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## New Onset Positive Autoantibodies Following Covid-19 Infection

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## Abstract

The World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic on March 11, 2020. Since the original outbreak in December 2019, over 100 million people have been confirmed to have been infected by COVID-19 and over two million people have died. The presentation seen in patients may vary widely based on multiple factors. Fever has been reported in up to 99% of patients, while other common symptoms seen are dyspnea, fatigue, anosmia, and myalgia. Around 80% of COVID-19 patients present with a mild respiratory illness that can be managed at home, while around 15% need basic hospital care and another 5% have a critical illness requiring more intensive support. While many patients have this classical presentation with respiratory symptoms, there are other clinical presentations and outcomes that have been documented. A link between COVID-19 and autoimmune diseases has been discussed as patients with COVID-19 that had a new onset of autoimmune antibodies and increased levels of common inflammatory markers during infection had the worst prognosis and outcome. Because of this possible link between COVID-19 and autoimmune diseases, our patient that presented with COVID-19 and eventual multiorgan failure was tested for autoimmune antibodies.

## Keywords

Autoantibodies, autoimmune diseases, COVID-19, SARS-CoV-2

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## Conflict of Interest Statement

All authors disclose no conflicts of interest.

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## CASE REPORT

# New Onset Positive Autoantibodies Following Covid-19 Infection

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## Abstract

The World Health Organization (WHO) declared the novel coronavirus (COVID-19) outbreak a global pandemic on March 11, 2020. Since the original outbreak in December 2019, over 100 million people have been confirmed to have been infected by COVID-19 and over two million people have died. The presentation seen in patients may vary widely based on multiple factors. Fever has been reported in up to 99 % of patients, while other common symptoms seen are dyspnea, fatigue, anosmia, and myalgia. Around 80 % of COVID-19 patients present with a mild respiratory illness that can be managed at home, while around 15 % need basic hospital care and another 5 % have a critical illness requiring more intensive support. While many patients have this classical presentation with respiratory symptoms, there are other clinical presentations and outcomes that have been documented. A link between COVID-19 and autoimmune diseases has been discussed as patients with COVID-19 that had a new onset of autoimmune antibodies and increased levels of common inflammatory markers during infection had the worst prognosis and outcome. Because of this possible link between COVID-19 and autoimmune diseases, our patient that presented with COVID-19 and eventual multiorgan failure was tested for autoimmune antibodies.

**Keywords:** Autoantibodies, Autoimmune diseases, COVID-19, SARS-CoV-2

## 1. Background

Since the initial outbreak in Wuhan, China, the knowledge regarding Coronavirus disease 2019 (COVID-19) has been steadily increasing. The viral agent responsible for causing this global pandemic driving disease is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which is an enveloped, positive-sense, single stranded RNA betacoronavirus.<sup>1</sup> Patients infected by COVID-19 may present with a wide array of symptoms, ranging from fever and fatigue to sepsis and multiorgan failure. Currently, the most effective way to prevent SARS-CoV-2 infection is via complete vaccination. For treatment, the United States FDA has approved Remdesivir, an antiviral drug, and monoclonal antibodies, such as bamlanivimab, and the combination of casirivimab and imdevimab.<sup>2</sup> Recently, there

has been debate about whether SARS-CoV-2 may stimulate auto-antibody production and induce autoimmunity activation. Different studies have shown that SARS-CoV-2 infection may lead to an increased amount of pro-inflammatory cytokines and classic inflammatory markers.<sup>3</sup> These studies also support the idea that these COVID-19 positive patients with higher levels of inflammatory markers have a poorer prognosis.<sup>3</sup> We report the case of a 43-year-old African American male patient that tested positive for COVID-19 on arrival and upon further testing, tested positive for autoimmune antibodies.

## 2. Case presentation

We present a 43-year-old unvaccinated African American male with a past medical history of congestive heart failure, hypertension, obstructive sleep apnea, obesity, and diabetes mellitus who

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presented to our emergency department complaining of shortness of breath. He was experiencing associated dizziness, diarrhea, loss of taste, and chest pain related to coughing. The patient noted progressively worsening symptoms one week prior to his onset of presentation. Upon initial presentation, his labs were significant for acute kidney injury, hypoalbuminemia, C-Reactive Protein (CRP) of 9.4 mg/dL, fibrinogen of 693 mg/dL, and COVID-19 Polymerase Chain Reaction (PCR) positive. EKG was unremarkable for any acute ST-T wave changes. Chest X-ray demonstrated right basilar pulmonary infiltrates.

On physical exam, the patient appeared in mild respiratory distress with an oxygen saturation of 86 % on room air, which improved to 93 % when placed on 2 L/min of oxygen via nasal cannula. His lungs were clear to auscultation bilaterally with decreased breath sounds in the right lower lobe. The patient was admitted due to acute hypoxemic respiratory failure secondary to COVID-19 pneumonia.

Throughout the course of the patient's hospital stay, oxygen requirements increased drastically. On the first day, he transitioned from 2 L/min to 35 L/min 100 % vapotherm with an oxygen saturation of 90 % and started on remdesivir 100 mg. The following day he was put on 100 % Bilevel Positive Airway Pressure (BiPAP) noninvasive mechanical ventilator support and achieved an oxygen saturation of 85 %. Despite being on 100 % fraction of inspired oxygen (FiO<sub>2</sub>) and BiPAP 20/10, the patient's hypoxia persisted and was intubated on day three as his oxygen saturation dropped to 60 %. Moreover, there was concern for kidney injury as his Blood Urea Nitrogen (BUN) and creatinine trended upwards, reaching levels of 113 mg/dL and 7.3 mg/dL respectively, which led to a nephrology consult and the start of dialysis. On day nine, the patient developed thrombocytopenia with a platelet level of 59, raising concerns for Heparin Induced Thrombocytopenia (HIT), however, testing for Heparin PF4 antibody resulted negative. Further testing revealed rhabdomyolysis as creatine kinase levels were >20,000, potassium was 5.8 mmol/L, and lactate dehydrogenase level was 859 U/L. A positive direct Coombs test revealed autoimmune hemolytic anemia and the patient was placed on prednisone 90 mg every 12 h. Troponin levels trended upwards to 269 pg/mL due to demand myocardial ischemia; an echocardiogram was performed to which an ejection fraction of 65–70 % with vigorous systolic function of the left ventricle, grade 1 diastolic dysfunction, reduced systolic function of the right ventricle, and an increased pulmonary arterial pressure of 55 mmHg was revealed.

An autoimmune workup was completed on day 17 of the patient's hospitalization. The workup was significant for elevated levels of both C3 and C4 and weakly positive ANA. On day 19, further autoimmune testing was conducted and Anti-RNP was found to be positive. Negative testing included anti-dsDNA, anti-Smith, anti-Sm/RNP, Jo-1 Ab IgG, anti-Ro, anti-La, and both anti-cardiolipin IgG and IgM Ab.

During the patient's prolonged hospital stay secondary to COVID-19 pneumonia and hypoxemic respiratory failure, he ultimately developed multi-system organ failure. The patient was pronounced deceased on day 23 of hospitalization.

### 3. Discussion

Autoimmunity can be induced by many different factors that may lead to a hyper-stimulated state of the immune system. There are three classifying factors that affect the immune system which may be divided into three primary groups: genetic, environmental, and hormonal; viruses are a major component of the environmental factors that may affect the immune system.<sup>4</sup> Virus-induced autoimmunity has been long studied and current data suggests viruses may initiate autoimmunity via numerous pathways, from molecular mimicry to immortalization of infectious B cells.<sup>5</sup> Some of the viruses that have this ability are Epstein-Barr virus, Cytomegalovirus, and Human Immunodeficiency Virus. This case report describes the new onset of autoantibodies following COVID-19 infection in a 43-year-old African American male.

The human immune system has developed numerous effective ways of responding to pathogens that may be introduced to the body. This normal immune response takes place when inflammatory pathways are activated. If this response is not properly regulated and instead is exaggerated, severe disease may ensue. One integral part of the immune response is the increase in quantity of pro-inflammatory cytokines, which function to recruit immune cells. COVID-19 infection is closely followed by an aggressive inflammatory response with a significant release of pro-inflammatory cytokines, known as a "cytokine storm".<sup>6</sup> A prospective study consisting of 41 documented confirmed COVID-19 cases in China concluded that levels of pro-inflammatory cytokines were elevated in patients that tested positive compared to healthy adults.<sup>7</sup> The presence of this "cytokine storm" has been linked with mortality in COVID-19 patients as the overproduction of pro-inflammatory cytokines can lead to Acute Respiratory Distress Syndrome (ARDS)

and widespread tissue damage to other organs subsequently leading to multi-organ failure and death.<sup>6</sup> Although, the exact mechanism for which SARS-CoV-2 triggers a strong immune response in some, is not yet fully understood.<sup>8</sup>

The link between COVID-19 and autoimmune diseases has recently been gaining attention. There are similarities between the two regarding both clinical manifestations and response to immunomodulatory treatment.<sup>9</sup> Also, the presence of autoimmune antibodies has repeatedly been witnessed in COVID-19 patients. A study conducted using a cohort of 40 COVID-19 patients determined there was a significant prevalence of ANA, ANCA, and ASCA IgA antibodies compared to healthy individuals.<sup>10</sup> Another study with a sample size of 29 patients concluded that almost 70 % of their cohort had developed autoimmune activation following COVID-19 infection.<sup>11</sup> It is important to note that these studies have limitations, such as their sample size. However, the prevalence of autoantibody production is not to be ignored. Sacchi et al., describe in their study that the presence of ANA and ANCA in COVID-19 infection resulted in a worse clinical outcome or death.<sup>10</sup> Additionally, the researchers noted that autoimmune rheumatic diseases are multi-organ-affecting diseases specifically highlighting pulmonary involvement, such as pulmonary interstitial disease. Furthermore, the researchers hypothesized that involvement of the lungs, through both COVID-19 infection and rheumatic disease, could provide an explanation for a lack of clinical improvement. Moreover, Vlachoyiannopoulos PG, Magira E, Alexopoulos H et al. discussed that in individuals with COVID-19 infection and autoantibody positivity displayed a mean sequential organ failure assessment (SOFA) score of 7.89<sup>11</sup> which is associated with a high mortality rate. The evidence that the various authors provide attempting to explain worse outcomes, death, and the new-onset autoantibody positivity in COVID-19 infection is convincing. Currently, it is hypothesized that molecular mimicry may be the cause of autoimmune phenomena observed in COVID-19.<sup>12</sup>

#### 4. Conclusion

The mechanism by which SARS-CoV-2 induces autoimmunity is not completely known, however, the limited studies conducted thus far on this topic support the association. Research has suggested that in those patients with an increased level of inflammatory markers and strong autoantibodies positivity (i.e., antinuclear antibodies and antineutrophil

cytoplasmic antibodies) due to COVID-19 infection, demonstrate worse clinical outcomes.<sup>10</sup> These results suggest a potential use of the pharmaceuticals normally used to treat autoimmune conditions and should be considered during COVID-19 infection with autoimmune positivity, potentially improving clinical outcomes.<sup>10</sup>

#### Consent

Written consent from this patient was obtained for the publication of this case report.

#### Conflicts of interest

All authors disclose no conflicts of interest.

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