Is COVID Evolution Due to Occurrence of Pulmonary Vascular Thrombosis?

Luca Saba, MD and Nicola Sverzellati, MD†*

Abstract: In this hypothesis paper, we suggest that severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) may induce intravascular pulmonary thrombosis, which may result in the rapid worsening of clinical conditions and, eventually, exitus. Previously published papers have demonstrated that increased levels of D-dimer at hospital admission correlate with a more severe disease (0.5 mg/L) or occurrence of death (1 mg/L). The potential prothrombotic action of the SARS-CoV-2 is supported by the topographical involvement of the lung regions with a predilection for the lower lobe with peripheral involvement. If this hypothesis is demonstrated, this could suggest the benefit of using antithrombotic/coagulation regimens for SARS-CoV-2 and, at the same time, the urgency to identify drugs that could alter the inflammatory storm, thus protecting the vessel wall.

Key Words: pulmonary thrombosis, COVID, lung

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In early December 2019, the first pneumonia cases caused by a novel enveloped RNA beta-coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) occurred in Wuhan,[1] the capital city of Hubei province; 4 months later, the World Health Organization (WHO) declared Coronavirus Disease 2019 (COVID-19) a global pandemic and a public health emergency. Data provided by the WHO Health Emergency Dashboard (April 14, 10.00 AM CET) report 1,935,646 confirmed cases worldwide since the beginning of the epidemic. Of these, 120,914 (6.25%) have been fatal.

The clinical features of the patients with SARS-CoV-2 mainly include lower respiratory tract illness with fever, dry cough, and dyspnoea, a manifestation similar to those of 2 other diseases caused by coronaviruses, severe acute respiratory syndrome (SARS), and Middle East respiratory syndrome (MERS).[2]

The main target of SARS-CoV-2 is the lung, with different radiologic patterns observed at different times throughout the disease course. It was reported that the time between onset of symptoms and the development of acute respiratory distress syndrome was as short as 9 days.[3]

In this paper, we suggest the hypothesis that SARS-CoV-2 induces an intravascular lung thrombosis and that its progression and evolution could induce the fast worsening of the clinical condition of the patients, which may eventually result in death.

The presence of an alteration in the coagulation status in patients affected by SARS-CoV-2 is reported in the *NEJM* paper by Guan and colleagues, who showed the clinical characteristics of 1099 patients. They reported that, at admission, the D-dimer levels were increased by ≥ 0.5 mg/L in 46.4% of the patients (59.6% patients with severe disease; 43.2% with nonsevere disease).[1] It is important to underline that these were the values reported at admission, and they may have varied during the subsequent days of hospitalization. Concordant findings were reported in a study published by the *Lancet* on March 11, wherein the authors found that patients who did not survive hospitalization for SARS-CoV-2 in Wuhan were more likely to be older, suffer from comorbidities, and have elevated D-dimer.[4] The odds of dying in the hospital increased with age (odds ratio, 1.10; 95% confidence interval, 1.03-1.17; per year increase in age), higher Sequential Organ Failure Assessment score (5.65, 2.61-12.23; $P < 0.0001$), and, in particular, with D-dimer levels exceeding 1 mg/L on admission (odds ratio, 20.04; 95% confidence interval, 6.52-61.56). It must be noted that some patients had normal or not dramatically high D-dimer values even in the presence of severe clinical conditions; in this regard, it may be speculated that the amount of fibrin alteration at the level of tiny subsegmental arterial vessels does not induce the same dramatic changes seen in classic pulmonary embolism (PE), as it is known that a correlation exists between D-dimer values and the location of PEs.[5]

As it has already been demonstrated with other viral infections, such as the influenza A virus (IAV), the presence of aggressive inflammation, known as a cytokine storm, is thought to cause most of the damage in the lungs during infection. Similarly, dysfunctional coagulation is a common complication in pathogenic influenza, which manifests through lung endothelial activation, vascular leak, disseminated intravascular coagulation, and pulmonary thrombosis.[6]

The presence of fibrin within the pulmonary arteries is generally defined as PE, and it is believed to originate from the embolization of fibrin fragments from a deep venous thrombosis. However, a deep venous thrombosis is often not found in patients with PE,[7] and several authors suggest it would be appropriate to refer to "pulmonary thrombosis" to explain the presence of fibrin in the pulmonary vessels not coming from the periphery.[8]

The potential prothrombotic action of the SARS-CoV-2 is supported by the topographical involvement of the lung regions. In fact, while authors report that, in SARS-CoV-2, all lung segments can be involved, there appears to be a predilection for the right lower lobe (225/849 affected segments among all patients) with peripheral distribution.[3] Moreover, other recently published papers showed similar patterns.[9,10] This observation seems to be concordant with the finding observed by several

From the *Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), Monserrato (Cagliari); and †Department of Medicine and Surgery, Division of Radiology, University of Parma, Parma, Italy.

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Correspondence to: Luca Saba, MD, Department of Radiology, Azienda Ospedaliero Universitaria (A.O.U.), di Cagliari—Polo di Monserrato s.s. 554 Monserrato (Cagliari) 09045, Italy (e-mail: lucasaba@tiscali.it).

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authors that the distribution of PE is dominant in the lower lobe.[11–13] If the formulated hypothesis is correct, the involvement of the lower lobe/peripheral distribution by SARS-CoV-2 is justified by the fact that it is the most frequent area of intravascular lung thrombosis.

If this hypothesis is correct, it could be possible to identify also other features usually observed in patients with PE (or pulmonary thrombosis), such as the presence of hypoxemia and hypocapnia, the first induced by ventilation-perfusion ratio inequality, the latter as the result of hyperventilation.[14]

In conclusion, this paper suggests the hypothesis that SARS-CoV-2 may induce lung intravascular thrombosis and that its progression could induce fast worsening of the patient's clinical condition with exitus. If this hypothesis is demonstrated, this could suggest using antithrombotic/coagulation regimens for SARS-CoV-2 and, at the same time, identifying drugs that could alter the inflammatory storm and protect the vessel wall. To demonstrate this hypothesis, computed tomography angiography examinations could be performed, and this would be possible with the commonly used radiologic technology.

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