Onset of rheumatoid arthritis after COVID-19: coincidence or connected?

COVID-19, caused by SARS-CoV-2, can lead to severe inflammation and has been suggested to induce autoimmune phenomena. Multiple studies have reported autoantibodies in patients with COVID-19, particularly anti-cardiolipin, anti-J2-glycoprotein 1 and antinuclear antibodies.1 2 Anti-citrullinated protein antibodies (ACPAs) and flaring of rheumatoid arthritis (RA) after SARS-Cov-2 infection have also been described.1 3 However, it is unclear how often ACPA occur after COVID-19 and whether they differ from ACPA normally found in patients with RA.

We have therefore performed a detailed investigation into ACPA positivity after COVID-19. To determine the seroprevalence of ACPA after COVID-19, ACPA was measured using routine tests or in-house ELISA in 61 patients visiting the post-COVID-19 outpatient clinic of the Leiden University Medical Center 5 weeks after hospitalisation. None of the patients tested positive for ACPA, except two patients previously diagnosed with ACPA-positive RA. Thus, we could not observe an increase in ACPA positivity after COVID-19.

Furthermore, we identified five patients across various Dutch rheumatology clinics presenting with polyarthritis compatible with RA after SARS-CoV-2 infection. To study the impact of COVID-19 on disease presentation, we closely examined their clinical phenotype and autoantibody characteristics (online supplemental table S1). All had suffered from moderate-to-severe COVID-19. On average, joint complaints started 6.6 weeks after infection, although two patients reported symptoms before infection. Four of five patients fulfilled the American College of Rheumatology 2010 criteria for RA. Three patients were phenotypically very similar to regular patients with new-onset RA. Patient 3 had a history of seronegative RA and had been in disease-modifying anti-rheumatic drug-free remission for 5 years. She flared 6 weeks after SARS-CoV-2 infection. Patient 2 had a remarkably different presentation. He was admitted with acute polyarthritis and high inflammatory markers 6 weeks after COVID-19. Pneumonia with reactive polyarthritis or septic polyarthritis was considered and treatment was started accordingly. The level of ACPA was low positive. The patient died unexpectedly after 2 days, and autopsy revealed dilating myocarditis of unclear underlying cause. No causative pathogen, or compelling evidence of autoimmunity, could be identified.

Previous studies have shown that patients with RA are most often either seronegative or triple-positive for rheumatoid factor, ACPA and anti-carbamylated protein antibodies. ACPA IgM and IgA are most frequently found within patients positive for ACPA IgG.4 Autoantibody measurements on sera of patients with post-COVID-19 polyarthritis using in-house ELISAs6 revealed patterns very similar to RA (figure 1A), with two patients being completely seronegative and three patients positive for a range of autoantibodies at presentation. Sera prior to presentation to the rheumatologist are not available.

A unique feature of ACPA IgG in patients with RA is that their harbour glycans not only in their Fc-part, but also in their variable domains (V-domains).1 We analysed the ACPA IgG V-domain glycosylation profiles of the above-mentioned three ACPA-positive post-COVID-19 polyarthritis patients and established RA patients (online supplemental table S1) using ultra-high-performance liquid chromatography.5 In all post-COVID-19 samples, the percentage of ACPA V-domain glycosylation was increased compared with total IgG (figure 1B), similar to regular RA. Inflammatory conditions, among which COVID-19, can induce changes in the composition of antibody Fc-glycans.6 A detailed examination of the specific ACPA IgG V-domain glycan traits revealed a significant decrease in bisecting N-acetylglucosamine-containing moieties (G2FBS1, G2FBS2) after COVID-19 (figure 1C), comparable to patterns described for total IgG Fc-glycosylation after COVID-19.6 The biological causes and consequences of these glycosylation changes currently remain unclear.

Limitations of this study include the small sample size and limited follow-up duration after COVID-19. Although autoantibody responses can develop rapidly after (SARS-CoV-2) infections, replication in a larger cohort with a longer follow-up would be valuable. Furthermore, part of the samples were measured in-house instead of commercial tests. However, the characteristics of these assays appear very comparable based on previous experience.

In conclusion, we found that the seroprevalence of ACPA is not increased after COVID-19 infection and that patients presenting with polyarthritis after COVID-19 resemble regular patients with RA, both regarding clinical phenotype and autoantibody characteristics. Based on these data, it appears that RA after COVID-19 may be coincidence rather than connected.

**Figure 1** (A) Auto-antibody measurements using in-house ELISAs: RF, ACPA and anti-CarP isotype levels per patient. White—seronegative, gradient light to dark blue—low to highest levels, normalised against the maximum detection limit of ELISA per antibody isotype. (B) Percentage of variable domain glycosylation (mean, SD). Average value of duplicates plotted. V-domain glycosylation in ACPA IgG after COVID-19 is significantly increased compared with total IgG (p<0.05; Mann-Whitney U test), no significant difference between ACPA IgG V-domain glycosylation after COVID-19 and regular RA (disease characteristics in online supplemental table S1). (C) Percentage of specific glycan traits of all ACPA IgG V-domain glycans (mean, SD). Average value of duplicates plotted. Glycan trait G2F52 without bisecting N-acetylglucosamine is significantly increased, while G2FBS1, a glycan trait with bisecting N-acetylglucosamine, is significantly decreased after COVID-19 (p<0.05; Mann-Whitney U test). Blue square—N-acetylglucosamine (B when bisecting), green circle—mannose, red triangle—fucose (F), yellow circle—galactose (G), purple diamond—sialic acid (S). ACPA, anti-citrullinated protein antibody; anti-CarP, anti-carbamylated protein antibody; RA, rheumatoid arthritis; RF, rheumatoid factor.
Letter

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