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Letter to the Editor

LETTER TO THE EDITOR

Targeting complement in severe coronavirus disease 2019 to address microthrombosis

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There is no approved therapy for coronavirus disease 2019 (COVID-19) [severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection], and the number of worldwide deaths on current standard therapy is staggering [1]. Current therapy is aimed at decreasing viral replication, supporting vital functions and addressing the most damaging consequences of the disease such as hyperinflammation (the so-called cytokine storm) and thrombosis. The latter two involve the use of anti-inflammatory therapies and heparin, respectively. We suggest that complement-blocking strategies such as eculizumab should be considered in severe cases not responding well to current therapy, including tocilizumab, in the context of clinical trials. Complement is thought to contribute to microangiopathies associated with infectious diseases [2].

Recent histological data from COVID-19 patients are compatible with acute respiratory distress syndrome (ARDS) [3]. Additionally, vascular congestion and inflammatory cell infiltrates were present [4], as well as microvascular thrombi in multiple organs including kidneys in patients who died of COVID-19 and SARS [5, 6]. Immunohistochemically, deposits of C5b-9, C4d and mannose-binding lectin-associated serine protease-2 have been found in the microvasculature of lungs and skin in patients with COVID-19 [7]. Furthermore, COVID-19 shares some features with entities that are complement mediated, such as disseminated intravascular coagulation, thrombotic microangiopathy (TMA) and antiphospholipid antibody syndrome. These include increased lactate dehydrogenase (LDH) , platelet disease, hypertransaminasaemia, anaemia and extrapulmonary involvement, such as the kidney or heart (Table 1) [5–10]. However, we have not found alterations in haptoglobin or the presence of schistocytes to date.

A related virus, SARS-CoV, promotes complement activation, increasing C5a levels and contributing to hyperinflammation [11]. Generally speaking, sepsis or critical injury (e.g. in the context of COVID-19) will activate immune cells that cause endothelial dysfunction, resulting in the activation of two molecular pathways: further inflammation and microthrombosis associated with complement activation and excess thrombin generation [2, 9]. Microthrombi may have different clinical manifestations depending on the most affected organ, such as ARDS in the lung, acute renal failure and haemolytic uraemic syndrome or acute myocardial infarction, among others [2]. While complement protects from infection, dysregulated complement activation could cause TMA and contribute to ARDS as suggested for other coronaviruses [2, 5, 12]. Additionally, in the context of inflammation, non-complement proteases, such as thrombin, a coagulation pathway protein [13], and proteases from neutrophils and macrophages can generate C5a from C5, independently from the plasma complement system [14]. We agree with Campbell that severe COVID-19 manifestations have commonalities with thrombotic microangiopathies that respond to the C5a complement inhibitor eculizumab [6, 15]. In this regard, anti-complement therapies should be part of clinical trials with well-defined entry criteria for a combined inflammatory–microthrombotic syndrome and integrating the approach within the current therapeutic algorithm for COVID-19 [1]. Indeed, two Phase 2 clinical trials testing eculizumab for

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Table 1. Comparison between clinical situations belonging to a combined inflammatory–microthrombotic syndrome related to COVID-19

Characteristics	COVID-19	TMA	DIC	APS
Anaemia	Often	Usually (haemolytic)	Often	Rare (haemolytic)
Thrombopenia	+	+++	++	+
Haptoglobin	Unknown	Low	Normal	Low/normal
LDH	High	High	Often high	High/normal
Hypertransaminasaemia	Yes	Yes	No	Rare
Schistocytes	Unknown	Yes	Yes	Rare
D-Dimer	High	Normal	High	Normal/high
Fibrinogen	High	Normal	Low	Normal/high
Coagulation tests	Altered	Normal	Altered	Altered
Anti-phospholipid antibodies	Rare	No	No	Anticardiolipin Anti-beta2-glycoprotein I Lupus anticoagulant
Histology	Endothelial damage Microvascular thrombi	Microvascular fibrin thrombi	Thrombosis in small and midsize vessels	Arterial and venous thrombosis
Serum complement (C3-C4)	Normal/high?	Low/normal	Low/normal	Low
Vascular complement deposition	C5b-9/C4d	C5b-9	No	C5b-9
Extrapulmonary involvement	Yes	Yes	Yes	Yes
Therapy	Supportive therapy Anticoagulant (heparin)? Eculizumab?	Supportive therapy Blood transfusion (RBC, FFP) PE/FFP haemodialysis (HUS) Eculizumab (aHUS) Description Rituximab (TTP)	Supportive therapy Blood transfusion (RBC, FFP, PC) Anticoagulant AC, rhTM	Anticoagulant Corticosteroids Intravenous immunoglobin Cyclophosphamide Rituximab? Eculizumab?

DIC, disseminated intravascular coagulation; APS, anti-phospholipid syndrome; RBC, red blood cells; FFP, fresh frozen plasma ; PE, plasma exchange; HUS, haemolytic uraemic syndrome; aHUS, atypical haemolytic uraemic syndrome; TTP, thrombotic thrombocytopenic purpura ; PC, platelet concentrate; AC, antithrombin concentrate; rhTM, recombinant human thrombomodulin.

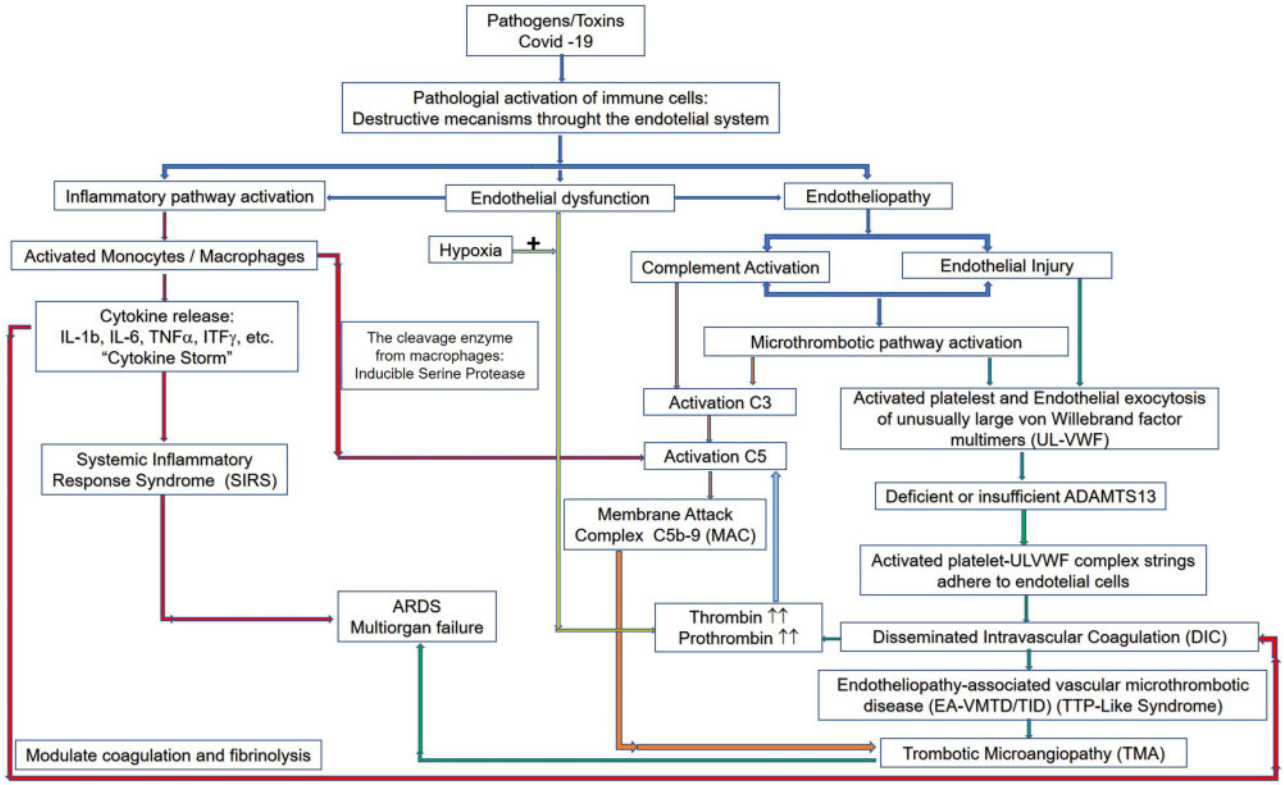

FIGURE 1: Proposed pathogenesis for COVID-19, adapted from Chang [2], which includes endothelial dysfunction as the origin of the damage and the two main pathways. The first is the inflammatory pathway that would be related to the activation of monocytes–macrophages triggering the 'cytokine storm' leading to a systemic inflammatory response syndrome that usually occurs in association with ARDS and, ultimately, multi-organ failure. The second is the microthrombotic , closely related to activation of the complement, platelet and coagulation disorders. Also, there are factors that interact with both pathways, for example, the inducible serine protease that activates C5; some cytokines favour the development of disseminated intravascular coagulation and hypoxia favours a prothrombotic state *per se* by stimulating thrombin.

patients with severe COVID-19 are scheduled to start soon or have started in April 2020 (NCT04288713, NCT04346797).

Furthermore, the relative contribution of anticoagulation and complement targeting should be defined [16]. It is likely that anticoagulation targets a relatively late event that may be driven by earlier complement activation and endothelial injury [2]. In order to clarify this hypothesis, we have designed a scheme (Figure 1).

CONFLICT OF INTEREST STATEMENT

The authors declare that there is no conflict of interest regarding the publication of this article.

REFERENCES

1. Siddiqi HK, Mehra MR. COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal. *J Heart Lung Transplant* 2020; doi:10.1016/j.healun.2020.03.012
2. Chang JC. Acute respiratory distress syndrome as an organ phenotype of vascular microthrombotic disease: based on hemostatic theory and endothelial molecular pathogenesis. *Clin Appl Thromb Hemost* 2019; 25: 107602961988743
3. Xu Z, Shi L, Wang Y *et al*. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 2020; 8: 420–422
4. Tian S, Hu W, Niu L *et al*. Pulmonary pathology of early-phase 2019 novel coronavirus (COVID-19) pneumonia in two patients with lung cancer. *J Thorac Oncol* 2020; doi:10.1016/j.jtho.2020.02.010
5. Su H, Yang M, Wan C *et al*. Renal histopathological analysis of 26 postmortem findings of patients with COVID-19 in China. *Kidney Int* 2020; doi:10.1016/j.kint.2020.04.003
6. Campbell CM, Kahwash R. Will complement inhibition be the new target in treating COVID-19 related systemic thrombosis? *Circulation* 2020; doi:10.1161/circulationaha.120.047419
7. Magro C, Mulvey JJ, Berlin D *et al*. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. *Transl Res* 2020; doi:10.1016/j.trsl.2020.04.007
8. Lippi G, Plebani M, Henry BM. Thrombocytopenia is associated with severe coronavirus disease 2019 (COVID-19) infections: a meta-analysis. *Clin Chim Acta* 2020; 506: 145–148
9. Wang D, Hu B, Hu C *et al*. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061–1069
10. Zhang Y, Xiao M, Zhang S *et al*. Coagulopathy and antiphospholipid antibodies in patients with Covid-19. *N Engl J Med* 2020; 382: e38
11. Wang R, Xiao H, Guo R *et al*. The role of C5a in acute lung injury induced by highly pathogenic viral infections. *Emerg Microbes Infect* 2015; 4: e28
12. Gralinski LE, Sheahan TP, Morrison TE *et al*. Complement activation contributes to severe acute respiratory syndrome coronavirus pathogenesis. *mBio* 2018; 9: e01753–18
13. Huber-Lang M, Sarma JV, Zetoune FS *et al*. Generation of C5a in the absence of C3: a new complement activation pathway. *Nat Med* 2006; 12: 682–687
14. Huber-Lang M, Younkin EM, Sarma JV *et al*. Generation of C5a by phagocytic cells. *Am J Pathol* 2002; 161: 1849–1859
15. Cavero T, Rabasco C, López A *et al*. Eculizumab in secondary atypical haemolytic uraemic syndrome. *Nephrol Dial Transplant* 2017; 32: 466–474
16. Tang N, Bai H, Chen X *et al*. Anticoagulant treatment is associated with decreased mortality in severe coronavirus disease 2019 patients with coagulopathy. *J Thromb Haemost* 2020; 18: 1094–1099

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