

# Could severe COVID-19 be considered a complementopathy?

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COVID-19 is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Acute respiratory distress syndrome (ARDS), observed in most critically ill cases with SARS-CoV-2, is a life-threatening inflammatory lung injury.<sup>1</sup> It necessitates hospitalisation, oxygen supplementation and in some cases mechanical ventilation, and is associated with high mortality rates, reaching around 40%.<sup>2</sup>

It is the effects of an over-reacting immune system, rather than the viral load, which are believed to cause ARDS. A cytokine storm characterised by proinflammatory cytokines, such as interleukin (IL)-1 and IL-6, together with hypercoagulability is seen in a majority of hospitalised patients. Elevated D-dimer, lactate dehydrogenase and fibrinogen and clinical thromboembolic manifestations, such as pulmonary emboli, are common features of severe COVID-19. Zhang *et al*<sup>3</sup> recently reported significant coagulopathy with multiple infarctions accompanied by prothrombotic antiphospholipid antibodies in three cases of COVID-19. Endothelial damage, another prominent manifestation in COVID-19, can initiate thrombotic microangiopathy (TMA), which contributes to mortality, as reported in COVID-19 autopsy studies.

The complement system is a critical part of the innate immune response to bacterial and viral infection,<sup>4</sup> but activation of the complement cascade can also lead to severe tissue damage. Gralinski *et al*<sup>5</sup> tested the role of complement in SARS-CoV pathogenesis using a mouse model. They were able to demonstrate that despite equal viral load, respiratory manifestations were significantly reduced in the absence of complement. Complement-deficient mice had reduced neutrophilia in their lungs and less systemic inflammation, consistent with the observation that SARS-CoV pathogenesis is an immune-driven disease. Increased complement activation on endothelial cells could be one of the mechanisms of the hypercoagulability

seen in these patients. Complement blockade has been proposed as a treatment for acute lung injury,<sup>6</sup> and anti-C5a antibody has been shown to protect mice from infection with Middle East Respiratory Syndrome Coronavirus (MERS-CoV).<sup>7</sup>

Patients with disseminated intravascular coagulation and TMA frequently exhibit complement activation and share the clinical consequences of thrombocytopenia, microangiopathic haemolytic anaemia and microvascular thrombosis. A number of haematological disorders, such as paroxysmal nocturnal haemoglobinuria and atypical haemolytic uraemic syndrome, are driven by complement and may be termed 'complementopathies'.<sup>8</sup> Recent evidence suggests that other conditions, such as catastrophic antiphospholipid syndrome, may also belong to the spectrum of complementopathies. These disorders are characterised by impaired regulation of complement as the main driving factor of disease pathogenesis, and complement inhibition improves significantly the course and prognosis of these diseases.

The possible role of complement in the pathogenesis of severe COVID-19 warrants further and deeper investigation of the genetic and immunological mechanisms that could contribute to tissue damage. Genetically determined complement dysfunction may account for aberrant activation of innate immunity in severe patients with COVID-19, and age-related changes in the expression and function of complement proteins as well as sex-related differences could partly explain the age predilection of the pathological changes and the clinical aggressiveness observed in the disease, as well as provide a link to the coagulopathy largely reported.<sup>9</sup>

In the light of this, use of complement inhibition, for example, eculizumab, a monoclonal antibody that binds with high affinity to the complement protein C5, thus preventing C5a formation, should be considered in critically ill patients with COVID-19, especially in those with signs of coagulopathy and complement



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consumption. A recent case series from Italy also demonstrated good efficacy of off-label use of eculizumab in four patients with COVID-19-associated ARDS.<sup>10</sup>

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