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See **Online** for appendix

Pulmonary intravascular coagulopathy in COVID-19 pneumonia

We read with pleasure the thoughtful Viewpoint by Dennis McGonagle and colleagues[1] on lung immunothrombosis during infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). However, some of the key pathogenetic events were not highlighted by the authors.

Evidence from the early stages of disease suggest the occurrence of diffuse alveolar damage with infiltrating multinucleated cells and few macrophages.[2] CT perfusion scans done in patients with early pneumonitis reveal microangiopathy that presents as hypoperfusion of the involved parenchyma (appendix). McGonagle and colleagues cite a study in which single-cell analysis showed no angiotensin-converting enzyme 2 (ACE2) expression in endothelial cells or alveolar macrophages.[1] However, other studies showed ACE2 expression in vascular endothelial cells in the lungs during infection with severe acute respiratory syndrome coronavirus (SARS-CoV),[3] or in the kidney during SARS-CoV-2 infection,[4] supporting the hypothesis that there is a receptor in all endothelial cells at the systemic level.

By infecting endothelial cells, the virus could alter the cells' function from the inside, as happens for other viruses. McGonagle and colleagues note that endothelial cells indeed express ACE2. The microangiopathy seen in patients with COVID-19 might therefore arise both from the inside (endothelial cells) and from the outside (platelets, cytokines, neutrophil extracellular traps, thrombophilic factors), resulting in, what we call endothelial leuko-thrombo-inflammation.

Alveolar haemorrhage can also occur in COVID-19 and an autopsy series from the USA showed foci of haemorrhage in all but one patient plus diffuse alveolar damage and mild-to-moderate infiltrates of CD4+ and CD8+ lymphocytes; CD4+ T cells were seen in aggregates around small blood vessels, some of which appeared to contain platelets and small thrombi. In addition, fibrin thrombi were present within the capillaries and small blood vessels with entrapment of numerous neutrophils. Neutrophil extracellular traps have been observed in the advanced phases of lung inflammation and one preprint paper reported the presence of CD61+ megakaryocytes.[5] Since platelets are normally produced in the lung, the thrombotic events are certainly facilitated. However, it is crucial to recall the hierarchical role of endothelial cells, which appear to be central regulators of the cytokine storm. In models of viral post-influenza inflammatory storms in the lung, triggering sphingosine-1-phosphate ($S1P_1$) receptors, which are expressed on endothelial cells and lymphocytes in the lung, suppressed cytokine production, innate immune cell recruitment, and cytokine release syndrome,[6] thereby decreasing lethality. Clinically, this finding could mean that, failing effective antiviral therapy (eg, remdesivir), treatments aimed at suppressing cellular aggregation or neutrophil extracellular trap formation and triggering $S1P_1$ signalling (eg, fingolimod) could be crucial in curtailing the endothelial leuko-thromboinflammatory storm before it starts, thus reducing the high mortality rate observed in patients with COVID-19 treated in intensive care units.

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We read with interest the Viewpoint by Dennis McGonagle and colleagues.[1] To account for unusual clinicopathological features of COVID-19 disease, particularly coagulopathy, the authors point to dysregulated immunity and systemic inflammation reminiscent of a cytokine storm or macrophage activation syndrome (MAS). Although the authors' contribution comes down firmly on the immunological side of the debate over whether COVID-19 coagulopathy is due principally to immune or endothelial dysfunction,[2] the common background assumption to both sides is that modelling COVID-19 using previously described clinical syndromes and traditional pharmacological and physiological mechanisms will lead to deeper insights into the disease.

We question this assumption on both clinical and physical-chemical grounds. McGonagle and colleagues themselves detail the many important ways in which MAS differs from COVID-19. Indeed, many key features of MAS, including hyperferritinaemia, only occur in the most severe COVID-19 cases. But the deeper problem in analysing COVID-19 pathogenesis, as reflected in the authors' usage of the term diffuse to describe virtually every aspect of the pathology of COVID-19, is that few truly discrete lesions exist in the bodies of patients with COVID-19. It is true that, late in the disease, alveolar damage occurs, as it is found at autopsy. But, in contrast to severe acute respiratory syndrome coronavirus (SARS-CoV), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) does not injure pneumocytes and other cells in the alveolar lining sufficiently to induce either early respiratory distress or radiographic evidence of alveolar inflammation and oedema.

Indeed, the unexpected preservation of lung compliance in the face of hypoxaemia suggests that SARS-CoV-2 has fairly modest effects on pneumocytes and other pulmonary cells. Otherwise, one would expect early and intense alveolar cellular inflammation and oedema. However, what is actually seen on CT is bilateral interstitial oedema and often virtually normal gas volume in the lungs on presentation. The absence of apparent alveolar damage on CT has led many authors to presume that hypoxaemia is not due to a failure of gas exchange at the alveolar-capillary interface, but instead to a more general vascular abnormality leading to ventilation-perfusion mismatch. The presence of viral inclusion structures in endothelial cells of pulmonary blood vessels has been taken as evidence that the primary target of viral damage is not the alveoli but the endothelium.

However, we believe SARS-CoV-2 does not directly damage the cells of the alveolus or endothelium but instead injures their loosely adherent extracellular surface layers.[2] As such layers are only understandable through physicochemical analysis, we suggest that COVID-19 presents such an unusual clinicopathological course that we need an entirely new conceptual framework to explain the disease. The most notable anomaly in COVID-19 presentation is profound hypoxaemia in the face of preserved lung compliance. Although abnormal hypoxic vasoconstriction could explain the hypoxaemia to some degree, little evidence exists for such aberrant vascular mechanisms until quite late in the disease course.

But could the virus somehow short-circuit gas exchange at the alveolar surface in a more direct way? In fact, although still little known, pulmonary surfactant has a gas exchange function,[3] which is more important than its better known surface-tension-lowering function. Although, according to older physical-chemical knowledge, damage to surfactant should lead to drastically impaired lung compliance, new knowledge strongly suggests that surfactant damage would mainly hinder gas exchange and have little, if any, effect on compliance.[4]

Paradoxically, SARS-CoV-2 appears to create less systemic inflammation and general cell damage than previous viruses that cause acute respiratory distress and might have evolved a way of undergoing replication cycles while sparing host cells. Therefore, we postulate that SARS-CoV-2 mainly injures the alveolar and endothelial surface layers. Such subtle damage would coherently explain the unusual combination of pulmonary and endothelial effects of SARS-CoV-2 infection, including alterations in blood viscosity and clotting tendency.[5] In the appendix, we outline the main anomalies in COVID-19 and compare current explanations with our surface-layer damage hypothesis.

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I read with interest the Viewpoint by Dennis McGonagle and colleagues,[1] in which they associate the changes that occur in the lungs of patients with COVID-19 with macrophage activation syndrome (MAS) and emphasise the possible occurrence of pre-terminal disseminated intravascular coagulation.

Coagulation disorders in patients with COVID-19 were initially thought to be due to systemic disseminated intravascular coagulopathy but evidence from autopsies instead shows that these disorders are due to a procoagulant event together with a severe inflammatory state.[2]

Serum ferritin is elevated in 71% of patients with catastrophic antiphospholipid antibody syndrome. Indeed, four well recognised clinical conditions exist that might be associated with high ferritin concentrations: MAS, adult-onset Still's disease, catastrophic antiphospholipid antibody syndrome, and septic shock.[3]

See **Online** for appendix

Adult-onset Still's disease has diagnostic criteria that do not correspond to the clinical presentation and disease course of critically ill patients with COVID-19. MAS is closely related to juvenile idiopathic arthritis, although