Diagnosis of COVID-19 associated arthritis in patients with or without underlying rheumatic and musculoskeletal disease supported by musculoskeletal ultrasound: a case series from three European centres

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Abstract

Objective

The coronavirus disease 19 (COVID-19) pandemic concerns the field of rheumatology in many ways. Arthritis in conjunction with COVID-19 is increasingly reported. However, clinical data are still limited and there is lack of a detailed characterisation of COVID-19 associated arthritis by musculoskeletal ultrasound (MSUS). This case series reports different forms of COVID-19 associated arthritis supported by MSUS in patients with or without underlying rheumatic and musculoskeletal disease (RMD).

Methods

From March 2020 to July 2021, adult patients (n=10) with arthritis timely related to COVID-19 were assessed in three European centres by clinical and laboratory values and additionally MSUS.

Results

In the group without underlying RMD (n=6), two patients presented with polyarticular arthralgia during severe COVID-19, swelling was rarely seen and MSUS demonstrated arthritis only in a few joints affected. The other four patients showed arthritis four to 16 weeks after mild or moderate COVID-19 (without hospitalisation): polyarthritis (n=1), oligoarthritis of the upper and lower limb (n=2), and in one case, late-onset rheumatoid arthritis (LORA) was newly diagnosed. In the group with an underlying RMD (n=4), an increase of disease activity was reported by MSUS during mild and mild-moderate COVID-19. In general, MSUS often presented power Doppler (PD) positive synovitis and tenosynovitis.

Conclusion

In our patients without underlying RMD, arthritides associated with COVID-19 are comparable to the clinical picture of a reactive arthritis (ReA) or other virus-related arthritides (e.g. parvovirus B19). New onset or flares of RMD possibly triggered by COVID-19 are noteworthy.

Key words

case series, COVID-19, reactive arthritis, virus-related arthritis, RMD, flares, musculoskeletal ultrasound

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Introduction

Since coronavirus disease 19 (COVID-19) outbreak at the end of 2019 and the development into a global pandemic, the influence of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection on rheumatic and musculoskeletal disease (RMD) course has been discussed in many publications (1, 2). Infection with SARS-CoV-2 can lead to a broad range of symptoms which in adults ranges from mild flu-like symptoms to life-threatening or fatal disease courses, the latter due to an acute respiratory distress syndrome (ARDS) (3). Especially in the hyperinflammatory state of severe COVID-19, immunomodulatory agents from the rheumatology field (*e.g.* interleukin (IL)-6 antagonists) are applied (4, 5). Increasing data indicate the occurrence of arthritis associated with COVID-19 resembling clinically both virus-related arthritis and reactive arthritis (ReA), respectively (6, 7). To date, a correlation with the severity of SARS-CoV-2 infection is not evident and a distinct definition of COVID-19 associated arthritis has not been made. During COVID-19, arthralgia and unspecific musculoskeletal symptoms are reported (8). Myositis as early sign of COVID-19 was also described (9). A possible pathophysiological link is the angiotensin-converting enzyme 2 (ACE 2), the major SARS-CoV-2 entry receptor in muscles and synovial tissue (10). Arthritis as an early symptom of COVID-19 has only rarely been presented, which could, however, not be well differentiated from acute illness-induced crystal arthropathy (11). In the context of musculoskeletal complications, post-COVID-19 critical illness myopathy needs also to be taken into account in patients after intensive care management (12). Additionally, musculoskeletal pain and arthralgia are present in long COVID, a further newly described disease entity (13). Moreover, sporadic case reports of new onset or flares of RMDs after COVID-19 disease have been published (2, 14-17). A further challenge for rheumatologists comes up with the possible influence of SARS-CoV-2 vaccination on courses of RMDs and the response to vaccination under disease-modifying antirheumatic drug (DMARD) therapy, respectively (18-21).

Clinical data on arthritis associated to COVID-19 are limited and there is a lack of characterisation by musculoskeletal ultrasound (MSUS). Thus, the objective of this case series is to present data on COVID-19 associated arthritis detected by MSUS and, furthermore, to make a contribution towards a detailed description of the clinical spectrum of COVID-19 associated arthritis considering pre-existing RMDs.

Patients and methods

Adult in- or outpatients with tender and swollen joints timely related to COVID-19 were selected. The patients were seen between March 2020 and July 2021 in three European centers: Clinical Unit of Rheumatology and Clinical Immunology, University of Rome Campus Biomedico (Italy), Academic Rheumatology Centre of the University Clinic of Turin (Italy) and the Department of Rheumatology and Clinical Immunology of the Charité – Universitätsmedizin Berlin (Germany). SARS-CoV-2 infection was confirmed either by reverse transcription polymerase chain reaction (RT-PCR) from nasopharyngeal swab (NPS) or SARS-CoV-2-specific antibodies. Clinical, laboratory and MSUS examinations were performed. The findings on MSUS were evaluated according to OMERACT definitions (22). Patients without inflammatory signs in MSUS (synovitis, tenosynovitis) were excluded from the study.

Case reports

In the following section, ten cases of patients with COVID-19 associated arthritis are presented. Table I summarises the detailed characteristics of the patients; see the Supplementary file for an extended version.

Case 1

A 53-year-old male with known psoriatic arthritis (PsA) treated with sulfasalazine (SSZ) and a concomitant chondrocalcinosis had low disease activity (Disease activity in psoriatic arthritis (DAPSA) 11.3) before contract-

Table I.

Case, Age (years)/ Sex (♀, ♂)	RMDs	Comorbidities (non-RMDs)	COVID-19 diagnosis	Severity of illness	Onset of Arthritis after COVID-19 diagnosis	Affected joints	Treatment arthritis	Outcome
Case 1, 53/♂	PsA, PA subset (LDA*under SSZ), Chondrocalcinosis		10/20 RT-PCR	Mild moderate	3 days	Right MCP2, right PIP3, left wrist	Restart SSZ, switch to ADA	LDA*after switch to ADA
Case 2, 58/♀	RA LDA** under MTX + (Abatacept)		11/20 RT-PCR	Mild	7 days	Right and left wrists, right MCP2-4, right PIP2, left MCP2-4, left PIP3	Restart MTX + Abatacept	LDA**
Case 3, 83/♂		Hypertension	02/21 RT-PCR	Severe	5 days	Right MCP5	GC (in the context of COVID-19)	Recovery
Case 4, 72/♀		IDA, Dyslipidaemia	03/21 RT-PCR	Severe	Concomitant	Right and left wrists, right and left knee joints, right and left shoulders, right MCP1-3, left MCP1, right and left IP1	GC (in the context of COVID-19)	Recovery
Case 5, 61/♂	RA (in remission under MTX + Sarilumab)		03/21 RT-PCR	Mild	3 days	Right wrist, right MCP3+4, right PIP2+3, left MCP4, left PIP2, right and left knee joints	Restart MTX + Sarilumab	Persistent HDA***, therapeutic change intended
Case 6, 60/♂		Tick bite (many years ago), Dyslipidaemia	03/20 RT-PCR	Moderate	16 weeks	MST: 30-60 min, arthralgia: right and left shoulder/knee joints, right MCP3, left MCP1, subjective swelling of finger/knee joints TJC 5/28 (right MCP3, left MCP1, left PIP3, right and left shoulder joints), SJC 2/28 (right knee, right MCP3)	NSAID, GC, MTX	LORA in remission
Case 7, 53/♀		Localised NSCLC in remission after lobectomy, history of Enchondroma of the left upper arm	11/20 Serology	Mild	8 weeks	MST: 60 min, arthralgia: right and left hip joints, right and left knee joints, right ankle joint; subjective swelling of the left knee TJC 0/28, SJC 0/28 (+ tender swelling of the right ankle)	NSAID, GC, SSZ, GC infiltration	Relapse, prolonged course
Case 8, 42/♀		Migraine, history of Sectio	12/20 RT-PCR	Mild	4 weeks	MST: 24 h, subjective symmetrical swelling of the wrists, finger joints, knee/ankle joints TJC 8/28 (right and left wrists, left MCP4, left PIP3+4, right PIP2-4), SJC 3/28 (right and left wrists, left MCP2 + right and left ankle joints)	NSAID, GC	Recovery
Case 9, 51/♀		Trigger finger D4 right hand, history of giant-cell tumor of the distal phalanx D2 right hand	12/20 RT-PCR	Mild	12 weeks	TJC 2/28 (right and left wrists) SJC 0/28	NSAID	Recovery
Case 10, 69/♂	pSS + SCLE overlap (under AZA)	Hypertension BPH, MGUS	12/20 RT-PCR	Mild	6 weeks	Arthralgia: right wrist, right MCPs; ubjective swelling right wrist, right MCPs, right PIPs	MTX	RA in remission

ADA: adalimumab; AZA: azathioprine; BPH: benign prostatic hyperplasia; D: digit; GC: glucocorticoid; HDA: high disease activity; IDA: iron deficiency anaemia; LDA: low disease activity; LORA: late-onset rheumatoid arthritis; MCP: metacarpophalangeal joint; MGUS: monoclonal gammopathy of undetermined significance; MST: morning stiffness; MTX: methotrexate; neg.: negative; NSCLC: non-small cell lung carcinoma; PA: polyarticular; RT-PCR: reverse transcription polymerase chain reaction; pos.: positive; PIP: proximal interphalangeal joint; PsA: psoriatic arthritis; pSS: primary Sjögren's syndrome; RA: rheumatoid arthritis; RMD: rheumatic and musculoskeletal disease; SCLE: subacute cutaneous lupus erythematosus; SJC: swollen joint count; SSZ: sulfasalazine; TJC: tender joint count.
* LDA based on Disease Activity Index for PsA (DAPSA), ** LDA based on Clinical Disease Activity Index for RA (CDAI), *** HDA based on CDAI

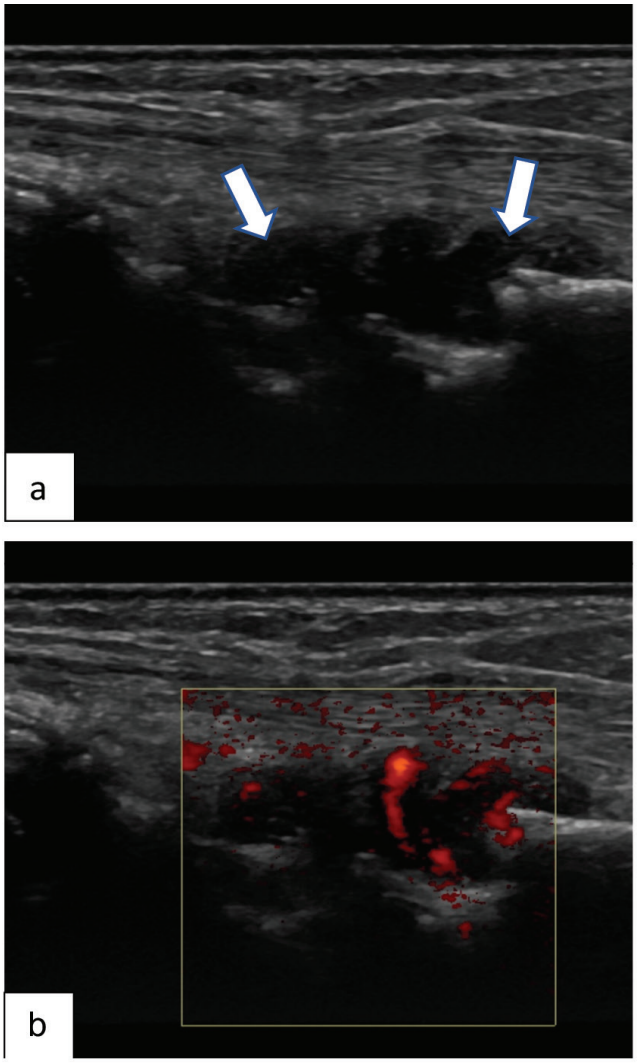

Fig. 1. Dorsal view of the wrist (radiocarpal and intercarpal joint) with moderate synovitis (below arrows) in grey scale (**a**) and power Doppler activity (**b**).

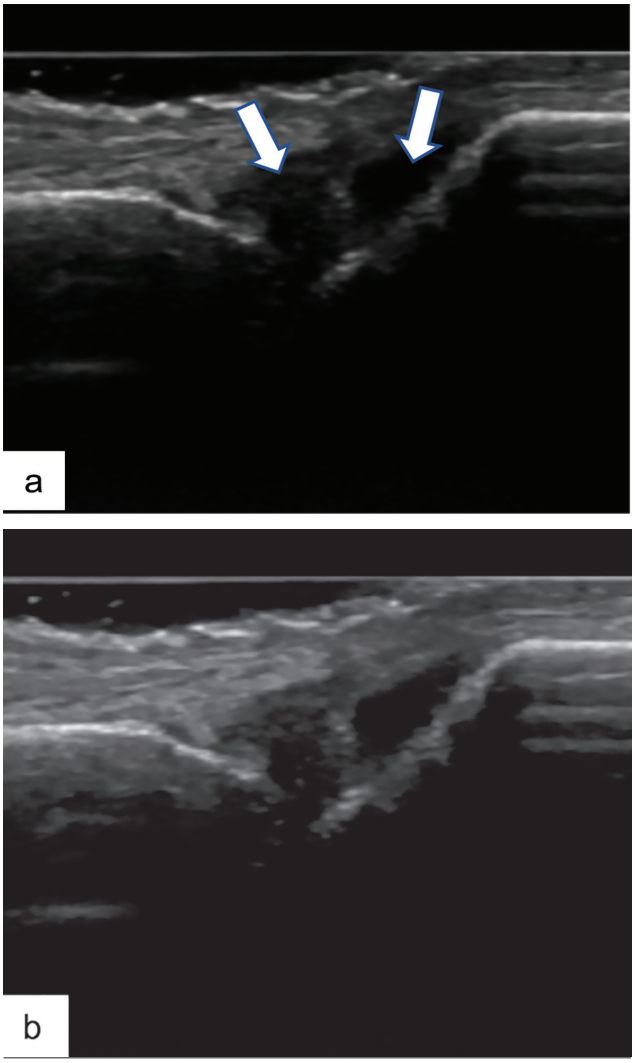

Fig. 2. Dorsal view of the MCP5 joint with moderate synovitis (below arrows) in grey scale (**a**) without power Doppler activity (**b**).

ing COVID-19 in October 2020. At that time, he had typical clinical symptoms such as fever, sore throat, fatigue, generalised body pain, dyspnoea, and diarrhoea. After respiratory and gastrointestinal symptom onset, a worsening of peripheral arthritis was reported (DAPSA 15.1 ≙ moderate disease activity). After eight days from articular symptoms onset, MSUS presented moderate synovitis of the right metacarpophalangeal joint (MCP)2 in grey scale that had not been evident in previous examinations. Temporarily paused SSZ was restarted after NPS for SARS-CoV-2 became negative. Due to persistent moderate disease activity, three months later adalimumab was started (after stop of SSZ) and low disease activity has been reached again.

Case 2

A 58-year-old female with longstanding rheumatoid arthritis (RA) had been under therapy with abatacept and methotrexate (MTX) and was in low disease activity (clinical disease activity index (CDAI) 5) before she fell sick by acute SARS-CoV-2-infection in November 2020. She reported fever, anosmia and dysgeusia. One week after discontinuation of abatacept and MTX due to the acute infection, a worsening of arthritis (tender joint count (TJC) 3/28, swollen joint count (SJC) 9/28) was obvious reflecting high disease activity (CDAI 26.5). Seven days later, MSUS demonstrated active synovitis in both hands and wrists (Fig. 1). After NPS for SARS-CoV-2 became negative, DMARD combination therapy with abatacept and MTX was restarted and the acute arthritis flare diminished.

Case 3

An 83-year-old male with hypertension as pre-existing condition and negative medical history for RMDs reported nausea, loss of appetite, fatigue, dyspnoea and desaturation due to COVID-19 in February 2021. After hospital admission, a non-invasive ventilation was temporarily required and the patient received glucocorticoids (GC). During hospitalisation, he complained of hand and lower limbs arthralgia. Despite the high number of tender joints, there were no clinically swollen joints apparent. MSUS reported synovitis of the MCP5 of the right hand (Fig. 2). Soon after NPS for SARS-CoV-2 be-

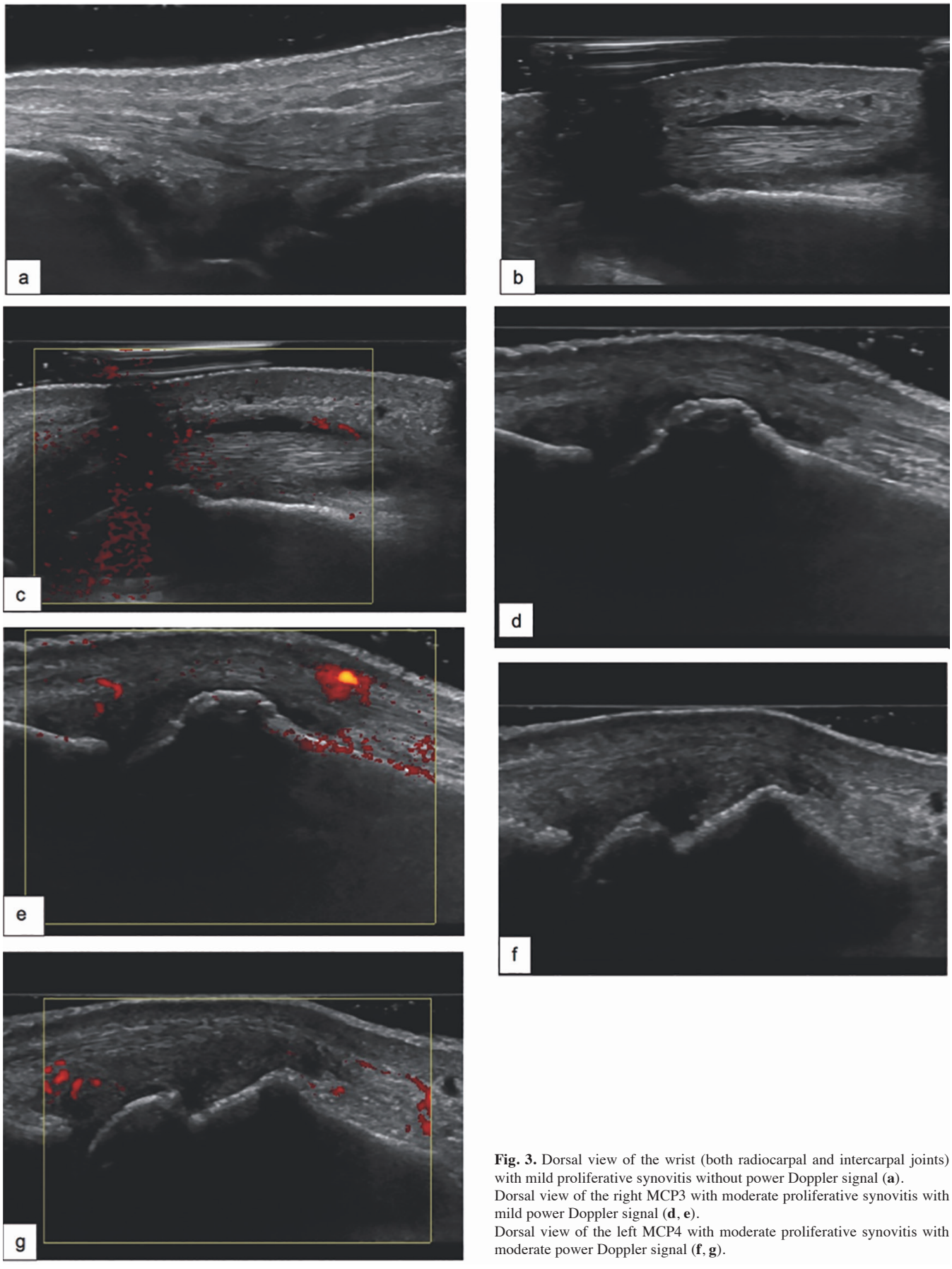

Fig. 3. Dorsal view of the wrist (both radiocarpal and intercarpal joints) with mild proliferative synovitis without power Doppler signal (**a**).
Dorsal view of the right MCP3 with moderate proliferative synovitis with mild power Doppler signal (**d**, **e**).
Dorsal view of the left MCP4 with moderate proliferative synovitis with moderate power Doppler signal (**f**, **g**).

came negative, musculoskeletal symptoms disappeared.

Case 4

A 72-year-old female with dyslipidaemia and iron deficiency anaemia, but no pre-existing RMD, was tested positive for SARS-CoV-2 in March 2021 and was hospitalised with respiratory failure, fever, severe fatigue and arthralgia. She showed twelve tender joints and two swollen joints. The MSUS examination presented mild synovitis in the wrist. During the hospitalisation, she has been treated with GC, which induced quick improvement of musculoskeletal pain and clinical arthritis.

Case 5

A 61-year-old male with RA in clinical remission under DMARD combination therapy with sarilumab and MTX reported low fever and rhinorrhoea in March 2021; NPS for SARS-CoV-2 was positive. Three days after stopping antirheumatic treatment, a severe worsening of joint pain and swelling occurred. Three weeks later, nasopharyngeal swab test for SARS-CoV-2 became negative and sarilumab and MTX were reintroduced (CDAI 28 one week after COVID-19 recovery). MSUS examination presented mild proliferative synovitis of the right wrist without power Doppler (PD) signal, as well as PD positive tenosynovitis of the second flexor tendon of the right hand and synovitis of the right MCP3 and left MCP4 (Fig. 3). Despite restart of the DMARDs after NPS for SARS-CoV-2 became negative, a high disease activity persisted. A therapeutic change is now planned.

Case 6

A 60-year-old male had a short episode of GC-sensitive polyarticular joint complaints two years before SARS-CoV-2 infection. In August 2020, about 16 weeks after a moderate COVID-19 disease with fever, cough, dyspnoea, anosmia and dysgeusia, he developed morning stiffness, symmetrical arthralgia (both shoulder and knee, right MCP3, left MCP1). Joint status presented five tender joints (TJC 5/28) and two swollen joints (SJC 2/28). Despite regular therapy with NSAIDs and GC, inflammation (synovitis/tenosynovitis) of the right MCP3 persisted, furthermore other joints (right wrist, right MCP2, right shoulder) became also affected (Fig. 4). It was decided to add MTX under the suspected diagnosis of a seronegative late-onset RA (LORA), and clinical remission could be achieved.

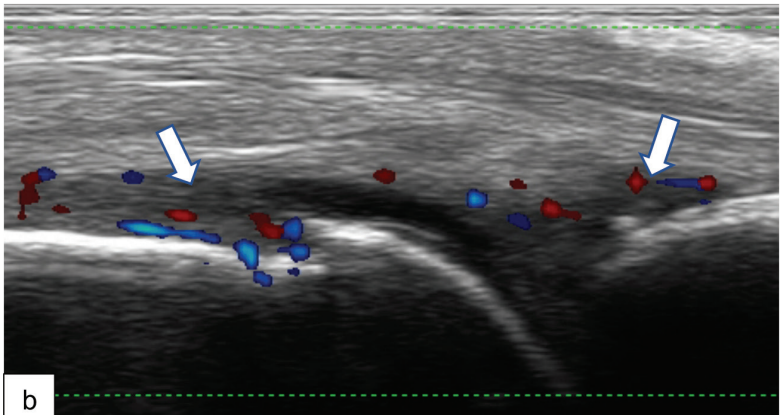

Fig. 4. Dorsal view of the MCP3 joint with moderate synovitis and moderate power Doppler activity.

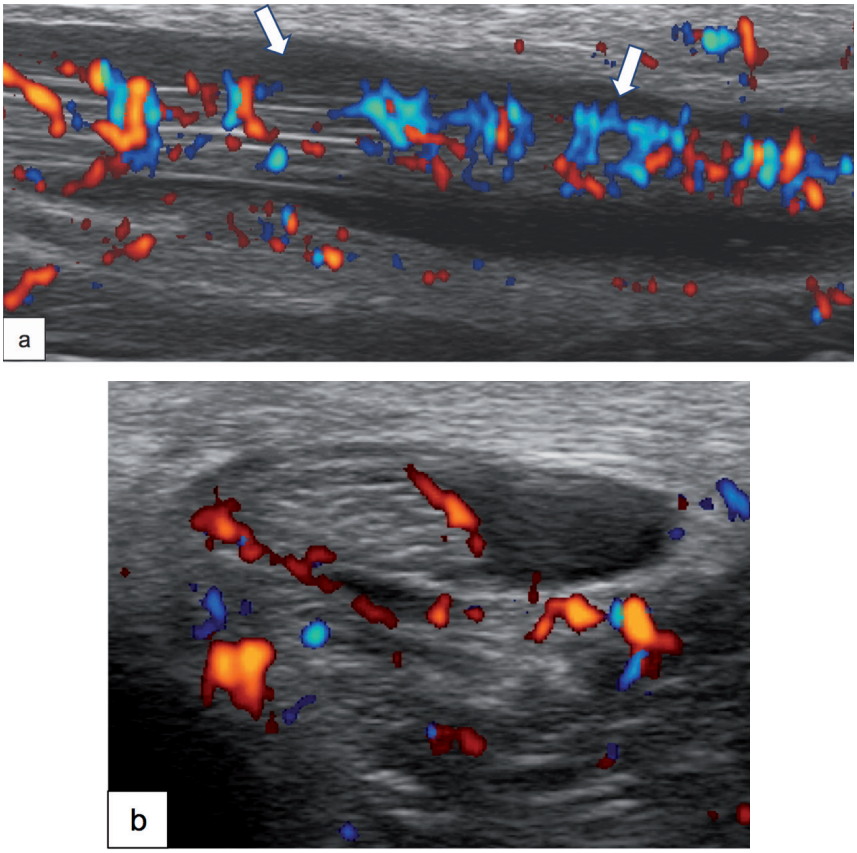

Fig. 5. Longitudinal (**a**) and transverse (**b**) view of the peroneus tendon brevis et longus with moderate tenosynovitis and moderate power Doppler activity.

Case 7

A 53-year-old female with localised non-small cell lung carcinoma (NSCLC) in remission after lobectomy and enchondroma of the left upper arm in medical history, but without a pre-existing RMD, was affected by mild COVID-19 confirmed by SARS-CoV-2-specific antibodies with subfebrile temperatures, cephalgia and myalgia in November 2020. About eight weeks later and nine days after SARS-CoV-2 vaccination (Comirnaty®, Biontech/Pfizer), morning stiffness, arthralgia of both hip and knee joints and the right

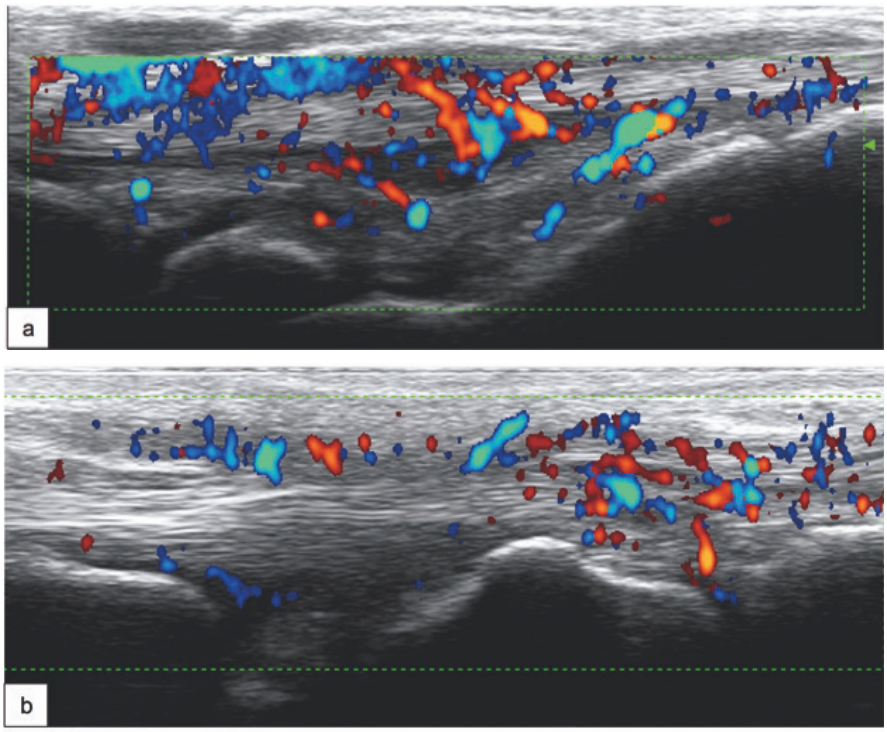

Fig. 6. Dorsal and ulnar view of the wrist with dominant tenosynovitis with high power Doppler activity of the extensor digitorum (**a**) and extensor carpi ulnaris tendon (**b**).

ankle joint occurred. MSUS showed PD positive tenosynovitis of the right peroneal tendons and a small effusion of the right tibiotalar joint (Fig. 5). NSAIDs were insufficient and triggered arterial hypertension, so that systemic GCs and SSZ were started and a temporary alleviation was reported. Under monotherapy with SSZ and aggravated tenosynovitis, a GC infiltration was performed which led to remission of inflammatory activity.

Case 8

A 42-year-old female with migraine and emergency cesarean in 2018 but without any pre-existing RMD was tested RT-PCR positive for SARS-CoV-2 from NPS in December 2020 and presented mild COVID-19 symptoms with cephalgia, rhinorrhoea, anosmia and dysgeusia. Four weeks later, morning stiffness and a symmetrical swelling of the wrists, finger, knee and ankle joints were reported. Concomitant symptoms were night sweat and fatigue. In physical examination, she had eight tender and five swollen joints (TJC 8/28, SJC 5/28). MSUS presented high inflammatory activity by PD in the wrist (Fig. 6) and finger joints. NSAIDs were insufficient, but under systemic GC a complete recovery was seen.

Case 9

A 51-year-old female with trigger finger (digit 4 right hand) and resected giant-cell tumour of the distal phalanx of the right index finger many years ago, but without pre-existing RMD suffered from mild COVID-19 in December 2020 (RT-PCR positive for SARS-CoV-2 from NPS) with flu-like symptoms (particularly sore throat and rhinorrhoea). Twelve weeks later, she complained about pain in her hands. In physical examination, tenderness in both wrists was observed. MSUS detected PD positive synovitis of the right wrist joint and synovitis of the right MCP2-5 (Fig. 7). Under NSAID therapy, a complete recovery was reached.

Case 10

A 69-year-old male with arterial hypertension, benign prostate hyperplasia (BPH) and monoclonal gammopathy of undetermined significance (MGUS) as well as known primary Sjögren syndrome (pSS) and subacute cutaneous lupus erythematosus (SCLE) without joint complaints in the past under azathioprine (AZA) suffered from mild COVID-19 in December 2020. COVID-19 was confirmed with positive RT-PCR for SARS-CoV-2 from NPS and cephalgia, myalgia, anosmia and dysgeusia were seen. Simultaneously, swelling of bilateral MCPs and PIPs occurred, about six weeks later followed by joint pain of the right wrist and persistent swelling of the right MCP3. MSUS reported synovitis and tenosynovitis of the right radiocarpal joint. Furthermore, the right MCP2-5 (Fig. 8) and both MTP1 showed synovitis. Complementary findings such as erosions and a chronic bursitis plus rheumatoid nodules of the right elbow were seen. The new onset of a rheumatoid factor (RF)-positive RA was postulated overlapping with pSS + SCLE. After therapy switch to MTX, remission was achieved.

Results

Ten adult patients (five female and five male) aged between 42 and 83 years (mean age 60 years) with COVID-19 associated arthritis were investigated. In four of them, an underlying RMD was known before COVID-19: RA (n=2), PsA (n=1) and pSS + SCLE (n=1). The reported SARS-CoV-2 infections occurred during March 2020 to March 2021 and were confirmed either by RT-PCR from NPS (n=9) or SARS-CoV-2-specific antibodies (n=1); assessments and follow-ups were performed from March 2020 to July 2021. The majority was evaluated in an outpatient setting (n=8), except for two patients who were assessed during hospitalisation due to severe COVID-19 characterised by requirement of oxygen supplementation. Severe COVID-19 treatment included GC application. The course of COVID-19 was mild in most cases (n=6).

The interval between SARS-CoV-2 infection and joint complaints covered few days to several weeks (maximum of 16 weeks). Arthralgia and joint swelling affected large and small joints, and upper and lower limbs were involved. Mono-, oligo- and polyarthritis, partially concomitant with tenosynovitis, was verified with MSUS. In one case, tenosynovitis of the right

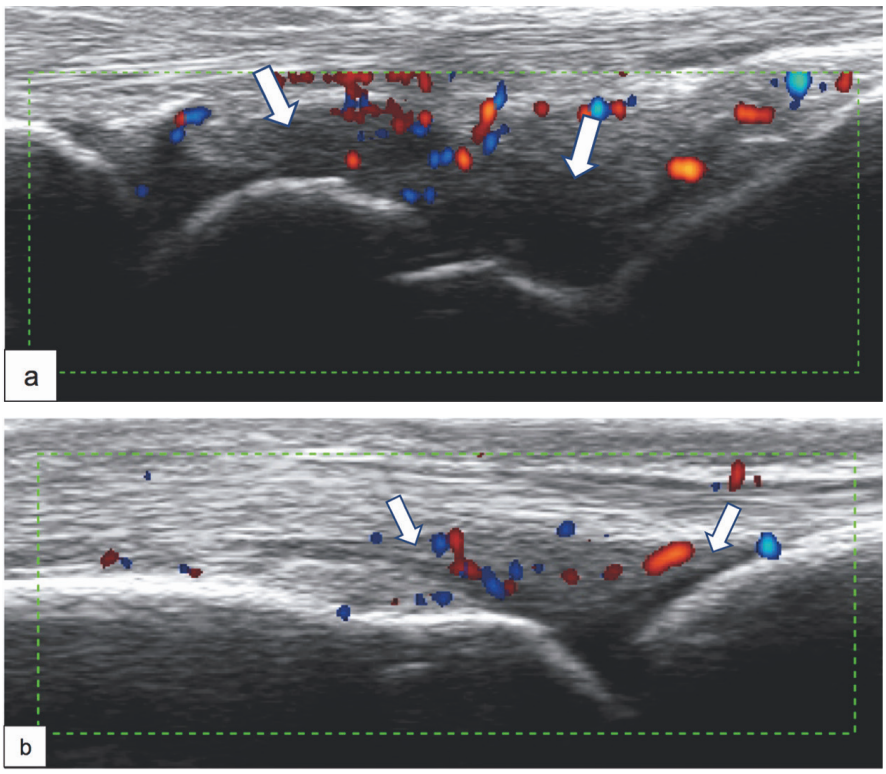

Fig. 7. Dorsal view of the wrist (radiocarpal and intercarpal joint) with moderate synovitis and mild to moderate power Doppler activity (**a**) and dorsal view of the MCP3 joint with moderate synovitis and moderate power Doppler activity (**b**).

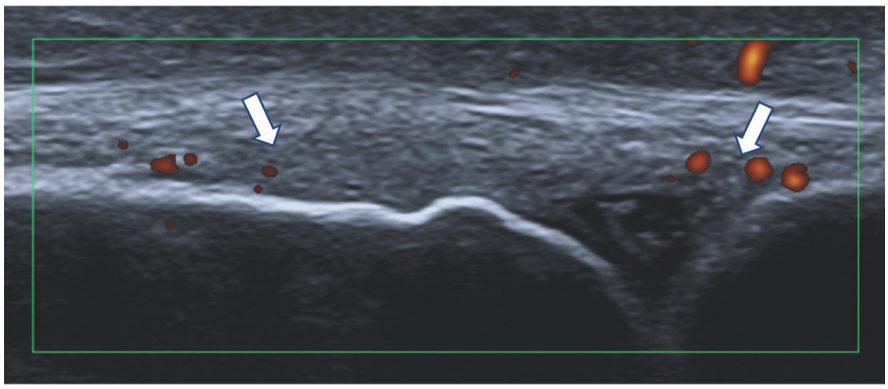

Fig. 8. Dorsal view of the MCP3 joint with moderate synovitis and mild power Doppler activity.

peroneal tendons was the major finding. Synovitis and tenosynovitis presented predominantly PD positive. Half of the patients experienced obvious partial or complete remission after treatment with NSAID, GC or after restart of DMARD therapy (temporarily paused during acute COVID-19). Half of the patients required start of a new DMARD or a DMARD-switch. In four of these patients, an underlying RMD had seen before or was newly diagnosed. Here, RA flares (n=2), a newly diagnosed LORA (n=1), and a newly diagnosed RA overlapping with longstanding pSS + SCLE (n=1) were causative. The patient with tenosynovitis of the right peroneal tendons took SSZ transiently.

Regarding the group without underlying RMD before COVID-19 (n=6), two patients presented with severe COVID-19. Their joint complaints occurred with a delay of few days during acute COVID-19 characterised by predominantly polyarticular arthralgia; swelling was rarely seen. MSUS proved arthritis in only few affected joints. Upon therapy with GC during COVID-19 and after respiratory reconvalescence, joint complaints completely disappeared. The other four patients without RMDs presented arthritis four to 16 weeks after SARS-CoV-2 infection. In two of them, polyarthritis was observed, in one case with good response to therapy with GC and in the other case, the diagnosis of LORA was made. One other case presented an oligoarthritis with recovery under NSAID and the aforementioned case with tenosynovitis of the right peroneal tendons also had an oligoarthritis. The prolonged and relapsing course and the SARS-CoV-2 vaccination nine days before onset of symptoms are notable here.

Concerning the subgroup with RMDs, three out of four patients showed an increase of disease activity with objectifiable synovitis by MSUS during mild and mild-moderate COVID-19. The patient with pSS + SCLE developed a RF-positive RA after mild COVID-19. Here, not only PD positive inflammation, but also erosions and rheumatoid nodules were documented in MSUS.

Discussion

Increasing data indicate the occurrence of arthritis associated with COVID-19 documented as single case reports, case series and review articles (6, 7, 23-25). However, clinical data are limited and there is lack of a detailed characterisation of COVID-19 associated arthritis confirmed by musculoskeletal ultrasound (MSUS). Thus, the objective of this case series is to present data on COVID-19 associated arthritis by MSUS. So far, best to our knowledge in only six publications authors presented MSUS findings by ultrasound images (7, 16, 26-29). In three other case reports the performance of MSUS and its findings were described, but no MSUS images for illustration and teaching purposes were published (25, 30, 31). In the case series of Ursini *et al*. with 35 patients, 60% of the COVID-19 associated arthritis was confirmed with MSUS or magnetic resonance imaging (MRI), but not presented by corresponding images (6). With this case series we want to objectify and illustrate MSUS-confirmed arthritis associated with COVID-19. Our MSUS findings revealed predominantly acute inflam-

mation, *e.g.* synovitis or tenosynovitis (often PD positive), which is consistent with the previous data.

Furthermore, we want to provide a detailed description of the clinical spectrum of COVID-19 associated arthritis. In general, arthritis in the context of infections is multiform. Bacterial infections cause septic arthritis, typically in the form of a monoarthritis with detectable causative pathogen in the joint cavity after infection with haematogenous spread, infection-related arthritis (*e.g.* after streptococcal tonsillitis), and ReA (32, 33). Disease definition and terminology of ReA have been changed since introduction (34). There are no standardised diagnostic or classification criteria. A symmetric mono- or oligoarthritis involving predominantly the lower limb following a symptomatic enteritis or urethritis are regarded as essential characteristics. The detection of the bacterial trigger infection is also required. In contrast to septic arthritis, synovial fluid is culture negative. ReA typically develops about one to six weeks post infection and can be associated with human leukocyte antigen (HLA)-B27 (35). Virus-related arthritis typically presents as symmetrical poly-articular arthritis that can principally mimic RA. Furthermore, in the majority of cases, a self-limiting course lasting several days to a few weeks is observable. In approximately one percent of patients with acute arthritis aetiologically a viral infection is assumed (36). Virus-related arthritis is caused on the one hand by direct invasion of synovial cells and on the other hand indirectly by an interaction of the cellular and humoral immune system (37). Moreover, the induction of autoantibodies like RF or anti-citrullinated protein antibody (ACPA) was demonstrated in the context of viral infections (38).

Consistent with previous findings, the clinical spectrum of COVID-19 associated arthritis is heterogeneous regarding the number and pattern of the joints affected, time to arthritis or disease course. Mono-, oligo- and polyarthritis, partly concomitant with tenosynovitis were seen. One of our patients presented with unilateral PD positive tenosynovitis of peroneal tendons 8 weeks after COVID-19, comparable to Di Carlo *et al.* (26). Notably, our patient reported joint complaints nine days after SARS-CoV-2 vaccination. Rarely, known vaccines are implicated triggering ReA (34). Polyarticular manifestation was identified, comparable clinical features affecting predominantly large and small joints respectively were described in previous case reports (39-41). COVID-19 associated arthritis has been occasionally accompanied with cutaneous phenomena: vasculitis, psoriatic skin lesions, but not in our presented cases (27, 39).

The interval between COVID-19 diagnosis and arthritis onset was a few days to 12 weeks, in one case complaints occurred during COVID-19. The variable lag time has been noted before, arthritis may occur during acute COVID-19, the recovery period or thereafter (7). The different time ranges might indicate different pathomechanisms.

Two of our patients (without underlying RMD) presented acute polyarthritis MSUS confirmed concomitant to severe COVID-19 with benign, self-limiting course after COVID-19 recovery and GC treatment. This clinical picture was compatible with an acute virus-related arthritis, such as parvovirus B19, hepatitis C virus, human T-lymphotropic virus type 1 (HTLV-1), rubella virus or the alphavirus Ross River virus (36). It must be pointed out that the synovial fluid or tissue of our two patients was not analysed. The detectability of viruses and its components in joints was shown for the viruses mentioned above, except for hepatitis C virus, but additionally for Epstein-Barr virus (38). In general, the pathogenicity is discussed as parvovirus B19 DNA was commonly shown in inflamed joints, but also in control samples of synovial tissue (42).

Four out of the six patients without underlying RMD showed a self-limiting course, similar benign courses were also predominantly found in literature (7, 25, 26, 28, 40, 41, 43-50). Nevertheless, insufficient response to therapy or prolonged courses are observable in our cohort and beyond (6, 30, 51). Persistence of arthritis or relapses under therapy tapering are suspicious of a developing RMD. This constellation applied to one of our patients, here a new onset of RA was diagnosed timely related to COVID-19.

However, an association between arthritis and the severity of COVID-19 is not deducible from our data due to the small number of cases and its heterogeneity.

We also want to highlight new onset or flares of rheumatic diseases possibly triggered by COVID-19. In this case series, three patients exhibited flares of their underlying RMD (2x RA, 1x PsA) developing increasing disease activity during COVID-19. Time to arthritis onset was three to seven days. In two of them there was a persistent arthritis despite restarting DMARD therapy after negative SARS-CoV-2 PCR. In the current literature there is one case of a 50-year-old female patient with seropositive RA in remission under MTX hospitalised because of severe COVID-19 who developed concomitant polyarthritis confirmed by MSUS and biopsy. The introduction of sarilumab (IL-6 antagonist) resulted in respiratory and articular improvement (16). Zhou *et al.* reported that COVID-19 in patients with PsA resulted in disease flares developing within two to three weeks (17). An association between respiratory virus infection and acute psoriasis flares has been discussed before. Sbidian *et al.* investigated in a pilot study patients with psoriasis flares temporary related to respiratory tract infections and identified mostly viral pathogens, *e.g.* Coronavirus, via RT-PCR from NPS (52). The cases 6 and 10 that are characterised by newly diagnosed RA (1x LORA, 1x RA overlapping with longstanding pSS + SCLE) post-COVID-19 might indicate the capacity of SARS-CoV-2 triggering RA. An increased RA incidence observed after epidemic coronavirus infections supports this hypothesis (53). These findings are in line with the common opinion that viral infections might be risk factors for developing RA (54). The potential links and pathophysiological overlaps between COVID-19 and RA are under investigation (55).

So far, clinical data are limited on this topic 'coincidence *versus* connection' of COVID-19 and RA (56). Perrot *et al.* reported a 60-year-old woman presenting

with polyarthritis about four weeks after mild COVID-19 treated with hydroxychloroquine and azithromycin. MSUS detected synovitis and laboratory findings revealed increasing levels of ACPA and C-reactive protein (comparing samples prior to and post arthritis onset). An ACPA-positive RA was diagnosed and a good clinical response under MTX was seen (14). Baimukhamedov *et al*. described the case of a 67-year-old man who developed polyarthritis several weeks after moderate COVID-19. Striking laboratory findings were newly elevated RF and increasing ACPA. Under MTX and methylprednisolone, remission was achieved. The diagnosis seropositive RA was discussed (57). Moreover, the case report of a 33-year old woman evolving an ACPA-positive palindromic rheumatism (PLR) following COVID-19 with transition to ACPA-positive RA after SARS-CoV-2 reinfection inspires the discussion of the relationship of the entities (58). In our cohort, the clinical phenotype of PLR and its distinct MSUS pattern with extracapsular inflammation, often without synovitis, were not evident (59, 60).

As mentioned above virus-related arthritis is typically self-limiting, but HTLV-1 related arthritis can take a chronic course (37). Additionally, because of the polyarticular pattern the differentiation between RA and virus-related arthritis is complicated. MSUS as a useful diagnostic tool in detecting erosions can be helpful in the assessment considering that erosive courses in virus-related arthritis are uncommon (61, 62). Erosions do not exclude viral aetiology, the capacity of HTLV-1 triggering erosive arthritides was mentioned (37, 63).

Limitation

The data presented originate from a rather small and heterogenous collective varying in age, comorbidities, severity of COVID-19 and its corresponding treatment. Besides these conditions, heterogenous findings were observed. Arthritis associated with COVID-19 in patients without underlying RMD resembles the clinical picture of ReA or virus-related arthritis. Predominant PD positive synovitis and also tenosynovitis detected by MSUS emphasise the inflammatory state. Thus, these findings reflect the heterogeneity of the current literature.

Conclusion

In summary it should emphasised that, with the COVID-19 pandemic the differential diagnosis of arthritis has been extended. With this report we want to increase awareness for arthritis associated with COVID-19 appearing as a symptom or a complication with features of the different entities. Flares or new-onset RMDs should also be considered. In this context we provide MSUS findings for complementary characterisation.

Collecting comprehensive clinical and laboratory information in combination with MSUS findings, and, if possible, synovial fluid analysis are essential to differentiate arthritis and to contribute towards a precise definition of the spectrum of arthritis associated with COVID-19. The increasing number of cases emphasises the relevance and need for further research efforts to establish a profound knowledge and for a better understanding of the current clinical heterogeneity.

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