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Rheumatological symptoms after COVID-19 pneumonia presenting as long COVID: What we need to know?

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Abstract

COVID-19 pandemic is in verge of over and evolved over last three years in different waves across the globe with various genetic mutants or strains. As of now, many COVID-19 recovered patients are lingering with residual symptoms of illness irrespective of disease severity called as long COVID. Nonspecific or vague and organic or topographical organ specific symptoms are very well described in literature in COVID-19 survived cases. Rheumatological symptoms are most documented in published data as sequel after COVID-19 illness. Clinical presentations of rheumatological symptoms are joint or musculoskeletal pain, chronic fatigue with minimal exertion and weakness or impaired quality of life. Pathophysiology involving in rheumatological manifestations would be persistent or dysregulated inflammatory response, immune activation or thrombogenic pathway abnormality after acute COVID-19 illness. Diagnosis is little difficult and needs prompt workup to rule out underlying rheumatological illness. Inflammatory markers and autoantibody analysis has documented role in work up and confirming the diagnosis in majority of cases. Management of these cases is still evolving and showed response to lifestyle modification, physiotherapy, and short course of steroids and multivitamins in various published studies.

Keywords: COVID-19; Sequel; Long COVID; Rheumatological symptoms; Inflammatory markers

1. Introduction

Long-term sequel of acute COVID-19, commonly referred to as long COVID, has affected millions of patients worldwide. Long COVID also called as post-COVID-19 syndrome [PCS], long haulers COVID or cases with 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. [1-3] It seems that the British guidelines offer the most convenient and practically oriented definition of PCS.[2] 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. A collection of long-term manifestations of COVID-19, including fatigue, shortness of breath, and loss of taste or smell, were identified by various follow-up studies from different countries and have been termed "post-acute COVID-19 syndrome" [1-3]

2. Basics of rheumatological symptoms in long COVID

Rheumatic symptoms as a long-term manifestation of COVID-19 have been frequently mentioned in published follow-up studies [3-12]. It was known that viral infection, such as parvovirus B19, hepatitis B and C, human immunodeficiency

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virus, and the alphaviruses, was recognized as an important cause of virally mediated arthritis, with a wide spectrum of rheumatic symptoms ranging from arthralgia to chronic arthritis. [13] Rheumatic symptoms after other coronavirus infection, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome, were also reported with an incidence of 10% and 32%, respectively. It is worth noting that, the incidence may be underestimated under the scenarios of high doses of glucocorticoids (cumulative doses during hospitalization of >1 g) [14-16].

3. Pathophysiology and possible link between rheumatological symptoms after COVID-19

As mentioned, Chronic inflammatory arthritis often evolves after specific infections caused by human immunodeficiency virus, some alphaviruses (Chikungunya, Ross River, Barmah Forest, Mayaro), hepatitis B or C viruses, and parvovirus B19. Pathophysiology of such arthritis 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" [17,18]. This term was proposed in 1978 by an Australian scientist Alan Ebringer to explain the pathogenesis of rheumatic fever [19]. The same mechanism is now viewed in connection with SARS-CoV-2 infection [20]. Numerous cases of arthritis post-SARS-CoV-2 infection have been reported in the literature [21,22]. A systematic review by Mexican authors compiled 99 reports of new-onset rheumatic musculoskeletal disease (RMD) post-SARS-CoV-2 infection [23]. 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 [24]. In most reports, arthritis after SARS-CoV-2 infection is viewed as reactive arthritis (ReA) which is a debatable diagnosis [25,26]. 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 [27].

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 associated viruses with RA development [28]. Another large Korean study of more than 24 000 patients with RA pointed to the triggering role of coronaviruses in the context of RA [29]. 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 [30].

4. Patterns of Rheumatological arthritis as long COVID after COVID-19

Three different patterns or possibilities of arthritis after COVID-19 disease is reported in literature. It is estimated that 31%-69% of COVID-19 survivors will experience long COVID symptoms after initial recovery from SARS-CoV-2 infection [31,32]. Generally, initial symptoms of long COVID symptoms include fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnoea (21%), anxiety (27%), chest pain, and arthralgia (18%). Correspondingly, a recent meta-analysis of 36 studies identified fatigue, cognitive impairment, joint pain, anxiety, and depression as primary clinical symptoms of long COVID [33]. A massive international survey found fatigue, malaise and cognitive impairment as the most prevalence symptoms experienced among individuals with reported long COVID [34].

4.1. RMD flare after COVID-19

Globally, this is most common pattern of rheumatological symptoms documented in long COVID care settings. 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

In this pattern, COVID-19 infection triggers the ongoing inflammation and will worsen the existing arthritis. 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 [35]. Authors [36] have demonstrated 1 of the most likely scenarios of association. 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. 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 [36].

4.3. Musculoskeletal Manifestations of Long COVID according to time frame

Various autoantibodies can be detected after episodes of SARS-CoV-2 pneumonia in 20%-50% of cases [37,38]. 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 [39]. 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.

5. Does rheumatological manifestations can be predicted during hospitalization?

COVID-19 pneumonia is heterogeneous disease with variable effect on lung parenchyma, airways and vasculature leading to long term effects on lung functions. Pathophysiological mechanism is immune activation, inflammatory, thrombogenic and direct viral affection to lungs and extrapulmonary tissues [40]. COVID-19 pandemic has been studied over last two and half years for its highly pathogenic nature of corona virus. Main hurdle for acquiring immunological memory after natural infection is genetic change in spike proteins of nucleocapsid of novel corona virus after certain interval resulting into different waves documented in different geographical settings. Dysregulation in the immune system can lead to an unappropriated local and systemic immune responses and subsequently the rapid spread of the virus, leading to severe COVID-19 disease.

Severity of illness increases with more lung parenchymal involvement as documented with chest imaging in proportion with inflammatory markers such as IL-6, CRP, Ferritin and LDH [41-44]. Authors have documented persistent smouldering infection as underlying mechanism for long COVID [45]. Second hypothesis is that mast cell activation syndrome could possibly contribute to long COVID symptomatology [46,47]. The third hypothesis put forth that sustained dysregulated immune system activation with subsequent chronic low-grade inflammation could lead to pathological consequences like autoimmunity leading to organ dysfunction [48,49]. Authors have documented long-lasting functional alterations of T-cells, with persistence of cytotoxic profile with decrease in dendritic cells revealed 7 months post-infection [50,51].

Residual excessive inflammation after infection & auto-antibodies against immunomodulatory proteins or against tissues are other proposed mechanism for long COVID [52,53]. Other possible hypothesis is persistence of SARS-CoV-2 in the lower gastro-intestinal tract was revealed in asymptomatic subjects several months after COVID-19, suggesting that residual viral proteins within tissues could possibly be the basis for a persisting immune reaction [54].

6. How inflammatory markers guide during follow-up in assessment of rheumatological symptoms?

Systemic autoimmune rheumatic diseases (SARDs), including rheumatoid arthritis (RA), connective tissue disease (CTD), idiopathic inflammatory myositis (IIM) and fibromyalgia (FM) and chronic fatigue syndrome (CFS), share similar symptoms with long COVID. Before confirming long COVID, SARD should be considered in a differential diagnosis as manifestations of several rheumatic diseases may mimic long COVID. Authors have documented that the blood abnormalities such as d-dimer, C-reactive protein (CRP), ferritin noted prior to hospital discharge had returned to normal in many patients at a median of 12 weeks follow-up [55,56]. Elevated IL-6 is associated with persistent pulmonary lesions in COVID-19 patients following their acute recovery [57]. Also, patients with evidence of pulmonary fibrosis after recovering from acute COVID-19 had a higher level of systemic inflammation at admission (ESR, CRP and d-dimer) and bone marrow suppression as evidenced by thrombocytopenia, leukopenia and low hemoglobin [58]. These parameters could be used as a potential biomarker for long COVID.

Authors have reported incidence of autoantibodies related to SARD in severe acute COVID-19 cases [59]. The most commonly observed autoantibodies in COVID-19 patients were antinuclear antibody (ANA), antineutrophil cytoplasmic antibodies (ANCA), anti-cardiolipin (aCL), anti-beta-2-glycoprotein-1 (anti-β2GP1) and anti-cyclic citrullinated peptide

(anti-CCP). The titer of the autoantibodies when present was generally low; for example, ANA ≤ 1/320 [21,22]. In a Dutch study of five patients who presented with inflammatory arthritis 6.6 weeks post COVID-19 infection, two patients had strongly positive and another patient had weakly positive anti-CCP antibodies [59]. However, serology status before the presentation was not available. Based on clinical phenotype and autoantibodies characterization, Derksen et al. proposed that the new onset of RA post-COVID-19 could be coincidence rather than causality [60].

Myalgia is a prevalent symptom during the acute COVID-19 infection. Myalgia is also a common symptom in patients with long COVID, SARD and FM. Unlike its presentation in patients with long COVID, myalgia in SARD, such as SLE, SS, scleroderma and mixed CTD, is commonly associated with other manifestations, such as Raynaud's, skin rashes and strongly positive autoantibodies. For example, a patient with generalized pain with malar rash and mouth ulcers raises the possibility of SLE. The autoantibodies commonly present in SARD include Ro and La, anti-centromere, anti-Scl-70 and anti-ribonucleoprotein (RNP), anti-smith (anti-sm) and anti-double-stranded deoxyribonucleic acid (ds-DNA), which are disease-specific. Clinically significant titers of these antibodies are less likely to be found in patients with long COVID [60]. If present, a weakly positive ANA is a false positive result with no clinical significance especially in the absence of CTD symptoms.

7. Do the different COVID-19 variants and vaccination have effects on rheumatological symptoms?

Both SARD and COVID-19 share a similar pathophysiological basis caused by exaggerated immune response characterized by cytokine stimulation and hyperactivity.[61] Both innate and adaptive immune systems play a key role leading to macrophage activation and cytokine storm. Molecular mimicry and cross-reactivity are thought to trigger an immune response in patients with COVID-19 in developing SARD. Vojdani et al. described cross-reactivity of human monoclonal autoantibody against SARS COV-2 spike protein, nucleoproteins and peptides [62]. Due to shared pathophysiology, immunosuppressive drugs such as corticosteroids, Janus kinase inhibitors, IL-1 and IL-6 blockers have been successfully used to treat inflammatory complications of COVID-19.

Genetic makeup of corona virus in different waves of pandemic has different rheumatological manifestations. Maybe, the genetic makeup of coronavirus was determining factor for overall outcome in the first and second waves, first was classical "Wuhan variant virus" and the second one was mutant "Delta variant" coronavirus; and as a mutant in the second wave was associated with increased morbidity and mortality and negligible mortality with Omicron variant [63]. Timely remdesivir use has documented in curtailing viremia and indirectly it has shown in preventing occurrence of long COVID and rheumatological symptoms possibility. Various myths regarding remdesivir use and its association with rheumatological symptoms has been observed in post COVID phase in those cases facing long COVID symptoms [64].

It is worth noting that there are also emerging cases of rheumatic-immune mediated inflammatory disease (R-IMD) following SARS-CoV-2 vaccinations reported recently [65]. More recently, a flare-up of well-controlled RA has been published following the administration of the SARS-CoV-2vaccination [66].

8. Management of rheumatological symptoms presenting as long COVID?

The possible causes of rheumatic symptoms following COVID-19 may be musculoskeletal disorders before COVID-19, gout, or rheumatic symptoms specific following the infection with SARS-CoV-2, which need to be further demonstrated by an orthopedist or rheumatologist through complete examinations. Long COVID will remain a diagnostic challenge, given the similarities it shares with SARD, including elevated inflammation markers, presence of autoantibodies and emerging evidence of organ-specific inflammatory changes on imaging [67]. A careful history, physical examination and appropriate investigations will enable clinicians to differentiate these conditions. However, due to the multi-organ involvement, clinicians should be educated about long COVID. The management of long COVID should involve a multidisciplinary approach due to the complexity of this clinical syndrome. Additionally, we recommend that clinicians should also be part of the MDT in long COVID clinics, including occupational therapists, physiotherapists, clinical psychologists and rehabilitation clinicians, to provide a holistic approach to the management [68].

The most prominent theories with therapeutic implications are summarized and displayed in Figure.1 [69]

Presently, there is no specific therapy for the most vexing and common manifestations of Long COVID including fatigue with post-exertional features, neurocognitive dysfunction, and somatic pain, though there are principles of management largely drawn from the management of other medically unexplained disorders. As there are no approved therapies for Long COVID, we are just at the beginning of a long process of drug discovery. There are now emerging clinical reports, largely anecdotal and observational, of a variety of therapies that should be interpreted with caution. Such observations

include improvement in Long COVID symptoms after subsequent COVID-19 booster vaccination [70]. Of particular interest are the role of the virus as a driver of Long COVID (largely based on the emerging data for viral persistence in Long COVID-19) [71], as well as a correlation of subsequent Long COVID with initial viremia of SARS-CoV-2 and Epstein-Barr virus in the acute phase of infection [71]. There are now emerging anecdotal reports of improvement in Long COVID in small numbers of patients following a course of oral nirmatrelvir, further supporting the urgent need for randomized and placebo-controlled trials [70]. Based on the growing data surrounding ongoing inflammation, as evidenced by modest but significant elevations of inflammatory cytokines and persistence of dysregulated interferon signaling, there is growing interest in immunomodulatory approaches to treatment; to date, there are no robust studies completed of any such agents.

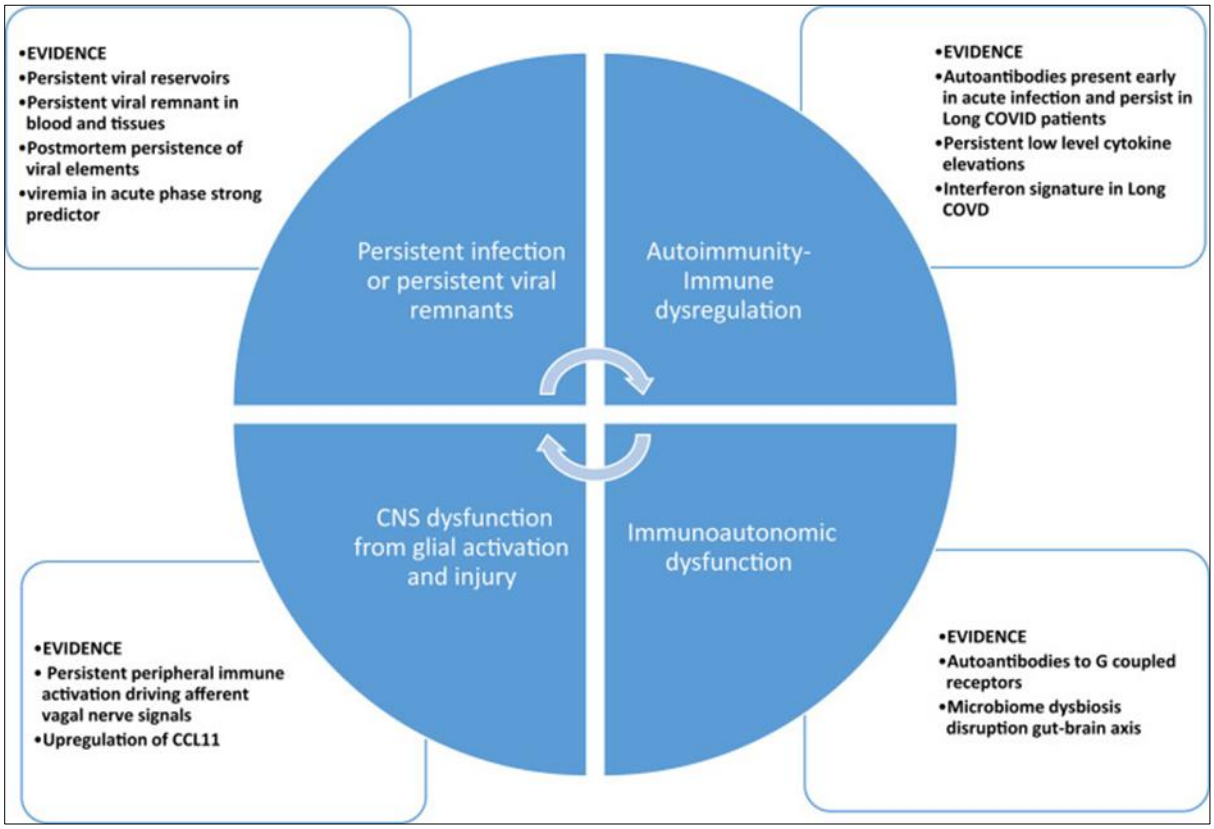

Figure 1 Proposed major pathogenic mechanisms in long COVID

Lastly, we recommend to assess inflammatory markers assessment in all cases suspected with any rheumatological symptoms during follow up in post covid care setting especially those having any long covid manifestations [72-78]. These markers have played significant role in assessment of cases form entry point to follow up and sequential change will guide to predict early chances of rheumatological symptoms in selected cases of recovered COVID-19 cases [79-81].

9. Conclusion

Rheumatological symptoms are more commonly documented after COVID-19 disease in follow up scenarios irrespective of disease severity and hospitalization. These are under evaluated due to lack of suspicion by patient and physician. Multidisciplinary approach is recommended during assessment of these cases to have successful treatment outcome. Steroids and hydroxychloroquine with or without analgesics is cornerstone of therapy. COVID Vaccination in important step in preventing these issues in post COVID care settings.

Learning points

- Rheumatological syndrome is known to occur after COVID pneumonia and now data is available its association with illness irrespective of diseases severity and hospitalization.

- Inflammatory markers patterns during initial COVID-19 pneumonia have direct correlation with rheumatological symptoms and can be suspected during hospitalization in indoor patients by analysing titers of these markers during evolution of pneumonia.
- Inflammatory markers analysis such as IL-6, Ferritin, D-Dimer, CRP and LDH at discharge has helped in majority of cases. Higher the titer of these markers, there will be more chances of long COVID in these cases.
- Inflammatory markers such as CRP, Uric acid and LDH are 'best laboratory clues' during follow up to pick up rheumatological symptoms early.
- Cases with history of antigenic mimicry and antigenic cross reactivity such as positive dengue serology were laboratory clue during hospitalization that these patients may develop rheumatological or autoimmune features in follow-up.
- Although Rheumatological syndrome that occurs with COVID-19 pneumonia is showing reversible nature over duration of time and few cases are showing persistent nature.
- All cases with rheumatological symptoms need prompt workup due to Immunological nature of disease. All cases should undergo analysis of rheumatoid factor, anti CCP, ANA and other tests to confirm exact type of disease-causing symptoms.
- Although ANA test is not confirmatory and specific to rule out Rheumatological syndrome, its high titre signifies towards immune nature of disease. ANA blot panel is more specific to label in exact nature of autoimmune disease.
- Steroids are cornerstone of treatment of Rheumatological syndrome with or without lung involvement and shown excellent response to steroids with hydroxychloroquine. Echocardiography is must in all cases to rule out cardiac dysfunction before initiation of treatment.
- Rheumatological syndrome which is rare vaccine related adverse event, and importantly it is reversible and managed with routinely available medicines and is having excellent prognosis. Vaccines has shown positive impact on controlling chances of rheumatological symptoms and now data is available regarding protective role of vaccine in preventing rheumatological symptoms.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest.

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