JIM Letter to the Editor

doi: 10.1111/joim.13123

Viral infections and their relationship with catastrophic antiphospholipid syndrome: a possible pathogenic mechanism of severe COVID-19 thrombotic complications

Dear Sir

The disease caused by SARS-CoV-2 (COVID-19) has different presentations and outcomes. Severe COVID-19 is commonly complicated by markedly elevated D-dimer, thrombocytopaenia and coagulation abnormalities that are considered to be regulated by various pro-inflammatory cytokines and similar to pneumonia induced by other pathogens [1], and are correlated with mortality. Recently, a small case series described aPL antibodies in patients with COVID-19 [2]. About 1% of APS patients develop a severe life-threatening clinical condition characterized by multiple thrombosis involving mainly small vessels, which has been described as catastrophic APS (CAPS). Patients with CAPS have in common: (i) clinical evidence of multiple organ involvement developing over a very short period of time; (ii) histopathological findings of multiple small vessel occlusions; and (iii) laboratory confirmation of the presence of aPL, usually in high titres. Although it is an uncommon disorder, its potentially lethal outcome emphasizes its relevance in clinical practice today. Most patients with CAPS are admitted in intensive care units with multiorgan system failure. The pathogenesis is not completely understood. Precipitating factors have been identified in more than 50% of patients, and include, by frequency, infections (49%), surgical procedures (17%), malignancies (16%), anticoagulation withdrawal (8%), pregnancy complications (8%), drugs (5%) and disease activity of systemic lupus erythematosus (SLE) [3]. Moreover, emerging infectious diseases (influenza A virus subtype H1N1) have recently been related to the presence of CAPS. CAPS has been recently included in the 'thrombotic storm' conditions together with *purpura fulminans* or haemolysis, elevated liver enzyme levels and low platelet count (HELLP) syndrome. This new concept defines a group of entities defined by an extreme prothrombotic phenotype and some patients with thrombotic storm presented high levels of acute phase reactants such as erythrocyte sedimentation rate, C-reactive protein, fibrinogen, ferritin and/or factor-VIII levels suggesting the evidence of an acute inflammatory state. Moreover, in sepsis, SIRS affects coagulation, particularly pro-inflammatory cytokines (TNF-α, IFN-γ and IL-1] which induce tissue factor expression on monocytes and endothelial cells, downregulates physiological anticoagulant pathways and inhibits fibrinolysis leading to microvascular thrombosis, and influences and modulates the inflammatory response.

Immune-mediated damage may be the predominant feature in severe COVID-19 and may resemble CAPS (Table 1). Initial reports from China [4] suggest that the abnormalities seen in COVID-19 may be associated with cellular immune deficiency, coagulation activation, myocardial injury and kidney injury. Moreover, in nonsurvivors, neutrophil count, D-dimer and creatinine levels continue to rise, which could hint to a sustained immune hyperactivation. The risk factors associated with the development of COVID-19-related ARDS and progression to death include older age, neutrophilia, organ and coagulation dysfunction. Severe COVID-19-associated pneumonia patients may exhibit features of systemic hyperinflammation designated under the umbrella term of macrophage activation syndrome. Elevated cytokine levels are associated with severe COVID-19, and thus, COVID-19 pneumonia may represent a novel viral macrophage activation syndrome-like immunopathology, where hyperinflammation may be the key to virus control. There may be a potential overlap between the severe pulmonary manifestations in COVID-19 and thrombi. In the Chinese experience [5], those with severe disease had a median platelet count of 137 000 compared with nonsevere with a median of 172 000. About 60% of patients in the severe group had severe thrombocytopaenia. D-dimer> 0.5 mg L^{-1} was found in two-thirds of patients with severe presentation. Data on comparison of the haematological

Table 1. *Similar clinical and pathophysiologic characteristics in CAPS and severe COVID-19*

Clinical characteristics	Pathophysiologic characteristics
Adult respiratory distress syndrome (ARDS)	Pro-inflammatory state Up-regulation of cytokines (high levels of IL-6, IL-1β and TNF)
Multiorgan dysfunction syndrome (MODS)	Coagulation dysfunction Elevated D-dimer Thrombocytopaenia Prolonged activated partial thromboplastin time Antiphospholipid antibodies
Macrophage activation syndrome (MAS) or cytokine storm syndrome (CSS)/secondary haemophagocytic lymphohistocytosis (HLH)	Pathogenic complement activation

parameters between mild and severe groups reveal significant differences in IL-6, D-dimer, glucose, fibrinogen, thrombin time and CRP. There was modest prediction accuracy of elevated IL-6 and D-dimer (combined area under the receiver operator characteristic curve 0.84).

In a joint webinar between the Chinese Cardiology Association and the American College of Cardiology on 28 March 2020 [6], the Chinese cardiologists described diffuse microvascular thrombi in multiple organs on autopsy, and therefore, anticoagulation has been recommended for patients with COVID-19 by an expert consensus in China. Noteworthy, a Dutch report of 184 patients revealed that the cumulative incidence of thrombotic complications in critically ill COVID-19 patients was 31%, of which the majority were venous (27%) and arterial (3.7%) despite all patients receiving thromboprophylaxis. Evidence of coagulopathy with prolongation of prothrombin and activated partial thromboplastin times was independent predictors of thrombotic complications. Endothelial dysfunction caused by infection and hypoxia may result in excess thrombin and induce a hypercoagulable state in patients with COVID-19. Tang et al. [7] analysed 449 patients with severe COVID-19. Ninety-nine received heparin for >7 days. Although on multivariate analysis D-dimer, age and prothrombin time were correlated with 28-day mortality, there was no statistical difference in overall survival in patients who received heparin versus no-heparin (30.3% vs 29.7%, $P = 0.91$). However, benefit was seen in subgroup analysis in those with D-dimer >6-fold the upper limit of normal (32.8% vs 52.4%, $P = 0.01$) and in those with increased sepsis-induced coagulopathy score (40% vs 64%, $P = 0.02$). A more recent case series [2] suggests the presence of aPL antibodies (aCL and aß2GPI) in COVID-19 patients; therefore, a possible underrecognized mechanism of thrombosis in patients with severe COVID-19 may be the production of aPL antibodies and development of its potential catastrophic variant. In conclusion, although thrombotic events in critically ill patients can occur due to a number of mechanisms, in clinical practice these are challenging scenarios to differentiate. We believe it is plausible that in at least a subset of patients with severe COVID-19, aPL antibodies may play a role leading to CAPS. Prospective studies are needed in this field to evaluate the prevalence of aPL antibodies and CAPS.

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