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Autoimmune and Autoinflammatory Connective Tissue Disorders Following COVID-19

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Coronavirus disease 2019 (COVID-19) is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). So far, a total of 768 million have been reported with COVID-19, with 6.9 million deaths worldwide. In addition to this pandemic, there have been several cases of new-onset autoimmune diseases (ADs) after COVID-19 affecting the endocrine system (Hashimoto thyroiditis and Graves' disease), musculoskeletal system (dermatopolymyositis, spondyloarthritis, and rheumatoid arthritis), nervous system (transverse myelitis, acute disseminated encephalomyelitis, and Guillain-Barré syndrome [GBS]), etc. Viral infection modifies the development and induction of ADs, like hepatitis C virus (HCV), Epstein-Barr-virus (EBV), influenza A virus (IAV), and parvovirus B19 (1, 2).

There are many autoantibodies in patients infected with SARS-CoV-2, such as anti-nuclear antibodies (biomarker for GBS) and anti-CCP antibodies (biomarkers for inflammatory arthritis /psoriasis /Grave's disease). Cytokine release syndrome is defined as the uncontrolled release of pro-inflammatory cytokines associated with SARS-CoV-2 infection, such as tumor necrosis factor-α and interleukins (ILs), leading to disrupting acquired and innate immune responses in humans, which causes intolerance to self-antigens (3). SARS-CoV-2 infection is linked to reduced and dysfunctional T-regulatory cells suppressing autoimmune events in cases with severe COVID-19 (1, 4-6). Because SARS-CoV-2 disrupts self-tolerance and, through cross-reactivity, stimulates autoimmune reactions that may lead to ADs.

Coronavirus disease 2019 is associated with many diseases, such as ADs, because SARS-CoV-2 disrupts self-tolerance and triggers autoimmune responses by cross-reactivity, leading to the development of ADs (7). Alopecia areata, systemic lupus erythematosus (SLE), vitiligo, vasculitis, and pediatric inflammatory multisystemic syndrome affect immunologic reactions after SARS-CoV-2 infection, proposing the presence of underlying immune dysregulations in COVID-19 patients (7, 8).

The SARS-CoV-2 infection is involved in cardiopulmonary failure, and its severity is an important factor causing patients' overall mortality; thus, extensive assessment of respiratory and cardiovascular outcomes after COVID-19 infection has been performed. There are similarities between COVID-19 and many ADs (7), but a comprehensive assessment of inflammatory or autoimmune diseases as post-acute sequelae of COVID-19 has yet to be established. Hence, the current nationwide, population-based study was done to estimate the risk and incidence of many autoinflammatory and autoimmune connective tissue disorders after COVID-19 (8, 9).

The psoriasis risk was slightly increased in the COVID-19 subcohort, including men and cases with severe COVID-19. Previous studies have reported exacerbation of pre-existing psoriatic lesions as well as elevated levels of T-helper (TH) 17-related cytokines in COVID-19 patients. Therefore, the TH17-skewed milieu due to SARS-CoV-2 infection can cause the pathogenesis of psoriasis (8).

There was an increase in the incidence of ANCA-related vasculitis in COVID-19 patients, which was in line with previous studies. Plausible mechanisms are viral-related hypercoagulability due to complement system activation, endothelial injury or infection, and the coagulation cascade dysregulation, resulting in vasculopathy. Also, long-term exposure to neutrophil extracellular traps may

induce anti-neutrophil antibodies (8).

According to another hypothesis, the release of cytokines triggers autoimmune reactions as bystander activation. IL-6 and IL-1 are associated with immune-related damage in cases with SARS-CoV-2 infection, and the effectiveness of antagonists of these cytokines in critically ill patients has been widely assessed. Dysfunctional angiotensin-converting enzyme 2 and its variants may contribute to an aberrant inflammatory microenvironment (8).

The risk of SLE was reduced in COVID-19 patients, which appears to contradict the results of other ADs in our research. The observation duration may not have been efficient in obtaining the full spectrum of SLE development. This is suggested by the cumulative incidence of SLE, which suggests that the onset of the disease occurs with a delay of approximately 100 days after the diagnosis of COVID-19. Also, SLE may be linked to the severity of COVID-19; higher mortality in critical COVID-19 cases may skew to a decreased risk of SLE (8).

The severity of the COVID-19 acute stage was related to AD outcomes. In general, the risks of the most common comorbidities were higher among the subgroups admitted to the ICU compared to the milder (non-ICU) cases. Coronavirus disease 2019 severity and death were associated with increased levels of various cytokines, such as IL-6 and tumor necrosis factor-α, suggesting a possible link to persistent autoimmunity (3).

We comprehensively assessed the risks of autoinflammatory and autoimmune connective tissue diseases in COVID-19 patients compared to controls, which highlighted them as potential post-COVID-19 sequelae. Long-term management of COVID-19 patients should include assessment of subsequent development of autoinflammatory and autoimmune connective tissue disorders.

Footnote

Conflict of Interests: The author is Editor-in-Chief of the journal.

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