Systemic lupus erythematosus and coronavirus disease 2019

Antonio La Cava*

Department of Medicine, University of California Los Angeles, 1000 Veteran Ave. 32-59, Los Angeles, CA, USA

Abstract

Coronavirus disease 2019 (COVID-19) is a contagious infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It manifests with variable clinical pictures ranging from asymptomatic to mild or uncomplicated illness to severe disease with possible multi-organ involvement, with respiratory and vascular systems being the most often affected. Since COVID-19 can affect patients with autoimmune rheumatic conditions, the concomitant presence of two diseases may have clinical characteristics whose knowledge may help facilitate clinical management. This review discusses the data available in the literature on COVID-19 in systemic lupus erythematosus (SLE) patients.

Keywords

systemic lupus erythematosus • coronavirus disease 2019

Introduction

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a coronavirus that spreads primarily through respiratory droplets, and possibly through fomites (the latter possibility not demonstrated conclusively). As of November 13, 2020, there have been over 53 million confirmed cases of SARS-CoV-2 infections globally and more than 1.3 million fatalities due to COVID-19, according to John Hopkins University (https://coronavirus.jhu.edu).

The gold standard for diagnosing COVID-19 is by real-time reverse transcription polymerase chain reaction (rRT-PCR) from a nasopharyngeal swab, although other testing strategies (e.g., immunoassays) have been used in smaller settings or are under development.

The clinical disease course of SARS-CoV-2 infection can be highly variable. Some infected individuals are asymptomatic (no disease manifestations) whereas most people have mild symptoms. For those who become symptomatic, the most common manifestations include cough, fever, and fatigue that generally develop after an incubation period of about 4–5 days. For some patients, the disease can worsen 5–10 days after onset of the initial symptoms and complicate into manifestations that can include hypoxia, respiratory failure including acute respiratory distress syndrome (ARDS), blood clots, septic shock, and multi-organ failure that can be fatal. For those that recover, long-term effects may include fatigue, low-grade fever, muscle weakness, cognitive issues, respiratory problems, and, in some cases, damage to organs (e.g., lungs and heart).

The management of COVID-19 generally focuses on infection control, supportive care, and ventilatory support as needed, in addition to the treatment of sequelae and complications.

Epidemiology of COVID-19 In SLE

A critical point that has to be definitely clarified is the real incidence of COVID-19 in patients with systemic lupus erythematosus (SLE), regardless of the patient’s treatment.

Despite the finding of a moderate increase in morbidity, a study that compared a large number of SLE patients to the general population could not conclusively inform on potential associations between SLE and COVID-19 cases, due to the variety of disease- and drug-related detrimental and protective factors potentially coexisting in patients with SLE.[1] This consideration
suggests that the incidence of COVID-19 might be similar in lupus patients as compared to the general population.[2]

While the global incidence of COVID-19 in SLE remains unknown, a study reported that 4% of the 450 patients in the Colombia Lupus Cohort had developed symptomatic COVID-19 infection.[3] However, with the lack of available larger datasets, general consensus on the incidence and prevalence of COVID-19 in the SLE population has not been reached. Some investigators suggested that lupus patients might be more susceptible to severe acute respiratory syndrome from SARS-CoV-2 infection and to a more complicated course of COVID-19[4] but others did not observe such correlation in SLE patients,[5] arguing that COVID-19 disease progression might not be exacerbated in lupus patients because of the comorbidity.[6] While a small study on four SLE patients found more severe manifestations of COVID-19 infection in lupus patients in association with respiratory comorbidities and glucocorticoid and tobacco exposure as predisposing factors,[7] there are currently insufficient data to draw conclusions about susceptibility and severity of COVID-19 infection in lupus patients.[8]

Regarding the hospitalization rate of SLE patients, one study reported a decline during the COVID-19 pandemic - although hospitalized patients had more severe symptoms and needed more intensive treatment for active SLE and infection[9] (this is consistent with the observation that disease flares and infection contribute to the main reason of hospitalization for SLE patients[10]). The authors interpreted those data by suggesting that SLE patients tended to avoid going to the hospital, and that social distancing restrictions/lockdown might have reduced respiratory tract infections, which are common triggers of SLE flares. In another study, the variables predictive of hospitalization in 226 SLE patients were similar to those identified in the general population, being infection the leading cause of hospitalizations and deaths.[11]

**COVID-19 and SLE**

Accumulating scientific evidence does not support the notion that severe COVID-19 can result from viral cytopathic effects. The multi-organ insults seem to rather occur because of the inappropriate immune response of the host.[12] In addition to the exaggerated immune response manifested by the cytokine storm elicited by SARS-CoV-2 infection, the acute phase of COVID-19 infection can at times be followed by a (not completely understood) second phase in which some patients display autoinflammatory conditions and autoimmune activation.[13] In this context, it is known that patients with autoimmune diseases have an increased risk of infection including viral infections,[14, 15] and acute viral infections can exacerbate pre-existing autoimmune conditions. Moreover, immunosuppressive therapies put autoimmune patients at higher risk of viral infection.

A meta-analysis of seven case-controlled studies showed that the risk of COVID-19 in autoimmune diseases was significantly higher than in control patients, and meta-regression analysis showed an association between the use of glucocorticoids and the risk of COVID-19, suggesting that an increased risk of COVID-19 in patients with autoimmune disease could be attributed primarily to the use of glucocorticoids.[16] However, currently available data seem to suggest that SARS-CoV-2 infection may not associate with an increased incidence of autoimmune flares. In all, the finding that the rate of viral infection and clinical course of SARS-CoV-2 infection seem comparable between autoimmune patients and the general population suggests that autoimmune conditions do not represent independent risk factors and/or that SARS-CoV-2 infection would associate with more severe outcomes in autoimmune patients.[17] In this context, autoimmune patients that develop severe COVID-19 are more likely afflicted by other comorbidities (which indeed represented independent risk factors for severe disease), in line with the finding that COVID-19 patients with comorbid conditions such as cardiovascular disease, diabetes, and underlying respiratory conditions (among others) are at higher risk for severe complications and death.

Some authors have suggested that lupus patients might be more prone to severe COVID-19 independently of their immunosuppressed state deriving from treatment. This would be due to the epigenetic dysregulation in SLE patients that causes hypomethylation and overexpression of angiotensin-converting enzyme 2 (ACE2), the functional receptor for SARS-CoV-2 spike glycoprotein.[4] This would facilitate viral entry and viremia, and increase the likelihood of cytokine storm — the latter also favored in lupus patients by a demethylation of interferon-regulated genes, nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB), and key cytokine genes.[4]

**COVID-19 and Lupus Autoantibodies**

Some have suggested that SARS-CoV-2 infection might trigger and/or simulate the production of autoantibodies and autoimmunity.[18] For example, a patient with IgG positivity for COVID-19 infection developed anti-nuclear antibodies (ANA) and atypical anti-neutrophil cytoplasmatic antibodies (ANCA), manifesting SLE and vasculitis that persisted after the viral phase.[19]

ANA positivity is present in 35–50% COVID-19 patients,[20, 21] and in severe COVID-19 patients the prevalence of anti-SSA/Ro is
20–25%.[21] Moreover, several studies document the presence of different anti-phospholipid (APL) antibodies (namely lupus anticoagulant (LA), anticardiolipin IgG/IgM, and anti-β2-glycoprotein-I) in COVID-19 patients, mostly associated with thrombotic phenomena[20–22] — a relevant finding considering that COVID-19 patients are at high risk of thrombosis. The high prevalence and increased incidence of LA in COVID-19 patients (85–87.7%) has been associated with thrombosis and confirmed by several groups.[22–26] However, one study did not find the significant associations between LA and thrombosis[25] reported by others.[26] A possible explanation for this discrepancy could be the concomitant use of immunomodulatory agents such as hydroxychloroquine,[25] a drug that modulates LA levels.[27] Although Siguret et al. found a moderately elevated prevalence of anticardiolipin/anti-β2-glycoprotein-I antibodies (12%) in COVID-19 patients — a magnitude similar to other studies[24] — the role of these antibodies in the pathophysiology of COVID-19-attributed thrombosis remains to be better defined. This is also because the frequent single LA positivity, mostly transient during (acute phase) COVID-19 infection, does not clearly associate with thrombotic complications.[28] Notwithstanding these considerations, anticoagulation therapy is advised in severe COVID-19 because of its association with decreased mortality.[29]

SLE Medications

Many lupus patients are treated with immunosuppressive drugs, to keep their disease under control, to avoid flares, and to prevent organ damage. In SLE patients, medications such as azathioprine, mycophenolate mofetil, and methotrexate, in addition to glucocorticoids and biologics such as belimumab and rituximab, are commonly used. Although immune suppression makes SLE patients more susceptible to infection,[30] there are no definitive data to suggest that the medication-induced immunosuppressed state in SLE predisposes patients to SARS-CoV-2 infection.

After lengthy investigations, hydroxychloroquine appears as not associated with a preventive effect against SARS-CoV-2 infection,[31, 32] whereas for steroids, moderate-dose dexamethasone might lower the risk of death in some COVID-19 patients receiving oxygen or mechanical ventilation.[33] Consistent with this, a lupus patient with lupus pneumonitis and superimposed COVID-19 infection was successfully treated with intravenous steroids.[34] On the contrary, a study suggested the possibility that treatment with rituximab might represent a possible risk factor for unfavorable outcomes in COVID-19 patients.[35]

Conclusions

Though much needs to be learned about COVID-19 in SLE patients, a progressive advancement of the field and an increasing knowledge — even when deriving from case reports or small lupus cohorts — have been helpful in advancing our current understanding of the two comorbidities. This can lead to an improved clinical management that could ultimately result in ameliorating the disease prognoses and outcomes.

Conflict of Interest

None Declared.

References

[1] Ramirez GA, Gerosa M, Beretta L, et al. COVID-19 in Systemic Lupus Erythematosus: Data from a Survey on 417 Patients. Semin Arthritis Rheum. 2020;50(5):1150–1157. doi: 10.1016/j.semarthritis.2020.06.012.
[2] Zen M, Fuzzi E, Astorri D, et al. SARS-CoV-2 Infection in Patients with Autoimmune Rheumatic Diseases in Northeast Italy: A Cross-Sectional Study on 916 Patients. J Autoimmun. 2020;112:102502. doi: 10.1016/j.jauto.2020.102502.
[3] Gartshtein Y, Askanase AD, Schmidt NM, et al. COVID-19 and Systemic Lupus Erythematosus: A Case Series. Lancet Rheumatol. 2020. doi: 10.1016/S2665-9913(20)30161-2.
[4] Sawalha AH, Zhao M, Coit P, Lu Q. Epigenetic Dysregulation of ACE2 and Interferon-Regulated Genes Might Suggest Increased COVID-19 Susceptibility and Severity in Lupus Patients. Clin Immunol. 2020;215:108410. doi: 10.1016/j.clim.2020.108410.
[5] Holubar J, Quintrec ML, Letaief H, et al. Monitoring of Patients with Systemic Lupus Erythematosus during the COVID-19 Outbreak. Ann Rheum Dis. 2020. doi: 10.1136/annrheumdis-2020-217919.
[6] Mathian A, Mahevas M, Rohmer J, et al. Clinical Course of Coronavirus Disease 2019 (COVID-19) in A Series of 17 Lupus Patients Under Long-Term Treatment with Hydroxychloroquine. Ann Rheum Dis. 2020;79(6):837–839. doi: 10.1136/annrheumdis-2020-217566.
[7] Wallace B, Washer L, Marder W, et al. Patients with Lupus with COVID-19: University of Michigan Experience. Ann Rheum Dis. 2020. doi: 10.1136/annrheumdis-2020-217794.
[8] Sawalha AH, Manzi S. Coronavirus Disease-2019: Implication for the Care and Management of Patients with Systemic Lupus Erythematosus. Eur J Rheumatol. 2020;7(Suppl 2):S117–S120. doi: 10.5152/eurjrheum.2020.20055.
Impact of Clinical and Autoimmune Conditions at the Crossroad of COVID-19 Pandemic on Hospitalisation of Patients with Systemic Lupus Erythematosus (SLE). Report from a Tertiary Hospital during the Peak of the Pandemic. Ann Rheum Dis. 2020. doi: 10.1136/annrheumdis-2020-218475.

Teh CL, Ling GR. Causes and Predictors of Mortality in Hospitalized Lupus Patient in Sarawak General Hospital, Malaysia. Lupus. 2013;22:106–111. doi: 10.1177/0961203312465780.

Fernandez-Ruiz R, Masson M, Kim MY, et al. Leveraging the United States Epicenter to Provide Insights on COVID-19 in Patients with Systemic Lupus Erythematosus. Arthritis Rheumatol. 2020. doi: 10.1002/art.41450.

Henderson LA, Canna SW, Schulert GS, et al. On the Alert for Cytokine Storm: Immunopathology in COVID-19. Arthritis Rheum. 2020. doi: 10.1002/art.41285.

Rodriguez Y, Novelli L, Rojas M, et al. Autoinflammatory and Autoimmune Conditions at the Crossroad of COVID-19. J Autoimmun. 2020;114:102506. doi: 10.1016/j.aut.2020.102506.

Doran, MF, Crowson CS, Pond GR, et al. Frequency of Infection in Patients with Rheumatoid Arthritis Compared with Controls: A Population-Based Study. Arthritis Rheum. 2002;46(9):2287–2293. doi: 10.1002/art.10524.

Katsuyama E, Suarez-Fueyo A, Bradley SJ, et al. The CD38/NAD/Sirtuin1/EZH2 Axis Mitigates Cytotoxic CD8 T Cell Function and Identifies Patients with SLE Prone to Infections. Cell Rep. 2020;30:112–123. doi: 10.1016/j.celrep.2019.12.014.

Akiyama S, Hamdeh S, Micic D, et al. Prevalence and Clinical Outcomes of COVID-19 in Patients with Autoimmune Diseases: A Systematic Review and Meta-Analysis. Ann Rheum Dis. 2020. doi: 10.1136/annrheumdis-2020-218946.

Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors Associated with COVID-19-Related Death Using Open SAFELY. Nature. 2020. doi: 10.1038/s41586-020-2521-4.

Gaggiannis D, Steinestel J, Hackenbroch C, et al. COVID-19-Induced Acute Respiratory Failure – An Exacerbation of Organ-Specific Autoimmunity? medRxiv. 2020. doi: 10.1101/2020.04.27.20077180.

Bonometti R, Sacchi MC, Stobbione P, et al. The First Case of Systemic Lupus Erythematosus (SLE) Triggered by COVID-19 Infection. Eur Rev Med Pharmacol Sci. 2020;24(18):9695–9697. doi: 10.26355/eurrev_202009_23060.

Gazzaruso C, Stella G, Mariani C, et al. High Prevalence of Antinuclear Antibodies and Lupus Anticoagulant in Patients Hospitalized for SARS-CoV2 Pneumonia. Clin Rheumatol. 2020;39(7):2095–2097. doi: 10.1007/s10067-020-05180-7.

Zhou Y, Han T, Chen J, et al. Clinical and Autoimmune Characteristics of Severe and Critical Cases of COVID-19. Clin Transl Sci. 2020;10.1111/cts.12805.

Ali OH, Bomze D, Risch L, et al. Severe COVID-19 is Associated with Elevated Serum IgA and Antiphospholipid IgA-ANTIBodies. Clin Infect Dis. 2020. doi: 10.1093/cid/ciaa1496.

Harzallah I, Deblquis A, Drénou B, Lupus Anticoagulant is Frequent in Patients with Covid-19. J Thromb Haemost. 2020;18(8):2064–2065. doi: 10.1111/jth.14867.

Gil MR, Barouqa M, Szymanski J, et al. Assessment of Lupus Anticoagulant Positivity in Patients with Coronavirus Disease 2019 (COVID-19). JAMA Netw Open. 2020;3(8):e2017539. doi: 10.1001/jamanetworkopen.2020.17539.

Siguret V, Voicu S, Neuwirth M, et al. Are Antiphospholipid Antibodies Associated with Thrombotic Complications in Critically Ill COVID-19 Patients? Thromb Res. 2020;195:74–76. doi: 10.1016/j.thromres.2020.07.016.

Helms J, Taquard C, Severac F. High Risk of Thrombosis in Patients in Severe SARS-CoV-2 Infection: A Multicenter Prospective Cohort Study. Intensive Care Med. 2020. doi: 10.1007/s00134-020-06062-x.

Olsen NJ, Schleich MA, Karp DR. Multifaceted Effects of Hydroxychloroquine in Human Disease. Semin Arthritis Rheum. 2013;43(2):264–272. doi: 10.1016/j.semarthritis.2013.01.001.

Devreese KJM, Linskens EA, Benoit D, Peperstraete H. Antiphospholipid Antibodies in Patients with COVID-19: A Relevant Observation? J Thromb Haemost. 2020;18(9):2191–2201. doi: 10.1111/jth.14994.

Tang N, Bai H, Chen X, et al. Anticoagulant Treatment is Associated with Decreased Mortality in Severe Coronavirus Disease 2019 Patients with Coagulopathy. J Thromb Haemost. 2020;18(5):1094–1099. doi: 10.1111/j.1860-897x.2019.17539.

Tsai CY, Li KJ, Hsieh SC, et al. What’s Wrong with Neutrophils in Lupus? Clin Exp Rheumatol. 2019;37(4):684–693.

Gentry CA, Humphrey MB, Third SK, et al. Long-Term Hydroxychloroquine Use in Patients with Rheumatic Conditions and Development of SARS-CoV-2 Infection: A Retrospective Cohort Study. Lancet Rheumatol. 2020;2(11):e689–e697. doi: 10.1016/S2665-9913(20)30305-2.

Favalli EG, De Luca O, Biggioggero M, et al. Role of Antimalarials in COVID-19: Observational Data from a Cohort of Rheumatic Patients. Ann Rheum Dis. 2020. doi: 10.1136/annrheumdis-2020-218068.

RECOVERY Collaborative Group; Horby P, Lim WS, et al. Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Report. N Engl J Med. 2020. doi: 10.1056/NEJMoai2021436.

Kichloo A, Ajadah M, Albosta M, et al. COVID-19 and Acute Lupus Pneumonitis: Diagnostic and Treatment Dilemma. J Investig Med High Impact Case Rep. 2020;8:2324709620933438. doi: 10.1177/2324709620933438.

Loare-Martos J, García-Fernández A, López-Gutiérrez F, et al. High Rates of Severe Disease and Death Due to SARS-CoV-2 Infection in Rheumatic Disease Patients Treated with Rituximab: A Descriptive Study. Rheumatol Int. 2020;40(12):2015–2021. doi: 10.1007/s00296-020-04699-x.