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Characteristics and Outcomes of COVID-19 in Patients With Antineutrophil Cytoplasmic Antibody–Associated Vasculitis

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The coronavirus disease 2019 (COVID-19) pandemic has not only stressed medical systems with its acute presentations but also conferred an additional permutation to the management of various established diseases. This includes patients with autoimmune disease requiring immunosuppression. The optimal management of immunosuppression during the pandemic and in those with acute infection still remains a matter of debate. We recently reported significant disruption on the chronic care of patients with antineutrophil cytoplasmic antibody–associated vasculitis (AAV) as a result of the pandemic, with a sizeable proportion of patients having their immunosuppression held and that the risk of disease relapse likely far outweighs the risk of COVID-19.[1] Also, with the use of protective equipment and adherence to social isolation restrictions, the incidence of COVID-19 in patients with AAV may be similar to that of the general population. The characteristics and outcomes of COVID-19 in patients with new and established diagnoses of antineutrophil cytoplasmic antibody remain largely unknown, with only few cases reported.

We prospectively followed 6 patients with COVID-19 on a background of established diagnosis of AAV from our institution. Additionally, we conducted a literature search for published cases of AAV patients with COVID-19, to report cumulative characteristics and outcomes of COVID-19 in this population.

RESULTS

Four cases of AAV diagnosed at the time of acute presentation of COVID-19, along with 8 cases of patients with a pre-existing diagnosis of AAV, have been reported in the literature (in addition, we report 6 cases with established AAV from our institution; n=14). With respect to the patients newly diagnosed with AAV (n=4), the median age was 41 years, with male and proteinase 3 antibody predominance (Table 1). All patients had evidence of acute kidney injury (median creatinine 5.5 mg/dl) with evidence of crescentic necrotizing glomerulonephritis on kidney biopsy. All patients received pulse steroids, with concomitant rituximab (RTX) administration in two, and cyclophosphamide administration. Two patients with severe alveolar hemorrhage required plasmapheresis, with 1 patient dying (this patient did not receive immunosuppression). The remaining 3 patients who received immunosuppression for AAV demonstrated evidence of clinical recovery.

In patients with established AAV presenting with COVID-19 (n=14), the median age was 54 years, with equal gender distribution and proteinase 3 predominance (n=12). Duration of antineutrophil cytoplasmic antibody diagnosis had a disparate range of 0.5–396 months (Table 2). Majority of patients (11 of 14) were on RTX and oral prednisone for maintenance therapy, with the median duration elapsed since last administration of RTX being 60 days. All patients had evidence of bilateral interstitial and ground-glass opacities on lung radiology, with only 1 patient requiring mechanical ventilation. Thirteen of 14 patients are in

Table 1. Demographics, clinical characteristics, and outcomes of patients with newly diagnosed ANCA-associated vasculitis and COVID-19

Case report	Age	Gender	Ethnicity	Peak creatinine (mg/dl)	ANCA type	Kidney Pathology	Lung radiology	ANCA Induction	RRT	Respiratory failure	COVID-19 Treatment	COVID-19 Outcome	Comments
Uppal[S4]	64	M	African American	7.9	MPO	Crescentic GN	Bilateral patchy infiltrates	Pulse steroids (MP 500 mg × 3) + RTX (1 g)	iHD	10 L NRB mask	Tocilizumab, convalescent plasma	AKI in recovery	Received only 1 dose of RTX post negative COVID-19 PCR
Uppal[S4]	46	M	South Asian	4	PR3	Focal necrotizing GN	Resolving peripheral GGOs	Pulse steroids (MP 1 g × 3) + RTX (375 mg/m^2) × 2	No	None	HCQ, azithromycin	AKI in recovery	Completed both doses of RTX (1 during hospital stay)
Moeinzadeh[S5]	25	M	NR	5.5	PR3	Crescentic proliferative GN	GGOs resemble diffuse alveolar hemorrhage vs. coronavirus infection	Pulse steroids (MP 1 g × 3) + CYC + PLEX + IVIG	No	None	HCQ, levofloxacin	AKI in recovery	PLEX given alveolar hemorrhage Commenced on CYC (day 10 post ANCA/ COVID-19 diagnosis) after negative COVID-19 PCR
Hussein[S6]	37	F	Middle eastern	NR	PR3	—	Patchy consolidation with a central and peripheral distribution, permeated by GGO and crazy paving pattern	Pulse steroids (prednisone 60 mg) + PLEX + IVIG	NR	MV	Ritonavir/ lopinavir	Patient died	PLEX given alveolar hemorrhage

AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; COVID, coronavirus disease 2019; CYC, cyclophosphamide; F, female; GGO, ground-glass opacity; GN, glomerulonephritis; HCQ, hydroxychloroquine; HFNC, high-flow nasal cannula; iHD, intermittent hemodialysis; IVIG, intravenous immunoglobulin; M, male; MP, methylprednisone; MPO, myeloperoxidase antibody; MV, mechanical ventilation; NR, not reported; NRB, nonrebreather mask; PCR, polymerase chain reaction; PLEX, plasmapheresis; PR3, proteinase 3; RRT, renal replacement therapy; RTX, rituximab; UA, urinalysis.

sustained clinical recovery, with 1 currently hospitalized with a positive clinical trajectory.

DISCUSSION

This combined case series review brings forward some pertinent aspects of the characteristics and outcomes of patients with newly diagnosed and established AAV diagnosis in the setting of COVID-19 infection. It is unknown if SARS-CoV-2 triggers autoimmunity. The emergence of pediatric multisystem inflammatory disease in temporal relation to SARS-CoV-2 infection is an example of SARS-CoV-2 triggering vasculitis.[4] In the newly diagnosed patient, the predominance of proteinase 3 provides further evidence for infectious antigen stimulation leading to generation of autoimmunity, especially in the setting of proteinase 3 AAV.[5] Additionally, both COVID-19 and AAV are associated with formation of neutrophil extracellular traps, providing further plausible mechanisms involved in the development of autoimmunity in the setting of the acute viral infection.[6,7]

Most importantly, these cases have provided possible strategies for management of immunosuppression at the time of a pandemic, where constant uncertainty regarding the same exists. In patients with new a diagnosis of AAV, treatment with pulse steroids with either RTX or cyclophosphamide shortly after acute presentation of COVID-19 led to overall sustained clinical recovery, with no worsening or recurrence of manifestations of infection. With respect to established AAV cases, the median duration elapsed since RTX administration was 60 days. Not only did all of these patients recover, but also only 1 on RTX maintenance required mechanical ventilation. This is in keeping with proposed theories that RTX may limit cytokine storm and prevent further worsening of clinical status.[2,3,8] Similar experience has been reported in patients receiving B cell–depleting therapies in diseases such as multiple sclerosis and pemphigus vulgaris, along with patients with other autoimmune diseases on biologic therapies.[S1–S3] The only caveat is to recognize that patients previously treated with RTX may demonstrate prolonged viral shedding devoid of any symptoms. This may influence recommendations for duration of quarantine for this population of patients so as to prevent inadvertent exposure to other individuals.

In conclusion, the use of immunosuppression in patients with COVID-19 in the setting of new and established diagnoses of AAV may not be associated with deleterious outcomes. Induction immunosuppression could be used shortly after improvement of acute COVID-19 presentation to treat newly diagnosed AAV. On the other hand, maintenance immunosuppression has the potential to attenuate the severe inflammatory effects of COVID-19 and may not be associated with worse outcomes.

DISCLOSURE

DG reports being consultant to ChemoCentryx and Aurinia. All the other authors declared no competing interests.

Table 2. Demographics, clinical characteristics, and outcomes of patients with COVID-19 on a background of established ANCA-associated vasculitis

Case report	Age	Gender	Ethnicity	Peak creatinine (mg/dl)	Duration of ANCA diagnosis (mo)	ANCA type	Lung radiology	ANCA maintenance	Last IS to COVID diagnosis (d)	RRT	Respiratory failure	COVID-19 treatment	COVID-19 outcome	Comments
Guilpain[2]	52	F	NR	NR	396	PR3	Bilateral interstitial pneumonia	RTX	1	No	MV	Lopinavir/ritonavir; HCQ	Recovered from respiratory failure; discharged on day 29 of admission	Received RTX a day prior to COVID presentation
Sharmeen[S7]	27	F	Hispanic	NR	1	PR3	Bilateral multifocal opacities	RTX, prednisone (20 mg)	60	No	NRB, 15 L	HCQ, tocilizumab	Recovered	On 20 mg prednisone at the time of COVID diagnosis
Schramm[S8]	25	M	NR	NR	2	PR3	Bilateral GGOs	RTX, CYC (induction), prednisone (60 mg)	9	No	Low-flow, 2 L	HCQ, lopinavir/ritonavir	Recovered	Nosocomial infection Ongoing 60 mg prednisone, 9 d after last of 5 cyclophosphamide infusions and 19 d after the last of 4 rituximab infusions
Daniel[3]	55	M	NR	NR	324	PR3	Bilateral GGOs (60% involvement)	RTX, prednisone (4 mg)	120	No	None	HCQ, azithromycin, lopinavir/ritonavir	Recovered, discharged home after 23 d	On 4 mg prednisone at the time of diagnosis
Leipe[S9]	63	M	NR	3.4	72	PR3	Bilateral GGOs	RTX, prednisone (5 mg)	14	No	Face mask, 6 L	None	Readmitted with worsening respiratory symptoms on day 14; eventual recovery	On 5 mg prednisone at the time of diagnosis
Shenavandeh[S10]	35	M	NR	NR	72	PR3	Multiple new left-sided peripheral GGOs in addition to the pre-existing right-side cavitary lesion	RTX, AZA, prednisone (7.5 mg)	NR	No	None	HCQ, azithromycin	Discharged after 4 d; recovered	On 7.5 mg prednisone at the time of diagnosis
Fallet[S11]	77	F	NR	NR	24	PR3	Scattered bilateral GGOs	RTX, MTX, prednisone 5 mg	30	No	None	None	Discharged after 6 d; recovered	—
Suárez-Díaz[S12]	64	F	NR	NR	72	MPO	NR	Prednisone 5 mg	90	No	None	None	Recovered at home	Treated for vasculitis relapse with RTX 90 d before COVID diagnosis
Current study	74	F	African American	1.5	108	MPO	Scattered bilateral GGOs	Prednisone 5 mg	–	No	MV	Remdesivir	Recovered	Renal biopsy showed mild necrotizing GN; received MP 40 mg × 10; RTX 2 mo after COVID diagnosis
Current study	48	F	Hispanic	0.7	72	PR3	Diffuse peribronchovascular and peripheral GGOs	RTX 500 mg, prednisone 8 mg	60	No	HFNC	Remdesivir, Dexamethasone	Recovered	—
Current study	81	F	African American	1.5	12	PR3	Scattered bilateral GGOs	AZA, prednisone 5 mg	—	No	HFNC	None	Recovered	—
Current study	45	M	Asian	1.3	60	PR3	Scattered bilateral GGOs	RTX, prednisone 5 mg	120	No	Low flow, 2 L	Remdesivir	Recovered	—
Current study	63	M	Caucasian	1.2	0.5	PR3	Scattered bilateral GGOs	See comments	7	No	Low-flow, 6 L	Dexamethasone, remdesivir, convalescent plasma	In-hospital	Received RTX 1 g and MP 500 mg × 3 for induction. Diagnosed with COVID a week after RTX and discharged from hospital.
Current study	36	M	Caucasian	1	54	PR3	—	RTX	80	No	None	None	Recovered at home	—

ANCA, antineutrophil cytoplasmic antibody; AZA, azathioprine; COVID, coronavirus disease 2019; CYC, cyclophosphamide; F, female; GGOs, ground-glass opacities; GN, glomerulonephritis; HCQ, hydroxychloroquine; HFNC, high-flow nasal cannula; iHD, intermittent hemodialysis; IS, immunosuppression; M, male; MP, methylprednisone; MPO, myeloperoxidase antibody; MTX, methotrexate; MV, mechanical ventilation; NR, not reported; NRB, nonrebreather mask; PR3, proteinase 3; RRT, renal replacement therapy; RTX, rituximab; UA, urinalysis.

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SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods

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