, Hepatitis C and Syphilis. Wrists plain radiographs were unremarkable. Based on the equivocal findings of synovitis with normal serology, a magnetic resonance imaging of the wrist was performed. Synovial enhancement surrounding the carpal bones confirmed the presence of synovitis (Fig. 1). At this point, a presumed seronegative inflammatory arthritis associated with COVID-19 infection was suspected.

Subsequently she was treated with low dose prednisone (10 mg daily). Unfortunately, she did not tolerate steroids due to emotional lability. She additionally underwent bilateral intra-articular corticosteroid injections of both wrists, with poor clinical response. A brief trial of hydroxychloroquine was started; however, this was discontinued upon

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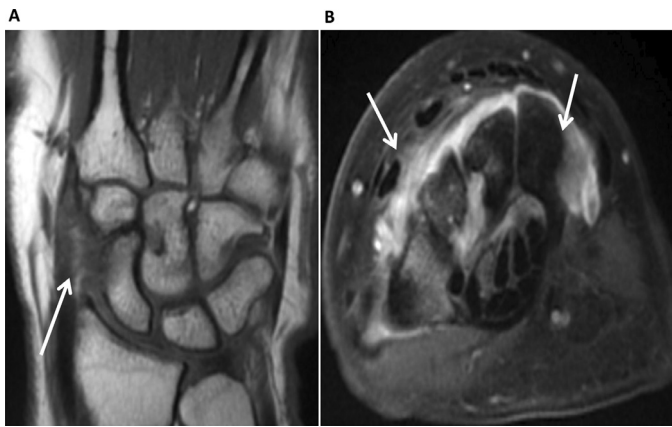


Fig. 1. Magnetic Resonance Imaging of the left wrist. (1A) T1W coronal sequence showed synovial hypertrophy and thickening (white arrow). (1B) Axial T1W fat suppressed postcontrast image at the level of carpal bones, demonstrated enhancing synovial hypertrophy along the dorsal aspect of the wrist (white arrows).

QTC prolongation. She was then switched to Methotrexate (MTX), but it was deemed ineffective after six months on a maximum dose (25 mg weekly). Repeat imaging showed unremitting wrist synovitis on ultrasound and magnetic resonance imaging. Therefore, Adalimumab (ADA) was added to MTX, yet again no significant response was observed after four months. A plan was made to initiate Upadacitinib, taper MTX and discontinue ADA. Ultimately, she discontinued the latter two immunosuppressive agents, however she later declined Upadacitinib given concern for an increase in cardiovascular risk. At her last follow up visit, two years after disease onset, arthritis remains stable with NSAID monotherapy. A repeat MRI of the wrist showed persistent enhanced synovial hypertrophy albeit with evidence of a slight improvement compared to prior images.

Discussion

Symptomatology of acute COVID-19 infection is broad, ranging from asymptomatic infection or mild flu-like illness to severe respiratory and multi-organ failure. Of interest, arthralgias are a common symptom of COVID-19 infection, however, inflammatory arthritis is infrequently observed. It is known that viral infections rarely cause arthritis, with an incidence of 1% in all viral syndromes [1]. Arthritis is generally self-limiting in nature, however, several viral illnesses, such as hepatitis C, HIV and Chikungunya virus, are known to be linked to chronic musculoskeletal symptoms [1]. While there is growing evidence about the effects of COVID-19 on patients with known rheumatic diseases, the role of SARS-CoV-2 on the development of inflammatory arthritis remains unclear [2].

Since the emergence of the pandemic, there have been numerous reports of incident inflammatory arthritis related to SARS-CoV-2 virus infection in adults. Nearly all such cases are characterized by a reactive arthritis syndrome, although de novo rheumatoid arthritis and psoriatic arthritis presenting within 3 to 4 weeks following SARS-CoV-2 infection have also been described [3].

To date, there are two other adult cases that disclosed arthritis as the initial manifestation of COVID-19 infection [4,5]. COVID-19 manifestations differed widely in all three cases but none of them reported severe disease (Table 1). Compared to our patient, the other two cases were in middle-aged men presenting with polyarthritis. The presence of autoimmunity was only found in Talarico’s case. Importantly, in contrast to our case, the other two patients had good response to initial immunosuppression. With that being said, Talarico’s patient had a relapse and Alivernini’s patient follow-up period was too short to know for certain if the arthritis resolved.

Table 1
Clinical characteristics of patients with arthritis as the initial manifestation of COVID-19 infection.

Author	Age/Sex	COVID-19 Sx	COVID-19 Rx	Type of arthritis	Serology	Arthritis Rx	Follow up period Outcome
Current case	55/F	Headache SOB Cough	Symptomatic	Oligoarthritis (wrists)	RF (-) ACPA (-) ANA/ENA (-)	NSAIDs, IA steroids, MTX, ADA	2 years Refractory
Alivernini (4)	61/M	Asthenia Anorexia Myalgia Pneumonia	Lopinavir-Ritonavir, HCQ	Polyarthritis (Knee, NR)	RF (-) ACPA (-)	NSAIDs, Baricitinib, Systemic steroids	12 days Improvement
Talarico (5)	45/M	Anosmia Dysgeusia Myalgia	Symptomatic	Polyarthritis (MCP, PIP, wrist)	RF (-) ACPA (+)	Systemic steroids	2 months Remission-Relapsed

F: female; M: male; NR: not reported; HCQ: hydroxychloroquine; RF: rheumatoid factor; ACPA: anti-citrullinated peptide antibody; ANA: antinuclear antibody; ENA: extractable nuclear antigens, MTX: methotrexate; ADA: Adalimumab; IA: intra-articular; MCP: metacarpophalangeal; PIP: proximal interphalangeal; Sx: symptoms; Rx: Treatment.

Conclusion

In summary, we detailed the case of a patient who presented with de novo inflammatory arthritis at the onset of COVID-19 infection. Although there have been two other cases reported in the literature, our case mainly differs in its oligoarthritis presentation, protracted course and lack of clinical response to multiple immunosuppressive agents. These early reports of de novo arthritis add to the growing body of literature regarding the association between new onset inflammatory arthritis and COVID-19 infection, highlighting the need for further investigation into the mechanisms at play, as the response to immunosuppressive drugs may vary compared to other forms of inflammatory arthritides.

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Declaration of Competing Interest

None

Data Availability

No data was used for the research described in the article.

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