EDITORIAL

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Significance of antinuclear antibodies in patients with COVID-19

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During the more than 3-year coronavirus disease 2019 (COVID-19) pandemic, many studies have reported an association between COVID-19 infection and autoimmune disease. Although most patients with COVID-19 are asymptomatic or with mild symptoms, some develop serious complications, such as acute respiratory distress syndrome or multiorgan injury, which are known to be related to a dysregulated immune response and increased levels of pro-inflammatory cytokines induced by SARS-CoV-2 [1]. Medications used to treat autoimmune diseases, such as corticosteroids, tocilizumab, and baricitinib, are widely used in patients with severe COVID-19. Autoantibodies known to occur in several autoimmune diseases have been detected in patients with COVID-19 during or after the illness [2]. In addition, several new autoimmune and autoinflammatory conditions have been reported, such as idiopathic inflammatory myositis or systemic lupus erythematous, after COVID-19 infections [3]. A study by Park et al. [4] in this issue of the *Korean Journal of Internal Medicine* draws attention to the relationship between COVID-19 infection and autoimmunity.

Inspired by several reports on the association between autoantibodies and COVID-19, some researchers have been investigating the clinical significance of antinuclear antibody (ANA) positivity in patients with COVID-19. However, those studies have been unsatisfactory because of a small sample size or a limited study design [5]. One prospective study evaluated the presence of ANA, anticytoplasmic neutrophil (ANCA) antibodies, and antiphospholipid (APL) antibodies in 33 consecutive patients with COVID-19 pneumonia [6]; 45% of patients were positive for at least one autoantibody, and 11 of 33 patients were positive for ANA. Although the presence of autoantibodies was related to a poor prognosis, ANA-positivity alone was not. Another study reported ANA positivity in 36.4% (48/131) of patients with COVID-19, but non-intensive care unit (ICU) patients had higher ANA titers than ICU patients [5]. Park et al. [4] reported that 77 cases (58.3%) among 132 patients with severe COVID-19 in their retrospective cohort were positive for fluorescent antinuclear antibody (FANA ≥ 1:80). These FANA-positive patients were older and had higher inflammatory marker levels and 28-day mortality than FANA-negative patients. A multivariate Cox regression analysis revealed that FANA positivity (hazard ratio [HR], 2.65; 95% confidence interval [CI], 1.04–6.74) was an independent predictor of 28-day mortality. The other predictors of 28-day mortality were age, underlying pulmonary disease, underlying hypertension, and blood levels of urea nitrogen, well-known predictors in patients with severe COVID-19. Remdesivir therapy was an independent predictor of reduced mortality (HR, 0.34; 95% CI, 0.15–0.74). The frequency of ANA positivity and its association with prognosis in COVID-19 patients varies among studies due to differences in patient characteristics such as age distribution, disease severity, and other factors, so caution should be taken when comparing results across studies.

This study is clinically attractive, as it had a relatively large sample size compared to previous studies and contained more information on the clinical features of hospitalized patients with COVID-19. However, several limitations must be considered. A transient increase in autoantibodies or ANA positivity in the response to viral infections is commonly seen and this is mediated by molecular mimicry of viral antigens [7]. In an epidemiological study in the USA, ANA prevalence in the general population ≥ 12 years was 13.8% and it increased with age [8]. Therefore, an external vali-

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dation study is needed with healthy or other viral-infected patients as control groups for a better predictive model for COVID-19 patients. Moreover, the presence of other autoantibodies, such as ANCA and APL, was not tested in that study, which could have added to our understanding of the autoimmune response in patients with COVID-19. Differences in the cut-off values for ANA positivity and in the use of different detection methods among studies also become another obstacle in comparing studies on autoimmunity in COVID-19 patients.

Another important question in the study of autoantibodies in COVID-19 patients is the serial change in autoantibodies over time, their relationship with long-term sequelae, and their association with the development of future autoimmune disease. A Canadian study measured ANA levels in 106 convalescent COVID-19 patients at 3, 6, and 12 months post-recovery and compared them to age- and sex-matched healthy controls (n = 22) and those who had other respiratory infections (n = 34) [9]. Patients with COVID-19 had higher detectable ANA and patients with a more severe acute phase developed a stronger autoimmune response 3 months post-recovery. The mean number of ANA autoreactivities per individual decreased between 3 and 12 months (from 3.99 to 1.55) with persistent positive titers associated with fatigue, dyspnea, and cough severity.

In conclusion, further studies are needed on the relationship between autoantibody positivity and the prognosis in COVID-19 patients, the effect of autoantibody positivity on the use of immunomodulatory drugs, and the association between autoantibody positivity and the development of autoimmune disease.

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