Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Editorial

Can SARS-CoV-2 trigger reactive arthritis?

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The SARS-CoV-2 virus-induced COVID-19 (coronavirus disease) pandemic has had a global societal impact and repercussions on rheumatological populations at different levels. The fear of infection of patients with rheumatological disease, due to rheumatological disease itself but also and above all due to the possible use of immunomodulating treatments, was at the center of the discussions and raised the question of the appropriateness of maintaining this treatment in the absence of signs of infection [1]. National and international recommendations have clearly positioned themselves in favor of maintaining rheumatological treatment in the absence of symptoms or evidence of infection with SARS-CoV-2 [1–3]. Slow-acting, biologic or targeted synthetic (JAK inhibitors) disease modifying anti rheumatic drugs (DMARDs) could be beneficial and have even been evaluated in the context of some forms of COVID-19 involving a "cytokine storm" [4,5].

On the other hand, the pandemic and confinement have had an impact on patient monitoring and adherence to treatment, and potentially indirectly on overall disease activity. For example, in the context of spondyloarthritis, an analysis of a questionnaire sent to patients who are members of a patient association in France showed that out of more than 600 responses, more than 60% of patients reported a worsening of their disease during the confinement period, significantly associated with a change in treatment [6]. This modification mainly concerned NSAIDs, and to a lesser extent the suspension of biological treatments for fear of the risk of infection. Another possible determinant of loss of disease control is a reduction in physical activity due to confinement. Psychological factors also need to be considered. A survey of a cohort of axial spondyloarthritis patients in the United States showed that, after adjustment, patients with high levels of stress and anxiety had significantly higher disease activity scores [7].

Available data on the incidence and severity of COVID in rheumatologic populations on targeted biological or synthetic DMARDs do not show an increased risk of infection in these patients compared to the general population [6,8].

The other rheumatologic side of COVID-19 is the induction of rheumatologic manifestations by or at a distance from SARS-CoV-2 infection. The rheumatological symptoms described during COVID are rare and hidden by other manifestations of the infection. Most often, they are arthralgia in the early phase of the disease [9]. In a Spanish series of more than 300 patients with proven COVID-19, arthralgias and myalgias were found in more than a quarter of the cases in the clinical presentation [10].

A few cases of acute arthritis or dactylitis have been reported, some of which may be suggestive of reactive arthritis. To date, six compatible cases are found in the literature, but an increase in reported cases is expected in the coming months. These 6 cases are summarized in Table 1 [11–16]. Indeed, some elements are in line with the classic or evocative aspects of reactive arthritis, defined as aseptic arthritis occurring after and distant from a site of infectious [17]. These include the predominance of males (5 cases out of 6), a delay of one to three weeks between the infection and the beginning of the rheumatological picture, a mono or oligoarticular inflammatory disease, predominant in the lower limbs, and the possibility of dactylitis or enthesitis. The joint fluid is sterile, without microcrystals. The evolution is reported to be favorable with NSAID treatment and intra-articular corticosteroid injections.

Some elements are however atypical for reactive arthritis: the advanced age in one patient, the absence of the HLA-B27 antigen in the 3 cases where the research was carried out. The COVID disease is benign in 3 cases and led to tracheal intubation in one case. The search for SARS-Cov-2 by RT-PCR in the synovial fluid is negative in 3 cases.

However, arthritis can be caused by different mechanisms. Cases of acute arthritis occurring at the onset of COVID symptoms have been reported. Alivernini et al. [18] reported a case of polyarthritis with a sudden onset, inaugural COVID-19 (treated with antiviral and hydroxychloroquine), improved by a combination of prednisone (10 mg/day) and baricitinib, which may suggest viral arthritis. Lopez–Gonzalez et al. reported 4 cases (males between 45 and 71 years of age), among 306 patients hospitalized with proven COVID-19 (1.3%), of arthritis starting between 8 and 27 days after the onset of COVID. In all 4 cases, joint fluid analysis led to the diagnosis of microcrystalline arthritis (gout 3 times, chondrocalcinosis once) [10]. These last observations illustrate the importance of rheumatological diagnosis.

The potential mechanisms at the origin of arthritis in a context of viral infection by SARS-CoV-2 remain at the hypothesis stage. The possibility of viral arthritis cannot be ruled out in the rare cases of early arthritis, but viremia is documented in only 15% of cases of COVID-19 [16] and has not been objectified in any published case with joint involvement. The presence of virus could not be detected by RT-PCR in synovial fluid in the 3 cases where this

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Table 1
Case reports in the literature of possible reactive arthritis after COVID.

Author (ref)	Gender Age	Comorbidities	COVID diagnosis	COVID treatment	Delay	Rheumatologic localization	Biology	Outcome
Saricaoglu [11]	M 73	Diabetes Hypertension Heart failure	Nasal RT-PCR	Ceftriaxone HCQ Azithromycin	8 days after end of COVID treatment	Dactylitis 1 right foot 2 left foot	Elevated CRP*	Resolution under NSAIDs
Liew [12]	M 47		Nasal RT-PCR		1 week	Right knee	SF negative cristal, Sars-CoV-2*	NSAID Intra-articular triamcinolone
Ono [13]	M 50	Steatohepatitis	Nasal RT-PCR intubation	Favipiravir cefepim vancomycin	21 days	Ankle arthritis Right Achilles enthesitis	SF negative cristal HLA-B27 negative*	Intra-articular steroids
Salvatierra [14]	F 16		Serology		3 weeks	Dactylitis 2,4,5 right foot	HLA-B27 negative	Resolution with NSAIDs
De Stefano [15]	M 30		Nasal RT-PCR	Symptomatic	10 days after resulotion of COVID symptoms	Arthritis right elbow, skin psoriasis	SF negative cristals, Sars-CoV-2* Sars-CoV-2 serology positive	Resolution in 6 weeks with NSAIDs
Yokogawa [16]	M 57	Hypertension Hyperlipidemia	Nasal RT-PCR	Symptomatic	17 days after onset of COVID symptoms	Arthritis right shoulder, left wrist knees	SF negative cristals, Sars-CoV-2*	Spontaneaous resolution after 10 days

SF: synovial fluid; NSAIDs: non-steroidal anti inflammatory drugs; HCQ: hydroxychloroquine; RT-PCR: real time polymerase chain reaction; *: other infections ruled out.

search was performed [12,15,16]. Histological and immunological analysis of a synovial biopsy in an early arthritis patient revealed an inflammatory synovial edema with perivascular and diffuse infiltrates expressing positivity for CD68 (histiocytic cells), CD3 (T cells) and CD138 (plasma cells) [18]. The mechanism of reactive arthritis is plausible, due to the clinical presentation, the delay between the onset (or diagnosis) of COVID and the onset of rheumatological manifestations, the usual negativation of nasopharyngeal RT-PCR at the time of onset of rheumatological involvement. Viral infections are known to potentially induce reactive arthritis patterns [17]. In this context, interleukin 17 could represent a link between the two conditions. Indeed, IL-17A is involved in the pathogenesis of both reactive arthritis and spondyloarthritis in general [17], but also in the hyperinflammatory state of COVID-19 [19]. However, cases of symptomatic SARS-CoV-2 infection have been reported in patients treated with an anti IL-17 monoclonal antibody for spondyloarthritis [19]. Finally, non-specific mechanisms deserve to be discussed. Arthritis may be reactive to a masked pulmonary or digestive infection as a consequence of COVID [13], or it may be a non-specific consequence of the "cytokine storm" that accompanies the symptomatic forms of the disease [20].

This new infectious disease may induce rheumatological manifestations, with the possibility of reactive arthritis. Although rare, they require special attention and the expertise of the rheumatologist for diagnosis. It also raises physiopathological issues that remain unresolved to date.

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Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Richez C, Flipo RM, Berenbaum F, et al. Managing patients with rheumatic diseases during the COVID-19 pandemic: the French Society of Rheumatology answers to most frequently asked questions up to May 2020. Joint Bone Spine 2020, http://dx.doi.org/10.1016/j.jbspin.2020.05.006.
[2] Landewé RB, Machado PM, Kroon F, et al. EULAR provisional recommendations for the management of rheumatic and musculoskeletal diseases in the context of SARS-CoV-2. Ann Rheum Dis 2020;79:851–8.
[3] Mikuls TR, Johnson SR, Fraenkel L, et al. American College of Rheumatology Guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: version 2. Arthritis Rheumatol 2020, http://dx.doi.org/10.1002/art.41437 [Online ahead of print].
[4] Felten R, Chatelus E, Arnaud L. How and why are rheumatologists relevant to COVID-19? Joint Bone Spine 2020;87:279–80.
[5] Benucci M, Damiani A, Infantino M, et al. Old and new antirheumatic drugs for the treatment of COVID-19. Joint Bone Spine 2020;87:195–7.
[6] Roux CH, Brocq O, Gerald F, et al. Impact of home confinement during the COVID-19 pandemic on medication use and disease activity in spondyloarthritis patients. Arthritis Rheumatol 2020, http://dx.doi.org/10.1002/art.41397 [Online ahead of print].
[7] Liew JW, Castillo M, Zaccagnino E, et al. Patient-reported disease activity in an axial spondyloarthritis cohort during the COVID-19 pandemic. ACR Open Rheumatol 2020, http://dx.doi.org/10.1002/acr2.11174 [Online ahead of print].
[8] Quartuccio L, Valent F, Pasut E, et al. Prevalence of COVID-19 among patients with chronic inflammatory rheumatic diseases treated with biologic agents or small molecules: a population-based study in the first two months of COVID-19 outbreak in Italy. Joint Bone Spine 2020, http://dx.doi.org/10.1016/j.jbspin.2020.05.003.
[9] Joob B, Wiwanitkit V. Arthralgia as an initial presentation of COVID-19: observation. Rheumatol Int 2020;40:823.
[10] López-González MD, Peral-Garrido ML, Calabuig I, et al. Case series of acute arthritis during COVID-19 admission. Ann Rheum Dis 2020, http://dx.doi.org/10.1136/annrheumdis-2020-217914.
[11] Saricaoglu EM, Hasanoglu I, Guner R. The first reactive arthritis case associated with COVID-19. J Med Virol 2020, http://dx.doi.org/10.1002/jmv.26296.
[12] Liew IY, Mak TM, Cui L, et al. A case of reactive arthritis secondary to coronavirus disease 2019 infection. J Clin Rheumatol 2020;26:233.
[13] Ono K, Kishimoto M, Shimasaki T, et al. Reactive arthritis after COVID-19 infection. RMD Open 2020;6:e001350.
[14] Salvatierra J, Martínez-Peñalver D, Salvatierra-Velasco L. COVID-19 related dactyitis. Joint Bone Spine 2020, http://dx.doi.org/10.1016/j.jbspin.2020.06.009.
[15] De Stefano L, Rossi S, Montecucco C, et al. Transient monoarthritis and psoriatic skin lesions following COVID-19. Ann Rheum Dis 2020, http://dx.doi.org/10.1136/annrheumdis-2020-218520.
[16] Yokogawa N, Minematsu N, Katano H, et al. Case of acute arthritis following SARS-CoV-2 infection. Ann Rheum Dis 2020, http://dx.doi.org/10.1136/annrheumdis-2020-218281.
[17] Wendling D, Prati C, Chouk M, et al. Reactive arthritis: treatment challenges and future perspectives. Curr Rheumatol Rep 2020;22:29.
[18] Alivernini S, Cingolani A, Gessi M, et al. Comparative analysis of synovial inflammation after SARS-CoV-2 infection. Ann Rheum Dis 2020, http://dx.doi.org/10.1136/annrheumdis-2020-218315 [Online ahead of print].
[19] Coskun Benlidayi I, Kurtaran B, Tirasci E, et al. Coronavirus disease 2019 (COVID-19) in a patient with ankylosing spondylitis treated with secukinumab: a case-based review. Rheumatol Int 2020;40:1707–16.
[20] Quartuccio L, Semerano L, Benucci M, et al. Urgent avenues in the treatment of COVID-19: targeting downstream inflammation to prevent catastrophic syndrome. Joint Bone Spine 2020;87:191–3.

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