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Original Contribution

Severe COVID-19: A multifaceted viral vasculopathy syndrome

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Highlights

- SARS-CoV-2 causes serious disease via two distinct mechanisms
- One mechanism is damage to the alveolar wall (microangiopathy) associated with high viral copy numbers
- The other mechanism is circulating viral capsid proteins that dock on ACE2+ endothelia
- The ACE2+ endothelia are most prominent in the subcutaneous fat and brain
- Endocytosis of spike protein by endothelia induces cell death, cytokine expression, and complement activation

Abstract

The objective of this study was to elucidate the pathophysiology that underlies severe COVID-19 by assessing the histopathology and the in situ detection of infectious SARS-CoV-2 and viral capsid proteins along with the cellular target(s) and host response from twelve autopsies. There were three key findings: 1) high copy infectious virus was limited mostly to the alveolar macrophages and endothelial cells of the septal capillaries; 2) viral spike protein without viral RNA localized to ACE2+ endothelial cells in microvessels that were most abundant in the subcutaneous fat and brain; 3) although both infectious virus and docked viral spike protein was associated with complement activation, only the endocytosed pseudovirions induced a marked up-regulation of the key COVID-19 associated proteins IL6, TNF alpha, IL1 beta, p38, IL8, and caspase 3 in endothelium. Importantly, this microvasculitis was associated with characteristic findings on hematoxylin and eosin examination that included endothelial degeneration and resultant basement membrane zone disruption and reduplication. It is concluded that serious COVID-19 infection has two distinct mechanisms: 1) a microangiopathy of pulmonary capillaries associated with a high infectious viral load where endothelial cell death releases pseudovirions into the circulation, and 2) the pseudovirions dock on ACE2+ endothelial cells most prevalent in the skin/subcutaneous fat and brain that activates the complement pathway/coagulation cascade resulting in a systemic procoagulant state as well as endothelial expression of cytokines that produce the cytokine storm. The data predicts a favorable response to therapies based on either removal of circulating viral proteins and/or blunting of the endothelial-induced response.

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Keywords

COVID-19; In situ; Spike protein; Endothelialitis; Complement

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