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SARS-CoV-2 Related ANCA-associated Vasculitis and Pauci-Immune Glomerulonephritis

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Abstract COVID-19 is primarily a pulmonary disease characterized by both pulmonary and extrapulmonary complications. While acute respiratory distress syndrome (ARDS) is the most common pulmonary complication, acute kidney injury is the most common extrapulmonary complication of acute COVID-19. In addition, COVID-19 is associated with a cytokine storm capable of stimulating an autoimmune disorder. Here we present an unusual case of P-ANCA associated vasculitis and diffuse, pauci-immune rapidly progressive glomerulonephritis in a 24-year-old COVID-19 patient, resulting in an (AKI) requiring hemodialysis. The patient improved clinically after starting hydrocortisone and rituximab. She was, however, still dependent on hemodialysis at the time of hospital discharge.

Keywords: *SARS-CoV2, Vasculitis, COVID-19 complications, Pauci-Immune Glomerulonephritis*

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1. Introduction

The COVID-19 pandemic has affected over 500 million people worldwide and led to the ultimate demise of 5.32 million people. As of December 16, 2021, 1 in 416 US residents had died of COVID-19. [1] This made COVID-19 the third leading cause of death worldwide, only exceeded by heart disease and cancer. [2] The growing number of COVID-19 survivors has introduced a new phase to the pandemic and the need to care for post-COVID complications in the first 30 days after and long-term complications past 30 days.

COVID-19 is characterized by both pulmonary and extrapulmonary complications. The most common extrapulmonary complication is AKI. [3] In Yang et. al, ARDS and AKI affected 67% and 29% of acutely-ill COVID-19 patients respectively. [3] In a meta-analysis of COVID-19 literature, AKI requiring renal replacement therapy was noted in 20-31% of critically-ill patients. Six months after initial infection, 35% of patients had decreased eGFR (<90 ml/min). Interestingly, 13% of patients with normal renal function during acute COVID-19 later developed new-onset renal impairment. [4]

The promotion of a hyper-inflammatory state in the setting of SARS-CoV-2 infection has been suggested as a pathogenic mechanism for the multi-organ system complications of COVID-19, especially in those with genetic predisposition to auto-immune disorders. [5]

ANCA-vasculitis associated with COVID-19 is rare, with only six published cases in the literature at the time of this writing including both P-ANCA crescentic glomerulonephritis (GN) and C-ANCA positive crescentic GN [Table 2].

Herein we present an unusual case of P-ANCA vasculitis in a patient with an underlying history of SARS-CoV-2.

2. Presentation

A 24-year-old female with no underlying medical history presented to the hospital with hemoptysis leading to respiratory failure. Patient was brought in with agonal breathing and immediately intubated. She subsequently became pulseless and CPR was initiated. Return of spontaneous circulation was achieved after one round of chest compressions and epinephrine administration. Patient was then placed on midazolam and fentanyl drips. As per her family, the patient was noted to have flu-like symptoms and hemoptysis in the preceding days prior to admission.

Patient was placed on a ventilator with the following settings: AC mode, RR of 22, TV of 450cc, FiO2 of 100%, and PEEP of 3 with 02 saturations of 100%. Vital signs showed a body temperature, heart rate, and blood pressure of 36°C, 98 beats/min, and 138/68 mmHg respectively. Initial ABGs prior to ventilation showed severe metabolic acidosis with pH 6.8, PCO2 26.4, PO2 238, and bicarb 4.3.

The patient was subsequently started on a sodium bicarbonate drip. Chest x-ray and CT were significant for bilateral infiltrates in lung bases (Figure 1). Empiric treatment with cefepime and vancomycin was started. Patient tested negative for COVID-19 with a COVID-19 PCR and positive for COVID IgG antibody. She was unvaccinated and had suffered from COVID-19 disease 6 months prior. Basic metabolic panel was significant for hyperkalemia (6.6 mEq/L), elevated blood urea nitrogen (136 mg/dL), and high creatinine (21.5 mg/dL). Urinalysis was positive for blood (2++) and proteinuria (300 mg/dL). The patient underwent emergent hemodialysis. She was also severely anemic with hemoglobin of 3.1 mg/dL, mean corpuscular volume of 89.2 fL, Iron 150 units, platelet count 358 10^3/ml transferrin of 143 mg/dL. Other complete blood count results included WBC 28.4, RDW 28.3, reticulocytes 4.4%, and immature reticulocytes 0.67. Coagulation labs was notable for PT 15.6, PTT 22.7, INR 1.4, D-Dimer 3708. The patient was transfused with four units of packed red blood cells and all anticoagulants were held due to a positive fecal hemoccult on admission and blood in the nasogastric tube. Other laboratory results are shown in Table 1.

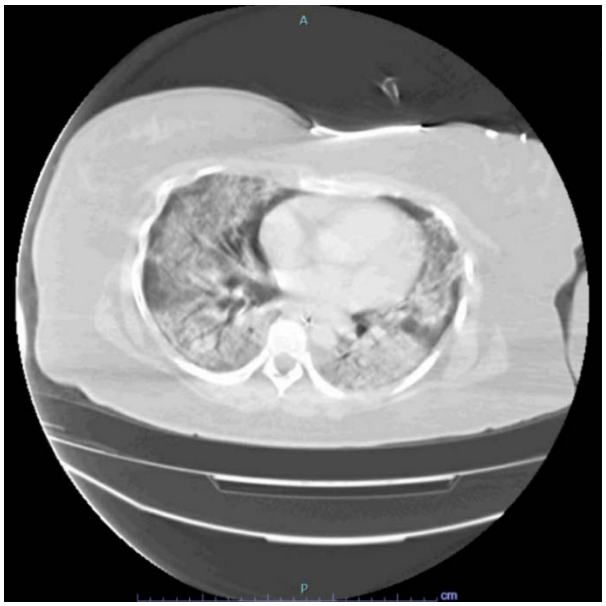

Figure 1. CT shows significant infiltrate in bilateral lung bases with partial consolidation

Table 1. Selective Laboratory Values

Parameter	Value on Admission	Value on Discharge	Reference Range
Basic Metabolic Panel			
Potassium	6.6	5.0	3.6-5.2 mEq/L
CO2	<5	19	23-30 mEq/L
BUN	136	77	2.5-7.1 mg/L
Creatinine	21.5	7.96	0.6-1.1 mg/dL
Complete Blood Count			
WBC	24	10.1	4.5-11 x 10^9/L
Hemoglobin	3.1	8.4	12-15.5 mg/dL
Hematocrit		24.4	35.5-44.9%
Platelet	356	113	-
Iron and Liver Function Tests			
Transferrin	143	-	204-360 mg/dL
TIBC	200	-	240-450 µg/dL
AST	162	34	0-35 U/L
ALT	137	127	7-55 U/L
Serologic Studies			
Perinuclear (P-ANCA)	1:320	-	Neg: <1:20
Cytoplasmic (C-ANCA)	<1:20	-	Neg: <1:20
Atypical P-ANCA	<1:20	-	Neg: <1:20
Anti-Myeloperoxidase (MPO) Abs	13.0	-	0.0-9.0 [iU]/mL
Antiproteinase 3 (PR-3) Abs	<3.5	-	0.0-3.5 [iU]/mL
Anti-GBM	3	-	Neg: 0-20
Other Tests			
Coronavirus OC43	Detected	-	Not detected
SARS-CoV-2	Not detected	-	Not detected
COVID Ab IgG	Positive	-	Negative
Rheumatoid factor	16	-	<14
CRP	10.71	-	<0.1 mg/dL
Troponin	0.95	-	<0.4ng/mL
Heparin PF4 Ab reactivity	0.166	-	0-0.4

Abbreviations: ANCA anti-neutrophil cytoplasmic antibodies, P-ANCA perinuclear ANCA, C-ANCA cytoplasmic ANCA, BUN blood urea nitrogen, TIBC total iron-binding capacity, Anti-GBM anti-glomerular basement membrane antibody, PR3 antiproteinase-3 antibody, APTT activated partial thromboplastin time, eGFR estimated glomerular filtration rate, CRP C-reactive protein, RBC red blood cells, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, COVID-19 Coronavirus disease 2019, OC43 common beta coronavirus , PF4 platelet factor 4.

Serologic studies revealed a high P-ANCA titer of 1:320 with an anti-MPO antibody titer of 13.0 U/mL. The C-ANCA titer and anti-glomerular basement membrane antibody were both negative. C-reactive protein was 10.71 and rheumatoid factor was 16. Bronchoscopy showed diffuse alveolar hemorrhage and acute inflammation with alveolar macrophages and bronchial cells. Seven sessions of plasmapheresis over two weeks were started based on the bronchoscopy results. Kidney biopsy detected crescentic glomeruli with mild tubular atrophy and interstitial fibrosis composed mainly of mononuclear cells. Electron microscopy of the kidney biopsy revealed ischemic type thickening of the basement membrane with no immune complex deposits and marked podocyte effacement. Based on the kidney biopsy and vasculitis studies, the patient was started on hydrocortisone 100mg IV q8h, rituximab 375 mg/m^2 weekly for four weeks. Patient continued to improve clinically and no longer needed supplemental oxygen on day of discharge (day 28). The creatinine level was stable at 7.96 mg/dL.

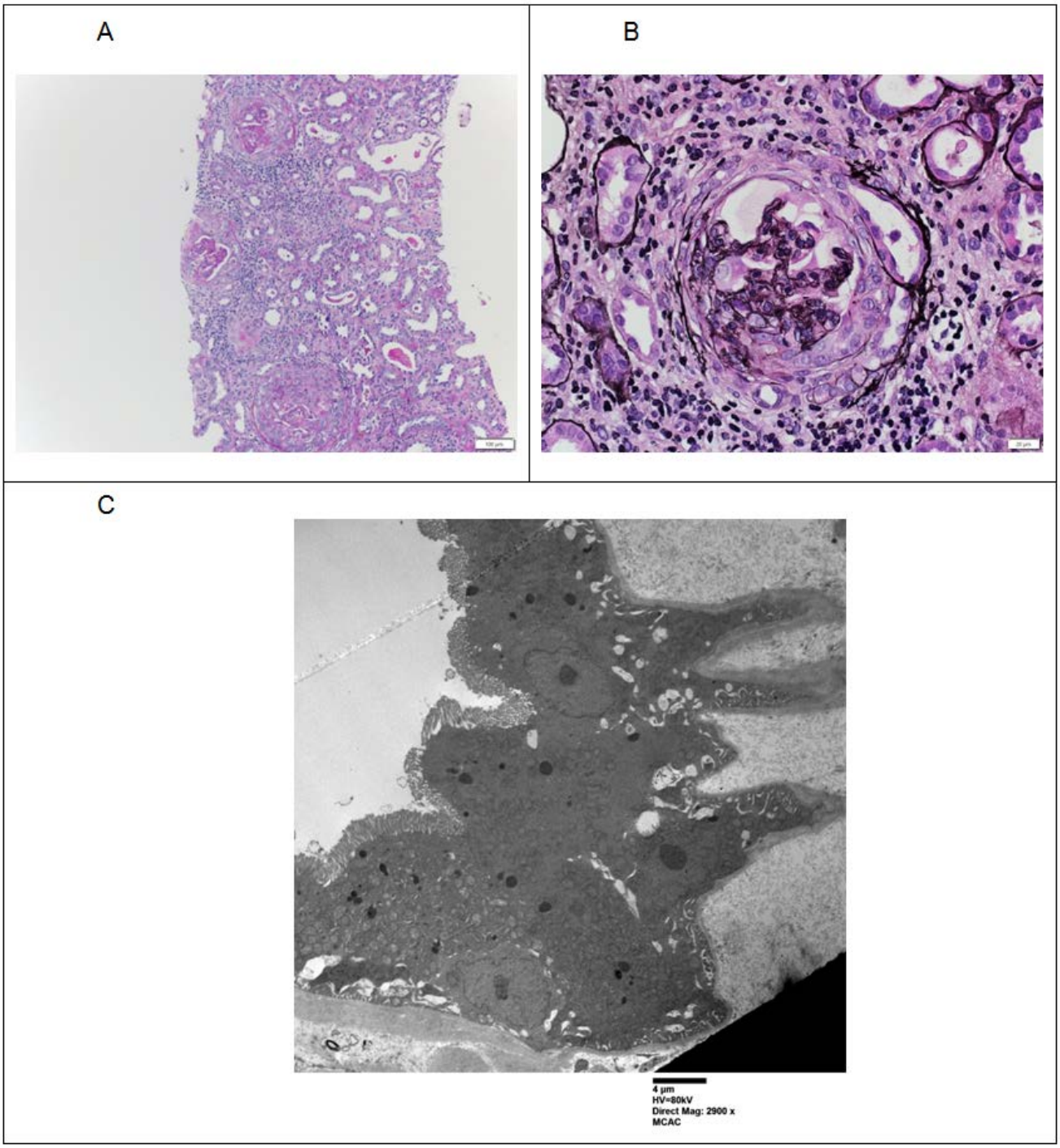

Figure 2. Kidney biopsy (A) Renal cortex demonstrating glomeruli with segmental to circumferential crescents in 14 out of 23 glomeruli sampled (PAS stained). (B) A glomerulus with cellular crescent (silver stained). (C) Protein reabsorption droplets within podocyte. Podocytes displayed marked foot process effacement involving 80-90% of the total peripheral capillary surface area.

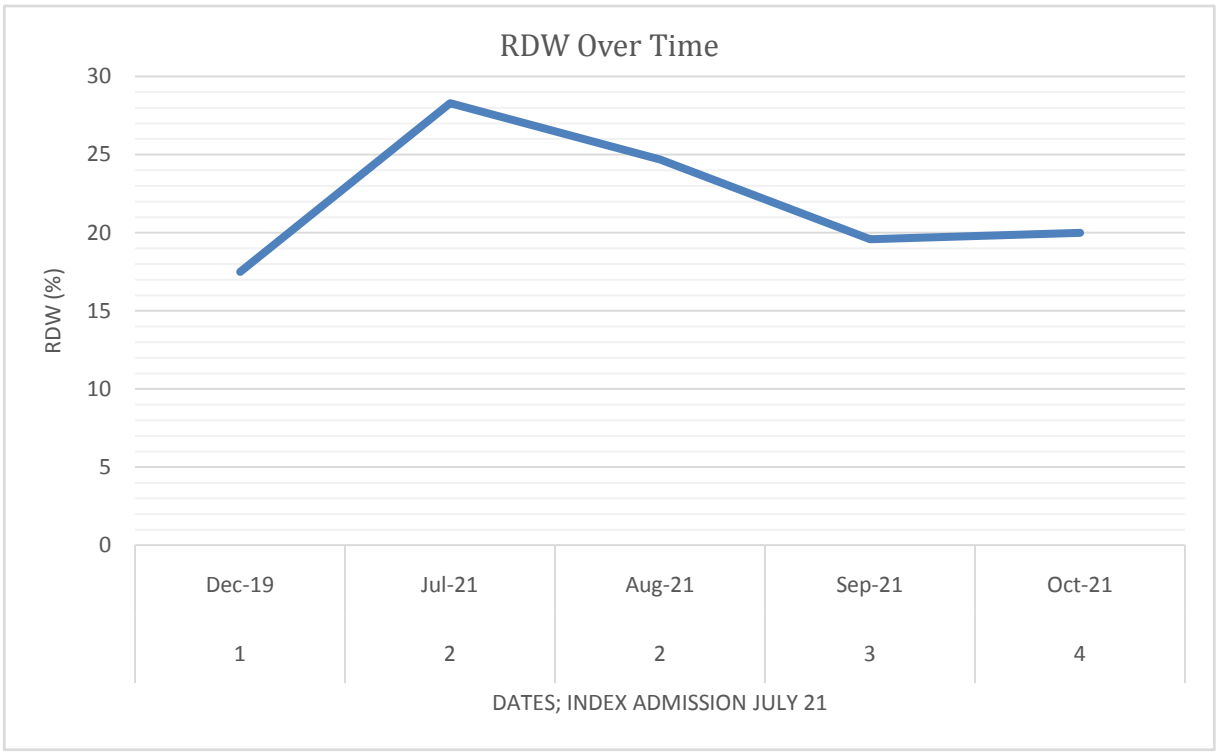

Figure 3. A graph of the patients RDW

After discharge patient was readmitted one month later for status epilepticus which was unresponsive to benzodiazepines and eventually aborted with a levetiracetam drip. In addition, she had elevated systolic blood pressure in the 200 range and was found to be thrombocytopenic. MRI was done, showing vasogenic edema involving the bilateral parieto-occipital lobe with areas of hemorrhagic conversion, minimal patchy restriction diffusion. This was likely posterior reversible encephalopathy syndrome (PRES). The PRES syndrome was most likely due to vasculitis vs uncontrolled hypertension. Currently, she is on an anti-hypertensive regimen to maintain systolic blood pressure in the 130-140 range. She is following up with nephrology and rheumatology specialists as needed.

In addition, on a readmission, patient was noted to have pancytopenia which was most likely attributable to rituximab and sulfamethoxazole-trimethoprim. Levetiracetam was also considered but was thought less likely.

The patient was diagnosed in the past with iron deficiency anemia due to her multiple C-sections. When the patient presented during her index admission, her anemia was likely attributed to acute blood loss compounded by vasculitis-induced-anemia. Our suspicion comes from analyzing her RDW where Kim et al predicted that an RDW > 15.4 % at diagnosis may increase the risk of severe vasculitis. [6] The patient's RDW at admission was 28.3% and after successful treatment with rituximab and iron supplementation her RDW was within normal range (Figure 3).

3. Discussion

Anemia is a frequent comorbidity of autoimmune and renal disease. Anemia of chronic disease (ACD) is secondary to the chronic inflammation of autoimmune disorders. Its pathogenesis may involve shortened life-span of erythrocytes, inadequate erythropoiesis, and changes to iron metabolism as a result of elevated hepcidin levels. Alternatively, renal anemia occurs in the setting of low erythropoietin or low glomerular filtration rates. The pathogenesis of both ACD and renal anemia involves inflammatory cytokines IL-1, IL-6, and TNF-alpha.

In a study by Kawamura et al, anemia was a frequent complication in patients with renal AAV. While the anemia was multifactorial, renal anemia and anemia of chronic disease were found in 92% and 56% of patients respectively. Patients with severe anemia, defined as Hgb less than 7.5 g/dl, had a significantly decreased length of survival compared to patients above that threshold. The severity of anemia was also significantly associated with the degree of renal dysfunction, as characterized by serum albumin, creatinine, eGFR, and the span of tubulointerstitial damage on biopsy. [7]

The pancytopenia that was noted on the readmission was likely due to the effects of the rituximab infusion received in the hospital and trimethroprim-sulfaxethazole.

COVID-19 associated ANCA-vasculitis is rare. This 24-year-old female with P-ANCA associated vasculitis and clinicopathologic diagnosis of diffuse, pauci-immune rapidly progressive GN with anti-MPO and P-ANCA positivity is - to our knowledge - the seventh case of COVID-19-associated ANCA-associated Vasculitis (AAV**)** at time of submission [Table 2]

Table 2. Published cases of COVID-19 Associated ANCA-Associated Vasculitis (Adapted from Izci Duran et al)

Case	Current	Izci Duran et al. [8]	Izci Duran et al. [8]	Uppal et al. [9]	Uppal et al. [9]	Moeinzadeh et al. [10]	Jalalzadeh et al. [11]
Age, years	24	26	36	64	46	25	46
Sex	Female	Male	Female	Male	Male	Male	Female
Race/Ethnicity	Hispanic	-	-	African-American	South Asian	Iranian	Hispanic
Comorbidities	None	None	None	None	DM	None	DM, scleroderma
Serology	MPO (P-ANCA)	MPO (P-ANCA)	PR3 (C-ANCA)	MPO (P-ANCA)	PR3 (C-ANCA)	PR3 (C-ANCA)	MPO (P-ANCA)
Lung involvement	Alveolar hemorrhage	Subpleural and parenchymal dispersed consolidative ground glass opacities	Bilateral cavitary lesions	Bilateral patchy infiltrates	Resolving peripheral ground-glass opacities	Alveolar hemorrhage	Bilateral pleural effusions and pulmonary infiltrates
Kidney pathology	Crescentic GN	Crescentic GN	Necrotizing crescentic GN	Crescentic GN	Focal necrotizing GN	Crescentic GN	Crescentic GN
Hemodialysis	Yes	Yes	No	Yes	No	No	No
Active COVID-19	No	Yes	Yes	Yes	Yes	Yes	No
Prior COVID-19	Yes, 6 mo prior to AKI	-	-	-	-	-	Yes, 6 mo prior to AKI
AAV Treatment	Fill out	Glucocorticoids, cyclophosphamide, plasma exchange	Glucocorticoids, cyclophosphamide	Glucocorticoids, rituximab	Glucocorticoids, rituximab	Glucocorticorticoids,	Glucocorticoids
COVID Treatment		Favipiravir	Favipiravir	Tocilizumab, convalescent plasma	Hydroxychloroquine, azithromycin	Hydroxychloroquine, levofloxacin, IVIG	
Ab titers on admission	MPO: 13.0 U/mL P-ANCA (1:320)	MPO: 80.6 U/mL P-ANCA (1:100)	C-ANCA (1:32)	MPO: 32.5 U/mL P-ANCA (1:640)	PR-3: 57.3 U/mL	C-ANCA (1:50)	MPO: 161.8 U/mL P-ANCA (1:1280)

Abbreviations: ANCA anti-neutrophil cytoplasmic antibodies, P-ANCA perinuclear ANCA, C-ANCA cytoplasmic ANCA, BUN blood urea nitrogen, TIBC total iron-binding capacity, Anti-GBM anti-glomerular basement membrane antibody, PR3 antiproteinase-3 antibody, APTT activated partial thromboplastin time, eGFR estimated glomerular filtration rate, CRP C-reactive protein, RBC red blood cells, SARS-CoV-2 severe acute respiratory syndrome coronavirus 2, COVID-19 Coronavirus disease 2019, OC43 common beta coronavirus , PF4 platelet factor 4.

Of the seven published cases of COVID-19 associated AAV, the average patient age was 38.1 years, with 57.1% male and 42.9% female. Two of the seven patients were Hispanic. Four patients, including the patient presented here, had P-ANCA serology. Of those that had P-ANCA serology, 75% ultimately required hemodialysis. Five of the seven cases were associated with an active COVID-19 infection. Notably, this case and that of Jalalzadeh et al. both involved crescentic GN in a Hispanic female patient with prior COVID-19 infection. The patient in Jalalzadeh et al did, however, have a known diagnosis of P-ANCA vasculitis ten years ago of which COVID-19 appears to have precipitated a recurrence. It is interesting to note that in both cases, the patients developed AKI approximately six months after recovering from COVID-19.

Autoimmune disorders such as ANCA-Vasculitis have long been hypothesized to have a triggering factor that initiates the disease process in genetically susceptible individuals. [12,13,14] The mechanism following SARS-CoV-2 infection includes bystander killing and formation of neutrophil extracellular traps (NETS). [12,13] Pro-inflammatory proteins are contained within NETS and directly cause endothelial cell injury by activating the complement system or indirectly by producing PR3 and MPO-ANCA. [12,13,15] The above mechanism is responsible for causing vasculitis. This has been confirmed by the presence of NETS on kidney biopsies of patients with AAV. Thus, SARS-CoV-2 could not only trigger a flare of AAV but also could start its onset. [12,13,15,16]

4. Conclusion

It is important for clinicians in the international community to be aware of the potential complications that underlie COVID long haul syndrome as they could potentially unmask an underlying autoimmune disorder. ANCA-associated vasculitis must be considered in the differential diagnosis of AKI after COVID-19 infection. In addition, severity of anemia in AAV with renal involvement may have utility as a prognostic marker. The prompt recognition and treatment of this condition is important to prevent morbidity and mortality years into the future.

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