

Post-Acute Sequelae of COVID-19 (PASC): Association with Inflammation and Autoimmunity

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Abstract

It has become increasingly evident that a high percentage of patients that recover from acute COVID-19 infection continue to suffer from a variety of persistent symptoms even months after viral clearance, the most common ones being fatigue, dyspnea, anosmia, dysgeusia, cognitive dysfunction, and psychological problems, including anxiety and depression. This syndrome, known as post-acute sequelae of COVID-19 (PASC), can severely affect quality of life and represents an important health care concern. The exact causes

for the symptoms observed in patients with PASC remain to be adequately characterized, but are likely to be associated with multiple factors, including residual disease and/or inflammation, organ damage, effects of hospitalization and/or prolonged ventilation, as well as effects of social isolation and stress. This mini-review discusses evidence that may link both inflammatory and auto-immune processes in the pathophysiology of PASC.

Introduction

Since the beginning of the COVID-19 pandemic at the end of 2019, great strides have been taken by the world's medical and scientific communities in the sequencing and characterization of the virus responsible, SARS-CoV-2, as well as in the pathophysiology of the disease. While much of the focus of research has been, understandably, on the management and treatment of the acute disease, the long-term consequences of COVID-19 infection are not well understood.[1-4] While many people recover quickly from COVID-19, it has become evident that many survivors of COVID-19 continue to experience a variety of symptoms weeks and months after clearing the virus, severely affecting their quality of life and placing a significant burden on already compromised health care systems. This set of symptoms in patients recovering from COVID-19 has received different names around the world, including post-acute sequelae of COVID-19 (PASC), long COVID, long-haul COVID, and post-COVID Syndrome.[5] An evolving definition of PASC has been suggested based on the persistence of symptoms or development of new symptoms beyond 3 or 4 weeks

from the onset of acute COVID-19 symptoms. It can be further divided into subacute/ongoing COVID-19—where symptoms persist 4–12 weeks beyond acute COVID-19—and chronic/post-COVID-19, where the abnormalities present or persist beyond 12 weeks after acute onset of COVID-19 and are not attributable to alternate diagnoses.[6, 7]

The symptoms suffered by PASC patients are many and appear to involve multiple organ systems. Some of the commonly reported symptoms are fatigue, dyspnea, anosmia, dysgeusia, cognitive dysfunction, and psychological problems, including anxiety and depression.[1-3] These symptoms could be related to residual disease and/or inflammation, organ damage, effects of hospitalization and/or prolonged ventilation, as well as effects of social isolation and stress.[1] Several studies with different follow-up periods have reported the incidence of persistent symptoms ranging from about one-third in outpatients up to 90 percent in hospitalized patients.[1-3, 8-12] These long-term sequelae have been reported in all age groups, and while they appear to be more common in patients who suffered severe COVID-19 or those with risk factors such as old

age, frailty, and pre-existing clinical conditions, they also occur in patients recovering from mild or moderate disease.[3, 9, 10, 13, 14] Current research efforts are directed at characterizing the causes and risk factors associated with PASC.

The Role of Inflammation

While the role of inflammation and autoimmunity in COVID-19 has been demonstrated by several studies [15, 16], their role in PASC remains poorly understood. It has been well established that hyperinflammation and immune dysregulation are associated with severe outcomes in hospitalized patients with acute SARS-CoV-2 infection and that COVID-19 is associated with a range of non-respiratory conditions affecting multiple organs, including the heart, circulatory system, kidneys, and liver, whose pathogenesis involves endothelial activation, activation of the coagulation cascade, and immune response against the virus.[1, 16, 17] Indeed, several prospective studies following patients after hospital discharge have suggested that some of the sequelae may be associated with organ damage and persistent inflammation. For example, Raman *et al.* [18] reported that serum markers of inflammation and severity of acute illness correlated with MRI evidence of multiorgan abnormalities and reduced exercise tolerance. The severity of illness during admission correlated moderately with inflammatory markers (procalcitonin, C-reactive protein [CRP], white blood cell count, neutrophil count, monocyte count) and signs of persistent inflammation/injury in the lungs, liver, and kidneys, as well as decreased exercise tolerance at follow-up assessment.

Several other studies have suggested that inflammatory responses may remain present, even after viral clearance. A study based on targeted mass spectrometry found that even in asymptomatic or moderately affected patients, there were significant remaining inflammatory responses 40–60 days post-viral infection that involved anti-inflammatory response or mitochondrial stress proteins, suggesting that inflammatory and biochemical pathways can remain perturbed in patients long after “recovery”.[19] Consistent with the persistence of inflammatory responses, persistent nasal inflammation has been reported five months after anosmia in COVID-19 patients.[20]

Neuropsychiatric sequelae may also have an inflammatory basis. The prolonged inflammatory responses in COVID-19 may pre-dispose patients to persistent depression and associated neurocognitive dysfunction.[21] Moreover, studies have shown that virus-infected monocytes can propagate neuroinflammation by releasing cytokines and promoting microglial activation.[22, 23] In addition, even in the absence of virus in the central nervous system (CNS), peripheral cy-

tokine transmigration into the CNS may cause neuropsychiatric symptoms.[24]

Finally, it is important to indicate that while inflammation seems to play an important role in the pathogenesis of PASC, it does not appear that PASC symptoms are necessarily associated with the strength of anti-viral immune responses. A study by Peluso *et al.* [25] in a cohort of individuals recovering from COVID-19 did not find significant differences between patients with and without PASC symptoms in long-term virus-specific T cell or antibody responses.

The Role of Autoimmunity

Several reports have suggested that some of the PASC may have an autoimmune origin. It has been proposed that SARS-CoV-2 may act as a trigger for the development of autoimmune or autoinflammatory dysregulation in genetically predisposed individuals.[26, 27] A retrospective study from China reported a 20–50% prevalence of autoimmune disease-related autoantibodies in a group of critically ill COVID-19 patients.[28] There are also reports of the association of several autoimmune diseases, such as immune thrombocytopenic purpura (ITP), Guillain-Barré syndrome (GBS), severe thrombotic events associated with anti-phospholipid antibodies, and Kawasaki-like inflammatory disease, with COVID-19.[26]

A role for molecular mimicry between COVID-19 antigens and self-antigens and/or bystander activation has also been proposed as a basis for autoimmune reactions arising from immune responses to shared peptide sequences.[29, 30] The heterogeneity of symptoms of PASC could have an origin in cross-reactive immune responses to viral sequences. A report by Kanduc *et al.* [31] suggested that immune responses following SARS-CoV-2 infection might lead to cross-reactions with pulmonary surfactant and related proteins, potentially contributing to SARS-CoV-2-associated lung diseases. Ehrenfeld *et al.* [26] also reported the presence of infiltrates of T lymphocytes, particularly CD8+ cells, in multiple organs in deceased COVID-19 patients, consistent with histological evidence of autoimmune reactions in COVID-19. Additional evidence for molecular mimicry is the generation of IgG autoantibodies following SARS-CoV-2 infection.[32] In addition, another study found that COVID-19 patients exhibit significant increases in autoantibodies compared to uninfected controls, including antibodies against immunomodulatory proteins, such as cytokines, chemokines, complement components, and cell surface proteins.[33]

One hypothesis attributes the development of autoimmunity post-COVID-19 to the loss of self-tolerance as a result of transient immunosuppression or an inadequate immune reconstitution in susceptible individu-

als.[34] Whether this autoimmune process is responsible for some of the PASC remains a possibility that needs to be explored.

Conclusions

Multiple lines of evidence suggest that lingering inflammatory and autoimmune processes elicited as result of SARS-CoV-2 infection may be involved in the

pathogenesis of at least some of the sequelae of COVID-19. Future research using prospective studies in patients suffering from PASC is needed to elucidate the contributions of inflammation and autoimmunity to their multiple symptoms and clinical presentations. Such research would contribute to our understanding of the pathophysiology of this syndrome and the predisposing risk factors while providing clues for potential therapeutic approaches and molecular targets.

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