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EDITORIAL

How long is long COVID

1 | INTRODUCTION

We live in the era of COVID-19 pandemic that took the lives of 6 584 230 people (https://www.worldometers.info/coronavirus/). All doctors, and especially rheumatologists, encounter a big issue of long COVID (post-COVID-19 syndrome [PCS], long haulers COVID, long-term effects of COVID-19). The estimated prevalence of PCS is about 20%–30% of the entire COVID-19 population, which is more than 100 000 000 people.[1,2]

Since the beginning of the pandemic, no globally acceptable definition of long COVID has been introduced, and there has not been consensus over the PCS duration and its diagnostic and classification criteria. The uncertainties surrounding PCS have challenged researchers, clinicians, and patients.[3,4] A clear-cut definition of PCS may guide clinicians to timely diagnose this condition and save financial and human resources which can be allocated to the global efforts against the pandemic and its consequences. What follows is a practicing rheumatologist's viewpoint that may stimulate discussion aimed at consensus statements over the issue of long COVID.

2 | LONG COVID DEFINITION

It seems that the British guidelines offer the most convenient and practically oriented definition of PCS.[2] The following modified definition may be globally acceptable:

- PCS (long COVID) is a systemic inflammatory syndrome with signs and symptoms that develop during or after an infection consistent with COVID-19, lasting from 12 weeks to 12 months, and not attributable to any alternative diagnosis.

The terms "post-COVID-19 syndrome" and "long COVID" can be interchangeably used in routine practice.

3 | LONG COVID MUSCULOSKELETAL MANIFESTATIONS

PCS often presents with musculoskeletal, pulmonary, gastrointestinal, and neurological symptoms.[5–7] Musculoskeletal manifestations are the most frequent, taking place in 30%–90% of cases.[8–10] Nonetheless, the structure of musculoskeletal manifestations in PCS is still uncertain,[2] without clear associations of joint and muscle pain with COVID-19 episodes. Empirically, the following scheme of musculoskeletal manifestations seems the most acceptable (Box 1).

As a rule, arthralgia and myalgia in PCS do not require targeted therapies, and differential diagnostic approaches are rarely considered.[11]

4 | INFLAMMATORY ARTHRITIS AND RHEUMATOID ARTHRITIS (RA) AFTER SARS-CoV-2 INFECTION

Chronic inflammatory arthritides often evolve after specific infections caused by human immunodeficiency virus, some alphaviruses (Chikungunya, Ross River, Barmah Forest, Mayaro), hepatitis B or C viruses, and parvovirus B19.[12–14] Pathophysiology of such arthritides is still not fully explored. Multiple organ system involvements and numerous confounding factors influence the course and outcomes of arthritis during and after viral infections. The most powerful mechanism of associated autoimmune reactions is "molecular mimicry".[15] This term was proposed in 1978 by an Australian scientist Alan Ebringer to explain the pathogenesis of rheumatic fever.[16] The same mechanism is now viewed in connection with SARS-CoV-2 infection.[17]

Numerous cases of arthritis post-SARS-CoV-2 infection have been reported in the literature. A systematic review by Mexican authors compiled 99 reports of new-onset rheumatic musculoskeletal disease (RMD) post-SARS-CoV-2 infection.[18] Most of the analyzed reports described signs of vasculitis and arthritis. Another systematic review from the USA synthesized information on 54 cases of inflammatory arthritis following COVID-19.[19] In our own practice, similar cases are observed on a daily basis, and some of these are now publicized.

In most reports, arthritis after SARS-CoV-2 infection is viewed as reactive arthritis (ReA) which is a debatable diagnosis.[20,21] ReA is a type of spondyloarthritis (SpA) after bowel or urogenital infections. Arthritis after COVID-19 is viral (post-viral, or virus-associated) when no other disease criteria are met.[22]

RA can be a RMD model with severe articular syndrome. We may consider RMD manifestations during and after COVID-19 through the prism of the RA model. A pre-pandemic systematic review convincingly

BOX 1 Main musculoskeletal manifestations of long COVID

- Myalgia
- Arthralgia
- Arthritis

associated viruses with RA development.[23] Another large Korean study of more than 24000 patients with RA pointed to the triggering role of coronaviruses in the context of RA.[24] Among the 8 investigated viruses, coronaviruses were significantly associated with occurrence of new cases of RA. Importantly, conclusion was drawn emphasizing a possible etiological role of respiratory viral infections in RA. It can be hypothesized that COVID-19 may also trigger some (autoimmune) rheumatic diseases. Such a hypothesis is now supported by numerous observations, including our own.[25] We now offer our scheme with several scenarios of arthritis post-COVID-19 (Box 2).

4.1 | RMD flare after COVID-19

Currently, this scenario is widely observed in routine practice. Viral load and discontinuation of immunosuppressive disease-modifying antirheumatic drugs act complementarily and result in rheumatoid flares. A common challenge is to distinguish RMD flare from *de novo* RMD.

4.2 | RMD debut after COVID-19

There are more than 10 published case reports of probable RA after SARS-CoV-2 infection, and the number of such cases may further increase. Clinicians will encounter a challenge of distinguishing coincidence from association.[26] We demonstrated 1 of the most likely scenarios of association.[27] Our patient was examined 3 months before the SARS-CoV-2 infection, and neither arthritis nor rheumatoid factor or anti-cytoplasmic antibody (ACPA) positivity were recorded at that time. After COVID-19, the patient developed polyarthritis and morning hand stiffness. During the initial post-COVID-19 examination, ACPA was in normal range (upper limit); but it rapidly increased and reached diagnostic levels on subsequent examinations. Notably, most patients elsewhere reported lacked records before COVID-19.

BOX 2 Arthritis after SARS-CoV-2 infection

1. RMD flare after COVID-19 (common).
2. RMD debut after COVID-19 (COVID-19 as a triggering factor).
3. Musculoskeletal manifestations of long COVID.

In our clinic, we have collected data of 5 cases with ACPA positivity after COVID-19, although their *de novo* RA diagnosis could not be reached due to the absence of examinations before COVID-19. We may consider such cases as rheumatoid flares of previously asymptomatic disease or discuss the third scenario, which is musculoskeletal manifestations of long COVID.

5 | MUSCULOSKELETAL MANIFESTATIONS OF LONG COVID. HOW LONG IS LONG COVID?

Various autoantibodies can be detected after episodes of SARS-CoV-2 pneumonia in 20%-50% of cases.[28] The overproduction of autoantibodies, including ACPA, can be transient. We have observed our own unpublished cases of oligoarthritis and polyarthritis post-COVID-19 accompanied by a slight increase in ACPA. Musculoskeletal manifestations of long COVID may occur in the presence of autoantibodies, satisfying criteria of certain RMDs. In such cases, distinguishing *de novo* RMD from PCS is a real challenge. A correct diagnostic decision can be reached with a sufficiently long observation. As such, there are still uncertainties surrounding temporal boundaries of PCS. Although 12 weeks as an initial temporary boundary is more or less certain,[2] there are no definitive approaches to the final boundary period. While most experts discuss 6–12 months periods for PCS, longer terms are also likely.[29] We consider 12 months after the onset of SARS-CoV-2 infection as a practically suitable time limit for PCS. Arthritis lasting 12 months after COVID-19 can be considered as a musculoskeletal manifestation of long COVID whereas a longer duration may point to a diagnosis of new-onset RMD. Arguably, the discussed time frames are conditional, and the diagnosis can be established earlier if certain sets of RMD criteria are met.

6 | CONCLUSION

Our cases and literature overview suggest that musculoskeletal manifestations of long COVID may raise concerns and warrant differential diagnostic approaches. At times, correct diagnosis cannot be reached in a short term, justifying a long follow-up in PCS. COVID-19 may be a trigger of rheumatic diseases. Long-term cohort studies amid the ongoing pandemic are warranted to track cases of RA and other RMDs and examine their temporal relationships with COVID-19.

KEYWORDS
arthritis, long COVID, post-COVID-19 syndrome, rheumatoid arthritis, SARS-CoV-2

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