Acute Kidney Injury With Endothelial Injury and Podocytopathy Following COVID-19 Vaccination

Soo-Young Yoon, MD,[1] Ji-Youn Sung, MD, PhD,[2] Jin Sug Kim, MD, PhD,[1] Kyung Hwan Jeong, MD, PhD,[1] and Hyeon Seok Hwang, MD, PhD[1]

Vaccination is established as the most effective way to prevent severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. However, kidney transplant patients may experience unexpected immune responses to vaccination. We report a case of acute kidney injury (AKI) in a kidney transplant recipient after a ChAdOx1 nCoV-19 vaccination.

A 57-year-old man who received a living kidney transplant from his spouse 9 years previously due to diabetic nephropathy was admitted with pitting edema 1 week after the ChAdOx1 nCoV-19 vaccination. Dark-colored gross hematuria was observed for 1 week and serum creatinine rose from 0.95 to 5.63 mg/dL with proteinuria (urine protein to creatinine ratio 6.03 μg/mg). Abdominal computed tomography scan with contrast enhancement showed no lesions indicative of gross hematuria. Serum anti-COVID-19 (coronavirus disease 19) IgM was detected, while donor-specific anti-HLA antibodies and serological tests for autoimmune renal diseases were negative. Platelet factor 4-heparin antibody test and brain magnetic resonance were assessed for vaccine-induced thrombotic microangiopathy, giving negative results.[1]

A percutaneous kidney biopsy demonstrated endothelial swelling of the arterioles, and acute proximal tubular injury involved 20% of the cortex with normal glomeruli (Figure 1A and B). There was a remarkable interstitial hemorrhage without inflammatory cell infiltration (Figure 1C). Immunohistochemical staining for C4d was minimally positive without peritubular capillaritis (Figure 1D). Immunofluorescence revealed staining for C1q in the vessels (2+) as well as C3 in the vessels (1+) and peritubular capillaries (1+) (Figure 1E and F). Electron microscopy showed diffuse foot process effacement, endothelial cell swelling, loss of fenestration, and schistocytes (Figure 1G and H). Immune-complex deposits in immunofluorescence and electron microscopic examinations were not noted. The patient also underwent genetic analysis of *APOL1* to identify high-risk variants for podocytopathy, but no mutations were observed. Despite a high dose of methylprednisolone pulse therapy and therapeutic plasma exchange followed by intravenous immunoglobulin, renal function did not recover.

Several recent studies have demonstrated that endothelial damage and activation of the complement system play a major role in the development of AKI in patients who experience a SARS-CoV-2 infection.[2,3] Interestingly, endothelial cell injury was the most noticeable biopsy finding in this patient, and endothelial cell dysfunction combined with interstitial hemorrhage was mainly responsible for AKI. The loss of barrier and fenestration of glomerular endothelial cell seemed to contribute to the hematuria clinically.[4]

Prominent proteinuria and foot process effacement without deposition of the immune complex were observed on kidney biopsy. A number of reports have stated that podocytopathy without demonstrable viral particles, tubuloreticular inclusions, and collapsing glomerulopathy indicate the implication of cytokines in podocyte injury with COVID-19 infection.[3,5] We speculate that immune stimulation against SARS-CoV-2 spike protein in vaccines is likely to attack podocytes.

Differences in antigenicity might also contribute the immune-mediated injury in the transplanted kidney. Because the antigenicity of the renal allograft was not identical to that of the patient's native organs, the activated immune system could be specific for renal allograft.

The present case demonstrated that SARS-CoV-2 vaccination triggered an immune response, causing endothelial dysfunction and podocytopathy in a renal allograft.

REFERENCES

1. Greinacher A, Thiele T, Warkentin TE, et al. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination. *N Engl J Med.* 2021;384:2092–2101.

Received 22 November 2021. Revision received 13 December 2021.

Accepted 13 December 2021.

[1] Division of Nephrology, Department of Internal Medicine, College of Medicine, Kyung Hee University, Seoul, Republic of Korea.

[2] Department of Pathology, College of Medicine, Kyung Hee University, Seoul, Republic of Korea.

This work was supported by grants from Kyung Hee University in 2020 (KHU-20201235).

All authors of this manuscript declare no conflicts of interest. The study was approved by the Ethics Committee of Kyung Hee University.

S.-Y.Y., J.S.K., K.H.J., and H.S.H. took care of the patient and S.Y.Y. and H.S.H wrote the article. J.-Y.S. performed the pathological analysis. All authors discussed and reviewed the article.

Correspondence: Hyeon Seok Hwang, MD, PhD, Division of Nephrology, Department of Internal Medicine, College of Medicine, Kyung Hee University, 23, Kyungheedae-ro, Dongdaemun-gu, Seoul 02447, Republic of Korea. (hwanghsne@gmail.com).

ISSN: 0041-1337/20/1064-e236

DOI: 10.1097/TP.0000000000004061

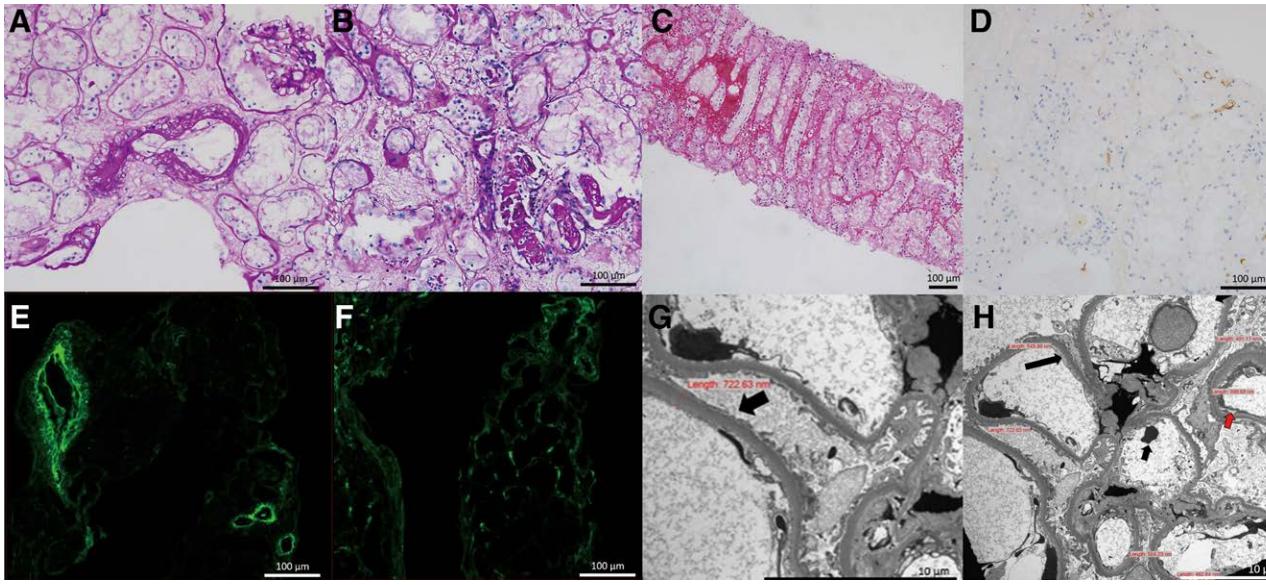

FIGURE 1. Patients' histopathological findings. A, Endothelial cell enlargement of the arteriole (periodic acid–Schiff stain; original magnification ×200). B, Acute tubular injury (periodic acid–Schiff stain; original magnification ×200). C, Diffuse interstitial hemorrhage (hematoxylin-eosin stain, original magnification ×100). D, Minimal C4d positivity (C4d immunohistochemical stain; original magnification ×200). E, C1q (2+) in vessels (immunofluorescence against C1q; original magnification ×200). F, C3 (1+) in the vessels and peritubular capillaries (immunofluorescence against C3; original magnification ×200). G, Diffuse foot process effacement (black arrow) (electron microscopy; original magnification ×3000). H, Endothelial cell swelling (long black arrows); fragmented red blood cell (short black arrow); subendothelial electron-lucent area (red arrow) (electron microscopy; original magnification ×3000). (A–F) Bars = 100 µm. (G, H) Bars = 10 µm.

2. Perico L, Benigni A, Casiraghi F, et al. Immunity, endothelial injury and complement-induced coagulopathy in COVID-19. *Nat Rev Nephrol.* 2021;17:46–64.
3. Nadim MK, Forni LG, Mehta RL, et al. COVID-19-associated acute kidney injury: consensus report of the 25th Acute Disease Quality Initiative (ADQI) Workgroup. *Nat Rev Nephrol*. 2020;16:747–764.
4. Jourde-Chiche N, Fakhouri F, Dou L, et al. Endothelium structure and function in kidney health and disease. *Nat Rev Nephrol*. 2019;15:87–108.
5. Kudose S, Batal I, Santoriello D, et al. Kidney biopsy findings in patients with COVID-19. *J Am Soc Nephrol*. 2020;31:1959–1968.