Clinical and peculiar immunological manifestations of SARS-CoV-2 infection in systemic lupus erythematosus patients

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Keywords:

Systemic lupus erythematous, SARS-CoV-2 infection, COVID-19, flare, disease activity

Key messages:

- SLE patients with major organ involvement tended to have asymptomatic SARS-CoV-2 infection.
- SARS-CoV-2 infection determined flares in a small number of patients.
- SARS-CoV-2 infection can trigger new onset autoimmune disease with atypical presentation.

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ABSTRACT

Objectives: The impact of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in patients with systemic lupus erythematosus (SLE) remains unclear and data on clinical manifestations after infection are lacking. The aim of this multicentre study is to describe the effect of SARS-CoV-2 in SLE patients.

Methods: SLE patients referring to 4 Italian centres were monitored between February 2020 and March 2021. All patients with SARS-CoV-2 infection were included. Disease characteristics, treatment, disease activity, and SARS-CoV-2 related symptoms were recorded before and after the infection.

Results: Fifty-one (6.14%) SLE patients were included among 830 regularly followed-up. Nine (17.6%) had an asymptomatic infection. Five (9.8%), out of 42 (82.6%) symptomatic, developed interstitial pneumonia (no identified risk factor). The presence of SLE major organ involvement (particularly renal involvement) was associated with asymptomatic SARS-CoV-2 infection (p-value=0.02). Chronic corticosteroid therapy was found to be associated with asymptomatic infection (p-value=0.018). Three SLE flares (5.9%) were developed after SARS-CoV-2 infection: one of them was characterized by MPO-ANCA positive pauci-immune crescentic necrotizing glomerulonephritis and granulomatous pneumonia.

Conclusions: SARS-CoV-2 infection determined autoimmune flares in a small number of our patients. Our data seem to confirm that there was not an increased risk of SARS-CoV-2 in SLE. Patients with asymptomatic SARS-CoV-2 infections were those having major SLE organ involvement. This may be explained by the high doses of corticosteroids and immunosuppressive agents used for SLE treatment.

INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China, in December 2019, and then spread worldwide. The World Health Organization (WHO) declared SARS-CoV-2 a pandemic in March 2020. SARS-CoV-2 has so far infected more than 139 millions of people and caused the death of almost 3 millions of them(1). In the following months, some risk factors for SARS-CoV-2 infection were identified in the general population (*e.g.* older age, male sex, non-white race, obesity)(2).

It is well established that patients with inflammatory rheumatic diseases (RDs) are at higher risk of infections than the general population because of associated comorbidities, underlying disease activity and concomitant immunosuppressive therapies(3). SARS-CoV-2 was shown to cause endothelitis resulting in vascular manifestations (*e.g.,* thrombosis) and immune system activation *via* toll-like receptors and complement system(4,5). At the beginning, the current pandemic aroused many questions for patients with RDs, such as systemic lupus erythematosus (SLE). In these patients, many factors associated with the disease were matter of concern, such as the well-establish role of viruses (*e.g.,* Epstein-Barr virus) in SLE pathogenesis(6–8), the higher susceptibility to infections(9), the risk of SLE flares after viral and bacterial infections(10), the presence of organ damage directly caused by SLE, the use of glucocorticoids (GCs), and immunosuppressive regimens.

Few new SLE cases, triggered by SARS-CoV-2 infection, have been so far reported(11). Conversely, as of today, studies were not able to detect an increased risk of SARS-CoV-2 in SLE patients(12). This could be explained by the fact that SLE patients could have adopted more protective behaviour than the general population and therefore this could have protected them from the infection(13,14). Besides GCs (more than 10 mg daily), no SLE-related risk factors have been identified(15). Moreover, some data about mortality in patients with RDs suggest caution about rituximab(15).

Various post-SARS-CoV-2 syndromes have been reported(16). Patients with pre-existing RDs may have flares during or after SARS-CoV-2 infection and it is an emerging consideration that RD patients might develop new and adjunctive autoimmune features(17).

The aim of the study was to describe the SARS-CoV-2 infection course on SLE patients in a multicentre cohort of Tertiary Hospitals of Northern Italy.

MATERIALS AND METHODS

Study design

Retrospective observational multi-centre cohort study.

Settings

Data regarding SLE patients, who have had a SARS-CoV-2 infection between February 2020 and March 2021 was retrospectively collected. The patients included in the study referred to 4 different SLE tertiary centres (Lupus Clinic of the Clinical Rheumatology Division of ASST Pini-CTO, Milan; IRCCS Policlinico, Milan; Ospedale Giovanni Bosco, Turin; Renal and Rheumatology Units, San Gerardo Hospital, Monza). The analysis is part of a study to collect observational data from SLE patients, that was approved by the Ethics Committee Comitato Etico Milano Area 2 (approval no. 0002450/2020).

Participants

All consecutive adult patients (over 18 years old) referring to participant centres with a diagnosis of SLE who had SARS-CoV-2 infection were included in the study. All patients provided written informed consent. SLE diagnosis was made in accordance with the 1997 SLE classification criteria of the American College of Rheumatology or those of the 2019 European League Against Rheumatism/American College of Rheumatology(18,19). Patients were considered to have had SARS-CoV-2 infection if a direct PCR on swab and/or a serological test for SARS-CoV-2 resulted positive. Patients were excluded if they had an overlap syndrome (*e.g.* rheumatoid arthritis and SLE).

Variables

Data regarding demographics, clinical and serological features of SLE, including organ involvement, disease duration, autoimmune profile, on-going treatment, disease activity before and

after SAR-CoV-2 infection, possible treatment modifications related to nasal swab positivity and comorbidities were collected and gathered in a database for statistical analysis. Moreover, when available, laboratory parameters (protein C reactive – CRP, erythrocyte sedimentation rate – ESR, ferritin, gamma globulins, interleukin 6 – IL-6) were collected at last follow-up visit before the SARS-CoV-2 infection and at the first follow-up visit after the infection. IL-6 dosage was available only for those patients referring to one centre (Ospedale Giovanni Bosco, Turin). Serum IL-6 levels were measured by immunoassay kit (Elecsys® IL-6, Roche Diagnostics). Information about SARS-CoV-2 infection (*i.e.*, clinical manifestations and hospitalization) were also recorded. Disease activity was assessed according to Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)(20). SARS-CoV-2 infection severity was assessed as previously defined(21)**.**

Statistical analysis

Descriptive statistic was used to summarize the patients' demographic and clinical data by using median, interquartile range, absolute numbers, and percentages. All these variables were then investigated as risk factors of the following outcomes: SARS-CoV-2 symptoms, COVID-19 pneumonia, and SLE flare after SARS-CoV-2 infection. The comparisons of continuous variables between groups of patients were assessed through Welch two sample t-test or Mann Whitney non-parametric test, as appropriate. The association between categorical variables was assessed by performing Chi square or Fisher's exact test, as appropriate. In order to identify subjects with similar profile and the association among the categorical variables, multiple correspondence analysis (MCA) was carried out(22). This multivariate analysis can also be seen as a generalization of principal component analysis (PCA) when the variables to be analysed are categorical instead of quantitative(23). No further modelling was conducted because of the limited number of individuals in each level of the investigated outcomes. A p value lower than 0.05 was considered as significant. All analyses were performed using R software, version 3.5.2, with package Rcmdr (version 2.5–1).

RESULTS

Characteristics before SARS-CoV-2 infection

Fifty-one patients, who had SARS-CoV-2 infection, were included in the study among 830 regularly followed-up patients. Disease history, laboratory parameters, demographic characteristics and therapy, collected at the last visit of follow-up before the SARS-CoV-2 infection, are reported in **table 1**. Included patients had a median age of 46.2 years with a SLE disease duration of 16.4 years. Most of patients were female (92.2%) and displayed history of ANA positivity (96.1%), anti-dsDNA (88.2%) positivity and low complement (52.9%). Median CRP was 0.20 mg/dL (IQR: 0.09-0.38), ESR 16 mm/h (IQR: 11-20), ferritin 152 mg/dl (IQR: 128-175), gamma globulins 85% (IQR: 14.35-17.58), and IL-6 24 pg/ml (IQR: 19-27). Thirty-four (66.7%) patients had experienced a major organ involvement (*i.e.*, kidney, central nervous system, lung) during the SLE history. Thirty-one patients (60.8%) were taking immunosuppressive drugs, 19 (37.3%) only GCs and/or hydroxychloroquine (HCQ), and 1 patient was without any SLE therapy. At time of SARS-CoV-2 infection, the majority of patient were in remission or low disease activity with a median SLEDAI-2K score of 2.

Clinical manifestations, therapy modifications and outcome of SARS-CoV-2 infection

The clinical manifestations of SARS-CoV-2 infection and its impact on SLE disease activity are reported in **table 2**. Nine (17.6%) patients had an asymptomatic SARS-CoV-2 infection, while 34 (66.7%) patients had a mild COVID-19, and 8 (15.7%) a severe-moderate COVID-19. Out of 42 symptomatic patients, 5 (9.8%) developed interstitial pneumonia(21) and 3 (5.9%) of them were hospitalized. In all patients with pneumonia the steroid dose was increased. Outpatients were treated with an oral course of antibiotics (macrolide). Among hospitalized patients, 2 received conventional oxygen therapy and 1 needed non-invasive positive pressure ventilation. Moreover, all 3 were treated with low molecular weight heparin and antibiotics.

Laboratory parameters were recorded at the first available follow-up visit after the infection: median CRP was 0.23 md/dL (IQR: 0.04-0.45), ESR 19 mm/h (IQR: 11-34.25), ferritin 216 mg/dL (IQR: 185-244), gamma globulins 16.9% (IQR: 15.6-17.9), and IL-6 56 pg/ml (IQR: 31-64). CRP (p=0.40) and gamma globulins (p=0.19) were not different from before the infection, whereas the levels of IL-6 (p=0.0003), ferritin (p=0.00003) and ESR (p=0.03) were statistically significant higher after the infection.

Thirty-nine (76.5%) patients out of 51 did not change the therapy during the SARS-CoV-2 infection. Nine (17.6%) patients stopped immunosuppressant therapy (*e.g.* azathioprine, mycophenolate, belimumab) during SARS-CoV-2 infection until a negative swab. An increased steroid dose was prescribed to 4 patients during the period of SARS-CoV-2 infection.

In our cohort, 3 patients had a disease flare after SARS-CoV-2 infection. One patient with a severe COVID-19 developed a severe disease flare, characterized by a typical picture of ANCA-associated vasculitis at renal and lung biopsy (all the details are reported below). One patient, after SARS-CoV-2 asymptomatic infection, had a severe disease flare with arthralgia and cutaneous vasculitis, successfully treated with GCs and azathioprine. One patient had a mild flare (transient proteinuria up to 3 gr daily with recovery without specific therapy) after a symptomatic SARS-CoV-2 infection.

Risk factors for symptomatic SARS-CoV-2 infection in SLE patients

Table 3 illustrates the distribution of the main demographic and clinical characteristics of the SLE patients stratified according to symptomatic/asymptomatic SARS-CoV-2 infection. Major organ involvement, in particular the renal one (p=0.008), was significantly more frequent (p=0.021) in asymptomatic patients (100%, n=9/9) when compared to individuals who had COVID-19 symptoms (59.5%, n=25/42). Concurrently, ongoing treatment with GCs and immunosuppressant overlapped the distribution of the SLE organ involvement in the 2 groups leading to a straightforward association between the anti-inflammatory/immunosuppressive therapy and asymptomatic

infection (4 and 23 out of 34 patients with organ involvement underwent GCs and/or immunosuppressive therapy, respectively). On the contrary, the remaining variables seem not to represent distinctive characteristics of the SARS-CoV-2 symptomatic profile. In this regard and on a strictly descriptive level, the multivariate analysis allowed to have an overall view of the relationships among all the clinical characteristics and to identify patients with similar profile (**Supplementary Figure S1,** available at *Rheumatology* online**)**. A substantial biologic variability of our cohort was explained by 2 underlying dimensions: the disease-related characteristics and the ongoing therapy. In this context, the major organ involvement and the treatment clearly defined the two profiles of SARS-CoV-2 infection.

Risk factors for COVID-19 pneumonia

In our cohort, only 5 patients (9.8%) developed SARS-CoV-2 related interstitial pneumonia. None of the considered parameters (*e.g.,* gender, age, disease duration, SLE organ involvement, serological SLE characteristics, SLE therapy, SLEDAI-2K score before the infection, or comorbidities) correlated with the risk of COVID-19 pneumonia. In the considered parameters, no difference was found between hospitalized and non-hospitalized patients.

CASE REPORT

A 56-year-old woman had been diagnosed SLE in 2001 based on antinuclear antibodies, anti-dsDNA antibody, low complement and lupus anti-coagulant positivity (ANCA, anti-ENA, anti-cardiolipin and anti-beta2glycoprotein I antibodies negative), malar rash, alopecia, arthritis and Raynaud phenomenon. She was treated with low-dose prednisone and hydroxychloroquine. Two years later, corticosteroids and antimalarial treatments were progressively stopped as sustained remission had been achieved. Regular follow-up visits confirmed persistent clinical remission with mild complement reduction, ANA positivity, and inconstant anti-DNA positivity since 2020.

In March 2020 she developed malaise, cough, and fever (maximum 38.5°C – no swab for SARS-CoV-2 performed – no specific therapy prescribed). In May 2020 fever and cough recurred, a lung computed tomography (CT) showed bibasilar consolidations, (swab for SARS-CoV-2 negative, SARS-CoV-2 IgG positive, CRP 6.4 mg/dL). The suspicion was SARS-CoV-2 pneumonia since the patient had been treated with several courses of antibiotic therapy with incomplete resolution of the clinical manifestations and persistence of bibasilar consolidations. In July 2020 she received a diagnosis of autoimmune thyroiditis and levothyroxine was started. At the end of November, for a new recurrence of chest pain, fever, and cough (swab for SARS-CoV-2 negative), a new lung CT was performed with evidence of multiple parenchymal consolidations and several nodules (**Figure 1**). A transbronchial lung biopsy revealed severe granulomatous inflammation with some multinucleated giant cells. The clinical conditions of the patient worsened, blood pressure increased, and rapid progressive kidney dysfunction developed with severe haematuria, anaemia, increased acute phase reactants and MPO-ANCA positivity (**Table 4**). Kidney biopsy was then performed with evidence of diffuse pauci-immune extra-capillary necrotizing glomerulonephritis (**Figure 2**). The patient received three intravenous methylprednisolone pulses of 750 mg each and rituximab (1 gr 14 days apart) followed by oral prednisone 0.5mg/kg/day with rapid resolution of the fever and of the other symptoms. One month after discharge, the patient was asymptomatic with a good control of blood pressure and a noticeable improvement on laboratory tests.

DISCUSSION

Our data seem to confirm that there is not an increased risk of SARS-CoV-2 in SLE patients. In this cohort, SLE patients with major organ involvements (with lupus nephritis being the most frequently observed) were those who experienced more often an asymptomatic form of the infection. SARS-CoV-2 infection determined flares in a small number of patients. Particularly, a patient with long-standing SLE developed a renal and pulmonary syndrome, atypical for SLE, more closely resembling a vasculitis.

Although statistically significant, the difference found between IL-6, ferritin and ESR levels before and after the infection did not seem biological relevant. Moreover, although increased with respect to pre-SARS-CoV-2 infection, ESR and ferritin values were still in the range of normality.

Considering the SLE intrinsic immunological abnormalities along with immunosuppressant therapies, the question of whether patients with SLE might have a different clinical SARS-CoV-2 infection outcome than the general population has risen among clinicians worldwide. It seems now evident that SARS-CoV-2 infection is characterized by a viral phase and a subsequent immunological response, supporting the hypothesis that the clinical spectrum of COVID-19 is a result of the heterogeneity in the immune reaction to the virus itself. The critical aspect of the most severe form of COVID-19 is the loss of the immune tolerance, leading to an exacerbation of the inflammatory components (the so-called cytokine storm)(24). In this regard, several therapeutic immunomodulatory approaches (*e.g.*, tocilizumab), usually administered in RDs, have been considered in the context of COVID-19(25). While overall results are still inconclusive, probably due to variability in dosing and heterogeneous inclusion criteria, it seems that some anti-rheumatic agents could have a role in the management of the immune response to SARS-CoV-2 infection.

In our cohort, patients with major organ involvement taking immunosuppressive regimens tended to experience asymptomatic SARS-CoV-2 infections; this fact might be explained by the concomitant ongoing SLE treatment (*e.g.*, high dose GCs) that could possibly have altered the immunological response to infection. This is only partially in line with what have been described in

other inflammatory conditions: in a cohort of 65 patients with systemic vasculitis, mainly ANCA-associated vasculitis, GCs at presentation and concomitant lung conditions were both associated with severe outcomes in COVID-19, while vasculitis disease activity and non-GCs immunosuppressant were not associated with severe outcome(26).

The case of a male SLE patient has been reported with articular and haematological involvement who developed Coombs positive haemolytic anaemia and anti-phospholipid antibodies positivity, after COVID-19(27). Here, we have reported the case of a female patient with a mild form of long-standing SLE in stable remission who developed a severe and atypical form of vasculitis after SARS-CoV-2 infection. This may suggest that in patients with an altered immunological substrate, SARS-CoV-2 may trigger immunological manifestations different from those expected.

Our study has some limitations, namely the number of patients included and the retrospective study design. Laboratory parameters were available only for some patients (*e.g.*, IL-6 were available for less than half of the patients) and at different time points after the SARS-CoV-2 infection: these aspects prevented the drawing of conclusions about the impact of the infection on inflammatory markers (CRP, ESR, ferritin…). In addition, because of outcoming information, our behaviour (*e.g.*, increased GCs, immunosuppressant suspension) might have changed over time and among centres towards SLE patients with SARS-CoV-2 infection.

Our data suggest a need to pay close attention to SLE patients with mild form, considering that they usually do not take immunosuppressant therapy and therefore they could be more exposed to develop an intense response to SARS-CoV-2 infection. Furthermore, our case report should remind clinicians that SARS-CoV-2 infection can trigger new onset autoimmune disease with atypical features in patients already prone to autoimmunity. The questions of whether these observations are reproducible in larger cohorts or, more critically, if they are somehow linked to immunological deregulations of SLE, are still open.

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Data availability statement

Data have been collected anonymously in an excel file that can be available upon request. Data about the case report could be subjected to some limitations due to privacy reasons.

BIBLIOGRAPHY

1. WHO coronavirus disease (COVID-19) dashboard. Available from: https://covid19.who.int. Data access: 15/4/2021.
2. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, et al. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;584:430–6.
3. Mageau A, Sacré K, Perozziello A, Ruckly S, Dupuis C, Bouadma L, et al. Septic shock among patients with systemic lupus erythematosus: Short and long-term outcome. Analysis of a French nationwide database. J Infect 2019 Jun;78(6):432–8.
4. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, et al. Covid-19 and autoimmunity. Autoimmun Rev. 2020 Aug;19(8):102597.
5. Merad M, Martin JC. Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. Nat Rev Immunol. 2020 Jun;20(6):355–62.
6. James JA, Robertson JM. Lupus and Epstein-Barr. Curr Opin Rheumatol. 2012 Jul;24(4):383–8.
7. Pisetsky DS. Role of Epstein-Barr virus infection in SLE: gene-environment interactions at the molecular level. Ann Rheum Dis. 2018 Sep;77(9):1249–50.
8. Harley JB, Chen X, Pujato M, Miller D, Maddox A, Forney C, et al. Transcription factors operate across disease loci, with EBNA2 implicated in autoimmunity. Nat Genet. 2018 May;50(5):699–707.
9. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, et al. Morbidity and mortality in systemic lupus erythematosus during a 10-year period: a comparison of early and late manifestations in a cohort of 1,000 patients. Medicine (Baltimore). 2003 Sep;82(5):299–308.

10. Tselios K, Tsioka R, Sarantopoulos A, Mouloudi E, Boura P. Influenza A/H1N1 septic shock in a patient with systemic lupus erythematosus. A case report. BMC Infect Dis. 2011 Dec 29;11:358.
11. Gracia-Ramos AE, Saavedra-Salinas MÁ. Can the SARS-CoV-2 infection trigger systemic lupus erythematosus? A case-based review. Rheumatol Int. 2021 Apr;41(4):799–809.
12. Fernandez-Ruiz R, Paredes JL, Niewold TB. COVID-19 in patients with systemic lupus erythematosus: lessons learned from the inflammatory disease. Transl Res J Lab Clin Med. 2020 Dec 19;
13. Favalli EG, Gerosa M, Murgo A, Caporali R. Are patients with systemic lupus erythematosus at increased risk for COVID-19? Ann Rheum Dis. 2021 Feb;80(2):e25.
14. Ramirez GA, Gerosa M, Beretta L, Bellocchi C, Argolini LM, Moroni L, et al. COVID-19 in systemic lupus erythematosus: Data from a survey on 417 patients. Semin Arthritis Rheum. 2020 Oct;50(5):1150–7.
15. Strangfeld A, Schäfer M, Gianfrancesco MA, Lawson-Tovey S, Liew JW, Ljung L, et al. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2021 Jan 27;
16. Flores-Alanis A, Cruz-Rangel A, Rodríguez-Gómez F, González J, Torres-Guerrero CA, Delgado G, et al. Molecular Epidemiology Surveillance of SARS-CoV-2: Mutations and Genetic Diversity One Year after Emerging. Pathog Basel Switz. 2021 Feb 9;10(2).
17. Kudose S, Batal I, Santoriello D, Xu K, Barasch J, Peleg Y, et al. Kidney Biopsy Findings in Patients with COVID-19. J Am Soc Nephrol JASN. 2020 Sep;31(9):1959–68.
18. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum. 1997 Sep;40(9):1725.

19. Aringer M, Costenbader K, Daikh D, Brinks R, Mosca M, Ramsey-Goldman R, et al. 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for systemic lupus erythematosus. Ann Rheum Dis. 2019 Sep;78(9):1151–9.
20. Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002 Feb;29(2):288–91.
21. COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines. National Institutes of Health.
22. Benzecri JP. Correspondence analysis handbook. New York: Marcel Dekker; 1992.
23. Greenacre M. Correspondence analysis in medical research. Stat Methods Med Res. 1992 Mar 1;1(1):97–117.
24. García LF. Immune Response, Inflammation, and the Clinical Spectrum of COVID-19. Front Immunol [Internet]. 2020 [cited 2021 Apr 18];11. Available from: https://www.frontiersin.org/articles/10.3389/fimmu.2020.01441/full
25. Nissen CB, Sciascia S, Andrade D de, Atsumi T, Bruce IN, Cron RQ, et al. The role of antirheumatics in patients with COVID-19. Lancet Rheumatol [Internet]. 2021 Mar 30 [cited 2021 Apr 18];0(0). Available from: https://www.thelancet.com/journals/lanrhe/article/PIIS2665-9913(21)00062-X/abstract
26. Rutherford MA, Scott J, Karabayas M, Antonelou M, Gopaluni S, Gray D, et al. Risk factors for severe outcomes in patients with systemic vasculitis & COVID-19: a bi-national registry-based cohort study. Arthritis Rheumatol [Internet]. [cited 2021 Apr 18];n/a(n/a). Available from: https://onlinelibrary.wiley.com/doi/abs/10.1002/art.41728
27. Raghavan S, Gonakoti S, Asemota IR, Mba B. A Case of Systemic Lupus Erythematosus Flare Triggered by Severe Coronavirus Disease 2019. J Clin Rheumatol Pract Rep Rheum Musculoskelet Dis. 2020 Sep;26(6):234–5.

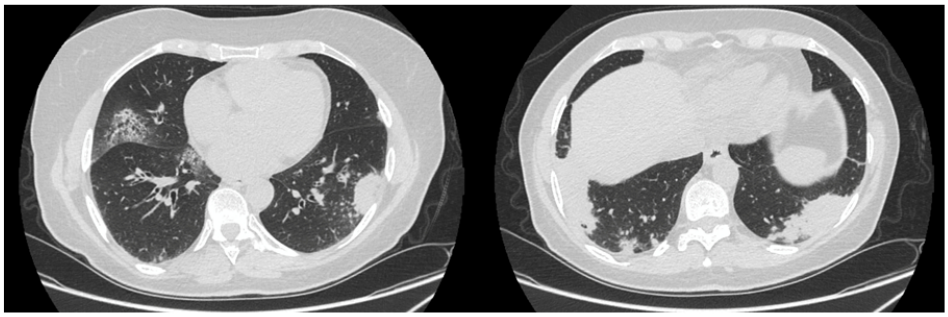

Figure 1. Pulmonary involvement: computed tomography images performed in December 2020 before bronchoscopy

254x190mm (96 x 96 DPI)

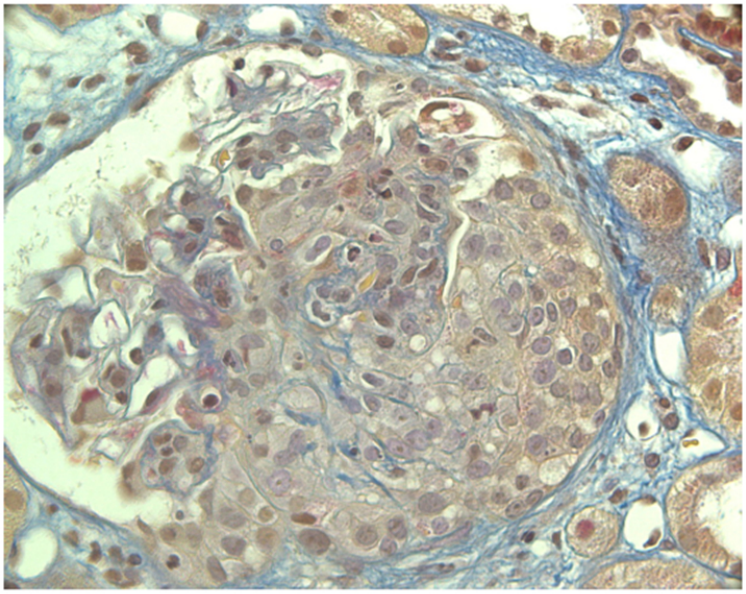

Figure 2. Kidney biopsy. Afog' stain. The glomerulus shows a large, almost circunferential cellular crescent. Partial of the Bowman capsule is disrupted.

figure 2 SLE covid

254x190mm (96 x 96 DPI)

Table 1. Demographic, comorbidities, SLE disease characteristics and therapies at the moment of SARS-CoV-2 infection.

Demographics	
Age, y, median (25th – 75th)	46.2 (40.5-52.7)
Disease duration, y, median (25th – 75th)	16.4 (5.0-22.3)
Gender, female, n (%)	47 (92.2)
Laboratory, median (25th – 75th)	
C-reactive protein, mg/dL[§]	0.20 (0.09-0.38)
Erythrocyte sedimentation rate, mm/h[#]	16 (11-20)
Ferritin, mg/dL[+]	152 (128-175)
Gamma globulins, %[++]	15.85 (14.35-17.58)
IL-6, pg/ml[+++]	24 (19-27)
Serology and organ involvement ever, n (%)	
ANA positivity	49 (96.1)
Anti-dsDNA antibodies positivity	45 (88.2)
Low complement (C3 and/or C4)	27 (52.9)
Anti-phospholipid antibodies positivity	16 (31.4)
Arthritis	42 (82.4)
Skin involvement	32 (62.7)
Renal involvement	31 (60.8)
Hematological involvement	18 (35.3)
Serositis	10 (19.6)
Lung involvement	5 (9.8)
Neurological involvement	4 (7.8)
Pulmonary arterial hypertension	1 (2.0)
Therapy, n (%)	
At least 1 immunosuppressant[*]	31 (60.8)
Corticosteroids	32 (62.7)
HCQ	45 (88.2)
ACEI/ARB therapy	21 (41.2)
Comorbidities, n (%)	
Arterial hypertension	21 (41.2)

Cardiovascular disease	6 (11.8)
Diabetes	2 (3.9)

[§]Available for 47 patients. [#]Available for 47 patients. [+]Available for 25 patients. [++]Available for 40 patients. [+++]Available for 21 patients. [*]Methotrexate, mofetil mycophenolate, cyclosporin A, azathioprine, belimumab, rituximab prior 12 months, intravenous immunoglobulin, cyclophosphamide.
ACEI: angiotensin converting enzyme inhibitors; ANA: anti-nuclear antibodies; ARB: Angiotensin Receptor Blockers; beta-B: beta-blockers; CCB: calcium channel blocker; HCQ: hydroxychloroquine; IL-6: interleukin 6; IQR: interquartile range; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SLE: systemic lupus erythematosus.

Table 2. Clinical manifestations of SARS-CoV-2 infection and SLE disease activity after SARS-CoV-2 infection.

Clinical manifestation of SARS-CoV-2 infection, n (%)	
Asymptomatic	9 (17.6)
Fever	31 (60.8)
Anosmia and/or ageusia	25 (49.0)
Cough	23 (45.1)
Diarrhea	4 (7.8)
Dyspnea	5 (9.8)
Interstitial pneumonia	5 (9.8)
Hospitalized	3 (5.9)
SLE disease activity	
SLEDAI-2K before SARS-CoV-2 infection, median (25th – 75th)	2 (0-2)
▪ Remission or low disease activity[§], n (%)	47 (92.2)
▪ Moderate or High disease activity[#], n (%)	4 (7.8)
SLEDAI-2K after SARS-CoV-2 infection, median (25th – 75th)	2 (0-4)
▪ Remission or low disease activity[§], n (%)	44 (86.3)
▪ Moderate or High disease activity[#], n (%)	7 (13.7)
SLE flare, n (%)	
SARS-CoV-2 infection with SLE flare	3 (5.9)
Asymptomatic SARS-CoV-2 infection with SLE flare	1 (2.0)
Symptomatic SARS-CoV-2 infection with SLE flare	2 (3.9)
Hospitalized SARS-CoV-2 infection with SLE flare	1 (2.0)

[§]Remission or low disease activity as defined according to SLEDAI-2K $\leq$ 4.

[#] Moderate or high disease activity as defined according to SLEDAI-2K > 5.

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SLE: systemic lupus erythematosus; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000.

Table 3. Distribution of demographic and SLE patient characteristics according to SARS-CoV-2 infection symptoms profile.

	Symptomatic SARS-CoV-2 (n=42)	**Asymptomatic SARS-CoV-2 (n=9)**	**p-value (p<0.05)**
Age, y, median (25th – 75th)	44.9 (40.1-52.7)	46.7 (43.6-52.7)	0.584
Disease duration, y, median (25th – 75th)	16.3 (5.5-21.9)	17.7 (4.0-22.5)	0.733
Female, % (n)	92.9 (39)	88.9 (8)	0.552
GCs, % (n)	54.8 (23)	100 (9)	0.018*
At least 1 immunosuppressant*, % (n)	54.8 (23)	88.9 (8)	0.072
HCQ	92.9 (39)	66.7 (6)	0.060
anti-dsDNA positivity, % (n)	88.1 (37)	88.9 (8)	1.000
aPL positivity, % (n)	33.3 (14)	22.2 (2)	0.701
Hypocomplementemia	52.4 (22)	55.6 (5)	1.000
Arterial hypertension	38.1 (16)	55.6 (5)	0.460
ACEi inhibitors, % (n)	42.9 (18)	33.3 (3)	0.720
Major organ involvement§, % (n)	59.5 (25)	100 (9)	0.021*
Renal involvement, n	52.4 (22)	100 (9)	0.008*
SLEDAI-2K before the infection, median (25th – 75th)	1 (0-2)	2 (0-4)	0.729

* Methotrexate, mofetil mycophenolate, cyclosporin A, azathioprine, belimumab, rituximab prior 12 months, intravenous immunoglobulin, cyclophosphamide.

§kidney, central nervous system, lung involvement.

ACEi: angiotensin converting enzyme inhibitors; aPL: anti-phospholipid antibodies; HCQ: hydroxychloroquine; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; SLE: systemic lupus erythematosus; SLEDAI-2K: systemic lupus erythematosus disease activity index 2000.

Table 4. Laboratory blood test history of SLE patients who received the final diagnosis of ANCA-associated vasculitis after SARS-CoV-2 infection.

	10/07/2020	05/11/2020	11/1/2021	05/03/2021
White blood cells, 10^9/L	4.2	4.6	9.9	6.2
Hemoglobin, g/dl	12.0	13.7	8.8	11.9
Platelets, 10^9/L	237	235	307	187
ESR, mm/h	49	19	124	12
CRP, mg/dL	0.3	0.1	1.76	0.11
C3 complement, mg/dL	-	94	118	97
C4 complement, mg/dL	-	9	17	8
TSH, mIU/L	13.7	-	1.06	-
Creatinine, mg/dL	1.09	0.97	2.83	1.43
ANA	1/640*	-	1/160	1/160
aPL	-	Negative	Negative	-
Anti-dsDNA ab	-	Negative	-	-
Urine sediment	Red blood cells	Normal	>100 urinary red blood cells /HPF, erythrocyte casts	20 urinary red blood cells No erythrocyte casts
Urine Protein,	0.3 mg/dl -	-	2128 mg/24h	1088 mg/24h
Anti-GBM ab	-	-	Negative	-
MPO-ANCA	-	-	Positive	Negative

*nuclear pattern

ESR: erythrocyte sedimentation rate; CRP: C-reactive Protein; TSH: thyroid-stimulating hormone; ANA: antinuclear antibodies; anti-ENA ab: antibodies to extractable nuclear antigens; aPL: antiphospholipid antibodies; anti-GBM ab: anti–glomerular basement membrane antibodies; ANCA: anti-neutrophil cytoplasmic antibodies.HPF: High power field