Is COVID-19 a Systemic Disease?

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Abstract: Background: Many observations denote that we should deal with COVID-19 as a systemic disease.

Methods: In the following report, we briefly discuss observations denoting “the systemic” nature of COVID-19.

Results: COVID-19 virology, the roles of ACE-2 receptor in COVID-19 pathogenesis, immunological aspects of the disease, endothelial dysfunction and coagulopathy, and autopsy studies denote the systemic nature of COVID-19.

Conclusion: Thinking of COVID-19 as a systemic disease, we will implement our ways of understanding and hence dealing with that disease. The most important public health solution is an effective vaccine for the broad population remaining at risk. As patients with COVID-19 present a broad spectrum of clinical presentation and distinct phenotypes, different strategies of management should be customized to the specific individual phenotypes. Further researches are highly needed to clarify the concept of “Is COVID-19 a systemic disease?”. Until that time, we think that clinicians should deal with COVID-19 as a systemic disease.

Keywords: COVID-19, systemic disease, immunity, pathobiology, ACE-2, coronavirus.

1. INTRODUCTION

The coronavirus infection COVID-19 first presented as an outbreak of atypical pneumonia in Wuhan, China, on December 12, 2019 [1]. Since then, it has spread globally to infect over 30 million people by September 17, 2020. This pandemic has impacted health and the economy worldwide on an unprecedented scale.

As the pandemic sweeps worldwide, clinicians start to realize that, whereas COVID-19 is primarily a respiratory infection, it has important systemic effects, including the cardiovascular and immune systems. This forces our mind to ask this important question; is COVID-19 a systemic disease?

In the following article, we try to answer this question in the light of many clinic-biologic and immunological observations. While we are constantly learning about the changing epidemiology, the rapidly evolving underlying science, together with insights from previous coronavirus infections, such as SARS-CoV-1 and MERS-COV, can help us to understand COVID-19 better and in turn, diagnose and treat our patients more efficiently.

2. COVID-19 VIROLOGY

SARS-CoV-2, the virus causing COVID-19, is a novel beta coronavirus (large RNA virus) that shares 80% sequence homology with the earlier SARS-CoV virus that caused the SARS outbreak 2003 [2]. However, SARS-CoV-2 has evolved several features that make it more efficient than SARS-CoV. The most critical receptor binding domain of SARS-CoV-2 preserved the overall configuration of the SARS-CoV binding domain, including 8 of the 14 residues being completely identical [3]. However, the 3D structure of the SARS-CoV-2 binding site shows that it is more compact, has improved binding stability, and potentially enhanced ACE-2 receptor binding affinity [3]. Another important difference is that SARS-CoV-2 contains a polybasic (furin) cleavage site inserted at the boundary of the S1/S2 subunits of the spike S-protein [4, 5]. This furin binding site is a feature shared by several recent highly pathogenic, viruses including avian influenza, and can enhance the virus’s ability to internalize into cells.

3. THE ACE-2 RECEPTOR

ACE-2 has been confirmed recently as the SARS-CoV-2 internalization receptor causing COVID-19 [5], in concert with the host’s TMPRSS2 membrane protease that primes the spike S protein of the virus to facilitate its cell entry [6]. ACE-2 is the same functional receptor of the earlier SARS-
CoV-1. However, the presence of TMPRSS2 significantly enhances viral infectivity [7]. It seems that protease inhibitors against TMPRSS2 can effectively block viral entry and infection of lung cells in vitro.

Interestingly, it was observed that ACE-2 has important immune-modulatory actions. ACE-2 can directly interact with macrophages in the setting of vascular and lung inflammation, as demonstrated by genetic manipulation in a model of SARS, as well as by the salutary anti-inflammatory effects of infusion of recombinant ACE-2 [8]. Indeed, ACE-2 reduces the levels of angiotensin II, which has pro-inflammatory and pro-oxidant effects. Therefore, ACE-2 is important in controlling excess systemic inflammation in the presence of danger signals [8].

As TMPRSS2 and ACE-2 facilitate SAR-CoV-2 entry, the co-presence of these two molecular entities in tissues explains, to a large extent, the tropism of viral proliferation. TMPRSS2 and ACE-2 are co-expressed in the lung, heart, gut smooth muscle, kidney, liver, neurons, and immune cells [9]. Thus, their distribution may explain the patients’ systemic symptoms and laboratory findings observed in COVID-19. Interestingly, circulating ACE-2 levels in patients is sex-dependent, being 50% higher in males than in females with heart failure [10]. Another intriguing association is the fact that in COVID-19 infections, the death rate of males is much higher, compared to females, despite adjustment for differences in risk factor profiles [11].

4. CLINICAL, HEMATOLOGICAL AND IMMUNOLOGICAL FINDINGS

It was observed that SARS-CoV-2 infection could generate a diverse range of responses in patients, ranging from completely asymptomatic virus shedding to a severe inflammatory response, including cytokine storm-like outcomes that are accompanied by high mortality [12]. Our current knowledge is that 81% of infected individuals have mild disease, 14% have severe symptoms requiring hospitalization, while 5% become critically ill requiring mechanical ventilation. These differences in response could be attributed to the degree of viral load, host immune response, age of the patient, and presence of co-morbidities. As per published recent data, there are 5 clinical phenotypes of COVID-19. Those phenotypes have distinct clinical presentations, prognostic features, and consequently, different management strategies [13]. Consequently, these different phenotypes could lead us to the concept that there will be a strong need for some sort of “phenotype-based tailored management”

On the extreme border, in patients with severe COVID-19, the “Cytokine storm” has been recently described and was characterized by increased plasma concentrations of IL-2, IL-7, IL-10, IL-18, interferon-γ-inducible protein 10, G-CSF, monocyte chemoattractant protein 1, tumor necrosis factor α (TNF-α), and macrophage inflammatory protein 1 alpha. This storm is the main mechanism for ARDS responsible for mortality in patients with severe COVID-19 [12].

Analysis of the inflammatory response to SARS-CoV-2 is interesting. A consistent finding is lymphopenia that occurs in over 80% of patients, the degree of which is a very important prognostic indicator early in the course of infection. In a parallel with the SARS-CoV-1 infection, in which lymphopenia was also observed to be highly prognostic, reports for SARS-CoV-2 showed an early reduction in T cells, in particular, a reduction in CD4+ more than CD8+ T cells [14]. Importantly, the recovery of lymphocyte count coincided with clinical improvement. Contrary to non-survivors, survivors from COVID infection demonstrated a nadir of lymphocytes count on day 7 from symptom onset and subsequent restoration. Therefore, serial assessment of the dynamics of the lymphocyte count may have predictive significance for patient outcomes [15]. A meta-analysis of nine studies had concluded that thrombocytopenia was significantly associated with the severity of COVID-19 [16]. Early analyses of patients succumbing to COVID-19 revealed marked reductions in circulating levels of CD4+ and CD8+ T lymphocytes and relative dominance of mononuclear cells (monocytes and macrophages) in target injury tissues, where the lung was primarily assessed [17].

5. VASCULAR ENDOTHELIUM, THROMBOSIS, AND COAGULOPATHY

Two major findings support that the SARS-CoV-2 virus targets the endothelium, one of the largest organs in the human body. First, ACE-2 is also expressed by endothelial cells [18]. Second, major clinical events were observed in COVID-19 patients (e.g., thromboembolic disease, high blood pressure, kidney injury, pulmonary embolism, and cerebrovascular stroke [19, 20].

Back to physiology, the endothelium prevents blood clotting by two mechanisms. First is providing an antithrombotic surface, maintained by heparan sulfate present in the matrix surrounding the cells through the expression of the tissue factor inhibitor, thrombomodulin. Second, by promoting fibrinolysis via the production of tissue-type plasminogen activator [21, 22]. On the other side, we identify endothelial dysfunction as a systemic condition in which the endothelium loses its physiological properties, including the tendency to promote vasodilation, fibrinolysis, as well as anti-aggregation [23].

Characteristically, it was observed that patients with COVID19 often have clotting disorders, with manifest organ dysfunction and coagulopathy, resulting in higher mortality [24, 25]. Analysis of coagulation profiles of samples collected from COVID-19 infected patients showed that non-survivors had significantly higher D-dimer and FDP levels and longer PT vs. survivors [26]. Moreover, the clinical diagnosis of disseminated intravascular coagulation (DIC) was observed in non-survivors during the late stages of hospitalization [26]. As expected, if DIC is attributable to systemic infection, it features an acute systemic over-inflammatory response, tightly linked to endothelial dysfunction [27].

Equally important, angiotensin II level in the plasma of COVID-19 patients was markedly elevated and linearly relat-
ed to viral load and lung injury; notably, angiotensin II is known to increase microvascular permeability, to induce the transcription of tissue factor in endothelial cells, and to activate platelets [27, 28].

Moreover, angiotensin II can trigger the release of several components of the complement system from endothelial cells, further confirming the key role of the endothelium in the pathogenesis of venous and arterial thrombotic phenomena in COVID-19 patients [29]. In the late stages of COVID-19, a dysregulated immune response is observed and plays a crucial role in endothelial dysfunction and thrombosis [30]. Quantitatively, endothelial cells represent one-third of the cell population of the lung, and physiologically, pulmonary endothelium represents a fundamental protective barrier between the blood and the interstitial space. Therefore, it is not surprising that pulmonary endothelial damage is considered the hallmark of ARDS [31].

The interaction between endothelial and immune cells could play a crucial role in COVID-19, especially in severe cases and in the late stages of the disease [12]. The cytokine storm might lead to abrupt hyperinflammatory and hypercoagulability states. Thus, the increased vulnerability of patients with CVD and/or diabetes might simply reflect the impact of this underlying chronic inflammation and its response during SARS-CoV-2 infection. If this is the scenario, then endothelial alterations could then be seen as an epiphenomenon.

Acute pulmonary embolism (PE), reported in COVID-19 patients [32], has been shown to be a cause of clinical deterioration in viral types of pneumonia, as well. Clinical implications for these observations denote that it is important to select COVID-19 patients at higher risk of PE, and practice computed pulmonary tomography angiography (CTPA) for the diagnosis of pulmonary thromboembolism especially in the case of a significant increase of D-dimer values. Anticoagulation could be a necessary therapy to control and reduce pro-thrombotic events, as well as to prevent PE [26, 33, 34].

6. AUTOPSY STUDIES

A group of articles has been published recently for autopsy studies performed for COVID-19 patients. Ackermann and colleagues [35] had examined 7 lungs obtained during autopsy from patients who died from COVID-19 and compared them with 7 lungs obtained during autopsy from patients who died from acute respiratory distress syndrome (ARDS) secondary to influenza A(H1N1) infection and 10 age-matched, uninfected control lungs. They found the pattern of diffuse alveolar damage with perivascular T-cell infiltration in patients who died from COVID-19–associated or influenza-associated respiratory failure. The lungs from patients with COVID-19 also showed distinctive vascular features, consisting of severe endothelial injury associated with the presence of the intracellular virus and disrupted cell membranes. The pulmonary vessels of patients with COVID-19 showed widespread thrombosis and microangiopathy. Alveolar capillary microthrombi were 9 times as prevalent in patients with COVID-19 as in patients with influenza [35]. In a study from the USA, autopsy findings on 23 patients with COVID-19 confirmed that COVID-19 is a systemic disease with major involvement of the lungs and heart [36]. The authors concluded that their autopsy findings support the concept that the pathogenesis of severe COVID-19 disease involves direct viral-induced injury of multiple organs, including heart and lungs, coupled with the consequences of a procoagulant state with coagulopathy.

7. OTHER OBSERVATIONS

The recent description in the literature of “atypical presentations” for COVID-19 makes us more logical to think that these atypical presentations could be one presentation of one “systemic disease”, rather than different or “atypical” presentations of the disease. Despite the majority of these reported atypical presentations represent case reports and low numbers of patients (at least in proportion to the majority of 4.6 million COVID-19 infected people globally); some of them represent real clinical challenges [37].

Lastly, our experience and knowledge with previous respiratory disorders, like chronic obstructive pulmonary disease (COPD), have passed in stages. It took many years to develop our standing of COPD from (simple chronic bronchitis-emphysema), to a systemic inflammatory disorder with many organs affection [38]. We think that a similar way of thinking could be applied to our understanding of COVID-19.

CONCLUSION

It can be concluded that no aspect of health care will be untouched by COVID-19. Thinking of COVID-19 as a systemic disease will implement our ways of dealing with the disease. For sure, it will affect our ways of therapeutic modalities. The most important public health solution is an effective vaccine for the broad population remaining at risk. Until a vaccine is developed, the best defense is avoiding infection altogether through frequent, thorough hand washing and social distancing. As patients with COVID-19 present a broad spectrum of clinical presentation and distinct phenotypes, different strategies of management should be customized to the specific individual phenotypes. Applying a personalized approach would benefit in the optimization of therapies and improving outcomes. Further researches are highly needed to clarify the concept of “Is COVID-19 a systemic disease?” Until that time, we think that clinicians should deal with COVID-19 as a systemic disease.

AUTHORS’ CONTRIBUTIONS

Sherif Mohamed and Nashwa Abd El-Aziz developed the idea, and all authors made a substantial contribution to the development and writing of this article. Sherif Mohamed, acting as the corresponding author, had the final responsibility for the decision to submit for publication. Khaled Saad, Ghada Elgohary, and Azza AbdElHaffez, contributed to the collection of data.
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REFERENCES


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