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Short Communication

Further Insights into the Pathogenesis of Cardiac Damage in SARS-CoV-2 Infection

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) continues to cause significant death and disability globally. After initial infection, approximately one fourth of patients develop cardiovascular complications including myocardial infarctions, stroke, arrhythmia, heart failure, and sudden cardiac death. Recent reviews and studies highlight the significance of innate immune mediators and cells in provoking microvascular injury in the heart and lungs of infected patients.

Keywords: SARS-CoV-2; Microvascular injury; Neutrophils; Heart; Complement; NETs

ABOUT THE STUDY

In severe infection with SARS-CoV-2, the virus is likely disseminated to other organs *via* infected monocytes and circulating vesicles from infected cells [1]. Because many ACE2 receptors are found in the heart, particularly on pericytes, the vasculature of the heart is a convenient target for viral proliferation and innate and adaptive immune system activation [2]. Because of SARS-CoV-2's molecular mimicry of human proteins with analogous peptide sequences, immune responses against SARS-CoV-2 can also be directed towards human proteins. In particular, molecular mimicry was revealed between the human SARS-CoV-2 and HEAT shock proteins (Hsp), which has been linked to Guillain-Barré syndrome and other autoimmune illnesses. The autoimmune response of SARS-CoV-2 to Hsp further damages the vascular endothelial lining throughout target organs like the heart, leading to activation of vascular endothelium with subsequent damage, coagulation, complement activation, and leukocyte infiltration [3].

We recently published a study of medical examiner cases who were either SARS-CoV-2 positive (COV^{+ve}) or negative (COV^{-ve}) at postmortem examination in 2020, prior to the availability of vaccine or other treatments. Many but not all of the COV^{+ve} patients died of the pulmonary consequence of this infection. We found a significant difference between COV^{+ve} and COV^{-ve} samples in the levels of staining for CD42, CD15, CD68, C4d, Fibrin, and Myeloperoxidase (MPO) ($p<0.001$). Visualizing each sample under a microscope revealed that the most prominent features were neutrophils (CD15, MPO) and MPO positive debris suggestive of Neutrophil Extracellular Traps (NETs). A similar distribution of platelets, monocytes, fibrin and C4d was seen in COV^{+ve} cases [4].

A recent review of other postmortem reports of immunohistochemical studies in COV^{+ve} and COV^{-ve} cases has come to similar conclusions. Thrombotic damage as well as evidence of SARS-CoV-2 infection of lung endothelium were implicated in most of the cited studies. Most of the cited studies demonstrated microthrombi in pulmonary capillaries along with complement components, macrophages, platelets and fibrin [5]. A cited study by Magro detected positive immunohistochemical staining for the membrane attack complex of complement (C5b-9, MAC) as well as C3d and C4d, colocalized with antibodies against the SARS-CoV-2 spike glycoprotein in pulmonary microvessels. MAC likely mediated the microvascular injury in these vessels [6].

In SARS-CoV-2 infection, complement has been shown to be activated by the classical, alternative and lectin binding pathways. Co-localization of SARS-CoV-2 spike protein and Mannose-Binding Lectin Serine Protease-2 (MASP-2) in pulmonary capillaries have been reported, substantiating this idea. Magro carried out an immunohistochemical assessment for the deposition of MAC, C3d, and C4d in lung, heart, liver,

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kidney, brain, and skin of 12 cases. All cases had significant endothelial and subendothelial microvascular deposition of C3d, C4d and MAC in the microvascular endothelium in these organs where they co-localized with the viral spike protein and the ACE2 receptor.

Thus, it has been clearly demonstrated that complement components lead to microvascular damage of infected organs such as lung, heart, kidney, liver and brain. Once complement is activated, cascading effects of leukocyte recruitment and coagulation activation potentiate the endothelial damage, culminating in microvascular clots and organ ischemic damage.

Pivotal in this process is the neutrophil recruitment triggered by complement activation that accelerates the inflammatory damage to microvascular endothelial cells. C3 activation is a point of convergence of all the complement pathways and leads to C3a, C5a, and MAC generation. C3a activates platelets while C5a and platelet-derived thrombin induce both neutrophil tissue factor and NETs that also carry active tissue factor. These thrombogenic Neutrophil Extracellular Traps (NETs) then induce endothelial cell activation with further tissue factor expression, generating a vicious cycle of procoagulant activity. Skendros have duplicated this sequence of events *in vitro*, using normal neutrophils and SARS-CoV-2 patient platelet-rich plasma co-cultured with human aortic endothelial cells. They show endothelial activation as well as thrombogenicity which could be blocked using thrombin, C5a, or NETosis inhibitors.

CONCLUSION

Recent reports as well as our recent study demonstrate that NETosis, complement activation, and cytokine generation during SARS-CoV-2 infection generate a thrombogenic environment which is the genesis of much of the organ damage in lungs and hearts as well as other organs.

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