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CASE REPORT

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Acute arthritis following SARS-CoV-2 infection: About two cases

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Key Clinical Message

Joint involvement in COVID-19 may occur at different stages of the disease and maybe represented by non-specific arthralgia or by acute arthritis. We report two cases of COVID-19 infection that were complicated by postviral reactive arthritis. Case 1: A 47-year-old male was presented 20 days after a COVID-19 infection with acute right knee arthritis. On biologic data, erythrocyte sedimentation rate and C-reactive protein were normal, and immunologic data were negative. A joint puncture was performed showing a turbid fluid. Testing for microcrystals was negative, as well as the synovial fluid culture. An infectious investigation was conducted, which was negative. The patient's complaints improved significantly, with analgesics and non-steroidal anti-inflammatory drugs (NSAID). Case 2: A 33-year-old female presented with acute left knee arthritis evolving for 48 h, free of fever, after a COVID-19 infection treated 15 days ago. On examination, besides knee arthritis, the osteoarticular examination was normal. A biological inflammatory syndrome was noted in laboratory tests. A yellow fluid with multiple PNN was detected in the joint fluid aspiration, with a negative culture. The patient was treated by analgesics and NSAID. The follow-up was highlighted by the arthritis resolution. Conclusion: Both of our cases are consistent with what has already been reported in the literature confirming the development of PostCOVID arthritis and strengthen the impending necessity of wider studies to identify rheumatologic manifestations in the short- and long-terms after surviving COVID-19.

KEYWORDS

acute arthritis, COVID-19, reactive arthritis, SARS-CoV2

1 | INTRODUCTION

In December 2019, COVID-19 infection was first reported as a pneumonia cluster from Wuhan, China, but quickly emerged to many countries worldwide, so that the World Health Organization (WHO) declared the disease as a pandemic in March 2020.[1,2] This pandemic has taken a heavy toll on the healthcare system across the world.[2]

The clinical course of COVID-19 is heterogeneous, but fever, dry cough, interstitial pneumonia, fatigue,

headache, and loss of taste and smell are the most frequently described symptoms.[3] Severity of clinical presentation also varies, while the majority of patients with COVID-19 have a favorable outcome, some develop severe pneumonia eventually leading to acute respiratory distress syndrome (ARDS) and respiratory failure,[4] requiring assisted ventilation in intensive care units in up to 12% of patients.[5]

Although much is known about acute manifestations of COVID-19, less has been reported about the evolution of the disease and the development of postinfectious complications. COVID-19 can lead to a wide variety of complications affecting pulmonary, neurological, cardiovascular, rheumatological, dermatological, and many other systems.[6] There are reports of several postinfection complications with COVID-19 including reactive arthritis (RA).[7–11] Joint involvement in COVID-19 may occur at different stages of the disease and may be represented by nonspecific arthralgia or by acute arthritis, as could happen in other viral diseases.[12] We report two cases of COVID-19 infection that were complicated by postviral ReA.

2 | CASE PRESENTATION 1

A 47-year-old male with a history of allergic asthma, osteomyelitis of the left lower third leg treated with an external fixator on April 2019, and a left bi-malleolar fracture that was orthopedically treated, 3 years ago. Twenty days before consultation, the patient was hospitalized in COVID unit of Taher Sfar University Hospital for management of COVID-19 infection. He had symptomatic treatment (oxygen therapy) with a favorable outcome. On 16th of October 2021, the patient was presented to the emergency department with acute right knee arthritis leading to significant functional impotence, impairing the ability to walk (Figure 1), and occurring in a context of apyrexia. He did not report a personal or familial history of chronic rheumatism or psoriasis. He denied any recent history of physical trauma, any extra conjugal sexual relationship, or infectious symptom such as dyspnea, odynophagia, or urine symptoms. The patient did not report any previous episode of arthritis, dactylitis, conjunctivitis, or uveitis nor inflammatory diarrhea. On biologic data, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were in the normal ranges (10 mm and 6 mg/L, respectively), so was the serum uric acid. Immunologic data were negative including antinuclear anti-bodies (ANA), rheumatoid factor (RF), anti-citrullinated peptide anti-bodies (ACPA). Knees, hip, feet, and hands X-rays in front and lateral views were normal without erosions or intra-articular calcifications. A joint puncture was performed showing a turbid fluid with 1500 white cells/mm^3, 60% of which were neutrophils (PNN) (Figure 2). Testing for microcrystals was negative, as well as the synovial fluid culture. An infectious investigation was conducted, including cardiac ultrasound, chest X-ray, urine cytobacteriological examination (UCE), blood cultures, Wright serology (for brucellosis infection) and viral serologies (B and C hepatitis, CMV, EBV, and VIH), PCR (real-time polymerase chain reaction) for coronavirus, as well as a tuberculosis assessment, and all of which were negative. The patient's complaints improved significantly, after immobilization and ice application associated with analgesics and nonsteroidal anti-inflammatory drugs.

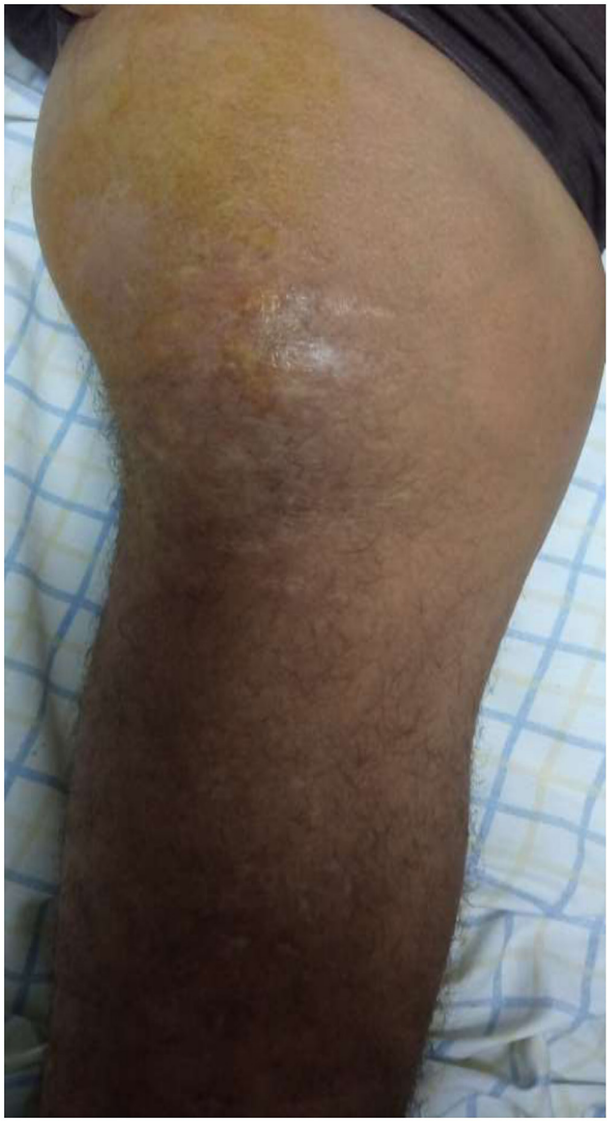

FIGURE 1 A picture of the swollen right knee of the first case.

3 | CASE PRESENTATION 2

A 33-year-old female with no previous history, who presented to the emergency department, on September 1,

FIGURE 2 A Picture of the aspirated joint fluid.

2021, with acute left knee arthritis evolving for 48 h, free of fever, with prolonged morning stiffness (more than 1 h). Symptoms hindered the patient's daily activities, reduced her walking perimeter and disturbed her sleep quality. Symptoms that occurred after a COVID-19 infection treated 15 days ago in ambulatory with a favorable course. On examination, there was no fever, and besides knee arthritis, the osteoarticular examination was normal particularly the spine, sacroiliac, and hip joints. There were no another extra-articular manifestation orienting toward rheumatic or autoimmune diseases particularly the systemic lupus erythematosus (SLE), spondyloarthritis (SpA), and Behcet disease (BD). A biological inflammatory syndrome was noted in laboratory tests with an ESR of 28 mm and a CRP of 18.6 mg/L. The knees, hip, feet, and hands X-rays in front and profile incidence were normal. A yellow fluid with multiple PNN was detected in the joint fluid aspiration, with a negative culture. PCR for coronavirus was negative, so was the infectious investigation. Diagnosis of SpA, SLE, and BD was eliminated by normal clinical examination, X-Rays, pelvis MRI, and immunologic investigations (ANA, RF, and ACPA). The patient was treated by analgesics and anti-inflammatory drugs. The follow-up was highlighted by the arthritis resolution in 3 weeks and the negativity of inflammation markers (ESR and CRP).

4 | DISCUSSION

The occurrence of postinfective and para-infectious arthritis following viral infection is not uncommon, but with the current pandemic, the incidence has increased.[6] The spectrum of musculoskeletal complaints associated with viral infection can range from mild arthralgia to chronic arthritis.[13]

Joint involvement in SARS-CoV-2 infection may occur at any time during the course of infection.[14] It may be an initial symptom of the infection, emerge during the acute phase (sometimes during hospitalization), or occur after recovery.[14] Coronaviruses generally appear to cause arthralgias and myalgias rather than true inflammatory arthritis.[15] Arthralgias are reported in 15% of COVID-19 patients, and myalgias in 44% of patients.[13] PCA, which was previously reported in October 2020 during the first wave of the COVID pandemic, has been well established as a clinical entity requiring medical attention.[16] Several clinical forms of PCA have been described.[17–19] It may present with mono- or oligoarticular involvement; however, clinical and epidemiological data of PCA indicate that monoarthritis was the most common form of involvement, with prominent involvement of the lower extremity joints.[17] The most frequently affected joints are the knee, ankle, and proximal interphalangeal joint[17] and such was the case in our patients, whose knee joint was affected. PCA is often diagnosed in young adults between the ages of 18 and 40 years,[20] such was the case with our 33-year-old female patient. The incidence of PCA is high in the male population.[17] The lag time between SARSCoV2 infection and arthritis onset varied between cases, usually, starting some days or a few weeks after the resolution of other infection manifestations and usually during the healing period (median: 18 days)[21] similar to that noted in both our patients, whose arthritis onset delay was, respectively, of 20 and 15 days. The predisposing factors for developing joint involvement following SARS-CoV-2 infection are still unknown, but in reviewing the literature, it appears that the virus' prolonged persistence, as evidenced by prolonged positivity of nasopharyngeal swabs for SARS-CoV-2, and its spread from the respiratory tract to other sites, including the gastrointestinal tract, could locally activate immunological and inflammatory pathways, and lead to the development of arthritis in some patients.[22]

Although different mechanisms have been suggested in the etiopathogenesis of virus-induced arthritis, the exact mechanisms by which COVID-19 could cause joint inflammation are only partially understood.[23] For a long time, it was assumed that SARS-CoV-2 infection resulted

in macrophage stimulation, which in turn caused the release of high levels of cytokines and chemokines that enhanced the inflammatory process.[23] Previous and current studies demonstrate that coronaviruses share molecular epitopes with human proteins (e.g., spike glycoprotein S) that play a key role in host cell invasion and evade immune response attacks, conferring immune invasive capacity to the infectious agent.[24] This molecular mimicry appears to be most prominent,[25] by triggering humoral and cellular self-reactivity in the host at the end of the process by which the epitope interacts between a viral agent and the host,[26] and it is well known to be responsible for eliciting autoimmune responses in susceptible individuals.[27] And this mechanism may be involved in the pathogenesis of acute systemic infection and virus-related post-infection immunological consequences.[28] Mimetic epitopes may also be present in the synovial membrane and cause acute local inflammation through similar pathways.[28] Other suggestive examples of diseases induced by molecular mimicry after COVID-19 come from recent publications reporting cases of Guillain-Barre and Miller Fisher syndrome.[29,30]

Other theories suggest that circulating immune complexes or a possible localization of the virus directly on the joint tissues are involved.[31] However, RT-PCR for the detection of SARS-CoV2 nucleic acids did not show that the virus was present in synovial fluid, validating the hypothesis of an immune-mediated process.

Given the worldwide frequency of COVID-19 and the large affected population, the number of reported PCA is small.[32] A credible justification for the lower incidence of musculoskeletal inflammation is COVID-19 treatment with corticosteroids, which likely attenuated the musculoskeletal manifestations.[32] Although hydroxychloroquine is ineffective for treating COVID-19, it has been shown to be effective in the management of systemic rheumatological diseases, especially with inflammatory joint involvement.[33] Most reported PCA cases show a prompt and complete response to nonsteroidal anti-inflammatory drugs, and this was also the case in our patients. Treatment duration can be extended for 2–4 weeks, as with other viral arthritis. However, steroid treatment is occasionally needed, and is preferred by intra-articular injection (in case of mono-oligoarticular involvement). In a few cases, systemic steroid is necessary, but generally for short periods.[34] Only a few cases of PCA have required immunosuppressive drugs (methotrexate and sulfasalazine).[35] Some patients with joint manifestations and severe lung involvement, as part of a hyperinflammatory syndrome, have been treated with IL-6 inhibitors or Jak inhibitors, with significant improvement in both lung and joint manifestations.[36]

In conclusion, as the number of patients recovering from COVID-19 increases, more and more data on postinfectious complications will emerge. Various autoimmune and rheumatic diseases have been reported in COVID-19 survivors. COVID-19 can also cause flare-ups of preexisting rheumatic diseases. Both of our cases are consistent with what has already been reported in the literature confirming the development of PCA and strengthen the impending necessity of wider studies to identify rheumatologic manifestations in the short- and long-terms after surviving COVID-19. Follow-up in the coming months will help to determine the chronicity of these inflammatory conditions. A better understanding of the immune consequences that accompany SARS-CoV-2 infection is required both to determine the immunopathogenic mechanisms capable of promoting or contrasting the development of rheumatic manifestations, and to adequately deal with such a complication.

AUTHOR CONTRIBUTIONS

Mouna Brahem: Conceptualization; methodology; supervision; validation; writing – original draft. **Olfa Jomaa:** Conceptualization; data curation; formal analysis; investigation; methodology; project administration; resources; software; visualization; writing – original draft; writing – review and editing. **Sondess Arfa:** Supervision; validation. **Rihab Sarraj:** Resources; software. **Ramy Tekaya:** Resources; software. **Olfa Berriche:** Supervision; validation. **Haifa Hachfi:** Supervision; validation. **Mohamed Younes:** Supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data openly available in a public repository that issues datasets with DOIs.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

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