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Can fibrinolytic therapy be clinically useful in severe pneumonia caused by COVID-19?

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The clinical course of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) meets the criteria for Acute Respiratory Distress Syndrome (ARDS) in many patients, the unfavorable course of which ultimately leads rapidly to death. In cases with fatal outcome, the pathophysiology of ARDS has been related to a hyperimmune reaction that increases the progressive worsening of lung function [1]. SARS-CoV-2 enters into alveolar epithelial cells through ACE2 surface receptors (also present in enterocytes, endothelial cells, and smooth muscle arteries) [2]. During the hyperimmune inflammatory reaction, activation of complement leads to the formation of C3a and C5a that elicit recruitment of lymphocytes, macrophages, monocytes, and neutrophils, responsible in turn for the massive local release of proinflammatory cytokines IL-1, IL-6, IL-8 and interferon-γ [3]. In addition, leukocytes mobilized at the injury site exert a potent proinflammatory effect, causing extensive vascular-endothelial damage, alveolar epithelial cell damage, and microvascular thrombosis [4].

The functional implications of the specific pathogenesis of ARDS contribute to a progressive worsening of the ventilation/perfusion imbalance and to the loss of reactive hypoxic vasoconstriction, with striking component of intrapulmonary microvascular thrombosis. Specifically, massive alveolar endothelial damage leading to a progressive pulmonary syndrome with microvascular thrombosis has been proposed as the primary mechanism of respiratory distress associated with COVID-19, suggesting the acronym MicroCLOTS (microvascular COVID-19 lung vessels obstructive thromboinflammatory syndrome) as the pathophysiological hypothesis of the atypical ARDS produced by COVID-19 infection [5]. In fact, direct viral infection of endothelial cells and diffuse endothelial inflammation in lung, heart, kidney, and small intestine have recently been described in three patients with SARS-CoV-2 infection who developed progressive respiratory failure and subsequent multi-organ failure [6].

A pattern of hematological, biochemical, inflammatory and immune biomarkers has been identified in patients with severe pulmonary disease compared to mild systemic disease. From the analysis of published studies, hematological parameters (lymphocyte count, neutrophil/lymphocyte ratio), inflammatory (CRP, IL-6) and specially biochemical (D-dimer, troponins) that show a hypercoagulable state, have been correlated with severe prognosis and fatal outcome in COVID-19 and could, therefore, be used as prognostic markers [7, 8].

In last months, pathologists at New Orleans [9] Milan [10] and Oklahoma [11] have reported the autopsy findings in 50 patients with PCR-confirmed SARS-CoV-2 infection and ARDS-consistent bilateral pneumonia. Age ranged from 32 to 86 years, and most of them had diabetes, hypertension or cardiovascular disorders comorbidities. The progressive worsening of lung function required intubation and mechanical ventilation. Death occurred in an average time of 16 days (range 5–31) from the onset of symptoms. On macroscopic inspection, areas of hemorrhage could be identified throughout the peripheral lung parenchyma. In some cases, small thrombi were also present. Histologic examination showed diffuse alveolar damage with mild-to-moderate lymphocytic infiltrate. The main relevant finding was the presence of platelet and fibrin thrombi within the alveolar capillaries and small arterial vessels (< 1 mm in diameter), that were observed in 86% of cases. In addition, patchy areas of hemorrhage 3–6 cm in size were also frequently observed.

A notable finding in one of the three autopsy reports was the presence of high number of CD61 + megakaryocytes (Mk) located within alveolar capillaries in association with platelets [9]. In response to viral infections of H1N1

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influenza and dengue, Mk have been shown to respond by overexpressing interferon-induced transmembrane 3 (IFITM3) restriction factor (producing platelets with the same over-expression) which induce an antiviral state in neighboring cells, thereby controlling the spread of the infection [12]. Evidence of direct SARS-CoV-2 infection of Mk is lacking, but the abundance of these cells in lungs suggests some relationship with the high amount of platelet-rich thrombi within alveolar capillaries and small vessels in these patients.

As pulmonary thromboembolism incidence is high in critically ill COVID-19 patients without prior classic thrombotic risk factors [13]; D-dimer level is significantly increased [14]; mortality rate might be reduced in severe COVID-19 patients treated with heparin [15]; and recurrent numerous pulmonary microthrombi are found at autopsy in many cases [9–11], taken altogether could suggest that refractory respiratory failure in these patients be pathogenically caused mainly by extensive pulmonary micro/macrothrombosis (and not so much by primary infectious/inflammatory damage). In COVID-19 pneumonia, pulmonary thrombosis can play a direct and significant role in the development of gas exchange abnormalities and multi-organ failure. Patients with severe respiratory failure exhibit an abnormal pattern of gas exchange compatible with alveolar dead space ventilation (regions devoid of gas exchange despite inspired air delivery) and intra-pulmonary shunt (significant mixture of non-oxygenated blood with oxygenated blood). Such anomalies strongly suggest the possibility of sudden-onset, severe pulmonary vascular involvement whose anatomical substrate would most likely be intrapulmonary disseminated acute microvascular thrombosis. The preserved lung function during the early phase of COVID-19 infection in patients with bilateral radiological opacity of the airspace suggests that pulmonary infiltrates may indeed represent areas of infarction and pulmonary hemorrhage.

Anticoagulation with low molecular weight heparin appears to be associated with lower mortality in the subset of patients who meet the criteria for sepsis-induced coagulopathy or have a remarkably high D-dimer as reported in observational studies. However, the relationship of heparin use at prophylactic doses with mortality rates is still supported by limited evidence and high-risk of confounding factors [16]. Beyond observational studies, randomized controlled trials are necessary to assign a causal association between heparin use and clinical outcomes in severe COVID-19 patients. However, in refractory respiratory failure in which disseminated intrapulmonary microvascular thrombosis may be the most significant mechanism in SARS-CoV-2-induced progressive respiratory distress, anticoagulant therapy may play a limited role in this terminal phase of the dying patient. Fibrinolytic agents could be a better alternative to promote the necessary clot lysis at this preagonal clinical stage, not to prevent the growth and extension of the thrombus mediated by anticoagulants.

According to the hypothesis of extensive intrapulmonary microvascular thrombosis as a pathophysiological basis of progressive respiratory failure in SARS-CoV-2 patients, two series of 'case reports' published in April reported on the response to fibrinolytic therapy with tissue plasminogen activator (tPA) in mechanically ventilated COVID-19 positive critically ill ARDS patients with D-dimer levels persistently elevated. In Mount Sinai hospital series [17], three out of four patients responded rapidly to an infusion of 50 mg tPA for 2 h (followed by 2 mg/h plus concomitant intravenous unfractioned heparin) with rapid improvement in alveolar ventilation and respiratory function (PaO_2/FiO_2 ratio). The fourth patient, after a similar initial improvement, died an hour later from biventricular thrombosis (not detectable on echocardiogram before tPA infusion). In the series at the University of Colorado [18], two out of three patients also responded after completing an infusion of 25 mg of tPA for 2 h and 25 mg for the following 22 h (followed by UFH 10 IU/kg/h; target APTT between 60 and 80 s) with a rapid and significantly improvement in the PaO_2/FiO_2 ratio (between 38% and 100%). The third patient showed improvement in respiratory function after tPA infusion too, dying of multiple organ failure three days later. No patient treated with tPA suffered bleeding complications in these series.

The scientific rationale for fibrinolytic therapy to improve lung function in seriously ill patients with COVID-19 is supported by several considerations, the main one is there are currently few ARDS therapies proven to be effective other than respiratory therapy [19]. If this fails mortality is near 100%. On the other hand, patients with COVID-19 on mechanical ventilation in the intensive care unit have been shown to have reduced level of fibrinolysis on thromboelastography in virtually all cases [20]. Fibrinolytic therapy on various animal models has been shown to be effective in acute lung injury in different preclinical studies [21], and a small phase 1 human clinical trial in patients with terminal ARDS (unrelated to SARS-CoV-2) showed that either urokinase or streptokinase led to a significant improvement in arterial blood oxygenation and to significant lower mortality rates than expected [22]. Tissue-type plasminogen activator (tPA) has higher clot lysis efficacy than urokinase and streptokinase without increased bleeding risk. Severe/life-threatening bleeding was 0.4–0.8% in myocardial infarction and submassive pulmonary embolism patients treated with 50 or 100 mg of tPA over 90 to 120 min followed immediately by a therapeutic heparin drip [23, 24]. Clearly, the risk of adverse events from tPA is far outweighed by the certainty of death in COVID-19 patients meeting eligibility criteria for this treatment [19].

Systemic administration of tPA would thus be potentially justified in critically ill patients with refractory respiratory

failure associated to COVID-19 infection. In these cases, fibrinolytic treatment can have an immediate physiological impact with significant improvement in alveolar ventilation, oxygenation, and shock. Fibrinolysis would improve alveolar ventilation by restoring blood flow in previously occluded regions. This redistribution would reduce the flow of dilated vessels, decreasing the shunt fraction and improving oxygenation.

In summary, the pathophysiology of SARS-CoV-2 could be explained in part by vascular endothelial dysfunction and pulmonary microthrombosis, potentially responsive to fibrinolytic treatment with tPA. This therapeutic option, under the indication of compassionate off-label use, should be carefully considered in the management of critically ill COVID-19 patients with severe refractory respiratory failure requiring intensive support. Given the gloomy prognosis of this condition, the compassionate use of tPA in critically ill COVID-19 patients not responsive to mechanical ventilation and/or heparin constitutes an alternative treatment we are obliged to ponder. This salvage therapeutic option could be decisive in patients with severe COVID-19 infection and refractory ARDS with no available treatment alternative.

Although consideration of therapies not recognized for this indication is justified by the unprecedented public health emergency that the global pandemic of COVID-19 represents, controlled clinical trials are urgently needed to define the tPA dose, route of administration, duration of treatment and especially if this potential therapy for SARS-CoV-2 refractory respiratory failure is effective with good benefit/harm ratio. A phase 2a multicenter randomized controlled trial of tPA in these patients is now underway [19].

Author contributions Both authors contributed equally.

Compliance with ethical standards

Conflict of interest Dr. Páramo has received speaker or other honoraria from Rovi, Daichii Sankyo, Octapharma and Stago. Bornstein has no conflict of interest.

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