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Adrenal Vascular Changes in COVID-19 Autopsies

Alina C Iuga, MD; Charles C Marboe, MD; Mine M Yilmaz, MD; Jay H Lefkowitch, MD; Cosmin Gauran, MD; Stephen M Lagana, MD

Department of Pathology and Cell Biology, Columbia University Medical Center, New York, NY (Dr. Iuga; Marboe; Yilmaz; Lefkowitch; Lagana); Department of Anesthesiology & Critical Care Medicine, Memorial Sloan Kettering Cancer Center, New York, NY (Dr. Gauran)

Corresponding Author:
Alina Iuga, MD
Assistant Professor of Clinical Pathology Department of Pathology and Cell Biology Columbia University Medical Center
630 West 168th Street, VC15-202
New York, NY 10032
ai2190@cumc.columbia.edu

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To the editor –

For the past two months, New York City has been the epicenter of the ongoing pandemic caused by SARS-CoV-2 virus (severe acute respiratory syndrome coronavirus 2). The disease (COVID-19) most acutely and severely affects the lungs, requiring mechanical ventilation in a subset of cases. Other organs, including the heart, kidneys, liver and gastrointestinal tract can also be involved. The pathophysiology and the extent of multiorgan involvement is poorly understood. We report pathological findings in the adrenal glands of the first five post-mortem examinations of patients with COVID-19 diagnosed on clinical grounds with confirmatory real-time polymerase chain reaction testing of nasopharyngeal swab. Two patients were brought to the emergency room in cardiac arrest and could not be resuscitated. Three were briefly hospitalized, two for 24 hours and one for 72 hours. There were four males and one female, ranging from 59 to 90 years of age and with the following co-morbidities: hypertension (5/5), diabetes (3/5), ischemic cardiomyopathy (3/5), chronic lung disease (2/5, one with chronic obstructive pulmonary disease and one with interstitial lung disease), prostate carcinoma (2/5) and recent spinal surgery (1/5). Blood cultures were negative in the three patients tested. On microscopic examination, acute fibrinoid necrosis of small vessels, mainly arterioles in adrenal parenchyma, adrenal capsule and in the immediately adjacent periaxillary adipose tissue was identified. Subendothelial vacuolization and apoptotic debris were present (see figures 1A-1C). No significant inflammation, adrenal parenchymal infarcts or thrombi were appreciated. The vascular pathology was disproportionately conspicuous in adrenal and not as easily identified in other organs examined.
Fibrinoid necrosis describes vessel wall necrosis with fibrin and serum protein accumulation conveying an eosinophilic amorphous appearance on histology. With Masson’s trichrome stain, the amorphous fibrinoid material is red, unlike collagen which stains blue (see figure 1D). Arteriolar hyalinosis is another term used to describe the accumulation of pink amorphous material in vessel walls. This is thought to relate to hypertension, but is not typically associated with vessel necrosis and endothelial apoptosis. Hyalinosis may explain some of the histopathology, however many of the vessels we observed were either necrotic or associated with apoptosis. It is unclear if the adrenal vasculopathy is due to hypoxia, abnormal vascular reaction and blood flow patterns, direct viral cytopathic effect, an immune-mediated injury or a combination of events. Acute fibrinoid necrosis is classically described in malignant hypertension (first by Volhard and Fahr\textsuperscript{1} in 1914), mainly in kidneys, and in immune-mediated vasculitides. While SARS-CoV-2 infection seems to affect more severely patients with a history of hypertension\textsuperscript{2}, most critically ill patients with COVID-19 need vasopressors for persistent hypotension\textsuperscript{3}. Two of the three hospitalized patients described had recorded high blood pressure values and one was hypotensive on arrival. Localized fibrinoid necrosis is also mentioned in a report of pathological findings in SARS virus infection\textsuperscript{4}. SARS-CoV-2 virus gains entry to the cell via the angiotensin-converting enzyme 2 receptor\textsuperscript{5}, which is most abundant in lung alveolar cells, but also present in endothelia and other tissues, providing a possible mechanism for vascular injury\textsuperscript{6}. Adrenal hormones are involved in modulating inflammatory responses\textsuperscript{7} and adrenal gland dysfunction has been described in patients with community-acquired pneumonia\textsuperscript{8}.
In general, adrenal function is not routinely assessed in an intensive care unit (ICU) setting. The most common indication for corticosteroid administration in ICU is refractory hemodynamic shock. According to several critical care societies, acute respiratory distress syndrome (ARDS) management can include corticosteroids, as they may decrease the time on a ventilator and reduce mortality. Corticosteroids are also administered if there is suspicion of adrenal insufficiency or if they are indicated due to an underlying condition. Currently, the World Health Organization and major critical care and infectious diseases associations advise against routine corticosteroid use in COVID-19 patients, mainly out of concern for slowing viral clearance. However, early reports from China and Europe suggested that corticosteroids are useful in severe COVID-19 and some experts posit that severe cytokine release syndrome seen in some patients warrants the use of corticosteroids or other targeted immunosuppressants.

It is interesting to consider that adrenal insufficiency secondary to the vasculopathy described here may contribute to the cytokine storm observed in patients with severe COVID-19. Clinical studies to further assess adrenal function in COVID-19 may help in understanding the pathogenesis of disease in severely affected patients and hopefully lead to therapeutic protocols that may rescue an increased number of patients.
References:


Figure legend:

A. Fibrinoid hyaline vasculopathy in periaondrenal vessels indicated by black arrow head (hematoxylin and eosin stain, H&E, 10x magnification).

B. Apoptosis in periaondrenal and adrenal vessels (black arrow head points to apoptotic endothelial cells) (H&E stain, 20x magnification).

C. Necrotic vessel with karyorrhectic debris at black arrow head (H&E stain, 20x magnification).

D. Masson's trichrome stain highlights fibrinoid hyaline material in red, indicated by the black arrow head (Trichrome stain, 20x magnification).