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REACTIVE ARTHRITIS IN A PATIENT AFTER COVID-19 INFECTION: A CASE REPORT AND REVIEW OF THE LITERATURE

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Summary

Reactive arthritis in a patient after COVID-19 infection: a case report and review of the literature

COVID-19 infection can lead to a wide variety of complications involving the majority of body systems, including the musculoskeletal one. One of its clinical manifestations of it is reactive arthritis. In the following, we present the clinical case of a 56-year-old woman with post-COVID-19 reactive arthritis and it's follow-up.

***Key words**: reactive arthritis, COVID-19 infection*

Rezumat

Artrita reactivă la un pacient după infecţia COVID-19: raport de caz

Infecţia cu COVID-19 poate duce la o varietate mare de complicaţii care implică majoritatea sistemelor corpului, inclusiv pe cel musculo-scheletal. Una dintre manifestările clinice ale acesteia este artrita reactivă. În cele ce urmează prezentăm cazul clinic al unei femei de 56 de ani cu artrită reactivă post COVID-19 şi monitorizarea acestuia.

***Cuvinte cheie:** artrită reactivă, infecţia COVID-19*

Резюме

Реактивный артрит у пациента после инфекции КОВИД-19: клинический случай

Инфекция COVID-19 может привести к самым разнообразным осложнениям, затрагивающим большинство систем организма, в том числе опорно-двигательный аппарат. Одним из клинических проявлений его является реактивный артрит. Ниже мы представляем клинический случай 56-летней женщины с реактивным артритом после инфекции COVID-19 и его последующее наблюдение.

***Ключевые слова:** реактивный артрит, инфекция COVID-19*

Introduction. It has been over two years since the first documented case of the COVID-19 virus was recorded. Since that time, our understanding of this virus has continually evolved; however, its wide-ranging effects are still unfolding. Like previously studied viral infections, severe acute respiratory syndrome-associated coronavirus-2 (SARS-CoV-2) has been shown to lead to a degree of autoimmunity in patients who are recovering from its effects. Due to its effects on the innate immune system such as the toll-like receptors and complement system, a varying degree of pro-inflammatory markers can become widespread in those who continue to recover from the virus [28]. COVID-19 can lead to a wide variety of complications affecting pulmonary, neurological, cardiovascular, rheumatological, dermatological, and many other systems. It is not yet clear how these complications will progress and whether they are reversible or not [4].

Conquering the early symptoms of COVID-19 may simply be the start of a long and challenging road to recovery as a substantial number of patients "long haulers" may have persistent post-COVID-19 symptoms [8,10]. Several studies reported post-COVID-19 reactive arthritis, vasculitis, and connective tissue illnesses, including lupus and inflammatory myositis. Others documented that, patients with COVID-19 with pre-existing rheumatic disorders may worsen or develop new autoimmune characteristics [13]. In this context, patients recovering from COVID-19 must be closely monitored for autoantibody production and rheumatic symptoms.

The mechanisms of post-viral arthritis are still unknown; these may include joint infection, immunologic complex formation, and immune dysregulation. Most researchers believe that molecular mimicry between SARS-CoV-2 epitopes and the synovial membrane causes local inflammation; other opinions speculate about the presence of circulating immune complexes or the virus's direct localization on joint tissue [18,24]. Furthermore, by boosting IL-6-related pathways, SARS-CoV-2 causes cytokine storm and macrophage activation syndrome. Antigen presentation and interferon-dependent routes can both be affected. Those altered inflammatory systems may elicit autoimmune processes in predisposed individuals [17]. Factors that predispose to arthritis as a result of SARS-CoV-2 infection are unknown; however, a review of medical literature, in line with the results of the current study, suggests that smoking affects mucosal surfaces, including the lungs, as well as synovial membrane and cartilage predisposing to arthritis [2,22]. In addition, studies reported that the incidence of viral arthritis was dependent on patients' age being more common in adults [23]. Likewise, Lokugamage et al. [25] stated that viral arthritis usually presents as a self-limiting bout of symmetric polyarticular arthritis or arthralgia. They also noted that toll-like receptors, which are abundantly expressed in the lung and bronchus, can recognize SARS-CoV-2 to produce IL-6. Thus, patients with COVID-19 may have inflammatory or autoimmune symptoms, such as arthritis [41]

The body of literature on the manifestations following COVID-19 is expanding and has ramifications in many disciplines. The medical community is still grasping the full picture of the aftermath of SARS-CoV-2 infection among recovered patients. Awareness about the possibilities of ReA in the immediate course of recovery from COVID-19 is essential as it may impede physical and occupational therapies, which are crucial in the recovery process. Moreover, in patients who have had a severe COVID-19 course and required intensive care management, ReA may coexist with the active or lingering symptoms of critical illness myopathy to further limit optimal gain from occupational therapies. It points to the importance of an adequate multidisciplinary team involving rheumatologists, physiatrists, pain physicians, and occupational therapies for efficient management in such scenarios.

Recommended first-choice treatment for reactive arthritis caused by other pathogens is NSAID's and glucocorticoids. If these agents are insufficient, disease-modifying anti-rheumatic drugs may be attempted. Although various rheumatic and musculoskeletal disorders associated with COVID-19 have been reported [1,11,27], there have been no controlled clinical studies on ReA associated with COVID-19.

Aim of the publication: To present the clinical case of a patient with post COVID-19 reactive arthritis.

Material and methods. We have examined an outpatient with manifestations of musculoskeletal system involvement after COVID-19 infection.

Inclusion criteria:

1. New onset of musculoskeletal symptoms after COVID-19 infection;
2. Fulfilment of both major criteria and a relevant minor criterion for definitive diagnosis of ReA;
3. More than 18 years old;
4. Informed consent of the patient.

Exclusion criteria:

1. Patient with previous history of rheumatic disorders;
2. Presence of positive serology for Chlamydia Trachomatis, Mycoplasma Hominis, Ureaplasma Urealiticum, Parvovirus, HBV, HBC, HIV;
3. Presence of positive serology for RF, anti-CCP, ANCA, ANA and subtypes ENA and subtypes,;
4. Presence of personal or hereditary history of psoriasis or IBD;
5. Patient refusal to participate in the study.

The subject was examined by general and specific methods of evaluation, as follows:

DAS-28

DAS stands for 'disease activity score', and the number 28 refers to the 28 joints that are examined in this assessment. The DAS28 is a composite score derived from 4 of these measures which includes:

1. SJC
2. TJC
3. ESR/CRP
4. PGA

According to the formula of the DAS, DAS28-ESR and DAS28-CRP were calculated and both DAS28 values were categorized as follows: > 5.1, high disease activity; ⩽ 3.2, low disease activity; and < 2.6, remission.

VAS

A Visual Analogue Scale (VAS) is one of the pain rating scales. The intensity of pain was measured over the last 7 days on a scale from 0-100mm. Where 0mm corresponds to an absence of pain and 100mm to extreme pain. A value of 0-30 mm was classified as mild pain, 30 mm-70 mm as moderate pain and >70 mm as severe pain.

TJC and SJC

The swollen joint count reflects the amount of inflamed synovial tissue and the tender joint count is associated more with the level of pain. Joint tenderness is defined as pain at rest that is induced by pressure at examination of the joints. Joint count includes the MCP, proximal interphalangeal (PIP), and distal interphalangeal joints of the hands, the metatarsal phalangeal (MTP) and distal interphalangeal joints of the feet, and the shoulder, elbow, wrist, hip, knee, ankle, tarsus, and temporomandibular, sternoclavicular, and acromioclavicular joint .

Clinical case.

First consultation

Patient E. M, 56 years old female was consulted by the rheumatologist in December 2021, with the complaints of arthritis of the left knee.

Medical history: the patient was diagnosed with a mild form COVID-19 disease 14 weeks ago, with symptoms of low grade fever (37.6oC, rhinorrhea, loss of smell and loss of taste). She was treated ambulatory by her family physician with Paracetamol and vitamin C and D. After 4 weeks from COVID-19 onset, the patient noted inflammatory knee pain.

Pathological antecedents: arterial hypertension 2nd degree treated with Bisoprolol and Indapamide, diabetes mellitus treated with Metformin.

Hereditary anamnesis: no particularities.

Bad habits: none.

Allergies: none.

Physical examination: the general state was good. Active attitude, clear conscience, normosthenic constitution, overweight (BMI – 29 kg/m2). Vital signs: temperature in the axillary fossa 36.5C, heart rate – 76 bpm, blood pressure – 123/78 mmHg. Musculoskeletal system: SJC – 1 left knee, TJC – 1 left knee, VAS pain was 65 mm and PGA 55 mm. The remainder of the physical examination was normal, with teguments and mucosa visible pink – pale, clean, normal pulmonary and cardiac stetacoustics, pulsatile peripheral arteries, supple abdominal pain, intestinal transit present, physiological motions.

The paraclinical stage reveals the presence of mild biological inflammatory syndrome by increased level of erythrocytes sedimentation rate (ESR) of 16 mm/hour and the serum C – reactive protein (CRP) of 6,6 mg/dl (normal < 5 mg/dl). The CBC was normal. Antibodies examination has shown that FR, anti – CCP, ANA, ANCA, complement C3 and C4, liver function tests such as ALT, AST, GGT, ALP were normal. Tests for hepatitis (anti HVC, anti Hbs and anti HBc antibodies) was proven to be negative. HIV test was negative as well CMV antibodies test'. Serology for Chlamydia Trachomatis, Mycoplasma Hominis, Ureaplasma Urealiticum were negative. US of the knee demonstrated synovitis – synovial hypertrophy and moderate joint effusion. Knee X-Ray revealed second degree osteoarthritis (figure 1).

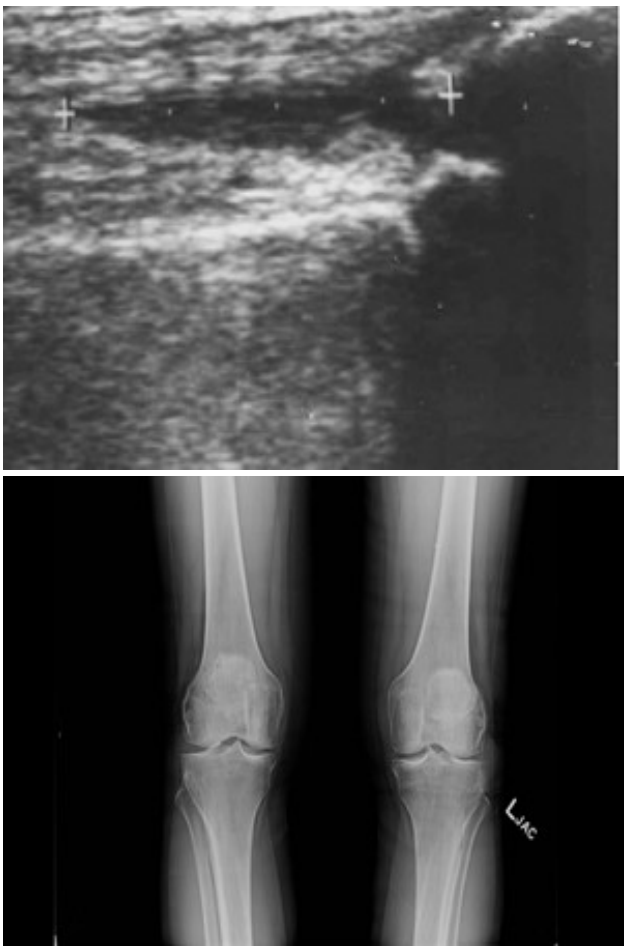

Figure 1. *Ultrasound knee joint showing synovial thickening*
Radiography of the knee showing second degree osteoarthritis

In this case, based on the clinical symptoms and the results of the paraclinical evaluation, a diagnosis of bilateral knee osteoarthritis with left knee synovitis was established.

For the treatment of the patient were recommended short period NSAIDs, left knee arthrocentesis with infiltration of Diprospan 2 ml and general recommendations of the management of knee osteoarthritis (knee orthesis, weight loss).

Second consultation

After 20 days the patient returned for rheumatology consultation. She reported that after joint arthrocenthesis the symptoms ameliorated for a short period of time. The disease flared with diffuse arthralgia and arthritis, involving symmetrically the hands, feet, despite taking permanently NSAIDs. Morning stiffness was more than 60 minutes. VAS pain scale was corresponded to intense pain 84 mm.

Joint examination showed: TJC 16, SJC 7.

In the repeated paraclinical examination, the ESR was 12 mm/h and CRP of 4.7 mg/dl.

Radiological examination of the hands and feet was in favor of ReA.

By analysing the clinical, paraclinical data as well as the mild responsiveness of the patient to the early treatment, the diagnosis post – COVID 19 ReA has been established.

It was then recommended to start treatment with DMARDs (Methotrexate 10 mg a week), low dose CS (Deflazacort 6 mg a day), folic acid, PPI and Ca + VitD.

Third consultation

After 1 month, the patient noticed an improvement of the joint syndrome – VAS pain was 31 mm, the duration of morning stiffness 10 minutes, she had no swollen joints and only 1 tender joint. ESR was 8 mm/Hg and CRP was negative. We have recommended to withdraw the GCS and to continue with Methotrexate intake (12,5 mg per week) plus NSAIDs.

Discussion on the clinical case. Reactive arthritis (ReA) is classically considered a sub-type of spondyloarthritis (SpA) that is precipitated after a gastrointestinal or genitourinary infection [19]. The usual presentation is monoarticular or oligoarticular arthritis involving large joints that occurs around 2–4 weeks after an infection. However, the term has been used in a wider context of an immune-mediated arthritis that may occur after any infection. The primary concept is that there is no direct invasion of the joints by any pathogen but the arthritis occurs as a result of induced changes in the immune system [21].

The American College of Rheumatology (ACR) or the European Alliance of Associations for Rheumatology (EULAR) does not have separate practice guidelines pertaining to ReA. The incidence is apparently declining in most high-income countries [22]. However, the rest of the world that depend on the ACR and EULAR recommendations may find this gap challenging. For example, Latin America had the largest proportion of patients with "peripheral spondyloarthritis" [27]. ReA from India has arthritis as the predominant feature in 95% of patients [42] while a report from Finland showed only arthralgia in two and arthritis in none of 17 patients with post-*Escherichia coli* musculoskeletal conditions [43]. Thus, there seem to be great differences in how clinicians from different parts of the world view ReA.

Only a small percentage of patients who have infections with organisms such as *Campylobacter*, *Salmonella*, *Shigella*, or *Yersinia* develop ReA [32]. Similarly, amongst millions who have developed SARS-CoV-2 infection, only a minor proportion develops arthritis.

The pathogenesis of viral associated arthritis is only partially understood but one of the mechanisms supposed to mediate the activation of the inflammatory process is molecular mimicry, well known to be responsible for eliciting autoimmune responses in predisposed individuals. Examples of molecular mimicry concerning SARS-CoV2 are reported [9] and this mechanism is hypothetically involved in the pathogenesis of both the acute systemic infection and the post-infective viral-related immunological consequences [3]. Previous and actual studies demonstrate that coronaviruses share molecular epitopes with human proteins (e.g., spike glycoprotein S) that play a key role to host cell invasion and escape immune response attacks, giving to the infectious agent an immune-evasive capacity [20]. Viruses have been long implicated in the breakdown of immune tolerance and precipitation of autoimmune disease [39]. SARS-CoV-2 activates CD14 + monocytes and PD-L1 + neutrophils via the Osteopontin-mediated inhibition of Interleukin-10. This pathway is involved in rheumatoid arthritis and thus provides a common pathway for the evolution of inflammatory arthritis. In Chikungunya viral infection, a prominent role of monocytes and anti-viral responses such as interferons has been postulated [40].

Interferon (IFN)-related pathways have been implicated in COVID-19 and these have a role in the initiation of rheumatoid arthritis. The TNF (Tumor Necrosis Factor)-induced animal models of rheumatoid arthritis are dependent on IFN and IFN response elements such as the IRF1 (interferon regulatory factor 1) transcription factor [8].

In addition, various autoantibodies have been reported in COVID-19. Some of these might have pathological potential and if they persist after the infection, they may lead to rheumatic manifestations like arthritis. At least 15 different autoantibodies

have been described in COVID-19 and 34 human peptides have similarities with SARS-CoV-2 proteins [18]. This may have implications for molecular mimicry in COVID-19.

TLR-3 and TLR-7 activation is presumed to be one of the first steps in SARS-Cov2 clearance. Nevertheless, the SARS-CoV2 infection relationship with TLRs is nothing but straightforward, as both clinical and experimental evidence seems to indicate that some unexplained TLRs alteration, either as inhibition or dysfunction, could sustain the defective immune response to viral infection and subsequent severe clinical manifestations [7,31,33]. Despite the knowledge we possess about the viral role in inflammatory arthritis, COVID-19 appears to operate following different immuno-pathogenic pathways. Furthermore, other immunological alterations are observed in COVID-19 patients, such as regulatory cells dysfunction and increased circulating T_H17 cytokines like IL-17 among all [29,44].

Post COVID-19 arthritis more commonly has a rheumatoid like phenotype affecting the wrists, ankles, and small joints of hands and feet. However, a spondyloarthritis-like presentation with axial involvement has also been reported [12]. It can also present as classical ReA with lower limb predominant oligoarthritis [40]. Isolate monoarthritis of a single metacarpophalangeal joint has also been reported [11]. Although ReA causes asymmetric oligoarthritis in the lower extremities, a mild form of upper limb arthritis can also occur. In contrast to this, Danssaert *et al.* [14] reported arthritis of unilateral hand joints without involvement of lower extremities. Liew *et al.* [26] described a patient with acute right knee arthritis manifesting 3 days after fever and simultaneously being positive for SARS-CoV-2 infection. Schenker *et al.* [36] and De Stefano *et al.* [15] described cases of ReA associated with cutaneous vasculitis and psoriatic skin lesions, respectively. The patient reported by Ono *et al.* [30] had severe respiratory distress requiring mechanical ventilation, whereas respiratory involvement was milder in the other five patients. Other manifestations of ReA include inflammatory back pain, dactylitis, enthesitis, tendinitis and bursitis. Arthritis persists for >6 months in 30–50% of patients [10]. There are no specific laboratory tests for ReA, and diagnosis relies on the typical clinical presentation with detection of the triggering infection [37]. However, the established definitive diagnostic criteria is based on the fulfilment of both major criteria and a relevant minor criterion, while a 'probable' diagnosis is characterized by both major criteria but no relevant minor criterion or one major criterion and one or more of the minor criteria.

ReA tends to occur most often in men between ages 20 and 50. The initial reports of post-COVID-19 ReA were in men past 50 years of age [20,26,35]. This is in contrast to the classical ReA that is most common between 15 and 40 years of age. Again, at least three cases of post-COVID-19 ReA have also been reported in the paediatric age group [24,38]. Unlike classical ReA, gender distribution appears equal between males and females. However, the total number of reported cases is too small for conclusive comments. The duration between COVID-19 diagnosis and ReA varied between cases. However, it was seen that arthritis generally appeared after acute infection and during the recovery period (median: 18 days). Clinical data of ReA indicate that oligoarticular involvement predominates, followed by monoarthritis with prominent involvement of the lower extremity joints [23,36]. Monoarthritis was the most common form of involvement in ReA cases after COVID-19, followed by oligoarthritis and polyarthritis at equal rates. The most commonly involved joints were the knee, ankle, and proximal interphalangeal joint. Lahu et al. [36] reported the most commonly involved joints in ReA to be the knee, talocrural (ankle), and metatarsophalangeal joints, which were consistent with the current results. The presence of polyarticular involvement with the involvement of the hand joints in ReA cases after COVID-19 is compatible with the clinical status of other viral-associated arthritises, which occur with a polyarticular pattern similar to rheumatoid arthritis [38].

Classical ReA is self-limiting in two-thirds of cases, but can damage the joints even in such a short period. Chronic ReA can have much worse sequelae. In the case of post-COVID-19 ReA, the manifestations appear more transient and self-limiting. This appears more similar to post-streptococcal ReA rather than classical ReA [1]. Also, some cases of post-COVID-19 ReA have different antibodies. There is a possibility that these may evolve into classifiable rheumatic diseases such as rheumatoid arthritis or lupus [2].

A 30–50% of patients with ReA carry HLA-B27. Although patients without HLA-B27 can develop ReA,, some degree of genetic susceptibility is considered necessary, since ReA occurs in only 7–15% of infected population-level subjects. The association of HLA-B27 and ReA is further illustrated by the fact that the prevalence of disease in HLA-B27-positive individuals is five times greater than in the general population. In HLA-B27-positive relatives of patients with ReA, the prevalence is an additional 10 times greater. Moreover, HLA-B27 positivity may be a poor prognostic factor, as a previous study has shown that the presence of HLA-B27 in ReA has been linked to more severe disease, higher frequencies of sacroiliitis and extra-articular manifestations, and an increased likelihood of persistent arthropathy (table 1).

Table 1.

Differences between classical and post-COVID 19-ReA [6]

	"Classical" reactive arthritis	**Post-COVID-19 reactive arthritis**
Age	15–40 years predominantly	Above 45 years predominantly, but reported in all ages
Gender	Male preponderance	Equal male–female distribution
Precipitating factor	Gut or urogenital infection	Respiratory tract infection
Inciting agent	Bacteria	Virus
Phenotype	Spondyloarthritis-like	Multiple phenotypes
	-Axial involvement	
	-Lower limb predominant oligoarthritis	
	Large joints	
Joint predilection	1/3rd become chronic (lasts beyond 3 months)	Small joints
Chronicity	Treated as other spondyloarthritis (limited evidence base)	Most resolve within 2 weeks to 3 months
Management	Dactylitis	Usually, low dose steroids with or without NSAIDs is sufficient (limited evidence base)
Extra-articular manifestations	Enthesitis	Unknown/limited
	Skin	
	Uveitis	
	Inflammatory bowel disease	

According to the majority of literature sources the patients had responded to non-steroidal anti-inflammatory drugs (NSAIDs) while some received intra-articular steroids or rapidly tapered oral steroids. Where outcomes are reported, usually, there was a response within the first week and the steroids / NSAIDs could be tapered down after 4 weeks. Only patients with rheumatoid arthritis-like phenotype with anti-citrullinated peptide antibodies had a chronic course and had to be given methotrexate [5,16,34].

Reports on axial involvement were depicted in the studies of Colatutto et al., Coath et al., and Shokraee et al. In these studies, the patients developed arthritis symptoms in a period of 2–3 weeks after being diagnosed with COVID-19. These patients were also presenting with new onset debilitating inflammatory back pain in the lumbar, thoracic and cervical regions, Symptoms improved with NSAIDs therapy over the following months while MRI remained positive.

In the studies by Liew et.al, Talarico et.al, Danssaert et.al, Schenker et.al, Houshmand et.al and Di Carlo et.al, patients presented also with symptoms of extra-articular manifestations of reactive arthritis such as balanitis, diffuse myalgia, urticaria as well as palpable pupura of the calves.

The case represents a 56 years old woman who presented with knee monoathritis shortly after COVID-19 infection, mild form of the disease. Regardless of the treatment with anti-inflammatory drugs, joint syndrome became poliarticular, involving symmetrically hands, knees and feet. In the exclusion of other cause of arthritis, a diagnosis of post COVID-19 ReA was established.

The clinical picture of our patient corresponds to the data regarding post COVID-19 ReA presented in the literature, where post COVID-19 arthritis was had commonly a rheumatoid like phenotype affecting the wrists, ankles, and small joints of hands and feet [12] and at the onset it can also present as classical ReA with lower limb predominant oligoarthritis or monoarthritis. Our patient did not respond to NSAIDs and intra-articular steroids, she required DMARD treatment. From the literature we know that only patients with rheumatoid arthritis-like phenotype had a chronic course and had to be given methotrexate [5,16,34].

Conclusions. Post-COVID-19 reactive arthritis is one of the many outcomes related to the SARS-CoV-2 infection. Clinical and laboratory presentation of the case reported in this article resembles reactive arthritis due to other pathogens, with few differences, this might be related to the diversity of pathophysiological mechanisms involved and still missing information about this infection.

Declarația de conflict de interese: autorii declară că nu există conflict de interese.

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