Correspondence on ‘Clinical course of coronavirus disease 2019 (COVID-19) in a series of 17 patients with systemic lupus erythematosus under long-term treatment with hydroxychloroquine’

Mathian et al described the clinical course and heterogeneity of COVID-19 in 17 systemic lupus erythematosus (SLE) patients. SLE subjects could be at higher risk of developing COVID-19, with more severe symptomatology and need for hospitalisation due to multiple underlying risk factors. Type-I IFN (IFN), including IFNαs, play fundamental roles in immunity and are crucial in antiviral responses. Defects in IFN signalling pathways, secondary to monogenic inborn errors or to blocking autoantibodies, promote immunodeficiency and recurrent infections. Dysregulation in type-I IFN pathway also plays key pathogenic roles in SLE. A recent report showed association between anti-type-I IFN autoantibodies in 10% of subjects with life-threatening COVID-19 in the general population. A comprehensive evaluation of multiple anticytokine autoantibodies showed the presence of anti-type-I IFN autoantibodies in 11% of SLE subjects in the pre-COVID-19 era. We hypothesised that SLE patients having anti-IFNα autoantibodies at baseline (prior to 2020) may be at higher risk of developing COVID-19, and that the presence of these autoantibodies may help in guiding management and preventive strategies.

Ten SLE females who developed COVID-19 between 1 April and 1 October 2020 were identified among lupus subjects followed at the National Institutes of Health, Bethesda, MD, USA under IRB-approved SLE natural history protocol 94-AR-0066 (online supplemental methods, table 1). Seven patients had mild to moderate COVID-19 symptoms that were managed at home with supportive care. Three patients had severe symptoms requiring hospitalisation, supplemental oxygen and/or steroids and convalescent plasma infusion. All patients had full recovery. Eight patients were on daily prednisone (range 5–20mg/day) when COVID-19 symptoms developed. Seven patients were taking hydroxychloroquine prior to COVID-19 and continued it during the infection. One patient (patient 2) had received rituximab in February 2020 and developed COVID-19 in May 2020. Another patient (patient 9) developed COVID-19 while on belimumab.

Biobanked plasma from healthy controls (HC; n=119) and the 10 SLE subjects were tested for anti-IFNα IgG autoantibodies by ELISA (online supplemental methods). Values 2 SD above mean in HC samples were considered positive. Anti-IFNα autoantibodies was detected in 4 out of the 10 SLE patients (patients 2, 3, 9, 10) who developed COVID-19 (40%; figure 1A). Longitudinal assessments of lupus plasma samples confirmed the presence of anti-IFNα autoantibodies preceding the infection as far back as 2017 (figure 1A). Patients with anti-IFNα autoantibodies had higher rates of hospitalisation requiring oxygen (two out of four) compared with those without (one out of six). Of the two patients (patients 2 and 9) who had received B-cell therapy in the prior years, both had persistent anti-IFNα autoantibodies. These results suggest that the prevalence of anti-IFNα autoantibodies is higher in those patients with confirmed COVID-19 than what has been previously reported in SLE.

We evaluated if the plasma positive for anti-IFNα autoantibodies could block IFNα signalling in vitro (online supplemental methods). Out of the four SLE subjects with anti-IFNα autoantibodies, half of the samples (two subjects; patients 3 and 9) blocked recombinant human IFNα-induced signal transducer and activator of transcription 1 (STAT1) phosphorylation in HC peripheral blood mononuclear cells (PBMCs) at 10% concentration (figure 1B). These patients had the highest anti-IFNα autoantibodies titers. None of the COVID-19 SLE plasma samples negative for anti-IFNα autoantibodies (n=6) inhibited STAT1 phosphorylation by rIFNα.

In this initial assessment, 40% of SLE patients who developed confirmed COVID-19 were positive for anti-IFNα IgG autoantibodies in samples obtained prior to SARS-CoV-2 infection. In general, positive autoantibodies were present several years before and in some patients persisted despite B-cell targeted therapy. Previous reports in the same cohort showed that SLE subjects had anti-IFNα autoantibodies prevalence of 11%. Therefore, those SLE patients who developed confirmed COVID-19 during this initial wave of the pandemic had enrichment in anti-IFNα autoantibodies. Plasma samples with the highest titers of anti-IFNα autoantibodies inhibited signalling of IFNα in vitro, suggesting that levels of these autoantibodies may affect their blocking ability. A worse outcome in COVID-19 patients positive for anti-IFNα autoantibodies in the general population was recently reported, and suggested that these antibodies may precede infection based on two prestored plasma samples. Our findings support this hypothesis, as SLE patients who

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Table 1: Clinical characteristics of SLE subjects with confirmed COVID-19

<table>
<thead>
<tr>
<th>Age</th>
<th>Gender</th>
<th>Race</th>
<th>COVID-19 in SLE</th>
<th>COVID-19 symptoms</th>
<th>Admission</th>
<th>Tx for COVID-19</th>
<th>Clinical manifestations of SLE</th>
<th>Autoantibodies</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 63 F C Hispanic Cough</td>
<td>No</td>
<td>IC, Dec</td>
<td>SLE, polyarthritis, arthritis, nephritis</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-SSB</td>
<td>Adenocarcinoma, pneumonia</td>
<td>Obesity, overweight</td>
<td></td>
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<tr>
<td>2 60 F H Rapid antigen</td>
<td>Yes</td>
<td>Oxygen, concomitant rhinitis, dyspnoea</td>
<td>SLE, respiratory failure, hypocomplementemia</td>
<td>Anti-IFNα, anti-Nucleosome, anti-DsDNA, anti-LAC, anti-RNP, anti-CL</td>
<td>Pulmonary embolism, throat, urinary infection</td>
<td>Overweight, hypertension</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 60 F H Rapid antigen</td>
<td>Cough, Fever, SLE, chest pain</td>
<td>Yes</td>
<td>Anti-IFNα, anti-DsDNA, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
<td></td>
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<tr>
<td>4 60 F AA Cough, Fever, Obstructive cough</td>
<td>No</td>
<td>Sputum, care</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>5 56 F C Rapid antigen</td>
<td>No</td>
<td>Sputum, care</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>6 49 F H Rapid antigen</td>
<td>No</td>
<td>Sputum, care</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
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<tr>
<td>7 60 F H Antihemophilic factor</td>
<td>No</td>
<td>Sputum, care</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
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<tr>
<td>8 50 F H Cough, SLE, chest pain</td>
<td>Yes</td>
<td>Oxygen, concomitant rhinitis, dyspnoea, loss of taste and smell, sore throat, cough</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
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<tr>
<td>9 50 F H SLE</td>
<td>Cough, chest pain</td>
<td>Yes</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity, diabetes mellitus</td>
<td></td>
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<tr>
<td>10 26 F H Cough, chest pain</td>
<td>No</td>
<td>Sputum, care</td>
<td>Anti-IFNα, anti-DsDNA, anti-Nucleosome, anti-LAC, anti-RNP</td>
<td>Pulmonary embolism, throat, upper respiratory tract, hypocomplementemia</td>
<td>Overweight, obesity</td>
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Systemic Autoimmunity Branch, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, Maryland, USA

Correspondence to Sarthak Gupta, National Institute of Arthritis and Musculoskeletal and Skin Diseases, National Institutes of Health, Bethesda, MD 20892, USA; sarthak.gupta@nih.gov

Twitter Sarthak Gupta @SarthakGuptaMD

Contributors SG, SN and MJK contributed to the conception and design of the study. SG, SN, JC and SH were involved in the acquisition of data. SG, SN, SH and MJK contributed to the analysis and interpretation of data. All authors contributed to drafting and/or revising the manuscript.

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ORCID iDs Sarthak Gupta http://orcid.org/0000-0001-8255-3554
Mariana J Kaplan http://orcid.org/0000-0003-2968-0815

REFERENCES


