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Pathological evidence of pulmonary thrombotic phenomena in severe COVID-19

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To the Editor

Between February and March 2020, the Journal of Thrombosis and Hemosthasis has published four papers addressing the intricate, complex and still little understood relation between COVID-19 and thrombogenesis (1-4).

SARS-Cov-2 induces in severe cases a cytokine storm that ultimately leads to the activation of the coagulation cascade, causing thrombotic phenomena (5). There is a further strong link between abnormal coagulation parameters (D-dimer and fibrin degradation products) and mortality. Tang et al. described that 71.4% of nonsurvivors and 0.6% of survivors showed evidence of disseminated intravascular coagulation (DIC), suggesting that DIC is a frequent occurrence in severe COVID-19 (4). The frequency of DIC in these patients is much higher than that reported for severe SARS (6).

There are ongoing widespread discussions among intensivists on the possible use of anticoagulant therapy, especially in severe patients with elevated D-dimer levels. Tang et al. showed that the use of heparin for 7 days

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or more resulted in decreased mortality in severe cases, especially the ones with SIC score > 4 or D-dimer > 6 fold of upper normal limit (2).

A pathological substrate confirming the presence and frequency of pulmonary thrombi in severe COVID-19, to provide more rationale to therapeutic management, is missing. Although the number of fatalities is in the range of tens of thousands worldwide, the autopsy studies are scarce and limited to few organs (7, 8).

It is comprehensible that few autopsies descriptions have been presented so far. Few centers have skilled pathologists to perform autopsies, besides the great risk of contagion during the procedure and the need for special security facilities in the autopsy rooms. In China, for instance, where the disease started, Zhu et al described that, since 2000, almost no autopsy has been performed in eight hospitals in large Chinese cities (9). Mostly a neglected procedure, the autopsy rapidly regains its importance when novel diseases arise and can be extremely useful in revealing patterns of tissue damage, systemic involvement, and also for further research on the pathogenesis of the disease.

São Paulo is the epicenter of COVID-19 cases in Brazil, with 304 deaths until 04/06/2020. Our large tertiary academic Clinical Hospital of the Faculty of Medicine of the University of São Paulo has allocated all of its 900 beds to receive patients with COVID-19 and, unfortunately, it is expected that a large number of deaths will still occur. Since February 2020, our group has performed minimally invasive autopsies in fatal cases of COVID-19, in order to characterize the pathology and pathogenesis of this new disease. We have developed a procedure for performing ultrasound-based minimally invasive autopsies (MIA-US) that samples tissues from several organs and, at the same time, reduces the risks of the autopsy procedure. In fact, MIA-US was applied during the recent 2018 yellow fever epidemic in Sao Paulo, Brazil, and showed a full diagnostic agreement with conventional autopsy (10). For COVID-19 cases, we analyze histological samples from lungs, kidneys, heart, liver, spleen, brain, skin and skeletal muscle. The procedure was approved by the institution's ethics board and was performed after informed consent from the next-of-kin. Here, we present some preliminary autopsy results that may provide new insights into the relation between COVID-19 and DIC.

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To date, we have studied 10 fatal cases, 5 men and 5 women, with a mean age of 67.8 years (33 to 83 years). Eight patients were over 60 years old and seven of them had comorbidities, including arterial hypertension, diabetes mellitus, ischemic heart disease and COPD. The average hospital stay was 5.4 days (0 to 15 days).

The general pulmonary histological picture in fatal cases of COVID-19 is exsudative/proliferative diffuse alveolar damage, with intense epithelial viral cytopathic effects involving alveolar and small airway epithelium, and little lymphocytic infiltration (Figure 1A). We observed a variable number of small fibrinous thrombi in small pulmonary arterioles in areas of both damaged and more preserved lung parenchyma in 8 out of 10 cases (Figure 1B to 1D). Endothelial tumefaction and a large number of pulmonary megakaryocytes in the pulmonary capillaries are other indicators of activation of the coagulation cascade. In addition, small fibrinous thrombi were rarely found in the glomeruli and superficial dermal vessels. There were few and small foci of alveolar hemorrhage, and pulmonary infarctions were not observed. Signs of secondary bacterial pneumonia were observed in 6 cases. As these are post-mortem transthoracic biopsies, we do not have access to large vessels and, therefore, we cannot exclude or confirm pulmonary embolisms.

In summary, our pathological observations support the current concept of hypercoagulative status in these critically ill patients, showing that the frequency of pulmonary microthrombosis is high. Hopefully, these findings may shed light on the complex therapeutic decisions on this subject.

The authors have no conflicts of interest

Legend for figure:

Figure 1. Diffuse alveolar damage in fatal COVID-19 (A). Fibrinous microthrombi in small sized pulmonary arterioles, observed in 8 out of 10 patients (B-D).

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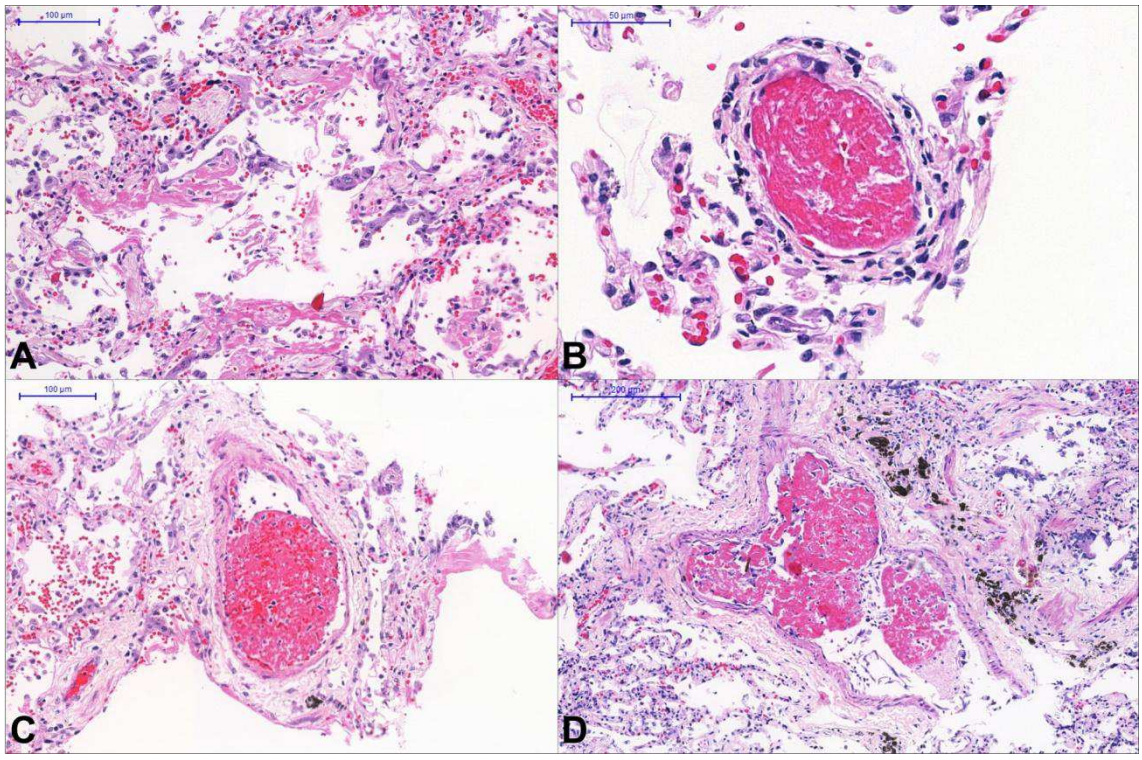
Figure 1:



Authors contribution:

MD: study design, data analysis and draft of the manuscript; ANDN: study design, tissue sample and data analysis; RAAM: study design, tissue sample; LFFS: study design, data analysis and figure; EPO: clinical data collection; PHNS: study design, tissue sample and data analysis; TM: study design, data analysis and draft of the manuscript; EMN: data analysis and draft of the manuscript.

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