Can SARS-CoV-2 induce reactive arthritis?

Sirs,

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is able to elicit the production of a large number of pro-inflammatory cytokines and, in predisposed subjects, the pathogenesis of SARS-CoV-2 severe manifestations (COVID-19) can be attributed to an excessive immune response in addition to the viral lytic effect on host cells (1). The musculoskeletal manifestations, mainly characterised by myalgia, in the course of COVID-19 have a variable prevalence, involving from 3 to 44% of subjects according to different case series (2, 3). These percentages concern the acute phase of COVID-19. Some authors have described the onset of acute polyarthritis during SARS-CoV-2 infection, suggesting the viral capacity to induce systemic autoimmune diseases (4).

The link between infections and the appearance of inflammatory joint manifestations is well known, especially in the context of reactive arthritis. Reactive arthritis falls within the context of spondyloarthritis, and is defined as arthritis triggered by an infection of a remote organ and not directly of the joint structures involved (5). Typically, a reactive arthritis occurs a few weeks after the infection that triggered it. The etiopathogenesis of reactive arthritis has not been clarified and it is believed to be due to an excessive stimulation of the immune system or an immune response to an antigen located at the joint level. To date, there are no internationally validated guidelines for the diagnosis and treatment of reactive arthritis (6).

The role of SARS-CoV-2 in inducing reactive arthritis is poorly known, although recently cases of reactive arthritis potentially induced by SARS-CoV2 have been described (7, 8).

This case report describes a likely reactive arthritis triggered by SARS-CoV-2 infection. The patient, a 55-year-old man, came to the rheumatologic care for the recent onset of a right ankle monoarthritis. In April 2020 the patient, in complete well-being, developed a mild form of COVID-19, with fever for three days without respiratory symptoms. The positivity of SARS-CoV-2 swab was recorded on April 8th 2020, when the fever was decreasing. After two weeks, SARS-CoV-2 detection resulted negative on two consecutive swabs. On May 15th 2020, the patient complained of swelling and pain in right ankle. The main abnormalities in laboratory findings were increased erythrocyte sedimentation rate (ESR) (67 mm/h) and C-reactive protein (CRP) (5.6 mg/dl), and mild lymphopenia ($1.26x10^3$/mcl). No personal or family history of rheumatic diseases, psoriasis, or microcrystal arthropathies has been recorded. In recent medical history, except for SARS-CoV-2 infection, there was no evidence of trauma, genito-urinary or gastro-intestinal infections.

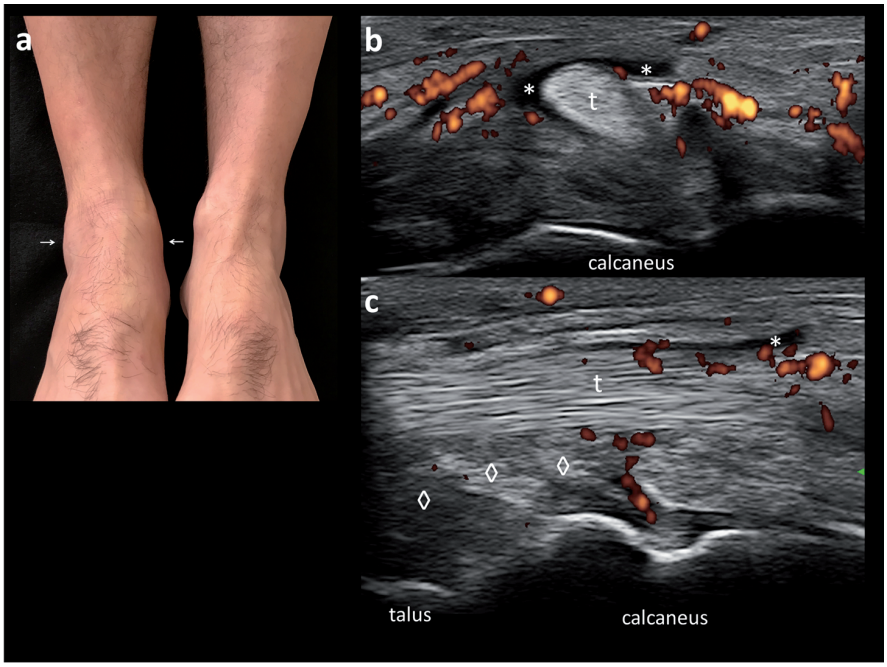

Fig. 1. Monoarthritis of the right ankle. (**a**) Clinical image of swelling (arrows). (**b**) Ultrasound scan (6-18 MHz ultrasound probe) of the medial aspect of the ankle revealing tenosynovitis of the posterior tibial tendon, with presence of exudate (asterisks) and peritendinous power Doppler signal. (**c**) Longitudinal ultrasound scan (6-18 MHz ultrasound probe) of the medial aspect of the ankle confirming the presence of tenosynovitis of the posterior tibial tendon with exudate (asterisk) and revealing synovitis of the subtalar joint, with presence of synovial hypertrophy (rhombi) and intra-articular power Doppler signal.

At the articular examination, the only remarkable finding was the presence of a synovitis of right ankle (Fig. 1A). Ultrasound evaluation (US) documented the presence of subtalar joint synovitis and coexisting tenosynovitis of the posterior tibial tendon sheath. Unfortunately, it was not possible to aspirate the synovial fluid, as it was present in small amounts in the posterior tibial tendon sheath, while the inflammation found at the subtalar joint was mainly due to a pattern of synovial hypertrophy (Fig. 1B and Fig.1C). US, also performed at the knees, wrists and metatarsophalangeal joints excluded the presence of deposits of monosodium urate or calcium pyrophosphate. Other laboratory investigations have documented the absence of HLA-B27 antigen, *Ureaplasma urealyticum*, *Mycoplasma hominis* and *Chlamydia trachomatis* in the genito-urinary system, and enterobacteriaceae (*Campylobacter jejuni, Shighella flexneri, Yersinia enterocolitica, Clostridium difficile, Salmonella spp*) in stool sample and sierology. The steroid treatment resulted in a prompt benefit on ankle monoarthritis, ruling out a septic etiology and supporting the reactive arthritis hypothesis. Currently the patient is asymptomatic with methylprednisolone 4 mg/day, and ESR and CRP are within the normal range.

Since it was not possible to isolate a causal bacterial agent, among those considered common in inducing reactive arthritis, and since no other apparent cause of ankle monoarthritis was detected, SARS-CoV-2 was considered the infectious trigger of reactive arthritis diagnosed in the patient. This conclusion is also supported by the time interval of few weeks between the onset of ankle monoarthritis and COVID-19. The main limitation in the discussion of this case report was the impossibility to perform a synovial fluid analysis, which would have allowed to definitively exclude a crystal-induced arthritis.

Although less common than bacteria, some viruses (HIV, Coxsackie, Echovirus) are able to trigger reactive arthritis (5). Some authors have recently report-

ed cases of polyarthritis during severe COVID-19 (4, 9), treated similarly to rheumatoid arthritis (9), or crystal-induced flares (10).

Given the worldwide expansion of the pandemic, rheumatologists are likely to face cases of SARS-CoV-2 reactive arthritis in the coming months (11).

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