Could severe COVID-19 be considered a complementopathy?

Katerina Chatzidionysiou, Elisabet Svenungsson, Francesca Faustini

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. It necessitates hospitalisation, oxygen supplementation and in some cases mechanical ventilation, and is associated with high mortality rates, reaching around 40%.

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. Increased 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’.

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.

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...
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.10

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**ORCID iD** Katerina Chatzidionysiou http://orcid.org/0000-0002-2669-1247

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