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REVIEW ARTICLE

Reactive arthritis before and after the onset of the COVID-19 pandemic

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Abstract

Most accepted definitions of reactive arthritis (ReA) consider it a type of spondyloarthritis (SpA) precipitated by a gut or urogenital infection. A wider definition considers any arthritis that occurs after a mucosal surface infection as ReA. There is limited consensus regarding a working definition, status of HLA-B27, or even classification criteria for ReA. This may also contribute to a lack of systemic studies or clinical trials for ReA, thereby reducing further treatment recommendations to expert opinions only. The emergence of post-COVID-19 ReA has brought the focus back on this enigmatic entity. Post-COVID-19 ReA can present at extremes of age, appears to affect both sexes equally and can have different presentations. Some present with small joint arthritis, others with SpA phenotype-either with peripheral or axial involvement, while a few have only tenosynovitis or dactylitis. The emergence of post-vaccination inflammatory arthritis hints at similar pathophysiology involved. There needs to be a global consensus on whether or not to include all such conditions under the umbrella of ReA. Doing so will enable studies on uniform groups on how infections precipitate arthritis and what predicts chronicity. These have implications beyond ReA and might be extrapolated to other inflammatory arthritides.

Key Points

- *Classical reactive arthritis (ReA) has a spondyloarthritis phenotype and is preceded by symptomatic gut or urogenital infection*
- *The demonstration of antigen and nucleic acid sequences of pathogens in synovium has blurred the difference between invasive arthritis and reactive arthritis*
- *Post-COVID-19 ReA has a transient phenotype and can have different presentations. All reported cases are self-limiting*
- *The large amount of literature reporting post-COVID-19 ReA calls for introspection if the existing definitions of ReA need to be updated.*

Keywords Infection-induced arthritis · Reactive arthritis · SARS-CoV-2 arthritis · Spondyloarthritis

Introduction

Reactive arthritis (ReA) is classically considered a sub-type of spondyloarthritis (SpA) that is precipitated after a gastrointestinal or genitourinary infection [1]. The usual presentation is monoarticular or oligoarticular arthritis involving large joints that occurs around 2–4 weeks after an infection [2]. 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.

The proposed definitions of ReA have under the umbrella of SpA, be it under the Amor or the European Spondyloarthropathy Study Group (ESSG) proposed criteria for "Spondyloarthropathy" [3] or the currently used ASAS (ASsessment in Ankylosing Spondylitis working group) criteria for peripheral SpA [4]. According to these definitions, the pathognomic features of SpA are required to label a patient as having ReA. These include sacroiliitis, uveitis, dactylitis, enthesitis, and HLA-B27 or family history of SpA, psoriasis, or uveitis [4, 5].

ReA allows us a distinctive opportunity to scrutinize and learn how an infective trigger precipitates an autoimmune phenomenon. A majority of ReA resolves within a

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few weeks to a few months. The rest assume a chronic form indistinguishable from other chronic autoimmune arthritides [6]. Thus, it also provides an opening to understand how the autoimmune process becomes self-sustaining and chronic.

ReA is a predominant problem of low-to-middle income countries where gut and urinary tract infections abound. Though it is reported from high-income countries, the phenotype is usually limited to arthralgia, tenosynovitis, dactylitis or often not-so-severe arthritis. The phenotype seen in the tropics is much different with the rapid development of secondary osteoarthritis or even evolution into ankylosing spondylitis [7]. However, with the COVID-19 pandemic, there are a lot of reports of post-COVID-19 ReA, re-igniting interest in this entity worldwide.

This perspective aims to explore how the concept of ReA has evolved over the last century, touching upon similar entities and finally how the COVID-19 pandemic is coercing us to re-look into the definitions of this enigmatic malady.

Search strategy

We have adhered to recommendations for narrative review searches [8]. We searched through Scopus and LitCovid/PubMed databases [9]. Non-English sources have not been consulted. Conference abstracts or non-peer reviewed sources were not included. To avoid confusion, we used the MeSH keyword "reactive arthritis" that includes "post infectious arthritis" for searches through LitCovid/PubMed. For Scopus, we used "reactive arthritis" OR "post infectious arthritis" in the search string.

History of ReA

The first descriptions of a post-infectious arthritis were made during the time of the First World war by Fiessinger and Leroy [10]. However, it was more commonly known with the eponym from a Nazi doctor who had first described a triad of urethritis, conjunctivitis, and arthritis. However, since he was convicted of war crimes, the eponym is not encouraged [11]. Also, a similar triad had already been described almost a century ago by Sir Benjamin Brodie in five cases [12].

More than half a century after the First World War, the concept of ReA was established as a non-purulent arthritis that occurred after a gastrointestinal infection without the direct invasion of the bacteria into the joints [13]. This concept was first contradicted by the finding of Chlamydia elementary bodies in the synovial cells of patients with ReA [14]. The tug of war over this concept has kept on going for a few decades. Now, it is clear that the entire live organism is not found in the joint but some antigen or genetic material, possibly carried by endosomes, may persist in the joint and lead to a sustained inflammatory reaction [15].

Current definitions and limitations

As the definition of ReA evolved, more and more entities were proposed for inclusion such as Lyme disease, gonococcal arthritis, post-streptococcal reactive arthritis, and rheumatic fever [16]. While it is true that Lyme disease and gonococcal arthritis may not fulfil the classical Koch's postulates to be defined as an "infection," both have unique characteristics clinical features. Clubbing them with ReA will neither help in the management nor further research. Similarly, the differences between ReA and post-streptococcal reactive arthritis are elaborated elsewhere [17].

The most commonly used definition of ReA has been provided by Braun and associates [18, 19]. This definition requires monoarthritis or oligoarthritis preceded by symptomatic diarrhoea or urethritis. For "definite" ReA to be diagnosed by the Braun criteria, an organism with known association with ReA needs to be demonstrated by culture or PCR. Even while these classification criteria were formulated, there was a lack of agreement on various points like the relationship of HLA-B27 with ReA, the existence of ReA without arthritis, or whether it should include only spondyloarthritis presentations or any arthritis [18]. More and more organisms are being added to the list of potential precipitants of ReA [20]. Also, the definition by Braun et al. does not consider the entity of "post-vaccination ReA."

The American College of Rheumatology (ACR) or the European Alliance of Associations for Rheumatology(EULAR) do not have separate practice guidelines pertaining to ReA as possibly the rheumatologists in Europe or the United States do not see severe cases of ReA[21–23]. The incidence is apparently declining in most high-income countries [24]. 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" [25]. ReA from India has arthritis as the predominant feature in 95% of patients [26] while a report from Finland showed only arthralgia in two and arthritis in none of 17 patients with post-*Escherichia coli* musculoskeletal conditions [23]. 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 [27]. Similarly, amongst millions who have developed SARS-CoV-2 infection, only a minor proportion develops arthritis. Understanding this may help unearth new verities about the immune system and tolerance mechanisms.

Clinical phenotype of post-COVID-19 ReA

Phenotype

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 [28]. It can also present as classical ReA with lower limb predominant oligoarthritis [29]. Isolate monoarthritis of a single metacarpophalangeal joint has also been reported [30]. Table 1 summarizes the different phenotypes, treatments given, and outcomes in various case reports of post-COVID-19 reactive arthritis from across the world.

Age and gender

The initial reports of post-COVID-19 ReA were in men past 50 years of age [31–33, 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 [41, 45]. Unlike classical ReA, gender distribution appears equal between males and females. However, the total number of reported cases is too small for conclusive comments.

Treatment and outcome

The majority of the patients had responded to non-steroidal anti-inflammatory drugs (NSAIDs) while some received intra-articular steroids or rapidly tapered oral steroids (Table 2). 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 [48–50].

Thus, the phenotype and outcomes of post-COVID-19 ReA appear to be different from those of classical ReA. These differences are summarized in Table 2.

Reactive arthritis after COVID-19 vaccination

Vaccination-induced autoimmunity is a concern since vaccines stimulate the immune system [51]. The first published case of ReA post-COVID-19 vaccination was reported in a 23-year-old woman after the inactivated Sinovac-CoronaVac vaccine [52]. We could identify a total of seven cases of inflammatory arthritis reported post-vaccination (Table 3).

Other post-COVID-19 inflammatory arthritis

We have reviewed post-COVID-19 rheumatic diseases at an earlier stage of the pandemic [57]. Post-COVID-19 peripheral nerve entrapment syndromes like carpal tunnel or tarsal tunnel syndromes have been hypothesized to be either due to localized demyelination, microangiopathy involving the vasa nervosum or an immune phenomenon targeting the adjacent synovial sheath [58]. An interesting group is the patients who have clinical phenotype and antibodies suggestive of rheumatoid arthritis developing post-COVID-19. These patients developed anti-cyclic citrullinated peptide antibody-positive arthritis after documented COVID-19 infection [48–50].

One concern was whether vaccination would cause a flare in persons with pre-existing autoimmune diseases [51]. Cases with flares of RA temporarily related to vaccination have been reported [59]. However, in a cohort of 724 patients with autoimmune rheumatic disease, only 4 patients had complained of a flare in joint pain. This was managed with NSAIDs and lasted less than a week [60].

In a cohort of 5493 RA patients from Hong Kong, a propensity-score weighted multivariate analysis did not show any association with COVID-19 vaccination and flare of RA [61].

Chronic arthritis after other viral infections

Several viruses are associated with acute polyarthritis that lasts less than 6–8 weeks [62]. In a small proportion of cases, such viral arthritis may become chronic such as in the case of HIV (Human Immunodeficiency Virus), Hepatitis B and C viruses [63, 64], parvovirus B19, and Chikungunya [65]. Some authors have argued that it may be better to label "COVID-19 associated arthritis" rather than "COVID-19 ReA" [66]. COVID-19 can also possibly precipitate arthritis in a susceptible individual. There is a case report of a lady with psoriasis and inflammatory bowel disease who developed arthritis post-COVID-19 infection [67].

Post-chikungunya or Parvovirus B-19 there can be an onset of arthritis indistinguishable from rheumatoid arthritis [68, 69]. A similar phenomenon has been reported post-COVID-19 too [48–50]. However, such anti-citrullinated antibody-positive RA has been reported only in 3 cases to date. The possibility of a coincidence cannot be excluded looking at the high incidence of COVID-19 infections and the not uncommon incidence of RA, but the point in support of a "reactive" arthritis is that the arthritis is seen after the acute COVID-19 infection. It is self-limiting. Had it been a direct viral arthritis, the synovitis should have occurred during the seroconversion phase. In acute COVID-19 infection, though arthralgia is common, documented arthritis has been rarely reported.

Possible pathogenic mechanisms

Viruses have been long implicated in the breakdown of immune tolerance and precipitation of autoimmune disease [70]. 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

Table 1 Summary of case reports and case series on post-COVID-19 ReA

First author	Age/sex	Joint pattern	Axial involvement	Other features	Autoantibodies	Treatment	Outcome	Sacroiliitis on radiography	HLAB27 positivity	Family history of SpA	Uveitis	Dactylitis	Enthesopathy
[31]	73/M	Left first metatarsophalangeal, proximal and distal interphalangeal joints	No	None	ANA, RF, anti-CCP negative	NSAID	Resolved in 21 days	NA	NA	NA	NA	NA	NA
[32]	47/M	Knee monoarthritis	No	Balanitis	NA	Etoricoxib and administered intra-articular triamcinolone	Not mentioned	NA	NA	NA	NA	NA	NA
[33]	50/M	Ankle arthritis	No	None	ANA, RF, anti-CCP,	NSAID, intra-articular	"Moderate improvement"	NA	Negative	NA	NA	NA	Achilles tendon enthesitis
[34]	45/M	Acute symmetric polyarthritis of wrists and proximal interphalangeal joints	No	Diffuse myalgia	NA	Methylprednisolone tapering dose	Complete remission in 3 months	NA	NA	NA	NA	NA	NA
[35]	60/M	Right knee arthritis	No	None	ANA, RF, anti-CCP, antibodies to extractable nuclear antigens negative	NSAIDs	Improved in 3 weeks; no relapse until 6 months	NA	Negative	NA	NA	NA	NA
[36]	53/F 58/F	Nil	Sacroiliitis	None	HLA-B8 and B57 positive Autoantibodies negative	NSAIDs	Intermittent NSAID use at 6 months	NA	Negative	NA	NA	NA	NA

Table 1 (continued)

First author	Age/sex	Joint pattern	Axial involvement	Other features	Autoantibodies	Treatment	Outcome	Sacroiliitis on radiography	HLAB27 positivity	Family history of SpA	Uveitis	Dactylitis	Enthesopathy
[37]	16/F	Nil	No	None	ANA, RF negative	Naproxen	Resolved in 5 days	NA	Negative	NA	NA	Dactylitis of three toes	NA
[30]	27/F	First metacarpophalangeal	No	None	NA	NSAIDs plus steroids	Resolved	NA	NA	NA	NA	NA	NA
[38]	57/M	Left wrist, the right shoulder and the bilateral knees	No	None	ANA, RF, anti-CCP negative	Not mentioned	Resolved spontaneously	NA	NA	NA	NA	NA	NA
[39]	37/F	Nil	No	Extensor tendosynovitis	ANA, RF negative	Hydromorphone	80% improvement at 2 weeks	NA	NA	No	NA	NA	NA
[40]	65/F	Symmetric polyarthritis of ankles, wrists and knee joints;	No	Palpable purpura on calves	Autoantibodies negative	Not mentioned	Not mentioned	NA	Positive	NA	NA	NA	NA
[41]	10/M	Both knees and his right elbow	No	Urticaria	ANA, RF negative	Antihistamines and acetaminophen	Improved in 72 h	NA	NA	No	NA	NA	NA
[42]	39/F	Distal interphalangeal and proximal interphalangeal joints	No	None	ANA, RF, anti-CCP negative	Celecoxib for two weeks	Doing well two weeks after stopping NSAIDs	NA	NA		NA	NA	NA
[28]	53/M	Nil	Bilateral sacroiliitis	None	NA	Intramuscular methylprednisolone and oral diclofenac	Resolved in 3 months	NA	Positive	NA	NA	NA	NA

Table 1 (continued)

First author	Age/sex	Joint pattern	Axial involvement	Other features	Autoantibodies	Treatment	Outcome	Sacroiliitis on radiography	HLAB27 positivity	Family history of SpA	Uveitis	Dactylitis	Enthesopathy
[43]	55/M	Right ankle	No	Tenosynovitis of the posterior tibial tendon sheath	NA	Oral methylprednisolone	Controlled on 4 mg methylprednisolone	NA	Negative	No	NA	NA	NA
[44]	53/M	Right knee, both ankles and the lateral side of the left foot	No	None	ANA negative	Ibuprofen and prednisolone	Maintaining on Ibuprofen	NA	Negative	NA	NA	NA	NA
[45]	8/M 6/F	Left hip arthritis in both patients	No	None	NA	Naproxen Ibuprofen	Recovered within a week	NA	NA	NA	NA	NA	NA
[29]	27/F	Bilateral knee, ankle and midfoot joints and small joints of hands	No	None	RF was positive in low titres. Anti-CPA, and ANA negative	NSAIDs plus steroids plus opioid analgesics	Resolved in 4 weeks	NA	Negative	NA	NA	NA	NA
[46]	58/F	Right hip	Right sacroiliitis	None	NA	Indomethacin and 80 mg IM depot prednisolone	Remission in 14 days	NA	NA	No	NA	NA	NA
[47]	53/F	Left knee	No	None	RF, anti-CCP, and ANA all negative	Diclofenac 150 mg/day; tapered by 6th Week	No relapse until 6 weeks	NA	Negative	No	NA	NA	Not available

Anti-CCP, anti-cyclic citrullinated peptide; *ANA*, antinuclear antibody; *NA*, not available; *NSAID*, non-steroidal anti-inflammatory drug; *RF*, rheumatoid factor

evolution of inflammatory arthritis [71]. In Chikungunya viral infection, a prominent role of monocytes and anti-viral responses such as interferons has been postulated [72].

Interferon (IFN)-related pathways have been implicated in COVID-19 [73, 74] 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 [75].

Also, various autoantibodies have been reported in COVID-19 [76]. 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 [77]. This may have implications for molecular mimicry in COVID-19.

Timelines of classic and post-COVID-19 reactive arthritides

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 [17]. 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 [57].

It is not necessary that all arthritis occurring post-COVID-19 should be reactive arthritis. The alternative is that it may be late-onset viral arthritis with actual invasion of the synovial space with the virus [78]. We could identify one study that reported the detection of SARS-CoV-2 RNA in a patient with wrist arthritis that had appeared 15 days after diarrhoea and upper respiratory tract symptoms [79]. However, other cases have not found such evidence [80]. Moreover, a post-mortem study also failed to find any viral RNA in synovial fluid or bone tissue in five patients who had died of COVID-19 [81].

Limitations

One limitation of this review is that the search strategy could miss cases of SARS-CoV-2 associated arthritis if the words "reactive" or "post-infectious" were not used. However, the main focus of the review was to assess how clinicians perceive and use the concept of reactive arthritis rather than only assessing SARS-CoV-2 associated arthritis.

Refining definitions for ReA

The definitions of ReA have been evolving gradually over the last half-century. Nevertheless, an ideal working definition still eludes us. Since this entity is not very common in high-income countries, there are possibly limited guidelines for this entity. The evidence base for treatment is also weak. The first and foremost requirement to fill in these deficiencies is a strong and universal definition of ReA.

Table 2 Differences between classical and post-COVID-19 reactive arthritis

	"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	
Joint predilection	Large joints	Small joints
Chronicity	1/3rd become chronic (lasts beyond 3 months)	Most resolve within 2 weeks to 3 months
Management	Treated as other spondyloarthritis (limited evidence base)	Usually, low dose steroids with or without NSAIDs is sufficient (limited evidence base)
Extra-articular manifestations	Dactylitis	Unknown/limited
	Enthesitis	
	Skin	
	Uveitis	
	Inflammatory bowel disease	

Table 3 Post-vaccination inflammatory arthritis

Reference	Age/sex	Vaccine	Temporal gap	Clinical features	Treatment	Outcome
[52]	23/F	CoronaVac	3 days after 1st dose; Again after the 2nd dose	Left knee monoarthritis	Celecoxib orally and intraarticular corticosteroid injections	Normal at 1-month follow-up
[53]	74/F	Sinovac	2 days after 2nd dose	Arthritis in the right wrist, 2nd–4th metacarpophalangeal and 2nd–4th proximal IP joints	10 mg/day prednisolone with tapering	No recurrence
[53]	76/M	Sinovac	1 week after 2nd dose	Arthritis in left hand all distal IP joints; hip; entire spine (previously diagnosed as ankylosing spondylitis)	10 mg/day prednisolone with tapering	No recurrence
[54]	72/F	Sinovac	3 weeks after vaccination	Arthritis in the left elbow, bilateral knees and right ankle	Prednisolone	Arthritis regressed in 2 weeks
[54]	79/F	Sinovac	5 days after the 2nd dose	Arthritis in both wrists, hand joints, and left ankle	Methylprednisolone	Had residual pain and swelling at 1-week follow-up
[55]	58/M	SPUTNIK-V	5 days after the 2nd dose	Left elbow	Non-steroidal anti-inflammatory drugs, physiotherapy, and intra-articular injection	Pain on active motion persisted at 1 month
[56]	38/F	SPUTNIK-V	20 days after the first dose with worsening after the 2nd dose	Arthritis in both shoulders and both knees initially. Involved small joints of hand and feet after the second dose	methotrexate, non-steroidal anti-inflammatory drugs, and methylprednisolone	Improved at 3 months follow-up

IP, interphalangeal joint

Though there is a definite association between COVID-19 and arthritis, the scientific rigor to establish causality is incomplete yet. Thus, any new definition should allow for reasonable doubt, but still be sufficiently solid to further studies in the field.

The advent of ultrasound in the detection of enthesitis can enable a more objective definition [82]. Also, radiographic features such as new bone formation at the site of enthesitis can be a possible marker [83]. Radiographic changes are late but ultrasound diagnosis can be early with validated OMERACT (Outcome Measures in Rheumatology Clinical Trials) definitions available [84].

Conclusion

The emergence of post-COVID-19 ReA and possibly post-vaccination ReA is forcing a paradigm shift in how we perceive this entity. Post-vaccination autoimmune diseases are being reported [85]. This leads to the question of whether individuals with genetic predisposition such as HLA-B27 positivity need to be segregated for different vaccines [52].

As the SARS-CoV-2 pandemic is transformed into an endemic due to wide-spread vaccination and emergence of less virulent strains, it will be interesting to study how this affects emergence of COVID-19 associated autoimmune conditions including ReA.

Finally, post-infectious arthritis may hold the key to understanding how the chronicity of arthritis develops. This may help in future preventive strategies. The first step has to be a coordinated effort across nations and various rheumatology societies to set up working definitions and enumerate thrust areas of research for ReA.

Author contribution All co-authors contributed substantially to the concept formulation, searches of relevant articles, and revisions. They approve the final version of the manuscript and take full responsibility for all aspects of the work.

Declarations

Conflict of interest SA has received honorarium as speaker from Pfizer, DrReddy's, Cipla, and Novartis (outside of the current work). All other authors declare no competing interests.

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