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(Case Report)

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# COVID-induced pulmonary renal syndrome with severe intra-alveolar hemorrhage

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## Abstract

Since the initial surge of COVID-19, there has been an increased number of connective tissue diseases and vasculitis associated with this diagnosis. These cases include systemic lupus erythematosus, lupus nephritis, antineutrophil cytoplasmic antibody (ANCA) associated vasculitis, polymyalgia, and giant cell arteritis. There are a number of presumed mechanisms behind that including the deregulation of the angiotensin-converting enzyme 2 as well as interferon related genes, leading to increased release of inflammation markers including cytokines as well as interleukin-6, complement activation and B cell proliferation and production of autoantibodies.

**Keywords:** COVID-19 infection; Respiratory Failure; Acute renal failure; Anti-Neutrophil cytoplasmic antibody

## 1. Introduction

Over the last four years, there have been a number of research articles relating COVID-19 infection to a number of organ system damage including pulmonary, renal, neurological, hematological and cardiovascular.This case report involves a 79-year-old Caucasian female patient who developed severe ANCA induced pulmonary renal syndrome one month post COVID-19 infection. The patient also developed complicating intra alveolar hemorrhage, progressive pulmonary failure, and renal failure requiring hemodialysis.

## 2. Case Study

A 79-year-old Caucasian female with a past medical history of chronic renal failure stage 3 secondary to hypertensive nephrosclerosis with baseline creatinine of 1.8 mg/dl and a mild proteinuria of 200 mg /day. Her initial evaluation showed a negative work up including anti-neutrophil cytoplasm antibody(ANCA) and Antinuclear Antibody (ANA).

The patient developed an upper respiratory tract infection with low grade temperature, rhinitis, mild diarrhea, and vomiting. She initially presented to an urgent care where she was diagnosed with COVID-19 using Polymerase Chain Reaction (PCR) test. Chest X-ray was unremarkable for any infiltrations. Her creatinine had increased to 2.2 mg/dl which was attributed to mild intravascular volume depletion. The patient was advised to go home and increase her fluid intake. Approximately five days later, she started feeling "better"and continued to progress for approximately four weeks until she started developing symptoms of severe fatigue associated with increased lower extremity edema. Due to increased shortness of breath, she went to the Emergency Department (ED). At the presentation, her oxygen saturation was recorded at 80 %. Due to her acute hypoxia, she was placed on a non rebreather oxygen mask set at 15 L/min. On physical examination, she was noted to be using accessory muscles with each breath and increased lung crackles were auscultated bilaterally throughout all lung fields. Bilateral lower extremities revealed increased pitting edema and portable chest x-ray showed extensive bilateral lung parenchymal infiltrations [figure1]. The patient's blood cultures

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were negative, blood urea nitrogen (BUN) was 111 mg/dl, creatinine was 4.37 mg/dl, and white blood cells (WBC) were 19,500. The patient's proteinuria increased to 3.6 grams/day, with urinalysis showing nephrotic and nephritic symptoms. Serological workup revealed a high level of ANA which was 1:2560, ANCA was positive with a titer of 1:1280, and Myeloperoxidase (MPO) antibody was also positive. Echocardiogram revealed a good ejection fraction with no evidence of valvular vegetation.

A kidney biopsy was obtained with findings suggestive of necrotizing crescentic glomerulonephritis [figure 2]. Initially, large doses of solumedrol were started at 500 mg intravenously every day for three days and then maintained with oral prednisone 60 mg daily. (Rituxan) or Rituximab was administered and continued as weekly injections times 4 doses. Despite the above measures, the patient's condition continued to worsen with progressive shortness of breath and hemoptysis. Breathing became very laborious requiring intubation and mechanical ventilation. During intubation a significant amount of blood was suctioned suggestive of intra-alveolar bleeding. Hematology results revealed a hemoglobin of 6.5 g/dl and platelets at 176,000 per microliter of blood. The patient subsequently became hypotensive, requiring emergent blood transfusion and intravenous administration of Norepinephrine (Levophed) for blood pressure support. Due to oliguria and worsening acute renal failure with creatinine of 5.5 mg/dl, slow continuous veno-venous hemodialysis was started along with plasma exchange. Despite receiving blood products and fresh plasma infusions, the patient's condition continued to deteriorate. She eventually experienced cardiopulmonary arrest with rescue efforts unsuccessful.

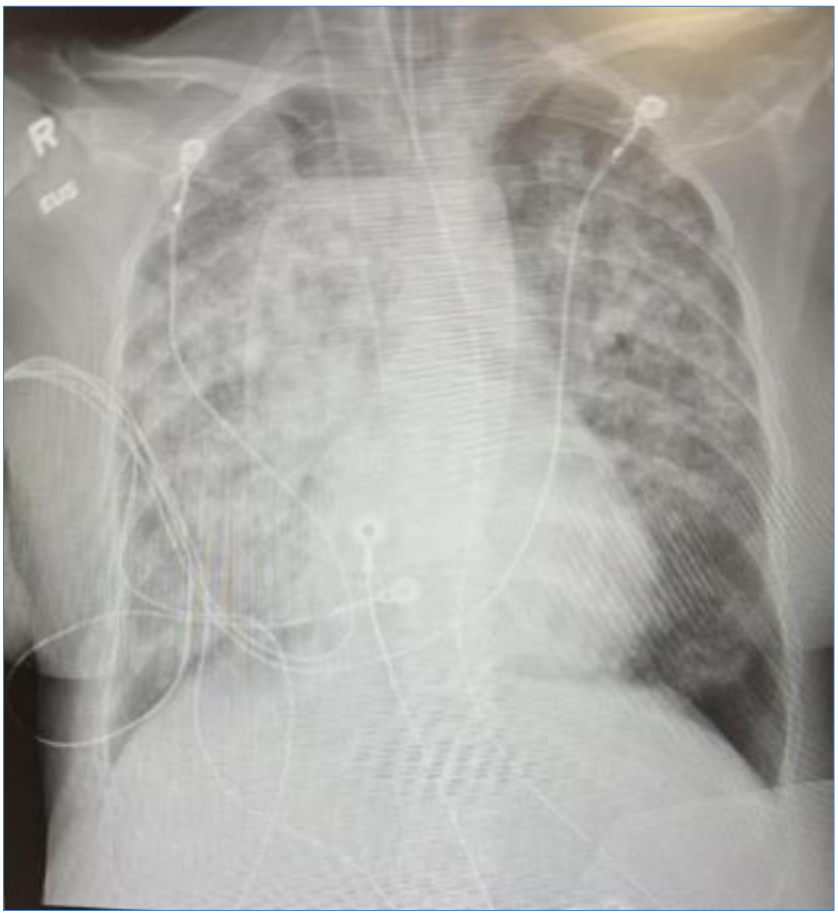


**Figure 1** Chest Radiograph

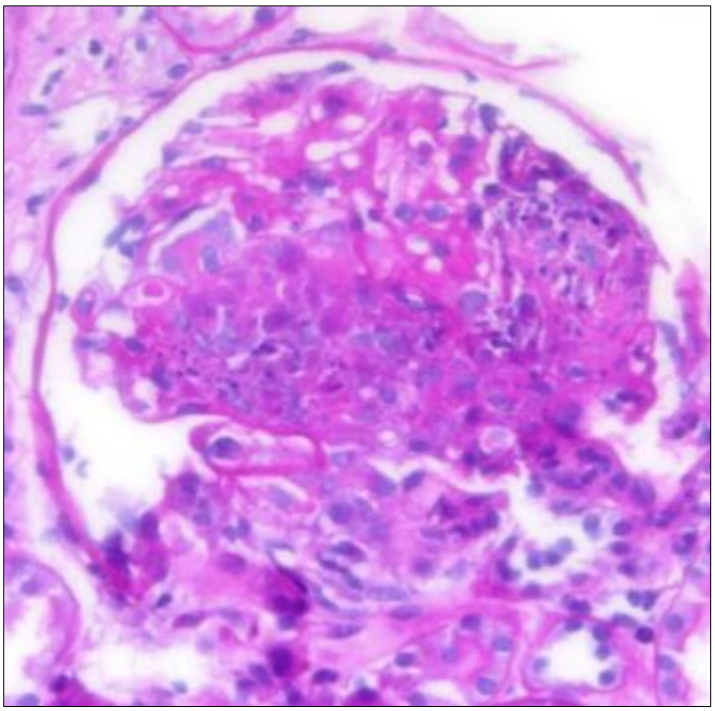

**Figure 2** Kidney biopsy with crescentic glomerulonephritis

## 3. Discussion

A recent study published in the Journal of the American Medical Association (JAMA) October 2023, stated that "a cohort study of 354,527 patients who had COVID-19 infection, when compared to the control group, were found to have a higher risk in developing autoimmune diseases including: vasculitis, alopecia, lupus, sarcoidosis, and inflammatory bowel diseases [1]. The novel COVID -19 virus is a single cell Ribonucleic acid (RNA) virus with a genome size ranging from 26,000 to 32,000 nucleotides: which are contained inside the virus envelope [2]. Four spikes of protein surround the envelope of the virus. These spikes are labeled as S, M, N, and E. The S spike protein then allows the virus to enter the host cell, which provides both M and E the ability to assemble the virus followed by the N spike which facilitates the RNA synthesis and replication.

There are several presumed mechanisms by which the COVID-19 virus triggers the immune system response. One of those mechanisms is the depletion of both B and T cells including CD8+ and CD4+ [3]. As a result of leukopenia, there is an overactivation of the T cell system causing the release of the inflammatory markers including IL1, IL6, IL8, TNF-alpha and interferon: all of which are believed to trigger an autoimmune response.

ANCA vasculitis, or antineutrophil cytoplasmic antibody mediated vasculitis, is an autoimmune disorder that affects small vessels. This disease includes a range of granulomatous formation to polyangiitis, with the involved blood vessels either rupturing or causing thrombosis and occlusion of the involved vessels [4]. Due to either genetic predisposition, exposure to environmental antigens, or infections there may be a formation of ANCA autoantigens that attach to the surface of neutrophils. As a result, the host starts recognizing these cells as antigens and triggers the production of ANCA antibodies. These antibodies attach to the autoantigens triggering the activation of the C5a complement pathway. This causes the ANCA carrying neutrophils to penetrate and attack the small blood vessels [5].

Antineutrophil cytoplasmic antibody mediated vasculitis includes several subtypes of diseases including Wegner's granulomatosis where the C-ANCA or anti-PR3 is positive in around 90% of the cases. The other one is the MPA or microscopic polyangiitis (Churg -Strauss disease) in which the myeloperoxidase (MPO) antibody is positive with a positive perinuclear antibody P-ANCA positive pattern [6].

The clinical manifestation of ANCA vasculitis includes upper respiratory tract symptoms: rhinitis, mastoiditis, saddle nose, pneumonitis, and pulmonary nodules with alveolar hemorrhages. Another serious manifestation is glomerulonephritis with nephrotic nephritic manifestations and worsening renal failure that is usually seen in crescentic glomerulonephritis

ANCA vasculitis if untreated carries a high mortality rate which can reach up to 80% [7].

Glucocorticoids intravenously are commonly used as a first line of treatment for acute vasculitis flare up. Once partial remission is achieved, it is usually switched to a tapering oral regimen. In addition to the induction with steroids, cyclophosphamide or Rituximab are introduced in tandem. However, recent studies have shown that Rituximab is superior to Cyclophosphamide with fewer side effects [8]. For remission maintenance, Mycophenolate or Azathioprine are commonly used to treat ANCA vasculitis. However, these medications are limited by both efficacy and toxicity. In an open-label controlled trial that included 42 European sites and enlisting 156 patients, it was concluded that Mycophenelate was less effective than Azathioprine in maintaining remission [9].

The plasma exchange role in treating ANCA vasculitis is still controversial with studies showing that it can decrease the incidence of kidney failure. However, it carries a higher risk of infection and there is no evidence that it changes the mortality rate. Therefore, discretion on behalf of the treating physician should be used when ordering the plasma exchange weighing both risks and benefits [10].

## 4. Conclusion

ANCA vasculitis can present as a complication of COVID-19 infection. Though it is a rare entity, it carries a very high mortality and morbidity. Early diagnosis and treating the associated complications can help change such a grim outcome.

## Compliance with ethical standards

### *Acknowledgments*

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### *Disclosure of conflict of interest*

There was no conflict of interest among corresponding authors

### *Statement of informed consent*

Informed consent was obtained from all individual participants included in the study.

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