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Acquired antineutrophil cytoplasmic antibody-associated glomerulonephritis after COVID-19 infection

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Acute kidney injury (AKI) is the most common renal complication in patients with coronavirus disease 2019 (COVID-19) [1,2]. Previous studies on patients with COVID-19 and AKI have shown that tubular epithelial injury is a prominent finding [3,4]. In addition, minimal change disease, or membranous nephropathy, is frequently reported as a form of glomerular involvement. However, the association between COVID-19 and crescentic glomerulonephritis (GN) has rarely been identified. We report a case of antineutrophil cytoplasmic antibody (ANCA)-associated GN in a patient with COVID-19. This study was approved by the Intitutional Review Board of Kyung Hee University Hospital (No. KHUH 2023-04-022).

A 66-year-old man visited our clinic for non-recovery of renal function. Before visiting our clinic, he received continuous renal replacement therapy and ventilator care for COVID-19 pneumonia, which presented as diffuse reticular opacities in both lungs. No antiviral treatment was administered. His renal function was not fully recovered after four weeks of COVID-19 management. Prior to the COVID-19 infection, his serum creatinine level was 0.84 mg/dL, and no abnormal findings were observed on urinalysis. He had no relevant medical history other than hypertension and had received a third dose of severe acute respiratory syndrome corona-virus-2 vaccine 4 months prior to infection.

On admission to our clinic, laboratory findings revealed a serum creatinine level of 2.46 mg/dL. Urinalysis showed microscopic hematuria; further, the urinary protein to creatinine ratio and 24-hr urine protein content were 0.95 g/g and 769 mg/day, respectively. All serologic tests including anti-proteinase 3 antibodies were negative, but an anti-myeloperoxidase (MPO) antibody test revealed a positive result of 2.60 index (positive ≥1.1).

A renal biopsy revealed six globally sclerotic glomeruli and one segmental sclerotic glomerulus on light microscopic examination (Fig. 1). Fibrous crescents were observed in three of four non-sclerotic glomeruli. No signs of acute tubular injury were observed. Electron microscopy revealed focal foot process effacement without immune deposits, and immunofluorescence staining results were negative. We administered methylprednisolone pulse therapy, and the patient received weekly rituximab treatment at 375 mg/m^2 for three cycles thereafter. Renal function did not further deteriorate, and serum creatinine level was 2.33 mg/dL 2 months after discharge.

Table 1 summarizes cases of ANCA-associated GN after COVID-19. Among these reports, we found that only one patient had an underlying autoimmune disease. However, most patients developed ANCA-associated GN in the absence of an autoimmune disease. These findings suggest

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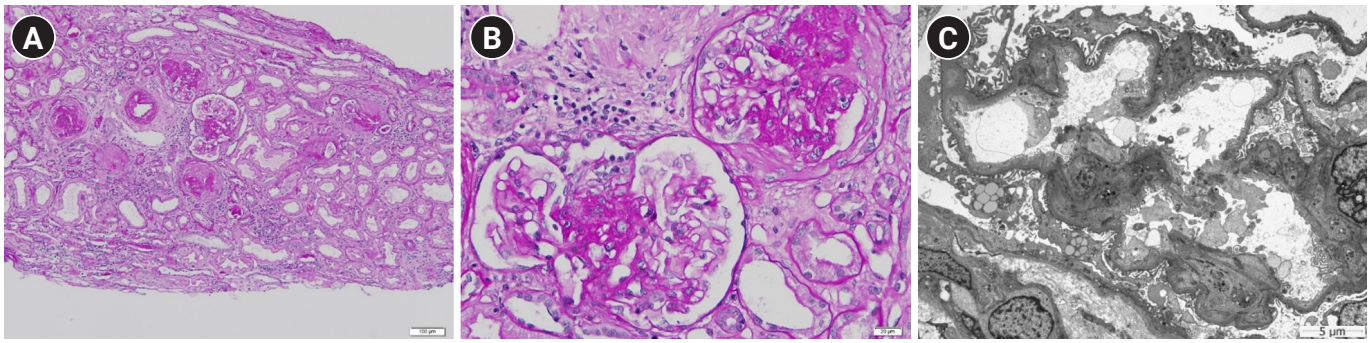

Figure 1. Histopathological findings of the patient. (A) Among the six glomeruli, three glomeruli (left lower) are globally sclerotic, two glomeruli have fibrous crescents, and the remaining glomerulus exhibits segmental sclerosis (periodic acid-Schiff (PAS) stain, ×100). (B) Both glomeruli show segmental sclerosis, and one (upper right) exhibits a fibrous crescent (PAS, ×400). (C) The epithelial foot process is focally effaced, and there are no electron-dense deposits (electron microscopy, ×2,500).

that COVID-19 alone has the potential to trigger pathologic immune activation, leading to ANCA-associated GN. Recent reports of ANCA-associated GN after COVID-19 vaccination further support this explanatory mechanism [5,6]. In this case, the lack of an underlying immune disorder also suggests that COVID-19 produced an anti-MPO antibody that caused crescentic GN on kidney biopsy.

The clinical presentation of COVID-19 is characterized by substantial cytokine release and a systemic inflammatory response [7]. Persistent fever, increased circulating inflammatory marker levels, and pulmonary infiltration are commonly observed in COVID-19 patients. Unfortunately, these clinical findings are similar to the symptoms and signs of ANCA-associated vasculitis, and COVID-19 pneumonic lesions make it difficult to distinguish from ANCA-associated lung involvement. In this case, ANCA-associated pulmonary involvement, if it actually existed, was not detected because of COVID-19 pneumonic lesions. Similar issues regarding difficulty of discrimination might also have occurred in previous reports on ANCA-associated GN after COVID-19.

In the present case, more than half of the glomeruli were globally sclerotic, suggesting that ANCA-associated glomerular injury was sustained during the active stage of the COVID-19 infection. However, detection of ANCA-associated GN may be complicated at the time of active infection. AKI is frequently observed in hospitalized COVID-19 patients, with a prevalence of 20% to 50% [3,4]. In addition, direct invasion of COVID-19 virus into podocytes or endothelial damage from the inflammatory response contributes to glomerular injury [3,8]. Consequently, the rapid decline in renal function and proteinuria may not be a specific sign of ANCA-associated GN in COVID-19 patients. Therefore, we recommend serological tests to identify the signs of ANCA-associated GN. Indeed, all reported cases of ANCA-associated GN showed positive serologic results for ANCA antibodies.

Immunosuppressive therapy was usually administered for ANCA-associated GN after COVID-19 in previously reported cases. Among them, seven patients (50%) showed partial recovery of renal function, and mortality did not occur. These findings imply that immunosuppressive therapy has clinical benefits and should be considered during active COVID-19 infection. In this case, it is expected that a greater clinical benefit could be obtained if early diagnosis and immediate immunosuppressive treatment began before progression to global sclerosis. Additionally, further studies are required to examine the role of antiviral treatment or vaccination in treating or preventing these types of complications.

In conclusion, AKI after COVID-19 infection could present as a form of ANCA-associated GN, and close monitoring is required for the presence of ANCA-associated GN in COVID-19. Early diagnosis with kidney biopsy and appropriate treatment are useful to prevent deterioration of renal function.

Table 1. Previously reported cases of ANCA-associated glomerulonephritis after COVID-19

Age (yr)/sex	Autoantibody	Underlying autoimmune disease	COVID-19 pulmonary manifestation	Treatment	RRT	Recovery of renal function	Antiviral treatment	Reference[a]
25/Male	PR3	None	Alveolar hemorrhage	MPD, plasmapheresis, cyclophosphamide	No	ESRD	Hydroxychloroquine	[1]
64/Male	MPO	None	Bilateral patch infiltrates	MPD, rituximab	HD	Partial	None	[2]
46/Male	PR3	None	Resolving peripheral ground glass opacities	MPD, rituximab	No	Partial	Hydroxychloroquine	[2]
46/Female	MPO	Scleroderma	Bilateral pulmonary infiltrates	MPD	No	ESRD	Unknown	[3]
60/Female	PR3	None	Alveolar hemorrhage	MPD, plasmapheresis, rituximab	No	Partial	None	[4]
26/Male	MPO	None	Alveolar hemorrhage	MPD, plasmapheresis, cyclophosphamide	HD	ESRD	Favipiravir	[5]
36/Female	PR3	None	Bilateral cavitary lesions	MPD, cyclophosphamide	No	Partial	Favipiravir	[5]
40/Male	PR3	None	Alveolar hemorrhage	MPD, Rituximab	No	Complete	None	[6]
60/Female	MPO	None	Alveolar hemorrhage	MPD, plasmapheresis, rituximab	No	Partial	Unknown	[7]
64/Female	PR3	None	Bilateral interstitial pneumonia	MPD, plasmapheresis, cyclophosphamide, rituximab	HD	Partial	Unknown	[8]
17/Male	MPO	None	Alveolar hemorrhage	MPD, plasmapheresis, cyclophosphamide	No	Complete	Remdesivir	[9]
61/Female	MPO	None	No	MPD, cyclophosphamide	No	Partial	None	[10]
26/Female	MPO	None	Alveolar hemorrhage	MPD, rituximab	No AKI	Complete	None	[11]
53/Male	MPO	None	Alveolar hemorrhage	MPD, cyclophosphamide	CRRT, HD	ESRD	Unknown	[12]

AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; ESRD, end-stage renal disease; HD, hemodialysis; MPD, methylprednisolone; MPO, myeloperoxidase; PR3, proteinase-3; RRT, renal replacement therapy.

[a]See the Supplementary material 1 (available online) for the references.

Conflicts of interest

All authors have no conflicts of interest to declare.

Data sharing statement

The data presented in this study are available on request from the corresponding author.

Authors' contributions

Conceptualization: HSH
Data curation, Investigation: JYL
Methodology, Visualization: JYL, HSH
Writing–original draft: JYL, HSH
Writing–review & editing: HSH
All authors read and approved the final manuscript.

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