Review

Post-COVID-19 Arthritis and Sacroiliitis: Natural History with Longitudinal Magnetic Resonance Imaging Study in Two Cases and Review of the Literature

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Abstract: Severe acute respiratory coronavirus-2 syndrome (SARS-CoV-2) is a well-known pandemic infectious disease caused by an RNA virus belonging to the coronaviridae family. The most important involvement during the acute phase of infection concerns the respiratory tract and may be fatal. However, COVID-19 may become a systemic disease with a wide spectrum of manifestations. Herein, we report the natural history of sacroiliac inflammatory involvement in two females who developed COVID-19 infection with mild flu-like symptoms. After the infection they reported inflammatory back pain, with magnetic resonance imaging (MRI) studies showing typical aspects of sacroiliitis. Symptoms improved with NSAIDs therapy over the following months while MRI remained positive. A literature review was performed on this emerging topic. To our knowledge, this is the first MRI longitudinal study of post-COVID-19 sacroiliitis with almost one year of follow-up. Predisposing factors for the development of articular involvement are unclear but a long-lasting persistence of the virus, demonstrated by nasopharyngeal swab, may enhance the probability of altering the immune system in a favourable background.

Keywords: sacroiliitis; arthritis; COVID-19; post-COVID-19 manifestations

1. Introduction

In December 2019, a new type of pneumonia emerged, caused by COVID-19, a member of coronaviridae family. The initial outbreak took place in Wuhan, but rapidly diffused worldwide, such that the World Health Organisation (WHO) declared the disease a pandemic in March 2020 [1–4].

Compared to the previous severe acute respiratory syndrome-related coronavirus (SARS-CoV) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV), SARS-CoV-2 is much more transmissive and dangerous, with a wide spectrum of systemic manifestations besides respiratory symptoms [1,2,5,6].

The disease caused by SARS-CoV-2 is often characterised by a dry cough, fever, dyspnoea, fatigue, general malaise, anosmia, ageusia, a sore throat, diarrhoea, nausea and vomiting. However, other symptoms have been reported in the literature [1,5–12].

Regarding articular involvement, some cases of arthritis have been described after SARS-CoV-2 infection, as could happen in other viral diseases, but further studies and long-term follow-up are required [13–39].
Articular involvement in COVID-19 can occur in different stages of the disease and it may be represented by non-specific arthralgia or by acute arthritis. These manifestations generally respond to non-steroid anti-inflammatory drugs (NSAIDs), but sometimes steroid treatment is required [15,16,23].

Sometimes patients can develop other musculoskeletal symptoms and signs, such as enthesitis, tenosynovitis or dactylitis [13–18,20–22,24,27,29–39]; isolated reactive inflammatory sacroiliac involvement after COVID-19 has been rarely recorded.

2. Case Reports

Herein, we report the natural history and long-term follow-up of two cases of sacroiliitis that developed after COVID-19 infection. They were two females aged 58 and 53, both working as healthcare professionals in a nursing home with old patients. They developed SARS-CoV-2 infection in March 2020 after work exposure, and were referred to our Rheumatologic Clinic for musculoskeletal symptoms such as inflammatory joint pain and myalgia, which started shortly after SARS-CoV-2 infection.

Demographic/clinical characteristics are illustrated in Table 1, while Table 2 describes laboratory tests at SARS-CoV-2 infection diagnosis and during the patients’ follow-up.

Finally, complete magnetic resonance imaging (MRI) follow-up is shown in Figures 1 and 2 for case report 1 and 2, respectively.

Table 1. Demographic and clinical characteristics of the two patients with reactive sacroiliitis post COVID-19 infection.

| Feature                                      | Patient 1                      | Patient 2                      |
|----------------------------------------------|-------------------------------|-------------------------------|
| Age, year                                    | 58                            | 53                            |
| Gender                                       | Female                        | Female                        |
| Comorbidity                                  | Autoimmune hypothyroidism     | Autoimmune hypothyroidism     |
| First COVID-related symptoms                 | End of March                  | End of March                  |
| First sacroiliitis symptoms                  | End of April                  | End of April                  |
| Improvement of peripheral pain and inflammatory back pain | End of May                  | End of May                  |
| Nasopharyngeal SARS-CoV-2 POSITIVE buffer (date, month/day) | 03/27, 04/04, 04/07, 04/17 | 03/27, 04/10, 04/17 |
| Nasopharyngeal SARS-CoV-2 NEGATIVE buffer (date) | 04/24, 04/28, 05/12, 05/19   | 04/24, 04/28, 05/12, 05/19   |
| Drugs for the infection                      | HCQ and azithromycin          | HCQ and azithromycin          |
| Treatment of the sacroiliitis                | NSAIDs                        | NSAIDs                        |
| Clinical outcome                             | Recovery                      | Recovery                      |
| First MRI                                    | June 2020, bilateral sacroiliitis | June 2020 unilateral sacroiliitis |
| Second MRI                                   | July 2020, bilateral sacroiliitis | July 2020 unilateral sacroiliitis |
| Third MRI                                    | January 2021, bilateral sacroiliitis | February 2021, unilateral sacroiliitis |

Legend: NSAID, non-steroidal anti-inflammatory drug; HCQ, hydroxynochomique; MRI, magnetic resonance imaging.
Table 2. Laboratory features at sacroiliitis diagnosis and during follow-up at our centre.

| LABORATORY FEATURES                      | Patient 1                  | Patient 2                  |
|------------------------------------------|----------------------------|----------------------------|
|                                           | First Visit (June 20)      | Second Visit (July 20)     | Last Visit (March 21) | First Visit (June 20) | Second Visit (July 20) | Last Visit (March 21) |
| Serology (UA/mL)                         | IgG 65.4 UA/mL             | IgG 75 UA/mL, IgM          | ND                     | IgG 32.2 UA/mL, IgM 1.9 UA/mL | IgG 17.3 UA/mL, IgM 0.9 UA/mL | ND |
| (Negative < 8; Borderline 8–12; Positive > 12) | IgM 2.76 UA/mL             | ND                         | ND                     | ND                     | ND                     | ND |
| Fibrinogen, mg/dL (normal range 180–380) | 248                        | 295                        | 250                    | 272                    | 406                    | 247 |
| CRP, mg/L (normal range 0–5.00)          | 1.20                       | 2.24                       | 1.41                   | 1.49                   | 4.56                   | 2.61 |
| IL1 beta, pg/mL (normal range < 0.001)   | 0.                         | 0.                         | ND                     | 0.                     | 0.                     | ND |
| IL6, pg/mL (normal range < 7)            | 0.9                        | 2                          | 2                      | 1.3                    | 2                      | 2   |
| IL2R, pg/mL (normal range 440–1435)      | 1346                       | 1446                       | ND                     | 904                    | 835                    | ND |
| IL8, pg/mL (normal range 6.7–16.2)       | 12.6                       | 13.9                       | ND                     | 19.2                   | 53                     | ND |
| IL10, pg/mL (normal range 1.8–3.8)       | 1.8                        | 2                          | ND                     | 2.1                    | 2                      | ND |
| TNF alpha, pg/mL (normal range 7.8–12.2) | 8.9                        | 13.2                       | ND                     | 11                     | 66                     | ND |
| IFN gamma, pg/mL (normal range < 0.99)   | 0.                         | 1.3                        | ND                     | 0.                     | 0.                     | ND |
| IP10, pg/mL (normal range 37.2–222)      | 112                        | 127                        | ND                     | 90.6                   | 96                     | ND |
| Haemoglobin, g/dL                        | 13.7                       | 13.4                       | 13.9                   | 13.8                   | 13.1                   | 13.3 |
| Leucocyte count, cell/mm³                | 3970                       | 4050                       | 4400                   | 3960                   | 4970                   | 5070 |
| Platelet count, cell/mm³                 | 197,000                    | 223,000                    | 202,000                | 321,000                | 305,000                | 357,000 |
| Antinuclear antibody (ANA)               | Negative                   | ND                         | Negative               | Negative               | Negative               | ND |
| Anti-SSA/SSB                             | Negative                   | ND                         | Negative               | Negative               | Negative               | ND |
| Rheumatoid factor (RF)                   | Negative                   | ND                         | Negative               | Negative               | Negative               | ND |
| CPK, IU/L (normal range 26–170)          | 187                        | 266                        | 171                    | 101                    | 147                    | 102 |

Legend: CRP, C-reactive protein; IL, interleukin; IL2R, interleukin 2 receptor; IFN, interferon; TNF, tumour necrosis factor; IP10, human interferon inducible protein 10; CPK, creatine phosphokinase; ND, not done.
Figure 1. Case report 1. Persistent MRI findings suggestive of bilateral active sacroiliitis in a 58-year-old patient with lower back pain. On the first MRI examination, subchondral bone marrow oedema at the iliac side of both sacroiliac joints was found, appearing as band-like hyperintensity on short-tau-inversion recovery (STIR) T2-weighted semi-coronal image (arrows in (a)) with corresponding hypointensity on turbo-spin-echo (TSE) T1-weighted semi-coronal image (b). Oedema was found to persist at a second MRI examination performed one month later (c,d), and increase after six more months (e,f), especially on STIR T2-weighted image (arrows in (e)).

Figure 2. Case report 2. Persistent MRI findings of unilateral active sacroiliitis in a 53-year-old woman with lower back pain. At the time of first MRI examination, subchondral bone marrow oedema at the iliac side of the left sacroiliac joint was observed, appearing as band-like hyperintensity on short-tau-inversion recovery STIR T2-weighted semi-coronal image (arrow in (a)) with corresponding hypointensity on turbo-spin-echo TSE T1-weighted semi-coronal image (b). Oedema was found to persist at subsequent MRI examinations performed after one month (c,d) and six months (e,f).
2.1. Case Report 1

At the end of March 2020, a 58-year-old woman complained of a dry cough without dyspnoea or fever and tested positive for a SARS-CoV-2-nasopharyngeal swab on March 27. She repeated the nasopharyngeal swab test several times until the first negative result, which occurred on April 24. Because of persistent positive swabs, she was treated with HCQ and azithromycin; on May 22 the patient performed a SARS-CoV-2 serological test showing negative IgM and slightly positive IgG, with limited sensibility and specificity. The patient suffered from autoimmune hypothyroidism treated with levothyroxine without other chronic therapy. She had no familial history for rheumatologic diseases, psoriasis or IBD.

At the end of April, she complained of inflammatory arthralgia and myalgia, especially in both shoulder and pelvic girdles, and bilateral buttock pain (right > left) with persistent dry cough. The patient reported that inflammatory pain was slowly and spontaneously improving from the end of May 2020 in the absence of chronic NSAID administration or other drugs.

At the end of May, upon physical examination she had bilateral sacroiliac joint pain without peripheral joint tenderness or swelling and no evocable tender points. Chest and abdominal examinations were normal.

Blood samples showed no inflammation and a mild elevation of CPK.

Extensive laboratory tests were performed, including cytokine profile, which did not provide further information regarding systemic inflammation (Table 1). Autoantibodies were negative. The patient presented HLA-B8 and -B57, while HLA-B27 was negative. The first MRI of shoulders and pelvic girdle (20 June 2020) showed bilateral sacroiliitis with bone marrow oedema, particularly on the left side (Figure 1a,b). Neither signs of bone damage nor alterations of the muscles were found.

In July 2020, the repeated MRI showed the same alteration as the first one (Figure 1c,d). She reported further improvement in articular and muscle pain but persistence of the same inflammatory back pain and at the clinical examination of sacroiliac joints, tenderness was still present.

Serological test for SARS-CoV2 was repeated, showing positive IgG and borderline IgM.

Blood samples were also repeated and no inflammation was found, but a mild elevation of CPK was confirmed. Serum cytokine profile was substantially normal, showing only a very mild increase in IL2R and TNF alpha at the second follow-up visit.

Because of sacroiliac joint pain, NSAIDs therapy was started in July for 10 days.

She was evaluated again in November 2020, reporting clinical recovery with only use of NSAIDs as needed.

MRI was repeated in January 2021 and it showed increased bone marrow oedema of the sacroiliac joints (Figure 1e,f). On physical examination, the patient still complained about mild low back pain. She continued to sporadically use NSAIDs, as needed. Blood tests showed no inflammation and normalisation of CPK.

2.2. Case Report 2

A 53-year-old female, working as a healthcare professional in the same nursing home as the previous patient, developed a dry cough without fever at the end of March 2020 and tested positive after repeated SARS-CoV-2 nasopharyngeal swabs (the first on March 27). She was treated with HCQ and azithromycin with the first negative result of the swab on April 24. A SARS-CoV-2 serological test performed on May 2020 showed negative IgM and slightly positive IgG.

In the middle of April, she developed very similar symptoms to her colleague, with a polymyalgic symptoms associated with inflammatory back pain.

In May, blood tests showed mild systemic inflammation (CRP 19 mg/L, normal values below 5 mg/L) and CPK elevation (412 IU/L), but they normalised one month later. Serum cytokine profile revealed only a very mild increase in IL8 at the first follow-up visit.

She stated that these symptoms were gradually and spontaneously improving from the end of May without any treatment. On clinical examination she had mild tenderness of
the sacroiliac joints. At the MRI performed on June 3rd, bone marrow oedema suggestive of sacroiliitis was found (Figure 2a,b). Serologic test for SARS-CoV-2 showed positive IgG and negative IgM. After blood tests, no inflammation was found, with normalisation of CRP and CPK. Considering the patient’s symptoms and MRI findings, NSAIDs therapy was initiated with subjective improvement. She repeated the MRI on July 3rd and it was unchanged (Figure 2c,d).

At the examination in November 2020, she was using NSAIDs occasionally. At the follow-up in January 2021 she reported mechanical low back pain and occasional use of NSAIDs, with mild tenderness of the sacroiliac joints upon physical examination; the MRI performed on February 2021 showed unchanged bone oedema and blood tests were normal (Figure 2e,f).

3. Materials and Methods

We conducted a PubMed search utilising the keywords “post-COVID-19 arthritis”, “post-COVID-19 sacroiliitis”, “reactive arthritis”, “reactive sacroiliitis”, “acute sacroiliitis”, “post-COVID-19 manifestations” and “post-COVID-19 rheumatic diseases”. About one hundred articles were evaluated and the most relevant were reviewed with more attention; significant data pertinent to the aim of our study were extracted and organised. In particular, the most significant articles were represented by reviews concerning reactive arthritis, post-viral arthritis, acute sacroiliitis and post-COVID-19 rheumatologic manifestations; case reports about post-COVID-19 arthritis were also considered.

Serum IL-6 (pg/mL) was measured by CE-IVD electrochemiluminescence immunoassay (Elecsys IL6, Cobas, Roche, Basel, Switzerland; physiological range < 7 pg/mL). All other soluble factors were quantified in the same sera of patients with a magnetic bead-based multiplex assay (Bio-Plex Pro™ Custom Human Cytokines and Chemokine Panel, procarta-Plex, Bio-Rad Laboratories, Hercules, California) according to the manufacturer’s instructions. All dosages were obtained in sera stored in aliquots at −80 °C.

4. Results

Case reports of supposed SARS-CoV-2-related arthritis are summarised in Table 3 [13–18,20–22,24,27,29–33,36–38].

We also included in our review case reports from Novelli and Baimukhamedov [34,35]. The first described the case of a 27-year-old woman who developed psoriatic spondyloarthritis triggered by SARS-CoV-2 infection. The patient developed peripheral arthritis and mild bilateral sacroiliitis confirmed on MRI; she was HLA-B27 negative and had a family medical history of psoriasis [34]. Baimukhamedov et al. reported the development of chronic arthritis, which fulfilled the classification criteria for seropositive rheumatoid arthritis, one month after COVID-19 infection [35].

Table 3 describes the characteristics of 19 cases, 12 males and 7 females, who were diagnosed as affected by SARS-CoV-2-related arthritis, without fulfilling the classification criteria for other arthritis.

The onset of the articular symptoms occurred two to four weeks after the infection in the majority of cases, while in two cases articular symptoms rose concomitantly to the diagnosis of COVID-19. The pattern of arthritis was usually mono-oligoarticular, mainly in the lower limbs (11/19), was polyarticular in 6/19 cases, one case had only extensor tendonitis of the right hand and another patient developed COVID-19-related dactylitis. Synovial fluid was negative for crystals. Autoantibodies, rheumatoid factor and antinuclear antibody were negative in all patients in whom these analyses were performed. HLA B27 was positive in one case.

Imaging study was not available in all patients. Five patients were evaluated by X-rays which revealed no erosions in all, while five patients were evaluated by ultrasound (US), which revealed synovitis, and three patients were studied by MRI, which showed signs of inflammation.
Table 3. Case reports of SARS-CoV-2-related arthritis.

| Sex and Age | Onset | Articular Involvement | SF Analysis | Presence of Crystals | SF Culture | RF and/or ACPA | ANA | HLA-B 27 | Synovial Biopsy | Imaging | Therapy | Outcome |
|-------------|-------|-----------------------|-------------|----------------------|------------|----------------|------|----------|----------------|---------|----------|---------|
| Talarico et al., 2020 [13] | M 45 | at COVID-19 diagnosis | polynuclear (bilateral MCP and PIP, right wrist) | yes | no | neg | neg | NA | NA | US: slight effusion of the involved joints | oral steroid treatment | arthritis after steroid suspension |
| Gasparotto et al., 2020 [14] | M 60 | 32 days after COVID-19 diagnosis | right knee and ankle | yes | no | neg | neg | neg | neg | NA | oral NSAIDs | recovered |
| Liew et al., 2020 [15] | M 47 | at COVID-19 diagnosis | right knee | yes | no | (neg GRAM stain) | neg | NA | NA | NA | X-rays: no erosion | oral NSAIDs and intra-articular steroid | long-term data not available |
| Yokogawa et al., 2020 [16] | M 57 | 15 days after diagnosis | right knee | yes | no | NA | neg | neg | neg | neg | NA | oral NSAIDs recovered |
| Di Carlo et al., 2020 [17] | M 55 | 4 weeks after COVID-19 infection | right ankle, subtalar joint synovitis | NA | NA | NA | NA | NA | NA | US: subtalar joint synovitis | oral steroid treatment | recovered |
| Ono et al., 2020 [18] | M 50 | 21 days after COVID-19 diagnosis | left and right ankle | yes | no | neg | NA | neg | neg | neg | NA | X-rays: no erosion | oral NSAIDs and intra-articular steroid | oral NSAIDs recovered |
| Jali et al., 2020 [19] | F 39 | 3 weeks after infection | DIP and PIP bilateral hands | NA | NA | NA | neg | neg | NA | NA | X-rays: normal MRI inflammation around the extensor involved | topical NSAIDs, oral opioid gabapentin | improvement without complete recovery, long-term data not available |
| Danssaert et al., 2020 [20] | F 37 | 12 days after COVID-19 diagnosis | tenosynovitis of the II, III, IV right hand extensor | NA | NA | NA | neg | neg | NA | NA | US: slight effusion of the involved joints | oral NSAIDs and oral prednisolone | recovered |
| Fraga et al., 2020 [21] | F 41 | 4 weeks after COVID-19 symptoms | polynuclear (small joints of the right hand) | NA | NA | NA | neg | neg | NA | NA | oral NSAIDs and oral prednisolone | recovered |
| Langhoff Hønge et al., 2020 [22] | M 53 | 4 days after hospital discharge for severe respiratory insufficiency | polynuclear (right knee bilateral ankles, lateral side of the left foot) | yes | no | neg | NA | neg | NA | NA | X-rays: fluid accumulation on the right knee | oral NSAIDs and oral prednisolone | recovered |
| Saricaoglu et al., 2020 [23] | M 73 | subacute | left I MTP, PIP, right II PIP, DIP | NA | NA | NA | neg | neg | NA | NA | X-rays: no erosion | oral NSAIDs | recovered |
| Parisi et al., 2020 [24] | F 58 | 25 days after COVID-19 symptoms | ankle arthritis | NA | NA | NA | neg | neg | neg | NA | oral NSAIDs | recovered |
| Alivernini et al., 2020 [25] | M 61 | at COVID-19 diagnosis | polynuclear | yes | no | NA | neg | neg | NA | Inflammatory infiltrates in the synovia | US: synovitis | baricitinib and oral prednisolone | recovered |
| De Stefano et al., 2020 [26] | M 30 | 10 days post COVID-19 symptoms | right elbow | yes | no | NA | neg | neg | NA | US: synovitis PD+ | oral NSAIDs | recovered |
Table 3. Cont.

| Sex and Age | Onset | Articular Involvement | SF Analysis | Presence of Crystals | SF Culture | SF RT-PCR for SARS-CoV2 | RF and/or ACPA | ANA | HLA-B 27 | Synovial Biopsy | Imaging | Therapy | Outcome |
|-------------|-------|-----------------------|-------------|----------------------|------------|-------------------------|---------------|-----|---------|-----------------|----------|----------|---------|
| Schenker et al., 2020 [32] | F 65  | 10 days after COVID-19 symptoms cessation | polyarticular (bilateral ankles, knee and wrists joints) | NA | NA | NA | neg | neg | pos | NA | NA | prednisolone | immediate steroid response, follow-up not available |
| Salvatierra et al., 2020 [33] | F 16  | 3 weeks after COVID-19 symptoms | IL, IV and V left toes dactylitis | NA | NA | NA | neg | neg | neg | NA | NA | oral NSAIDs | recovered |
| Shokraee et al., 2021 [36] | F 58  | 2 weeks after COVID-19 symptoms initiation | right hip | NA | NA | NA | NA | NA | NA | NA | NA | oral NSAIDs and prednisolone | recovered |
| Cincinelli et al., 2021 [37] | M 27  | 2 weeks after COVID-19 diagnosis | I MCF | NA | NA | NA | NA | NA | NA | NA | NA | oral NSAIDs | recovered |
| El Hashami et al. (case 2) [38] | M 57  | One month after COVID-19 infection | left wrist | NA | NA | NA | neg | neg | pos | NA | MRI: wrist synovitis | oral prednisolone and oral NSAIDs | recovered |

Legend: M, male; F, female; SF, synovial fluid; RF, rheumatoid factor; ACPA, anti-citrullinated protein/peptide antibody; ANA, antinuclear antibody; Neg, negative; DIP, distal interphalangeal joint; MTP, metatarsophalangeal; NSAIDs, non-steroidal anti-inflammatory drugs; PIP, proximal interphalangeal joint; PD, power doppler; US, ultrasound; NA, not available.
In some of these cases, synovial fluid analysis was not performed, so we cannot exclude the presence of crystals. Lopez Gonzalez et al. reported four cases of crystal-induced arthritis (MSU and CPP crystals detected with polarised light microscopy of the synovial fluid) during hospitalisation for SARS-CoV-2 infection [23,28].

Alivernini et al. also performed synovial biopsy in two patients, but in one of them an exacerbation of RA arthritis during SARS-CoV-2 infection was diagnosed, so we did not include this case [30].

Most of those cases resolved with NSAIDs or with corticosteroids (administered orally or with intra-articular injection). One case was treated with topical NSAIDs, oral opioid and gabapentin, one case was treated with baricitinib and corticosteroids and, finally, one case did not require any treatment.

Sacroiliac joint involvement after COVID-19 infection was reported in three cases, [34,38,39]; all of them fulfilled the classification criteria for psoriatic arthritis [34], or HLA-B27-positive axial spondyloarthritis [38,39]. Moreover, in the case report by Coath et al., COVID-19 infection was not confirmed by nasopharyngeal swab [39].

Notably, the case reported by De Stefano et al. presented transient psoriatic skin lesions, and in the patient treated by Cincinelli et al., nail psoriasis was previously diagnosed [31,37]. However, the authors did not conclude a psoriatic arthritis diagnosis with sufficient certainty in either case.

Finally, Salvatierra et al. described a case of SARS-CoV-2-related dactylitis in a sixteen-year-old girl that resolved without NSAIDs [33].

5. Discussion

Articular involvement in SARS-CoV-2 infection may occur at different times, since it could be an initial symptom of the infection, emerge during the acute phase (sometimes during hospitalisation) or manifest after recovery.

When it appears during the active phase of the infection, it is generally represented by non-specific arthralgia, while it could develop into acute arthritis when arising in the healing period; this feature deviates from classic viral-related arthritis, where joint involvement usually occurs during the viremia period with acute manifestations of the infection, as observed by Gasparotto and Ono, and assimilates this clinical manifestation to post-infectious arthritis [14,18].

The relationship with HLA-B27 positivity did not emerge for COVID-19-related arthritis, while its influence on reactive arthritis is well known.

Since 1999, the term “reactive arthritis” can be applied only to the clinical picture and the microbes associated with HLA-B27 and spondyloarthritis [40]. Thus, the term post-COVID-19 sacroiliitis is more appropriate.

Post-COVID-19 arthritis may present with mono- or oligoarticular involvement, with a predilection for lower limb joints. Generally, it begins some days or a few weeks after the resolution of other manifestations of the infection [13–18,20–22,24,27,29–33,36–39]. As observed by Di Carlo et al., other possible features of post-viral arthritis are represented by enthesitis, dactylitis and tenosynovitis [17,33].

Post-COVID-19 arthritis generally responds to NSAIDs, prolonged for 2–4 weeks, like other viral arthritis. However, steroid treatment is sometimes required, preferably administered with intra-articular injection (if there is mono-oligoarticular involvement); in a few cases, systemic steroid is necessary, but generally for short periods [13–18,20–22,24,27,29–33,36–39].

Only a few cases of SARS-CoV-2-related arthritis required immunosuppressive drugs (methotrexate and sulphasalazine) [35,36].

Some patients with articular manifestations and severe lung involvement, in the context of hyperinflammatory syndrome, have been treated with IL-6 inhibitors or with Jak inhibitors, with significant improvement in both pulmonary and articular manifestations [30].

While peripheral joint symptoms have been much investigated, axial involvement related to COVID-19 is still unclear.
Novelli et al. reported a case of psoriatic spondyloarthritis triggered by SARS-CoV-2 infection and Coath and El Hasbani reported two cases of HLA-B27-positive axial spondyloarthritis that emerged closely after COVID-19 [34,38,39].

To our knowledge, our study is the first longitudinal study with MRI in post-COVID-19 sacroiliitis. Other previous case reports of sacroiliitis documented by MRI after COVID-19 included cases of seronegative spondyloarthritis, all fulfilling the classification criteria for psoriatic arthritis or axial spondyloarthritis [34,38,39].

Our patients complained of typical inflammatory lower back pain after the resolution of infectious symptoms, with clinical features of acute sacroiliitis (insidious onset, night pain, morning stiffness, improvement with exercise and NSAIDs, radiation to buttocks), as described after different infections or in the context of reactive arthritis or seronegative spondyloarthritis [41]; other differential diagnoses were excluded by personal and familiar history and laboratory tests. Both the patients were negative for HLA-B27. Sacroiliitis was then confirmed by MRI, that showed bone marrow oedema in typical sites of sacroiliac joints, and the patients responded well to NSAIDs. Even if it is well known that bone oedema can be seen in a substantial fraction of healthy people and that our patients could be at risk for developing lower back pain and even MRI abnormalities due to their work, the pre-test probability made the MRI findings more likely to be true rather than false positive [42].

On the other hand, sometimes MRI remains positive after clinical resolution in seronegative spondyloarthritis [41,43].

Whether persistence of bone marrow oedema represents the persistence of inflammatory activity (or its chronicity), or is a result of previous inflammation that requires more time to disappear, is unclear. Follow-up of those patients is ongoing to monitor both clinical and imaging evolution.

Generally, imaging findings are not specific, since X-rays are negative and ultrasound can reveal synovitis, enthesitis or tenosynovitis. Data on MRI are scarce, since only three other cases have studied sacroiliitis with MRI [34,38,39].

The exact mechanism through which COVID-19 might cause arthropathies is not completely understood.

Most authors assume the existence of molecular mimicry between viral epitopes and the synovial membrane causing local inflammation; other theories speculate about the presence of circulating immune complexes or possible localisation of the virus directly on joint tissue [14,44].

Interestingly, a mechanism involving molecular mimicry of heat shock proteins/molecular chaperones, similar to that described in immune adverse events secondary to immunotherapy for cancer, could be hypothesised. In fact, tumour cells can display on their surface heat shock proteins/molecular chaperones that are mimicked by SARS-CoV-2 molecules. Molecular mimicry between SARS-CoV-2 and tumoural proteins can elicit an abnormal immune reaction by cytotoxic cells against the virus that cross-react with the tumour cells [45].

In reactive arthritis, chlamydial heat shock protein 60 mimics host self-proteins and thus can contribute to initiation and maintenance of autoimmune/autoinflammatory diseases [46].

Heat shock proteins have been repeatedly implicated in the pathogenesis of rheumatoid arthritis, and increased Hsp27 and Hsp90α mRNA levels have been found in rheumatoid arthritis synovial tissues [47,48].

At the moment, the relationship with HLA-B27 positivity is not clear for COVID-19-related arthritis, while its influence on reactive arthritis is well known [49–51].

Predisposing factors to develop articular involvement consequent to SARS-CoV-2 infection are still unknown, but by evaluating medical literature, it seems that longer persistence of the virus, as demonstrated by the protracted positivity of nasopharyngeal swab for SARS-CoV-2, and its spreading from the respiratory tract to other sites including the gastrointestinal tract, might locally activate immunological and inflammatory pathways.
that could lead to the development of arthritis in some patients, including seronegative spondyloarthritis, which has been linked to an altered intestinal microbiome [52,53].

Moreover, as described in many studies, SARS-CoV-2 is able to activate in different ways the immune system; in particular, it can induce interleukin-6 (IL-6)-dependent pathways leading to cytokine storm and macrophage activation syndromes; in addition, it might alter interferon signalling in some cases [19,54–58].

Those altered inflammatory systems may elicit autoimmune processes in predisposed individuals.

A mild elevation of some cytokines was identified in our patients; in particular, IL2R, TNFalpha and IL8, which have been clearly linked both to COVID-19 and inflammatory arthritis [59].

Despite negativity of specific antibodies and different clinical features, COVID-19 shares similarities with rheumatoid arthritis, in particular regarding the cytokine pattern involved in the inflammatory process, so inhibitors of these molecules could be used in selected groups of patients, as used for the treatment of rheumatoid arthritis [19,55,60,61]. Nevertheless, endemic human coronaviruses seem to be associated with an increased risk of developing rheumatoid arthritis, as described for other viral agents such as parainfluenza virus and metapneumovirus [62]; therefore, the SARS-CoV-2 pandemic might potentially lead to increasing cases of rheumatoid arthritis in the near future [63–65].

Hopefully, when an antiviral therapy is available, patients with persistent positivity of SARS-CoV-2 on nasopharyngeal swab, even if asymptomatic, could be treated to obtain a faster virus clearance, since the occurrence of post-infectious manifestations may be decreased by reducing the spread and the exposure of the human immune system to the virus.

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