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Renal side effects of COVID-19 vaccines in patients with immunoglobulin A nephropathy

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Although kidney-related complications are not a common side effect of coronavirus disease-19 (COVID-19) vaccination, complications such as abnormal urinalysis and worsening renal function have recently been reported in patients with underlying chronic glomerulonephritis [1]. Herein we report a case of gross hematuria and exacerbation of proteinuria after COVID-19 vaccination in a patient with known immunoglobulin A nephropathy (IgAN) (Fig. 1).

A 27-year-old female presented with brown-red hematuria 2 days after the second dose of messenger RNA (mRNA) COVID-19 vaccine (Pfizer-BioNTech). Hematuria did not appear after the first dose. Chills and myalgia were felt several hours after vaccination, however, improved quickly within 24 hours of injection. Laboratory findings were as follows: urine blood, 3+; urine red blood cell (RBC), >20/ high power field (HPF); urine protein, 4+; random urine protein-to-creatinine ratio (PCR), 2.295 g/g; and serum creatinine, 0.69 mg/dL. On the 4th day post-vaccine, gross hematuria resolved with conservative treatment. On the tenth day, laboratory findings were as follows: urine blood, 3+; urine RBC, 11–20/HPF; and random urine PCR, 0.541 g/g. The initial IgAN diagnosis (Oxford MEST-C classification as M1-E0-S1-T0-C0) was made 1.5 years before this event during an evaluation for asymptomatic urinalysis with normal kidney function (urine RBC, 11–20/ HPF; urine PCR, 0.543 g/g; and serum creatinine, 0.57 mg/dL). The patient was receiving treatment with losartan 50 mg per day and proteinuria and kidney function were stable (urine PCR, 0.17–0.18 g/g and serum creatinine, 0.65 mg/dL) until this event. Gross hematuria self-resolved without intervention and proteinuria level improved, but proteinuria did not return to baseline and remained higher than usual.

Table 1 summarizes cases that showed renal complications after COVID-19 vaccination in patients with IgAN. We observed some important findings. First, gross hematuria can be the first manifestation of newly diagnosed IgAN in previously healthy patients. Second, IgAN flares can relapse after just single injection; however, de novo IgAN only follows a second injection. Third, the latent period from injection to gross hematuria was short (even within a day) in all cases. Fourth, increased proteinuria and serum creatinine level can accompany gross hematuria. Finally, all cases of gross hematuria occurred in patients who received the mRNA COVID-19 vaccine, not other vaccine types.

The pathogenesis of gross hematuria in IgAN is not fully understood. The present consensus 'multi-hit hypothesis' theoretically explains the pathogenesis as a four-step model: elevation of circulating galactose-deficient IgA1 (Gd-

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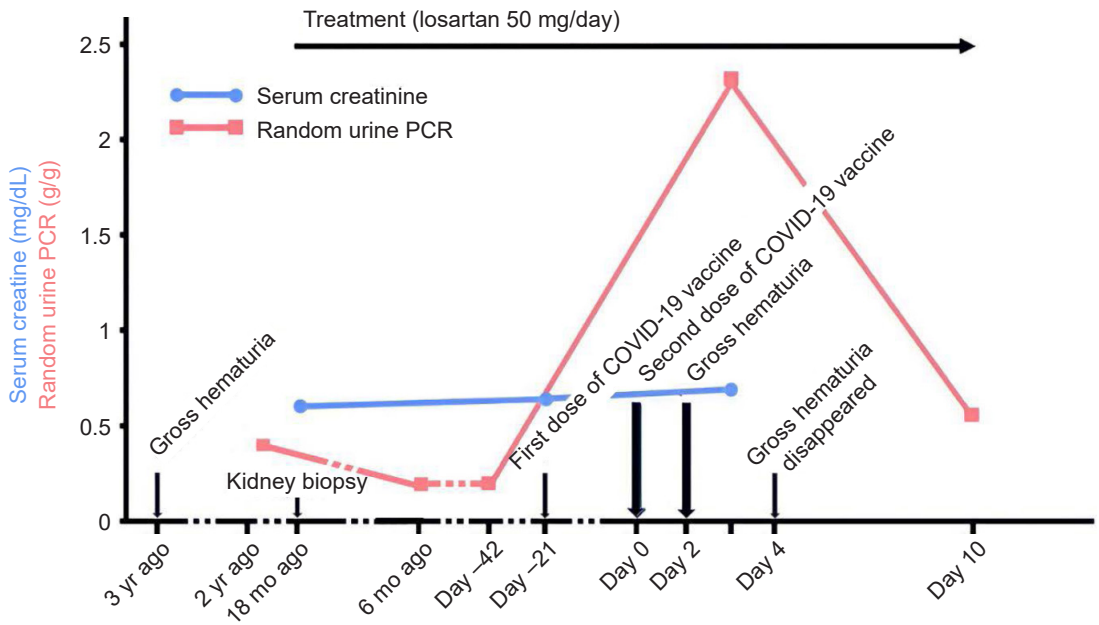

Figure 1. Clinical course of the patient. Immunoglobulin A nephropathy was diagnosed 18 months earlier. Gross hematuria appeared two days after the second messenger RNA coronavirus disease 2019 (COVID-19) vaccine dose with a peak increase in random urine protein-to-creatinine ratio (PCR). Although urine PCR improved quickly, a complete recovery to the previous state was not seen. Serum creatinine levels were stable before and after vaccination.

Table 1. Reported cases of gross hematuria following COVID-19 vaccination in IgAN patients

IgAN	Age (yr)/sex	Vaccine	Dose	Latent period (day)	Systemic sign/ symptom	Initial sign	Duration of gross hematuria	Residual sign	Report[a]
Known	22/male	MO	1st	2	Arthralgia	H, P	ND	No	Perrin et al., 2021
			2nd	2					
Known	41/female	PB	1st	2	Leukocytosis	C	ND	No	Perrin et al., 2021
Known	13/male	PB	2nd	<1	Vomiting	H, C	2 days	No	Hanna et al., 2021
Known	38/female	MO	2nd	1	Fever	H, P	3 days	P	Negrea et al., 2021
Known	38/female	MO	2nd	1	Fever	H	3 days	No	Negrea et al., 2021
Known	52/female	PB	2nd	1	Fever	H, P	5 days	P	Rahim et al., 2021
Known	ND/male	PB	2nd	1	Fever	H, P	3 days	No	Plasse et al., 2021
Known	22/female	MO	2nd	<2	ND	H, P	<1 month	P	Park et al., 2021
Known	39/female	MO	2nd	<2	ND	H, P	<1 month	No	Park et al., 2021
Known	27/female	PB	2nd	2	Pancytopenia	H	ND	No	Perrin et al., 2021
Known	ND/male	PB	2nd	6	Myalgia	H, C, P	ND	C, P	Plasse et al., 2021
Known	78/female	MO	ND	7	Diarrhea	H	15 days	No	Obeid et al., 2021
Known	27/female	PB	2nd	2	Fever	H, P	4 days	No	Presenting case
De novo	39/male	MO	2nd	Immediately	Fever	H, C, P	weeks	H	Anderegg et al., 2021
De novo	17/male	PB	2nd	<1	Hypertension	H, C, P	5 days	C, P	Hanna et al., 2021
De novo	41/female	PB	2nd	1	Myalgia	H, C, P	ND	ND	Tan et al., 2021
De novo	50/male	MO	2nd	1	Rash	H, C, P	<1 month	C, P	Park et al., 2021
De novo	50/female	MO	2nd	2	Fever	H, C, P	5 days	ND	Kudose et al., 2021
De novo	19/male	MO	2nd	2	ND	H, C	2 days	ND	Kudose et al., 2021
De novo	30/male	MO	2nd	1	Fever	H, P	2 days	P	Abramson et al., 2021

C, increased creatinine; COVID-19, coronavirus disease-19; F, female; H, gross hematuria; IgAN, immunoglobulin A nephropathy; M, male; MO, Moderna; ND, no data; P, increased proteinuria; PB, Pfizer-BioNTech.
[a]See the Supplementary material (available online) for the references below.

IgA1) level; production of anti-glycan antibody against Gd-IgA1; formation of an immune complex consisting of Gd-IgA1 and anti-glycan antibody; and, finally, deposition of an immune complex in the glomerular mesangium [2]. However, the role of mRNA COVID-19 vaccines in the pathogenesis of IgAN remains unclear. Considering the short latent period from injection to gross hematuria and the finding that neutralizing antibody does not increase during the 7 days after the first injection in the serum of vaccinated patients [3], it is reasonable to postulate that gross hematuria is not associated with neutralizing antibody, but with more immediate immunologic factors such as cytokines or IgA1 anti-glycan immune responses [4].

There have been reports of other glomerulonephritis (including Henoch-Schönlein purpura) relapse or new diagnosis after viral vector-based COVID-19 vaccines (manufactured by Oxford-AstraZeneca) [1,5–7]; however, all gross hematuria in patients with IgAN were reported only after an mRNA COVID-19 vaccine. The reason for this remains to be elucidated. In viral vector-based COVID-19 vaccines, the gene encoding the spike protein of severe acute respiratory syndrome coronavirus-2 is delivered to host cells by an adenovirus vector [8]. For the preexisting anti-adenovirus antibody that circulates in majority of population and can be cross-reactive with various serotypes of adenovirus, vaccine immunogenicity can be attenuated by preexisting antibody [8]. However, mRNA COVID-19 vaccines use a lipid nanoparticle as delivery vehicle (not adenovirus); therefore, interference from a preexisting antibody is not relevant to immunogenicity [8]. We assume that such differences in vaccine mechanism and immunogenicity may be one potential answer to question of why gross hematuria is reported after only a specific type of vaccine in IgAN patients.

The present case described gross hematuria and exacerbation of proteinuria without acute kidney injury following mRNA COVID-19 vaccine in an IgAN patient. To the best of our knowledge, this is the first such case report in Korea. Our findings suggest the following important points: First, gross hematuria can occur as the first manifestation of de novo IgAN even within a day after mRNA COVID-19 vaccine injection. Second, patients should be warned about the possibility of relapse or de novo IgAN before their first or second dose of mRNA COVID-19 vaccine, respectively. Third, serial assessment of urine protein and PCR for increased proteinuria and serum creatinine should be performed in at-risk patients. Finally, kidney biopsy, if indicated, should be performed to diagnose de novo IgAN. Further study is required to clarify the role of mRNA COVID-19 vaccines in the pathogenesis of IgAN.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Authors' contributions

Conceptualization: JSP, EYL
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