Glomerular endothelial injury following vaccination for SARS-CoV-2

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Short Title: Glomerulonephritis by SARS-CoV-2 vaccination

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Several cases of IgA nephropathy (IgAN) which developed gross hematuria following vaccination for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were reported [1–3]. In them, the vaccination was presumed to have triggered IgA1 response and exacerbated glomerulonephritis (GN). However, injected intramuscularly, the vaccines unlikely trigger this mucosal-immune-system response [4]. We report a case of crescentic GN where renal histological findings suggested that vaccination-induced potent immune cell responses caused the exacerbation.

A 65-year-old female with no known past medical history developed gross hematuria, which was preceded by fever and myalgia, the next day after the second administration of the Pfizer-BioNTech SARS-CoV-2 vaccine. While the symptoms resolved, two days later, urinalysis showed proteinuria of 0.93 gram per gram of creatinine (g/gCr), and hematuria of...
more than 100 red blood cells per high-power field (RBC/HPF). Serum chemistry showed creatinine concentration (sCr) 1.38 mg/dL, IgA 279 mg/dL, IgG 1412 mg/dL, IgM 103 mg/dL, C3 99 mg/dL, C4 39 mg/dL, and CH50 53.2 U/L.

Renal needle biopsy was performed five days after the vaccination. Light microscopic examination of the biopsy samples detected a cellular glomerular crescent in one glomerulus among the 23 glomeruli observed (Supplementary Figure. 1A) and diffuse mesangial matrix expansion with mild focal increase in mesangial cellularity (Supplementary Figure. 1B). Immunofluorescence examination revealed mesangial staining of IgG, IgA, IgM, and C3 (Supplementary Figure. 1C). Further examination by transmission electron microscopy revealed diffuse subendothelial widening and podocyte foot process effacement but no dense deposits on glomerular capillaries (Figure. 1).

Based on the histological findings, oral prednisolone therapy was started with a dose of 0.8 mg/kg. Two weeks after the start of the therapy, her proteinuria, hematuria, and sCr decreased to 0.29 g/gCr, 30–49 RBC/HPF, and 1.01 mg/dL, respectively. Thereafter, the dose of prednisolone could be reduced without exacerbation of the GN.

Having had mesangial matrix expansion and IgA staining, the case would have had latent IgAN. However, the absence of electron dense deposits on glomerular capillaries at the time of the renal biopsy (5 days after the vaccination) suggests that IgAN would not have been responsible for the crescent formation; glomerular capillary deposition could be observed until 4–10 days after the induction of the GN in the experimental antibody-mediated crescentic GN [5]. Since nucleoside-modified-mRNA vaccines would induce potent immune cell responses [6], the immune cell responses rather than IgA1 response would have caused the crescent formation. Releasing several cytokines, the responses would have caused vascular endothelial injury, which would present diffuse subendothelial widening and crescent formation.
In the reported cases of IgAN exacerbation following SARS-CoV-2 vaccination, the vaccination was presumed to have triggered the IgA1 response [1–3]. However, in them, renal histology was not examined within 10 days after the vaccination. Hence, whether IgA1 response participated in the exacerbation was not clarified, and the vaccination-induced immune cell responses might have caused the exacerbation. To clarify the cause of the exacerbation following SARS-CoV-2 vaccination, an early-phase renal histological examination (at least <10 days and preferably <4 days after the vaccination) is necessary [5]. If glomerular capillary deposition were not observed, the glomerular endothelial injury by the vaccination-induced potent immune cell responses rather than IgA1 response would be the primary cause of the exacerbation.

PATIENT CONSENT
The patient gave informed consent to publish her case.

CONFLICT OF INTEREST STATEMENT
The authors declare that no conflict of interest exists.

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FIGURE LEGENDS

FIGURE 1: Electron microscopy findings of renal biopsy.

Subendothelial widening with podocyte foot process effacement (arrow heads) but no glomerular capillary deposition.