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Lung Injury in COVID-19—An Emerging Hypothesis

Abdulrahman Alharthy, Fahad Faqihi, Ziad A. Memish, and Dimitrios Karakitsos*

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ABSTRACT: Lung injury with COVID-19 may be due to a complex underlying pathophysiology. Cytokine release syndrome appears to be a catalyst of different inflammatory pathways promoting lung parenchymal injury and thromboembolic phenomena ("dual hit" injury). Recently, severe neurological manifestations such as acute disseminated encephalomyelitis, which may be not linked to lung pathology, have been identified in COVID-19, contributing thus further to the versatility of its clinical features.

KEYWORDS: *COVID-19, Cytokine release syndrome, Interstitial pulmonary edema, Acute disseminated encephalomyelitis, Thromboembolic disease*

INTRODUCTION

We have recently shown that patients with life-threatening SARS-CoV-2 disease (COVID-19) had associated cytokine release syndrome (CRS)[1] as outlined in Table 1. Lymphocytopenia and increased levels of inflammatory mediators are early predictors of extensive lung involvement and death.[2−4] A minority of COVID-19 patients have fulminant disease, which is characterized by acute respiratory distress syndrome (ARDS), multisystem organ failure (MSOF), neurological manifestations, thromboembolic phenomena, and CRS. Recently, it has been interestingly hypothesized that the inflammation of nucleus tractus solitaries might elicit an exacerbation of neurogenic pulmonary edema and microvascular thrombosis in critically ill COVID-19 patients.[5,6] However, in a recent series, patients with severe COVID-19 have demonstrated features of acute disseminated encephalomyelitis (ADEM) with hemorrhagic changes,[7] which has not been related to the severity of lung involvement, and it has been partially attributed to diffuse endothelial dysfunction related to the viral binding to the ACE-2 receptors.[8,9] However, neurogenic pulmonary edema could indeed occur in patients with severe COVID-19 pneumonia although it should not be characterized as a form of ARDS, but rather as a noncardiogenic interstitial lung edema with peripheral lung zone distribution, which could be observed in viral pneumonitis and after brain injury.[10] On clinical grounds, this noncardiogenic pulmonary edema has been mainly a diagnosis of exclusion. In COVID-19, although the main distribution pattern of ground-glass opacities and consolidations is peripheral and on the lower lung lobes as has been reported by numerous chest computed tomography (CT) studies, atypical lung involvement patterns may occur.[11−14] In a prospective, longitudinal lung ultrasound study in severe COVID-19 pneumonia, we have recently outlined a diverse lung involvement in several lung zones.[15] Hence, we believe that the lung injury due to COVID-19 could be attributed to multifactorial pathophysiologic mechanisms.

Table 1. Criteria for Defining Cytokine Release Syndrome in COVID-19[a]

one or more of the following criteria should be present[b]
C-reactive protein >100 or > 50 mg/L but doubled in the past 48 h
lymphocyte count < 0.6×10^9/L
serum Interleukin-6 (IL-6) ≥ 3× upper normal limit
ferritin > 300 ug/L (or surrogate) with doubling within 24 h
ferritin > 600 ug/L at presentation and LDH > 250 U/L
elevated D-dimer (>1 μg/mL)

[a]Abbreviations: CRS, cytokine release syndrome; LDH, lactate dehydrogenase. [b]We define as low risk for developing CRS the presence of one criterion, moderate risk the presence of two to three criteria and high risk the presence of more than three criteria.

AN EMERGING HYPOTHESIS

The lung involvement in COVID-19 could lead to ARDS requiring intubation and intensive care unit admission. The pathogenesis of lung involvement may be attributed to various mechanisms. First, the virus could cause lung parenchymal injury resulting in pneumonitis barring interstitial lung and/or alveolar inflammation features. Also, the virus could directly bind to the ACE-2 receptors facilitating endothelial dysfunction. The associated CRS could exacerbate both lung parenchymal and microvascular inflammation, promoting thus refractory forms of ARDS with associated hypercoagulable states and microthrombosis.[16−18] Interleukin-6 (IL-6) is a pivotal cytokine in the development of CRS. In our pilot series of patients with life threatening COVID-19, the median values

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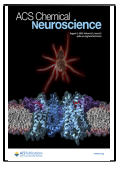

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of IL-6 that have been measured were 159 pg/mL (normal: 1−7 pg/mL), which have been decreased to normal with associated clinical improvement when we have applied therapeutic plasma exchange using the Spectra Optia Apheresis System equipped with the Depuro D2000 Adsorption Cartridge (Terumo BCT Inc., USA).[19] This adsorption cartridge contains activated uncoated coconut shell (carbon granules) charcoal (100 g) and the nonionic resins Amberlite XAD-7HP and Amberchrom GC300C. These can remove interferon-γ, interleukin-3, -10, -1B, -6, -8, and tumor necrosis factor α.[20] Moreover, tocilizumab, a monoclonal antibody against IL-6, has been tried in severe COVID-19 cases, albeit with variable results.[21−23] Hence, we suggest that COVID-19 associated CRS may be the catalyst of two parallel inflammatory pathways: one promoting parenchymal lung injury and another one facilitating thromboembolic phenomena, resulting thus in a "dual-hit" lung injury.[24−26] The interstitial lung edema observed in COVID-19 could be associated with the evolving viral pneumonitis per se with contributing cardiogenic and noncardiogenic underlying mechanisms. Cardiac dysfunction with associated pulmonary edema (i.e., myocarditis, arrhythmias, and stress cardiomyopathy) has been previously reported in COVID-19.[27−33] Although the occurrence of severe ADEM in COVID-19 has not been linked necessarily to lung pathology,[7] neurogenic pulmonary edema due to the catecholamine storm after a severe brain injury in COVID-19 cannot be excluded as a clinical entity. In our prospective lung ultrasound study of severe COVID-19 pneumonia, we have encountered interstitial pulmonary edema in variable lung and pleural zones of distribution. Moreover, the extent and quality of the pulmonary edema observed has been constantly changing as the pneumonia evolved over time (5 weeks).[15] Further studies are clearly required to shed more light on the complex pathophysiology of the SARS-CoV-2 clinical syndrome with associated cytokine storm (Figure 1).[34]

CONCLUSION

Currently, the pathophysiology of lung injury in COVID-19 appears to be complex, multifactorial, and partially understood. CRS is a key factor affecting the interplay between different inflammatory routes that need further exploration. The versatility of clinical features such as cardiac dysfunction, thromboembolic disease, and neurological manifestations along with the lung injury, and other systemic sequelae of SARS-CoV-2 infection may represent an evolving clinical syndrome, which requires further studying and analysis.

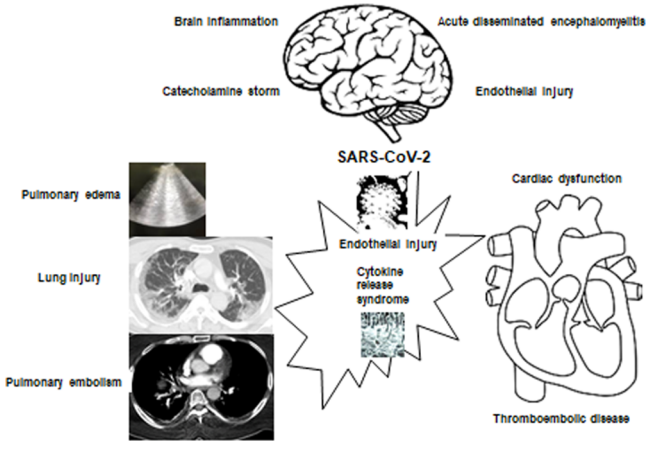

Figure 1. Simplified illustration of the versatile SARS-CoV-2 clinical features. The "dual-hit" lung injury is presumably facilitated by the associated cytokine release syndrome in COVID-19.

AUTHOR INFORMATION

Corresponding Author

Dimitrios Karakitsos − *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia;* orcid.org/0000-0003-3370-7099; Email: karakitsosdimitrios@gmail.com

Authors

Abdulrahman Alharthy − *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia*

Fahad Faqihi − *Critical Care Department, King Saud Medical City, Riyadh, Saudi Arabia*

Ziad A. Memish − *Critical Care Department and Research and Innovation Center, King Saud Medical City, Riyadh, Saudi Arabia*

Complete contact information is available at: https://pubs.acs.org/10.1021/acschemneuro.0c00422

Author Contributions

All authors contributed to data acquisition, analysis, and interpretation. All authors reviewed and approved the final version of the manuscript.

Notes

The study was approved by the Institutional Review Board of King Saud Medical City, Riyadh, Kingdom of Saudi Arabia [H-01-R-053, IORG0010374#, serial number: H1RI-29 April-2020].

The authors declare no competing financial interest.

LIST OF ABBREVIATIONS

ARDS, acute respiratory distress syndrome; CRS, cytokine release syndrome; COVID-19, SARS-CoV-2 disease; ADEM, acute disseminated encephalomyelitis; IL-6, interleukin-6

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