Complement Induced Endotheliopathy Associated Vascular Microthrombosis in Coronavirus 2019 Disease

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TO THE EDITOR—The recent article by de Nooijer, et al [1] correlates complement activation with morbidity and mortality in COVID-19. The authors discuss cytokines, inflammation, coagulation, and thromboembolic events, but never reach any conclusions regarding the path by which complement activation causes severe and sometimes fatal disease.

The final component of the complement pathway is the membrane attack complex (MAC) or terminal complement complex (TCC). MAC plays an important role in the early response to pathogens. This response is a critical defense mechanism against some extracellular pathogens, such aa *Neisseria meningitides*, with vulnerable cell membranes that can have pores created by MAC. Host cells are protected primarily by a membrane protein called CD59 which blocks the final addition of C9 which is necessary for the final formation of MAC. With many invading microbes, complement activation is intensified and CD59, as well as other lesser defense mechanisms, can be overwhelmed, resulting in endothelial cell damage by MAC. This endotheliopathy initiates two distinct pathways. The first is an inflammatory response marked by the release of interleukin-6. The second is a microthrombotic pathway heralded by the release of unusually large von Willebrand factor (ULVWF). The long multimers of von Willebrand factor extend from the surfaces of endothelial cells and trap activated platelets forming microthrombi. Microthrombogenesis has been proposed as the pathophysiological mechanism responsible for the acute respiratory distress syndrome (ARDS) as well as the multi-organ dysfunction syndrome (MODS) [2]. Diffuse alveolar damage, which is the histopathologic correlate of ARDS, has been found to be the predominant histopathology in COVID-19 [3]. Special stains have shown von Willebrand factor in the thrombi of small vessels and capillaries in the lungs of autopsied COVID-19 patients [4]. Tissue factor is not involved in microthrombogenesis. Furthermore, there is no coagulopathy as factor VIII is normal or elevated in COVID-19 patients rather than decreased as would be expected in a consumptive coagulopathy [5]. This is consistent with other microthrombotic disorders which have been found to have normal or elevated levels of factor VIII [6].

The authors mention the high incidence of thromboembolic events in COVID-19 patients in their discussion. These are macrothrombotic events and are to be distinguished from the previously discussed microthrombotic features of COVID-19. Macrothrombosis occurs when the pathways of microthrombogenesis and fibrinogenesis (coagulation pathway) merge to form macrothrombi [7]. The coagulation pathway commences with subendothelial and extravascular injury which releases tissue factor. The vascular injury can be caused by numerous factors including needle sticks and vascular catheters.

Lastly, the authors comment on the possible use of C5 inhibitors as therapy. Eculizumab has been used successfully in at least two small trials [8,9]. These trials, while successful, note the increased risk of bacteremia and bacterial pneumonia.

***Conflict of interest*.** Both No reported conflicts of interest. Both authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest.

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References

1. De Nooijer AH, Grondman I, Janssen NAF, et al. Complement activation in the disease course of coronavirus disease 2019 and its effect on clinical outcomes. J Infect Dis **2021**;223:214-24.
2. Chang JC. Acute respiratory distress syndrome as an organ phenotype of vascular microthrombotic disease: based on hemostatic theory and endothelial pathogenesis. Clin Appl Thromb Hemost **2019**:1-20.
3. Hariri LP, North CM, Shih AR, et al. Lung histopathology in coronavirus disease 2019 as compared with severe acute respiratory distress syndrome and HINI influenza: a systemic review. Chest **2021**;159:73-84.
4. Fox SE, Akmatbekov A, Harbert JL, el al. Pulmonary and cardiac pathology in African American patients with COVID-19: an autopsy series from New Orleans. Lancet Respir Med **2020**; dot.org/10.1016/S2213-2600(20)30343-5.
5. Stefeky JA, Christensen BB, Gogakos T, et al. Marked factor V activity elevation in severe COVID-19 is associated with venous thromboembolism. Am J Hematol **2020**;95:1522-30.
6. Chang JC. Disseminated intravascular coagulation: new identity as endotheliopathy-associated vascular microthrombotic disease based on in vivo hemostasis and endothelial pathogenesis. Thromb J **2020**;18:25.
7. Hawley HB. Sepsis produces micro thrombosis and not coagulation: implications for sepsis therapy. Ann Pub Health Rep **2020**;4:87-91.
8. Annane D, Heming N, Grimaldi-Bensouda L, et al. Eculizumab as an emergency treatment for adult patients with severe COVID-19 in the intensive care unit: a proof-of-concept study. EClinMedicine **2020**;28:100590.
9. Diurno F, Numis FG, Porta G, et al. Eculizumab treatment in patients with COVID-19 preliminary results from real life ASL Napoli 2 Nord experience. Eur Rev Med Pharmacy Sci **2020**;24:4040-7.