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First Diagnosis of Immunoglobulin A Nephropathy Following SARS-CoV-2 mRNA Vaccination in Japan

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INTRODUCTION

The SARS-CoV-2 mRNA vaccine has been effective against COVID-19.[1,2] However, following mass-scale SARS-CoV-2 mRNA vaccination, several immune-mediated disorders, including newly diagnosed or exacerbated cases of IgA nephropathy (IgAN), have been reported worldwide.[3–6] Majority of the reported IgAN cases associated with SARS-CoV-2 mRNA vaccination show gross hematuria; however, the commonality in the kidney histopathological findings remains uncharacterized. In this study, patients first diagnosed with IgAN by kidney biopsy due to gross hematuria following SARS-CoV-2 mRNA vaccination at 6 medical centers were evaluated. The details of study methods are shown in the Supplementary Methods.[S1-S4]

RESULTS

Clinical characteristics of patients are shown in Supplementary Table S1. Among the 28 eligible patients, the median age was 42 (interquartile range, IQR: 29–50) years and 22 patients (79%) were females. Twenty-one patients (75%) had a medical history of microhematuria and/or proteinuria, and 3 patients (11%) had systemic hypertension. Two patients (7%) had been treated with renin-angiotensin-aldosterone system inhibitors.

All patients had mild to moderate degrees of reactions associated with the SARS-CoV-2 mRNA vaccination, such as fatigue, fevers, or myalgia, and presented with gross hematuria within 2 days of vaccination. Most patients (89%) experienced gross hematuria after the second dose of vaccination. The median duration from the onset to disappearance of gross hematuria was 2 (IQR: 1–3) days. Isolated microhematuria and both microhematuria and proteinuria were identified in 4 cases (14%) and 23 cases (82%), respectively. A mild to modest decrease in estimated glomerular filtration rate was identified in 5 cases (18%). The median serum creatinine and estimated glomerular filtration rate values were 0.69 (IQR: 0.59–0.93) mg/dl and 74 (IQR: 60–90) ml/min per 1.73 m^2, respectively. The median urinary protein-to-creatinine ratio was 0.82 (IQR: 0.36–1.24) g/g creatinine. More than one-half of patients (71%) had microhematuria of ≥50 per high-power field. The median urinary protein excretion at the time of kidney biopsy was 0.27 (IQR: 0.10–0.67) g/d. One month after kidney biopsy, the median estimated glomerular filtration rate increased to 79 (IQR: 62–87) ml/min per 1.73 m^2, and the median urinary protein-to-creatinine

Table 1. Kidney biopsy histopathological findings

Case	Days from GH to biopsy	Number of glomeruli in biopsy specimens	Mesangial hypercellularity	Endocapillary hypercellularity (%)	Global GS (%)	Segmental GS (%)	Adhesion (%)	Crescent (%)			IF/TA (%)	Arteriosclerosis (0-2)	Oxford classification (M/E/S/T/C)	IgG		IgA		IgM		C3		C1q		EDD	
								FC	FCC	CC				Mes	Peri	Mes	Peri	Mes	Peri	Mes	Peri	Mes	Peri	Mes	Peri
1	35	20	Diffuse	0	10	0	15	0	10	0	20	2	1/0/1/0/1	-	-	2+	-	+	-	+	-	-	-	+	-
2	14	18	Focal	0	17	0	0	0	0	0	10	0	0/0/0/0/0	-	-	3+	-	+	-	+	-	-	-	+	-
3	32	21	Diffuse	9.5	19	4.8	4.8	4.8	4.8	0	10	1	1/1/1/0/1	-	-	2+	-	+	-	2+	-	-	-	+	-
4	21	31	Focal	0	3.2	0	3.2	0	6.5	3.2	5	0	0/0/1/0/1	+	-	2+	-	2+	-	2+	-	-	-	+	-
5	65	47	Diffuse	0	6.3	2.1	6.3	2.1	2.1	2.1	20	0	1/0/1/0/1	-	-	2+	-	-	-	2+	-	-	-	+	-
6	16	26	Focal	0	23	0	0	0	0	0	20	0	0/0/0/0/0	-	-	2+	-	±	-	2+	-	-	-	+	-
7	2	26	Focal	0	3.8	3.8	8	0	0	0	10	0	0/0/1/0/0	-	-	2+	-	+	-	2+	-	-	-	+	-
8	20	13	Focal	82	15	18	0	0	0	0	60	2	0/1/1/2/0	-	-	3+	-	+	-	+	-	-	-	+	-
9	84	27	Focal	0	0	0	0	0	0	0	0	0	0/0/0/0/0	-	-	2+	-	-	-	2+	-	±	-	+	-
10	30	17	Diffuse	82	12	5.9	18	0	5.9	0	20	0	1/1/1/0/1	-	-	3+	3+	+	+	2+	2+	-	-	+	+
11	87	37	Focal	0	2.7	0	8.1	0	5.4	0	10	2	0/0/1/0/1	-	-	3+	-	2+	-	+	-	-	-	+	-
12	19	19	Focal	5.3	0	10.5	15.8	5.3	5.3	0	10	0	0/1/1/0/1	-	-	2+	-	+	-	-	-	-	-	+	-
13	31	20	Focal	0	5	5	0	0	0	0	10	2	0/0/1/0/0	-	-	2+	-	-	-	+	-	-	-	+	-
14	64	54	Focal	1.8	3.7	0	3.7	0	1.8	0	10	0	0/1/1/0/1	-	-	2+	-	-	-	2+	-	-	-	+	-
15	32	36	Focal	2.8	2.8	0	0	0	2.8	0	20	0	0/1/0/0/1	-	±	2+	-	-	-	2+	+	-	-	+	-
16	123	14	Focal	0	0	0	0	0	0	0	20	0	0/0/0/0/0	±	-	+	-	±	-	+	-	-	-	+	-
17	30	69	Focal	5.8	15.9	0	0	0	0	0	20	0	0/1/0/0/0	-	-	2+	-	-	-	2+	-	-	-	+	-
18	36	16	Focal	12.5	18.8	0	6.3	0	0	0	10	0	0/1/1/0/0	-	-	2+	-	-	-	2+	-	-	-	+	-
19	36	48	Focal	6.3	20.8	0	4.2	0	0	0	10	0	0/1/1/0/0	-	-	2+	-	-	-	2+	-	-	-	+	-
20	100	60	Focal	1.7	16.7	0	0	0	0	0	10	0	0/1/0/0/0	-	-	2+	-	-	-	2+	-	-	-	+	-
21	82	22	Focal	0	0	0	0	0	0	0	10	0	0/0/0/0/0	±	-	2+	-	+	-	2+	-	-	-	+	-
22	45	70	Focal	0	8.6	0	0	0	0	0	10	0	0/0/0/0/0	-	-	+	-	-	-	+	-	-	-	+	-
23	85	21	Focal	9.5	19	0	0	0	0	0	10	0	0/1/0/0/0	-	-	2+	-	-	-	2+	-	-	-	+	-
24	32	32	Focal	0	3.1	0	3.7	0	0	6.3	10	0	0/0/1/0/1	-	-	2+	-	±	-	+	-	-	-	+	-
25	26	26	Focal	0	7.7	0	0	0	7.7	3.8	10	0	0/0/0/0/1	-	±	2+	+	-	-	+	±	-	-	+	-
26	25	27	Focal	0	0	0	0	0	0	0	10	0	0/0/0/0/0	-	-	2+	+	-	-	+	±	-	-	+	-
27	54	40	Diffuse	0	12.5	0	0	0	0	2.5	25	0	1/0/0/0/1	+	+	2+	+	±	±	+	-	-	-	+	-
28	60	54	Focal	0	7.4	0	3.7	0	0	0	20	0	0/0/1/0/0	-	+	2+	+	-	±	2+	-	-	-	+	-
Mean	46	33		7.8	9.1	1.8	3.6	0.4	1.9	0.6	14.6														
(SD)	(30)	(17)		(21.3)	(7.4)	(4.1)	(5.2)	(1.4)	(2.9)	(1.5)	(10.6)														
No. of cases			5 /28	11 /28	23 /28	7 /28	13 /28	3 /28	10 /28	5 /28		5 /28	5/11/115/1/12 /28	2 /28	2 /28	28 /28	5 /28	10 /28	1 /28	27 /28	2 /28	0 /28	0 /28	28 /28	1 /28

C, cellular and/or fibrocellular crescents score; CC, cellular crescents; E, endocapillary hypercellularity score; EDD, electron dense deposit; F, fibrous; FC, fibrous crescents; FCC, fibrocellular crescents; GH, gross hematuria; GS, glomerulosclerosis; IF/TA, interstitial fibrosis and tubular atrophy; M, mesangial hypercellularity score; Mes, mesangial and/or para-mesangial area; NA, not available; Peri, peripheral area; S, segmental glomerulosclerosis and/or adhesion score; T, interstitial fibrosis and/or tubular atrophy score.

ratio decreased to 0.15 (IQR: 0.065–0.73) g/g creatinine. Isolated microhematuria and both microhematuria and proteinuria persisted in 13 cases (46%) and 13 cases (46%), respectively.

The histopathological findings from kidney biopsies are summarized in Table 1. The mean duration from the onset of gross hematuria until kidney biopsy was 46 ± 30 days. Diffuse mesangial hypercellularity was observed in 5 patients (18%), cellular crescent in 5 patients (18%), fibrocellular crescent in 10 patients (36%), segmental glomerulosclerosis in 7 patients (25%), adhesion in 13 patients (46%), and endocapillary hypercellularity within glomeruli in 11 patients (39%). Overall, 24 patients (86%) presented with chronic glomerular lesions such as global and/or segmental glomerulosclerosis, and 18 patients (64%) presented with acute glomerular lesions such as cellular crescent, fibrocellular crescent, or endocapillary hypercellularity. The Oxford classification scores for mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis and/or adhesion (S), interstitial fibrosis and/or tubular atrophy (T), and cellular and/or fibrocellular crescents (C) (MEST-C) were measured as described previously.[S4] According to the Oxford classification, M1 was observed in 5 patients (18%), E1 in 11 patients (39%), S1 in 15 patients (54%), T2 in 1 patient (4%), and C1 in 12 patients (43%). Immunostaining revealed that IgA deposition was identified in mesangial and/or paramesangial area in all the 28 kidney biopsies, with IgA deposition in glomerular capillary area in 6 kidney biopsies. Of these, C3 deposition was identified in 27 patients (96%), IgG deposition in 3 patients (11%), whereas no C1q depositions were observed. In all 28 cases, electron dense deposition was identified in mesangial and/or paramesangial area by electron microscopy.

To assess the effects on the renal histopathological findings specific to SARS-CoV-2 mRNA vaccination, the Oxford MEST-C scores assigned to the current cases were compared with those of 771 patients with IgAN who were recruited in the Japan IgAN prospective cohort study, a multicenter, cross-sectional study of 44 hospitals in Japan.[7] In the Japan IgAN prospective cohort study, M1 was observed in 246 cases (32%), E1 in 272 cases (35%), S1 in 609 cases (79%), T1 + T2 in 88 cases (11%), and C1 + C2 in 357 cases (46%). There was no significant difference in the Oxford scores between the Japan IgAN prospective cohort study score proportions and those observed in our patients, except our current cases less frequently obtained the S score than those evaluated in the Japan IgAN prospective cohort study (Figure 1).

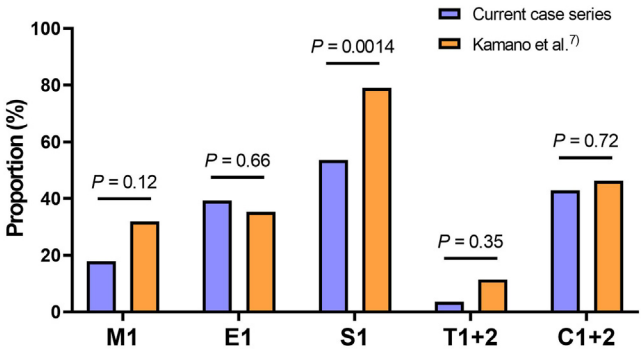

Figure 1. Comparison of Oxford classification scores between our cases and those in Japan IgAN prospective cohort study. There were no significant differences in Oxford scores between the 2 studies, except for the S score, which was less frequent in our cases. M1, mesangial hypercellularity present; E1, endocapillary cellularity present; S1, segmental glomerulosclerosis and/or adhesion present; T1 + T2, interstitial fibrosis and/or tubular atrophy present; C1 + C2, cellular and/or fibrocellular crescents present.

DISCUSSION

Regarding patients with IgAN presenting with gross hematuria following SARS-CoV-2 mRNA vaccination, there was active debate about whether they relapse or present *de novo* onset. Most of the previously reported cases presented with gross hematuria within 3 days following the second dose of vaccination (Supplementary Table S2), and gross hematuria disappeared spontaneously.[3–6,S5–S21] In addition, more than one-half of newly diagnosed IgAN cases were reported to have had medical history of microhematuria and/or proteinuria. These clinical features were consistent with those observed in the current cases. Our cases showing predominant medical history of urinary abnormalities suggests that most patients have undiagnosed latent IgAN, which manifested following SARS-CoV-2 mRNA vaccination.

The distribution of MEST-C Oxford histopathological classification was similar to that identified in a previous large-scale Japanese cohort study of IgAN with a usual diagnostic process, except for the S lesions, which were less frequent in our current case series. The S lesions in IgAN are formed as a resultant scarring secondary to glomerular inflammation and/or podocyte injury.[8] Gross hematuria occurring immediately following vaccination may have motivated the patient to visit the hospital, resulting in an earlier diagnosis of IgAN before the establishment of S lesions. It is noteworthy that patients with S lesions were frequently associated with persistent proteinuria in subgroup analyses of our cases (Supplementary Table S3). Given that persistent proteinuria is a well-established predictor of kidney disease outcomes in IgAN,[9] these results may indicate the significance of

performing kidney biopsy in patients showing gross hematuria following SARS-CoV-2 vaccination.

Immunostaining results showed that IgG deposition might be less frequent in current case series. The glomerular IgG deposition in patients with IgAN was variably reported at a rate of 15% to 45%.[S22–S25] The glomerular IgG deposition rate of 11% in the current case series was significantly lower than that reported in previous studies (Supplementary Table S4). Because of limitations such as the lack of long-term follow-up data, the clinical significance of the low IgG deposition rate in our cases is currently unknown and requires further investigation.

To our knowledge, our study is the first to focus on the histopathological features of patients with IgAN presenting with gross hematuria following SARS-CoV-2 vaccination, which is the largest case series study ever reported. The main limitation is inherent to data collection in retrospective studies with several potential biases, including the variation in the period from the appearance of gross hematuria to kidney biopsy, the selection bias of kidney biopsy indication, and the absence of a comparison group.

In conclusion, the patients presenting with gross hematuria following SARS-CoV-2 mRNA vaccination who were diagnosed with IgAN by a biopsy were characterized by medical history of urinary abnormalities and histopathological observation of both acute and chronic glomerular lesions in the kidney. In addition, histopathological findings of the kidneys in the current cases were similar to those in a large-scale Japanese cohort study of IgAN independently diagnosed from SARS-CoV-2 mRNA vaccination, which suggested that these patients had undiagnosed latent IgAN before the vaccination. Further accumulation of cases and follow-up observation of long-term clinical courses are required to further clarify the IgAN pathogenesis and kidney outcomes associated with SARS-CoV-2 mRNA vaccination.

DISCLOSURE

All the authors declared no competing interests.

AUTHOR CONTRIBUTIONS

Research idea and study design was conceptualized by SY, NT, HU, AS, and MO; data acquisition was done by SY, HU, AS, MO, and RA; data analysis and interpretation was performed by SY, NT, HU, AS, MO, KH, TS, KJ, HSaeki, HSuzuki, and ST; statistical analysis was performed by SY; supervision was done by HSaeki, HSuzuki, YS, and TY. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.

SUPPLEMENTARY MATERIAL

Supplementary File (PDF)

Supplementary Methods.

Supplementary References.

Table S1. Baseline characteristics at presentation following gross hematuria.

Table S2. Reported cases of biopsy-proven IgAN with gross hematuria following SARS-CoV-2 mRNA vaccination.

Table S3. Comparison of clinical and pathological findings between improved proteinuria group and persistent proteinuria group.

Table S4. Comparison of glomerular immunofluorescence findings in IgA nephropathy.

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