

COVID-19-Related Arthritis: Difference between Viral Arthritis and Reactive Arthritis

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Abstract

Sterile arthritis has been reported in patients with Coronavirus Disease (COVID-19). However, some patients had been inappropriately diagnosed with 'Reactive Arthritis (ReA)' instead of 'viral arthritis'. ReA is a form of sterile arthritis that occur secondary to an extraarticular infection in genetically predisposed individuals. The extra articular infection is typically a bacterial infection of the gastrointestinal or genitourinary tract. The definition, diagnostic criteria, and list of causative bacteria were proposed at the Fourth international workshop on reactive arthritis held in 1999. The clinical features of patients with COVID-19-related arthritis do not only fit with the definition and diagnostic criteria. The clinical course of extraarticular infection and subsequent self-limiting arthritis is sometimes similar for both viral arthritis and ReA. However, the duration of arthritis is generally much shorter in viral arthritis than in ReA. Therefore, it should be necessary to understand that COVID-19-related arthritis falls into a distinct category of 'viral arthritis' that is different from ReA.

Keywords: COVID-19; Reactive arthritis; SARS-CoV-2; Spondyloarthritis; Viral arthritis

Introduction

Postinfectious arthritis is a broad group of non-suppurative arthritis induced during and after an extraarticular infection by various microorganisms. Classical ReA (formerly Reiter's syndrome), infection-related arthritis, and viral arthritis or postviral arthritis is considered independent entities that are classified within postinfectious arthritis. However, the definition and classification of postinfectious arthritis remain misleading entities, especially concerning terminology.

The term ReA is sometimes incorrectly used interchangeably with postinfectious arthritis, especially viral arthritis. In other words, some authors inappropriately consider postinfectious arthritis to be a large group of ReA. Viral infections are known to have both clinical features and a complex immunological relationship similar to various autoimmune diseases. However, the terms 'viral arthritis' or 'postviral arthritis' is not widely used or understood in clinical practice. Thus, viral arthritis is sometimes misdiagnosed [1] (Figure 1).

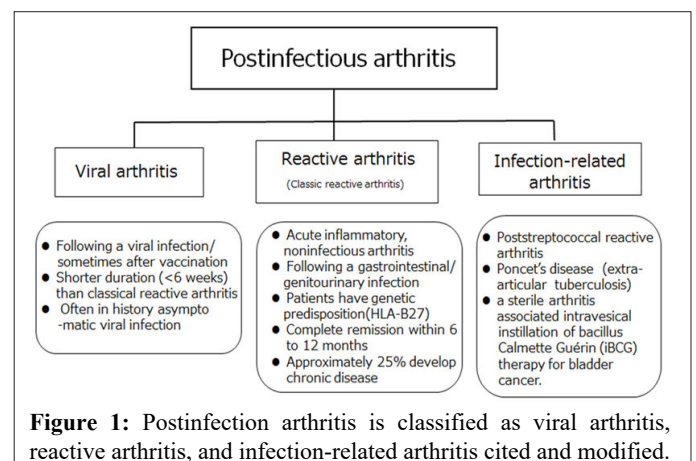


Figure 1: Postinfection arthritis is classified as viral arthritis, reactive arthritis, and infection-related arthritis cited and modified.

More than 30 cases of COVID-19-related arthritis have been recently reported, with more than half of them diagnosed as ReA. However, the cases do not fit with the established definition and traditional diagnostic criteria of ReA [2].

Viral arthropathy and myalgia following COVID-19 are commonly reported, and some viral infections induce clinical manifestations similar to those of well-defined rheumatic diseases [3,4]. However, there is few papers show that COVID-19-related arthritis is viral arthritis instead of ReA, leading to widespread misdiagnosis of ReA. This mini-review presents our opinions based on the original definition of ReA and the difference between viral arthritis and ReA.

Literature Review

The concept, definition, and diagnostic criteria of ReA

Ahvonon, et al. defined ReA as aseptic or non-suppurative arthritis following microbial infection of sites other than the joints. This is a well-known concept of ReA that is simply based on a pattern of developing arthritis after an extraarticular bacterial infection [5].

At the Fourth International Workshop on Reactive Arthritis, the designation of Reiter's syndrome was discarded because Hans Reiter was accused of war crimes with the Nazi Party [6]. The eponym was replaced with the term ReA which was introduced by Ahvonon, et al. The definition and diagnostic criteria for ReA were proposed by Braun and associates at the workshop (Table 1) [2,5]. This is the most commonly used definition and diagnostic criteria of ReA [7-11].

The Berlin diagnostic criteria for reactive arthritis		
Typical peripheral arthritis epredominantly lower limb, asymmetric oligoarthritis Plus	Evidence of preceding infection	
	a) Where clear clinical diarrhoea or urethritis within the preceding four weeks, laboratory confirmation is desirable but not essential	b) Where no clear clinical infection, laboratory confirmation of infection is essential
Exclusion criteria: Patients with other known causes of mono/oligoarthritis, such as other defined spondyloarthropathies, septic arthritis, crystal arthritis, Lyme disease and post-streptococcal reactive arthritis. The diagnosis of reactive arthritis does not require the presence of HLA-B27 or extra-articular features (conjunctivitis, iritis, skin lesions, non-infectious urethritis, cardiac and neurological features) or typical spondyloarthopathic features (inflammatory back pain, alternating buttock pain, enthesitis, iritis) but these should be recorded if present.		

Table 1: The Berlin diagnostic criteria for reactive arthritis and its exclusion criteria.

A panel of experts attending the workshop determined a specific list of possible causative gastrointestinal and urogenital pathogens. These included *Chlamydia trachomatis*, *Yersinia*, *Salmonella*, *Shigella*, *Campylobacter*, *Escherichia coli*, and *Clostridioides* (formerly *Clostridium*) *difficile* [10]. Although other bacteria and viruses were proposed, they are not included as causative agents of ReA by this definition [4].

Bacterial, immunological, and genetic factors including Human Leukocyte Antigen (HLA)-B27, play an important role in the pathogenesis of ReA. Therefore, ReA is not only a pattern of acute inflammatory arthritis following an infection outside the joint but also the specific clinical entity (classic ReA) defined at the workshop. Further, ReA is categorized as one of the diseases of Spondyloarthritis (SpA) that consisted of axial SpA including ankylosing spondylitis, psoriatic arthritis and SpA with inflammatory bowel diseases.

The clinical feature of ReA refers to a constellation of arthritis, enthesitis, mucocutaneous lesions, and ocular symptoms of sterile inflammation occurring after a urinary or gastrointestinal infection [7-11]. Peripheral arthritis is typically induced in ReA, found predominantly in lower limbs and large joints, and it asymmetrically develops in less than 5 joints. The typical disease duration is 3 months-5 months. Most patients either achieve complete remission or have little active disease within 6 months-12 months after presentation and 15%-20% of patients may likely experience chronic persistent arthritis [12].

Additionally, it was proposed at the workshop that, except for septic arthritis, any other post infectious non-suppurative arthritis, such as post streptococcal ReA, Poncet's disease, and aseptic arthritis induced by intravesical instillation of Bacillus Calmette-Guérin (iBCG) therapy for bladder cancer, were proposed to be referred to as "infection-related arthritis" not but ReA [13]. Therefore, post infectious arthritis is fundamentally categorized as ReA (classic ReA), infection-related arthritis, and post infectious viral arthritis [1] (Figure 1).

Based on this established definition, and diagnostic criteria, arthritis induced by a Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection, which has recently been reported, does not fit with the criteria of ReA described in the literature and textbook should be categorized as 'viral arthritis'. Therefore, the term ReA is now widely used but often inappropriately spread [14].

Viral arthritis

Viral arthralgia and viral arthritis occur commonly in patients infected with parvovirus B19, hepatitis B virus, Human Immunodeficiency Virus (HIV), flaviviruses, and alphaviruses and some patients demonstrated arthritis that is very similar to Rheumatoid Arthritis (RA) and other rheumatic diseases such as ReA [15,16]. Among the virus-induced arthritides, ReA associated with an HIV infection is often reported and discussed in the literature. However, ReA is found to be related to other bacterial infections that patients with HIV are exposed to, not to the HIV infection itself [17,18].

Pathogenesis of viral arthritis

Various mechanisms of viral arthritis have been discussed including direct entry into joint cells or tissues, Immune Complex (IC) formation, by directly or indirectly causing immune dysregulation, and molecular mimicry. Rubella, rubella vaccine virus, parvovirus, enterovirus, and chikungua virus have tropism for synovial tissue, allowing the direct invasion to the joint [16,19]. Both parvovirus and enteroviruses have been isolated from joint fluid. Alphavirus and Ross River virus persist in synovial macrophages. Viral particles act as the antigenic component of IC and IC preferentially deposits in the joints and skin which causes arthritis and skin rash. This type of presentation commonly occurs in cases of hepatitis B, hepatitis C, and parvovirus infections [20].

Interestingly, a mechanism of molecular mimicry refers to a significant similarity between certain pathogenic molecules of a virus or viral vaccine and specific human proteins. This similarity may lead to immune cross-reactivity, wherein the reaction may harm similar human proteins, essentially causing an autoimmune disease. Many authors assume the existence of molecular mimicry between viral epitopes and synovial membranes causing local inflammation [21]. Recently, 28 human proteins harboring regions homologous to SARS-CoV-2 peptides have been studied and reported [22].

Considering the mechanisms of IC formation, immune dysregulation, and molecular mimicry, it can be understood that the development of arthritis could take several days to a few weeks from the onset of SARS-CoV-2 infection. In a patient-reported analysis, 69.1% of patients with COVID-19 reported arthralgia during a SARS-CoV-2 infection, 9.9% of patients reported arthralgia after COVID-19, and 20.9% had arthralgia both during and after COVID-19 [3]. This biphasic illness is a well-known pattern or course of ReA, but it easily confuses or misleads the diagnosis of 'viral arthritis' as ReA. This is another especially important feature of viral arthritis which is not widely understood in medical practice.

Recently, Kuschner, et al. [23] reported the detection of RNA of the SARS-CoV-2 in the synovial fluid in the case of COVID-19. This is the first report demonstrating the presence of SARS-CoV-2 RNA in the joint. Therefore, this evidence does not support Ahvonen, et al.'s concept of ReA [5].

Cytokine and chemokine

The exact mechanisms for joint inflammation are not fully understood, however, a SARS-CoV-2 infection leads to stimulation of macrophages which in turn causes a release of high levels of cytokines such as IL-6, IL-1, IL-8, TNF, and other chemokines, such as granulocyte-macrophage colony-stimulating factor, CXCL10 (IP10), and CCL2 (MCP1), which all leads to the development of and increase the inflammatory response [24]. Interleukin 17A has been involved in the pathogenesis of reactive arthritis and other SpA in general, and also in the hyper inflammatory state of COVID-19 [25]. Therefore, it is not surprising that COVID-19 can sometimes induce musculoskeletal and skin manifestations of SpA. In fact, up to one-third of HIV-infected persons with psoriasis develop psoriatic arthritis [26].

Clinical manifestation of COVID-19-related viral arthritis

The clinical features of COVID-19-related arthritis have been reported by Gracia-Ramos, et al. [4]; among their 32 patients, 3 had axial involvement and 29 had peripheral involvement (9 monoarticular and 20 polyarticular), and in a few patients, concomitant enthesitis (n=3), psoriatic lesion (n=2) and balanitis (n=1) were found. According to the classification criteria, patients were satisfied with RA, 3 with axial SpA, and only 6 with peripheral SpA. However, the remaining 17 patients did not fulfill the Assessment of SpondyloArthritis international Society classification criteria for SpA, as they had isolated arthritis in the context of post-COVID-19 arthritis [4]. After the arthritis was resolved, no treatments were administered in most patients, except in patients with RA. Based on this review and other reports, the clinical presentation of COVID-19-related arthritis is not similar to that of ReA. Moreover, COVID-19-related arthritis generally demonstrates a milder disease presentation than that of ReA.

Duration of arthritis

Both viral arthritis and ReA follow a self-limiting course. Viral-induced acute arthritis is generally described in the textbook as arthritis that remits within 6 weeks. However, it is not the case with ReA induced by bacteria. The natural history of ReA suggests that most patients achieve complete or near complete remission within 12 months. Approximately 25% develop chronic disease and require on-going treatment [10,27]. We analysed the duration of arthritis in patients with COVID-19-related arthritis reported in 2021 by PubMed.

In 22 of 32 patients, the duration of arthritis could be identified. The mean and median durations were 17 and 14 days, respectively, with a range of 2 days~30 days.

The bacteria that cause ReA to invade and persist in the host cell are called intracellular bacteria. Although intracellular bacteria could not be cultivated, some molecules of the bacteria within the host cells are activated themselves to involve in persistence within the host cells with an interaction of immune responses associated with HLA-B27 molecules [28]. This is one of the explanations for the generally longer duration of arthritis in ReA [29].

Discussion and Conclusion

COVID-19-related arthritis is classified as viral arthritis or postviral arthritis rather than ReA based on the 1999 definition and diagnostic criteria of ReA. The difference between viral arthritis and ReA can be explained by several reasons. First, the causative microorganisms in ReA are bacteria rather than viruses, and urogenital or enteric bacterial infections induce ReA as defined at the workshop. In a recent review article, although other bacteria and viruses have been proposed in some reviews, they are not among the causative agents of ReA based on the classical definition. Additionally, various other bacterial and viral infections have been recently suggested of triggers of postinfectious arthritis but they are by convention not considered as 'ReA'.

The clinical manifestations of SpA have been reported in only a few cases during or after COVID-19. No patients presented with the classic triad of reactive arthritis formerly termed 'Reiter's syndrome' (conjunctivitis, arthritis, and non-infectious urethritis). In a previous study, HLA-B27 is poorly observed among 8 patients tested, and only two patients (25%) were HLA-B27 positive.

Both viral arthritis and ReA exhibit a self-limiting disease course. However, the most prominent difference is the duration of arthritis. Viral arthritis usually remits within 6 weeks, whereas complete remission of ReA usually takes 6 months~12 months. Approximately 30% of ReA patients develop a chronic form of arthritis; however, these patients do not include those with COVID-19-related viral arthritis.

Since the term ReA is sometimes inappropriately used interchangeably with viral arthritis. There is a fundamental need to understand the separate categories of viral arthritis and ReA.

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