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Looking beyond pulmonary disease in COVID-19: A lesson from patients with cystic fibrosis

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ABSTRACT

Coronavirus disease 2019 (COVID-19) caused more than 52.775.271 million confirmed cases, 1.293.106 deaths, globally, and afflicted 208 countries, areas, or territories; and almost three months have passed since the World Health Organisation (WHO) declared COVID-19 as a pandemic. Despite the dramatic and global impact of the *Coronavirus*, the knowledge about the SARS-CoV-2 infection has been improved remarkably. Herein, we provided the rationale for SARS-CoV-2 infection as endothelial dysfunction rather than respiratory disease. Accordingly, we strongly invited the researchers to look beyond pulmonary injury and shift their attention from respiratory disease to endothelial disorder. This strategy could be particularly relevant to identifying therapeutic weapons stabilizing the endothelium rather than the lungs.

Introduction

Coronavirus disease 2019 (COVID-19) caused globally more than 52.775.271 million confirmed cases, 1.293.106 deaths, and afflicted 208 countries, areas or territories; and, almost three months have passed since the World Health Organisation (WHO) declared COVID-19 as a pandemic [1]. Despite to the dramatic and global impact of the *Coronavirus*, the knowledge about the SARS-CoV-2 infection has been improved remarkably. Clinical manifestations of COVID-19 range from asymptomatic to mild, moderate, severe, and critical. Symptoms may appear 2–14 days after exposure to the virus. Fever or chills, cough and difficulty breathing are the most commonly reported clinical symptoms [2–4]. Gastrointestinal symptoms have been also reported in children and adolescents diagnosed with COVID-19. Diarrhea and vomiting have been reported in about 8%-9% of cases, reaching more than 20% in some studies [5,6].

Compare to them, the high prevalence of respiratory symptoms is due to the evidence that the respiratory system offers a more efficient means of spreading and the protein angiotensin-converting enzyme 2 (ACE2), a co-receptor for *Coronavirus* entry, is expressed in the lungs [7]. Accordingly, the COVID-19-mediated respiratory disease draws attention to himself and enormous efforts have been made in understanding the mechanisms underlying lung involvement in COVID-19, the sequelae stemming from the disease, and therapeutic strategies to counteract the disease. However, it is all true here? Are we sure we are moving in the right direction? Are we looking at SARS-CoV-2 infection from the right perspective? We are very doubtful, and, probably, we are missing something.

The hypothesis/theory

At our Respiratory Unit, we are daily working with patients affected by cystic fibrosis (CF) which, in accordance with the Centers for Disease Control and Prevention (CDC) guidelines, are included in the cluster of people at higher risk of COVID-19-mediated serious illness [8]. Fortunately, despite their underlying health condition, patients with CF referring to our Hospital have been spared from the disease, and a similar trend has been globally reported [9]. Globally, to the best of our knowledge, COVID-19 has been confirmed only in fifty-eight patients with CF (age range, 6–28 years) [10]. Ten of them were notified in Italy, five patients with CF have been reported to have SARS-CoV-2 infection in Germany. Three patients with CF were also notified in Spain [11]. The remain confirmed patients have been notified in Canada, France, Ireland, Netherlands, New Zealand, United Kingdom (UK), and United States (US) [12]. No case was reported in Australia [12]. Currently, CF patient registries throughout Europe have collected data about people with CF who become infected with SARS-Cov-2, causing the illness COVID-19. Up to 30 November 2020, two hundred ninety-eight with CF have had COVID-19, two hundred twenty-three out of two hundred ninety-eight were PCR-confirmed cases with data available, 79 patients were hospitalised and 12 of them needed intensive care, and 5 died [13]. Globally, 80% of them were symptomatic for SARS-CoV-2 at presentation, with more than 60% having a fever. Four out of 58 patients were admitted to the Intensive Care Unit (ICU), and three of all them required oxygen while one out of four required invasive ventilatory support. No death was reported [12]. Therefore, the disease course does not seem to differ apparently from the general population, even less severe. Considering the reported evidence, we wondered if COVID-19, defined as "a lung disease caused by a novel coronavirus first detected in late 2019" [2], is really a pulmonary disease. If so, we would have expected a more severe disease in patients with underlying pulmonary disease, such as CF. In this regard, authors reported that among the 31 Genotype-Tissue Expression (GTEx) human tissues, the small intestine, testis, kidneys, heart, thyroid, and adipose tissue show the highest expression

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of ACE-2 protein, while blood, spleen, bone marrow, brain, blood vessels, and muscle have the lowest ACE-2 expression levels. In the colon, liver, bladder, adrenal gland, and lung ACE-2 showed medium expression levels [14]. Thus, it is reasonable to hypothesize that the lung is not the primary target of infection but rather, being the major site of respiratory droplet deposition, it supports the replication of SARS-CoV-2. The release of virions in a compartment with close proximity to the pulmonary capillary bed, in fact, allows a systemic spread of the virus to distant organs, especially in the context of chronic inflammation [15]. Considering the chronic systemic inflammatory response occurring in CF, patients experience a pulmonary disease and early vascular ageing [16,17]. Whether in healthy subjects, endothelial cells act as a semi-permeable barrier, as a key regulator of angiogenesis, coagulation, vascular tone, and inflammatory responses, endothelial cells properties change upon CFTR dysfunction [18]. Vascular inflammation, oxidative stress, endothelial dysfunction and reduced bioavailability of nitric oxide (NO), increased endothelial permeability, prothrombotic and hypercoagulability status, and excessive angiogenesis contribute to disease progression [18-22]. However, although findings suggest that early vascular ageing may be implicated in CF, we hypothesized that vascular senescence can be protective from COVID-19. In light of the endothelial cell dynamics in vascular ageing, we hypothesized that a lower ACE-2 expression might occur in the damaged endothelium of patients with CF, therefore, their underlying systemic and chronic inflammatory disease could become a "protective measure" for COVID-19. Moreover, we also believe that due to the reduction in ACE-2 expression in the colon, small intestine, and blood vessels, the ACE-2 expression in airway epithelium even if sufficient to viral entry cannot allow an adequate viral spreading. In summary, taking into account both our clinical experience and the epidemiologic trend globally reported as well as the hypothesis previously argued by other authors [10,23,24], we support the hypothesis that the endothelium, and not lung, is a key target organ of COVID-19.

Evaluation of the hypothesis/idea

Twelve out of 58 CF subjects globally notified were from post-lung transplant patients, who were on average 6 years post their transplant [10]. Thus, what lessons we learn from the COVID-19? Lung transplantation is a life-saving procedure for patients with end-stage lung disease; however, it burned by both acute and chronic allograft rejection, thus, immunosuppressive regimens are employed to reduce the rate of rejection although they are not without adverse effects, including drug-specific toxicities, as well as opportunistic infections and malignancy. Accordingly, COVID-19 may pose a great risk to transplant recipients [25–27], therefore, it was very surprising that transplanted CF patients did not develop a more severe COVID-19 course. After lung transplantation, a "sterile" inflammatory condition, involving oxidative stress and immune response, ultimately resulting into a breakdown of the endothelial and epithelial barriers, and, consequently, into oedema and defective gas exchange, has been widely described [28]. Therefore, we speculated that transplanted CF patients, in addition to their baseline CF-mediated endothelial damage, show a further endothelial injury due to the ischemia/reperfusion damage after lung transplantation. In turn, the disruption of endothelial and epithelial barriers, probably, leading to lower ACE-2 expression, could become a further "protective measure" for COVID-19. These findings could prove that the endothelium, not the lung, is a key target organ of COVID-19. In fact, while studies demonstrated an improvement in lung function after lung transplantation, with a significant increase both in forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) in the transplanted subjects [27], studies did not support a recovery of the endothelial barrier [15,28], so, failing the ACE-2 expression, the viral entry into the host cells can be inadequate. Studies found that the density of ACE-2 in the tissue correlated with the severity of the disease in that tissue [15,29–32]. Accordingly, we hypothesized that a lower ACE-2 expression, probably occurring both in the lung tissue and vascular endothelium damaged over time by a chronic disease, such as CF, and an acute event, such as lung transplantation, cannot permit the viral entry. Both conditions would provide paradoxically an adequate protection from the COVID-19-mediated acute respiratory disease.

Consequences of the hypothesis and discussion

Currently, there is no validated evidence on the treatment and prevention in children infected with SARS-CoV-2. In critically ill adult patients, tocilizumab, convalescent plasma, low-molecular-weight heparin, anti-oxidant agents, and antiviral drugs have been used as potential treatments against the inflammatory status, cytokine storm, microangiopathic thrombotic inflammation, disseminated intravascular coagulation, and viral replication cycle [33–39]. Herein, we provided the rationale for SARS-CoV-2 infection as endothelial dysfunction rather than respiratory disease. Accordingly, we strongly invite the researchers to look beyond pulmonary injury and shift their attention from respiratory disease to endothelial disorder. This strategy could be particularly relevant to identifying therapeutic weapons stabilizing the endothelium rather than the lungs.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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