Microthrombotic Complications of COVID-19 Are Likely Due to Embolism of Circulating Endothelial Derived Ultralarge Von Willebrand Factor (eULVWF) Decorated-Platelet Strings

To the Editor: COVID-19 is a pandemic caused by the virus SARS-CoV-2. Serious complications of COVID-19 are characterized by acute respiratory distress syndrome (ARDS), pneumonia and rapidly progressing to multiorgan dysfunction syndrome (MODS).

The pathophysiology of COVID-19 is not fully understood yet and neither vaccine nor clearly effective antiviral treatment is available at this time. Based on the endothelial pathogenesis of viral sepsis, which includes ARDS as seen in severe acute respiratory syndrome (SARS) due to SARS-CoV and Middle east respiratory syndrome due to MERS-CoV,[1,2] we believe COVID-19 associated ARDS is also caused by endotheliopathy-associated vascular microthrombotic disease (EA-VMTD), which also involves multiorgan dysfunction syndrome (MODS) that has been reported as the cause of death.[3] We suspect these complications are secondary to disequilibrium state (for various reasons[4,5]) between insufficient ADAMTS13 and excessive exocytosis of ultra large von Willebrand factor multimers (ULVWF) from Weibel-Palade bodies present endothelial cells due to COVID-19-induced endotheliopathy.

Endothelial derived ULVWF multimers anchored to the endothelial surface of the vascular wall recruit platelets and initiate microthrombogenesis within the microvasculature, leading to large microthrombi strings composed of platelet and eULVWF complexes like "beads-on-a-string structures"[6] where platelets firmly adhere to eULVWF, instead of roll on eULVWF strings.[4] Platelets, once adhered to eULVWF strings, are rapidly activated causing platelet aggregation and also recruit leukocytes in a P-selectin dependent manner.[4] These aggregates grow until they become sufficiently large and can no longer be held onto the eULVWF strings against the force of blood flow and released from endothelial cells into the circulation.[4] It appears to us that in COVID-19 microthrombotic disease, large amounts of circulating complexes of endothelial derived ULVWF decorated platelet microthrombi strings are filtered in the microvasculature (embolism) or develops in the microvasculature in situ causing microthrombotic occlusion. During our data search, we have come across several articles published by Chang, including on endotheliopathy causing vascular microthrombotic disease based on a novel concept of "TTP-like syndrome"[7]

The genesis of EA-VMTD in TTP like syndrome is suspected to be triggered by complement activation and terminal complement complex (C5b-9, membrane attack complex, MAC) may play a key role in producing endotheliopathy.[7] Magro and colleagues reported that COVID-19 patients has demonstrated generalized thrombotic microvascular injury involving the lungs and skin showing intense complement activation and C5b-9 deposition in the tissue.[8] Also, recent pathology reports of COVID-19 diseased lungs showed extensive platelet-rich clotting with adherent mononuclear cells and extensive fibrin clotting,[9] which appear consistent with involvement of NETosis.[10] In another case report from Switzerland, a patient with severe COVID 19 had massive elevation of VWF antigen and activity (555% and 520%, respectively) and increased Factor VIII clotting activity (369%).[11] These findings support vascular endotheliopathy causing exocytosis of ULVWF and associated increase in Factor VIII causing microthrombotic disease/embolism.

COVID-19 clinical syndrome appears very much consistent with EA-VMTD presenting

with ARDS and MODS as well as micro-macro-thrombotic complications, including peripheral ischemia/gangrene involving fingers and toes and skin necrosis.[8,12]

We believe that an appropriate therapy may not be anticoagulation but should include antimicrothrombotic therapy targeting endotheliopathy and primary hemostasis in the early stages of the disease (platelet adhesion, activation, and aggregation; especially eULVWF) like recombinant CD59 (membrane attack complex inhibition factor [MACIF]), recombinant ADAMTS13, Glycoprotein IIb/IIIa receptor blocker, therapeutic plasma exchange, and perhaps anticomplement therapy (in selected cases) and others; these needs to be validated in clinical trials prior to clinical application.

Of note, ADAMTS13 is a zinc containing protease. We noted that zinc and calcium concentrations play a significant role (in vitro) in ADAMTS13 activity in citrated plasma and recombinant ADAMTS13 activity with no added chelators (recombinant ADAMTS13 activity can enhance up to 200 folds); whereas in high zinc concentrations, ADAMTS13 gets deactivated.[13] We suggest this finding merits an urgent clinical trial since it appears to us as the best possible cost-effective treatment for COVID-19 microthrombotic complications.

In this view of clinical pathophysiology of sepsis in COVID-19, we would like to enlighten the relationship between endothelial pathogenesis of coronaviral sepsis and vascular microthrombotic disease and would urge the medical community to immediately explore appropriate therapeutic options.

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