Systemic lupus erythematosus flare following SARS-CoV2 infection: the implication of IFNα and anti-IFNα autoantibodies

Sirs,

The SARS-CoV2 pandemic brought back the unresolved question of whether and how a viral infection may trigger autoimmune diseases1. Type 1-interferon and autoantibodies to IFNα (anti-IFNα) are involved in both systemic lupus erythematosus (SLE) and COVID-19 pathogeny (2-5). To give insight into the complex relationship between COVID-19 and SLE, IFNα, anti-IFNα and anti-dsDNA antibodies were tested overtime in a patient who experienced a SLE flare following COVID-19.

In January 2019, a 20-year-old woman was admitted for acute pericarditis. Testing for antinuclear antibodies (ANA) was not performed at this time. She was treated with colchicine and aspirin then discharged. In April 2020, the patient was hospitalised for a mild COVID-19 that recovered without treatment. In August 2020, she presented malar rash, sore mouth, chest pain and arthritis. Laboratory tests showed elevated levels of anti-dsDNA antibodies at 159 IU/ml and SLE was diagnosed. Serum complement levels and urinary protein/creatinine ratio were normal. Oral glucocorticoids (starting at 0.5 mg/kg/day) and hydroxychloroquine (HCQ) led to a complete clinical remission. In January 2021, the patient was admitted for a severe infection with SARS-Cov-2 α variant, while still under steroids (10 mg/day) and HCQ. Supplemental oxygen was required. The patient recovered without SLE relapse.

Serum specimens from January 2019 until June 2021 could fortunately be retrieved and analysed (Fig. 1). In January 2019, serum was already positive for ANA, anti-Sm and anti-dsDNA antibodies, confirming that pericarditis was the heralding manifestation of SLE. Interestingly, high titre of anti-IFNα was also detected in January 2019 prior to COVID-19 (Fig. 1). Consistent with a potential protective role of anti-IFNα in SLE[3], lupus disease remitted without specific treatment at that time. Conversely, the presence of anti-IFNα may predispose to COVID-19 by blocking the action of this crucial antiviral cytokine (2, 5) and the patient displayed a first SARS-Cov-2 infection in April 2020. As an apparent consequence of type I interferon overproduction induced by the virus (5), the titre of anti-IFNα decreased after COVID-19 while IFNα level remained high (Fig. 1). The decrease in anti-IFNα titre may have contributed in turn to the lupus flare observed 4 months after COVID-19. Eventually, while the patient was still receiving steroids and HCQ, IFNα levels decreased and paralleled both diminished lupus activity and anti-dsDNA titres. Unfortunately, the patient suffered highly symptomatic COVID-19 reinfection during the "second wave" of the pandemic in France in December 2020. Thus, the first infection failed to induce a protective humoral immunity as assessed by the lack of circulating N-protein and S-protein specific IgG detected in October 2020. The second infection occurred while the patient was under steroids and HCQ making it more difficult to decipher the variation causes of circulating IFNα and anti-IFNα at this time. However, the second COVID-19 happened while anti-IFNα were still detectable in serum and was followed by an apparent rebound of IFNα level in March 2021. Eventually, in June 2021 anti-IFNα titre rose to its "protective" level for SLE (195 U/ml) while SARS-CoV-2 seroconversion had occurred and SLE was still in remission (Fig. 1).

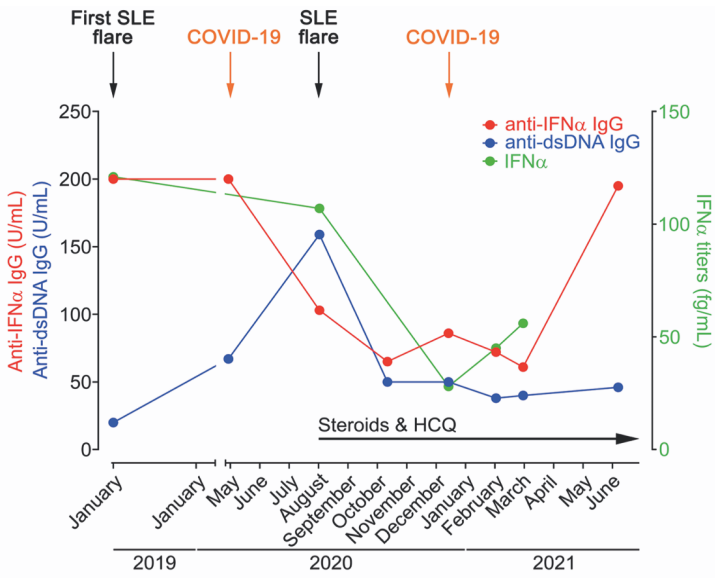

Fig. 1. IFNα, anti-IFNα and anti-dsDNA time course in a 20-year-old SLE patient with COVID-19. IFNα was measured by SIMOA technology (threshold 32 fg/ml), anti-IFNα by in house ELISA as described[2] (positivity threshold >10 UA/ml), anti-dsDNA by FEIA (positivity threshold >15 UI/ml).

Although a causative link cannot be demonstrated, the chronology of events indicates an original mechanism by which a viral infection may promote SLE flares. Indeed, a high titre of anti-IFNα – known to inhibit IFNα signalling (3) – may protect against lupus flare but predispose to COVID-19. In such setting, strong IFNα production induced by a virus like SARS-Cov-2 may overpass the protective role of anti-IFNα in SLE and thus contribute to lupus flare. Although our group reported no clear-cut evidence for a higher risk of severe COVID-19 in SLE (6), this observation suggests that SLE patients with anti-IFNα may be at risk for lupus flare following COVID-19.

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References

1. PUXEDDU I, FERRO F, BARTOLONI E *et al.*: COVID-19: the new challenge for rheumatologists. One year later. *Clin Exp Rheumatol* 2021; 39: 203-13.
2. BASTARD P, ROSEN LB, ZHANG Q *et al.*: Autoantibodies against type I IFNs in patients with life-threatening COVID-19. *Science* 2020; 370: eabd4585..
3. GUPTA S, TATOULI IP, ROSEN LB *et al.*: Distinct functions of autoantibodies against interferon in systemic lupus erythematosus: a comprehensive analysis of anticytokine autoantibodies in common rheumatic diseases. *Arthritis Rheumatol* 2016; 68: 1677-87.
4. CROW MK: Type I interferon in the pathogenesis of lupus. *J Immunol* 2014; 192: 5459-68
5. HADJADJ J, YATIM N, BARNABEI L *et al.*: Impaired type I interferon activity and inflammatory responses in severe COVID-19 patients. *Science* 2020; 369: 718-24.
6. MAGEAU A, ALDEBERT G, GYSEL DV, PAPO T, TIMSIT J-F, SACRE K: SARS-CoV-2 infection among inpatients with systemic lupus erythematosus in France: a nationwide epidemiological study. *Ann Rheum Dis* 2021; 80(8): 1101-2.