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Should all COVID-19 patients be approached in the same way?

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TO THE EDITOR:

Since the first reports of coronavirus disease (COVID-19) in Wuhan, China, in 2019, it has become clear that hypoxemic respiratory failure is the most severe clinical manifestation of COVID-19.[1] A high incidence of cases of severe acute respiratory syndrome (SARS) or acute respiratory distress syndrome (ARDS) in a short period of time among patients exposed to a wet market in Wuhan raised the possibility of a highly contagious infectious disease caused by a new coronavirus, which was later designated SARS coronavirus 2 (SARS-CoV-2).[2]

Given that COVID-19 causes severe respiratory failure, is highly transmissible, and results in a high number of deaths from respiratory disease, different therapeutic modalities have been employed. Identification of the etiologic agent of COVID-19 and of pathophysiological mechanisms of COVID-19–related lung parenchymal injury led to two different therapeutic approaches: treatments aimed at reducing viral load and replication (remdesivir and plasma from patients who recovered from COVID-19); and those aimed at reducing the pulmonary inflammatory response to SARS-CoV-2 (including chloroquine, corticosteroids, and tocilizumab [an anti-IL-6 receptor antibody]).[3] However, the efficacy of these treatments has yet to be established in controlled clinical trials.

A third therapeutic approach has recently been proposed, namely, treatment of SARS-CoV-2–induced pulmonary vascular disease. Autopsy studies have shown the presence of endotheliitis[4] and thrombosis in the pulmonary microvasculature.[5] Elevated D-dimer levels have been correlated with poor prognosis in patients with COVID-19,[6] indicating the relevance of vascular disease in the clinical course of COVID-19. Gattinoni et al.[7] showed that, despite the severity of hypoxemia, lung compliance is relatively preserved in cases of COVID-19–induced ARDS. However, unlike what has been reported in other causes of ARDS, pulmonary shunt fraction is surprisingly high, suggesting that vascular disease plays a role in the severity of COVID-19. In this scenario, it is tempting to consider the possibility of treating vascular disease in patients with COVID-19. In a retrospective study conducted in China, heparin was reported to play a potential role in the treatment of vascular disease in patients with COVID-19.[8] However, this treatment approach has yet to be evaluated in prospective controlled studies.

COVID-19 arrived in Brazil in mid-March 2020, and clinical experience demonstrated a wide variety of pulmonary manifestations.[9,10] With regard to inclusion in randomized clinical trials and clinical management, it might be inappropriate to treat vascular disease in patients with predominantly parenchymal involvement. Patient selection for inclusion in prospective studies, clinical support, and specific treatment modalities can be essential to achieve the expected result. Figure 1 shows chest CT scans of two patients. Patient A presented with severe hypoxemia but no lung parenchymal changes that might account for it, as well as presenting with markedly elevated D-dimer levels, all of which were suggestive of concomitant vascular disease as the underlying cause of hypoxia. Should this patient have received treatment aimed at reducing the lung parenchymal inflammatory process despite the fact that the underlying condition appeared to be pulmonary vascular disease? Patient management included hospitalization, ventilatory support, and prophylactic heparin. In contrast, patient B presented with extensive lung parenchymal changes, without hypoxemia or elevated D-dimer levels, and was therefore managed at home. Should patients without evident vascular disease receive anticoagulation therapy? Both patients responded well to treatment at 10 days and are clinically well at this writing. The aforementioned cases suggest that COVID-19 has varying phenotypes (i.e., parenchymal and vascular), and this has an impact on the clinical management of the disease. However, there is currently no evidence for a phenotype-based approach to COVID-19 treatment.

Given that several pathophysiological pathways are involved in the development of COVID-19, indiscriminate treatment of COVID-19 patients can lead to negative results in clinical studies and unsatisfactory individual clinical outcomes. Proper identification of the pathophysiological mechanism of lung injury in patients with COVID-19 might prove essential to appropriate clinical management and the interpretation of the results of clinical trials currently underway. However, it should be born in mind that definitive conclusions on the efficacy and safety of COVID-19 therapeutic strategies other than ventilatory support await results of ongoing prospective clinical trials.

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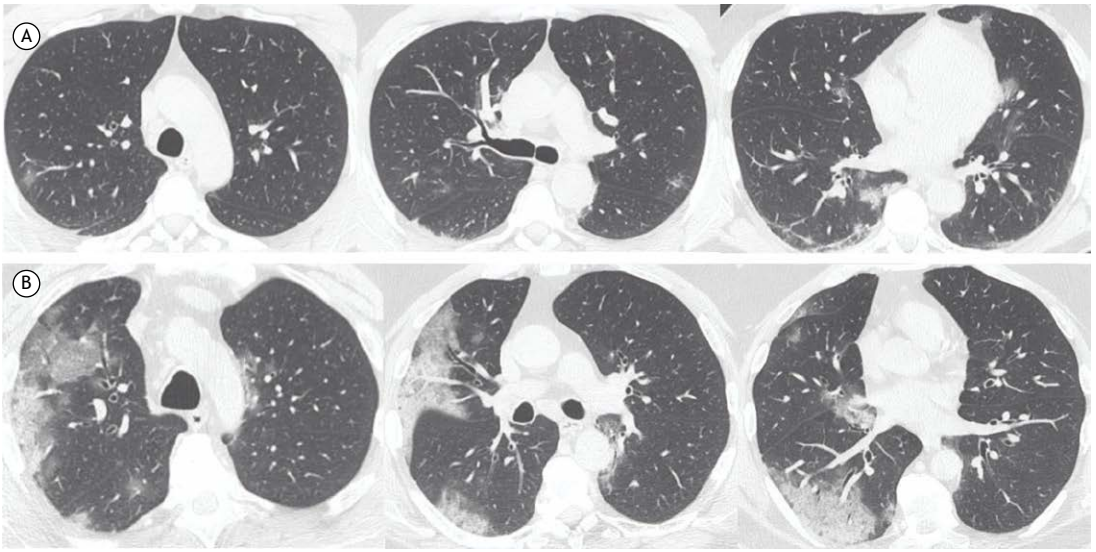

Figure 1. Chest CT scans of two patients with COVID-19, both of whom had an approximately 10-day history of respiratory symptoms. In A, a 48-year-old male patient with no comorbidities and an SpO_2 of 89% on room air, as well as a D-dimer level of 2,600 ng/mL. In B, a 62-year-old male patient with hypertension and diabetes, as well as an SpO_2 of 95% on room air and a D-dimer level of 420 ng/mL.

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