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Introduction: mRNA COVID-19 vaccine is more effective than traditional vaccines owing to superior immune activation. Nevertheless, the impact of mRNA COVID-19 vaccine on triggering *de novo*/relapsing glomerulonephritis (GN) is limited. We report a case series of patients who developed new or relapsing GN postvaccination.

Methods: We evaluated baseline characteristics, vaccine type, and clinical outcomes of 13 patients from our institution who had a new diagnosis or relapse of their GN post-mRNA COVID-19 vaccination.

Results: Of 13 patients, 8 patients were newly diagnosed with having GN and 5 patients had relapse. Median age was 62 years (range 19–83 years). Autoimmune disease (38%) was the most prevalent underlying disease followed by cancer (23%). Most patients were White males. IgA nephropathy (IgAN) was the most common GN in our series (5 patients, 38%) followed by membranous nephropathy (MN) (3 patients, 23%). There was 1 patient with IgAN who had evidence of IgA deposits before vaccination suggesting the immune activation after vaccination triggered a flare of the disease. Our case series also included the first case report of tip-variant focal segmental glomerulosclerosis (FSGS), NELL-1–associated MN, and atypical anti–glomerular basement membrane (GBM) nephritis. A total of 77% developed acute kidney injury (AKI) with most being Kidney Disease: Improving Global Outcomes stage 1 (67%). Outcomes are favorable with 80% responding to therapy.

Conclusion: New cases and relapse of GN can present shortly after mRNA COVID-19 vaccination. New cases of IgAN may result from unmasking of undiagnosed IgAN owing to robust immune activation rather than development of new deposits.

Kidney Int Rep (2021) **6**, 2969–2978; https://doi.org/10.1016/j.ekir.2021.09.008 KEYWORDS: COVID-19; glomerulonephritis; IgA nephropathy; minimal change disease; mRNA vaccine; SARS-CoV-2 © 2021 International Society of Nephrology. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

R apid and mass SARS-CoV-2 vaccination has been one of the pivotal strategies to curb the COVID-19 pandemic. The use of recently developed mRNA vaccine, such as BNT162b2 (Pfizer) and mRNA-1273 (Moderna), has provided effective protection against severe COVID-19 infection.^{1,2} mRNA vaccines use lipid nanoparticle as a vehicle to deliver genetically modified mRNA. Once injected, the mRNA is translated into target protein resulting in robust immune response.³ These vaccines thus far have been found to have excellent safety profile, and the most common immediate and short-term side effects for both mRNA vaccines

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have mostly involved injection site reaction. Severe reactions have been rare.^{1,2} Since mass-scale vaccination, however. several immune-mediated reactions. including cases of myocarditis and newly diagnosed or relapsed GN, have been reported.4,5 Most cases have been associated with mRNA vaccines (Pfizer and Moderna) and adenovirus vector deliveries.^{6–14} Nevertheless, rare cases of GN related to inactivated virus vaccine (CoronaVac from Sinovac) have also been reported.¹⁵ The most common reported GN thus far is IgAN. But whether COVID-19 vaccine results in an immune response that triggers IgA antibody (Ab) production and formation of new deposits in the kidneys or whether the immune response to the vaccine only unmasks the presence of previously formed deposits is unclear. In this case series, we report 13 cases of newly diagnosed or flares of GN post-COVID-19 mRNA vaccines and provide a literature review of all the reported

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GN cases thus far. We also provide evidence in 1 case of "new" IgAN wherein the deposits were present previously. We also report on 3 new diagnoses after COVID-19 vaccination, including a case of NELL-1– associated MN, a case of primary FSGS, and a case of atypical anti-GBM nephritis.

METHOD

Patient Selection

Patients who were either newly diagnosed or had a relapse of their GN after vaccination are reported in this case series. All patients had their kidney pathology results reviewed at the Mayo Clinic, Rochester, Minnesota. Clinical data and baseline characteristics, vaccine type, onset of symptoms, laboratories on presentation, treatments, and outcomes are based on review of medical records.

Literature Review

We searched all literature since the inception that reported newly diagnosed or relapse of GN after any type of COVID-19 vaccines through PubMed. We then extracted baseline characteristics, laboratories on presentation, treatments, and outcomes.

Statistical Analysis

We report continuous data with median and range. Categorical data are found with number and percentage. We used descriptive statistics in this report as the sample size is quite small and no analytical statistics were implemented.

RESULTS

Baseline Demographic and Clinical Characteristics of Newly Diagnosed and Relapsed GNs

There were 13 patients reported in this case series. Of these, 8 of 13 cases (62%) were newly diagnosed with having GN whereas 5 of 13 cases (38%) were relapses. The median age was 62 (19-83) years. Most patients were White (12 of 13, 92%) and male (9 of 13, 69%). Autoimmune disease (38%) was the most common comorbidity in our series followed by cancer (23%). The autoimmune diseases included diabetes mellitus type 1, Crohn's disease, ulcerative colitis, primary sclerosing cholangitis, and psoriatic arthritis. IgAN was the most common GN in our case series (5 of 13, 38%). The second most common GNs were MN (3 of 13, 23%) and primary podocytopathy (2 cases of minimal change disease [MCD] and 1 case of primary FSGS) (3 of 13, 23%). In addition, 54% of our patients received mRNA-1273 (Moderna) and the other 46% received BNT162b2 (Pfizer) vaccine. Most

patients presented after the second dose (10 of 13, 77%). The median time of onset varied. Median time of onset in those newly diagnosed with having GN was 1 week after the first dose and 4 weeks after the second dose. In contrast, all of our relapse cases occurred after the second dose with median onset of 3 weeks. AKI, edema, and macroscopic hematuria were common presentations. Median serum creatinine level was 1.6 (0.6–2.5) mg/dl. Baseline clinical characteristics of each patient are found in Table 1.

Clinical Characteristics of Patients With Newly Diagnosed GNs

Of newly diagnosed cases (8 patients), there were 4 cases of IgAN, 1 case of MCD, 1 case of NELL-1-associated MN, 1 case of myeloperoxidase-antineutrophilic cytoplasmic Ab (ANCA) crescentic GN, and 1 case of atypical anti-GBM nephritis. The clinical characteristics of these patients are found in Table 1. There were 5 patients who presented after the second dose of the vaccine (range 2-6 weeks) and 3 patients who presented after the first dose (range 1-2 weeks). The main presenting symptom in patients with new diagnosis of IgAN included AKI and gross hematuria. Furthermore, 1 patient had a symptom of pericarditis in addition to gross hematuria at the time of presentation. There was also 1 patient who had a history of inflammatory bowel disease which raised possibility that he may have had IgA deposits in the kidney before undergoing vaccination and likely had asymptomatic IgAN. This patient also had history of renal cell carcinoma and had undergone partial nephrectomy 7 years before his vaccination. Results of his serum creatinine and urine studies had been normal at the time and in follow-up (last value from 1 year before vaccination). To evaluate for the presence of IgA deposits before vaccination, the nephrectomy sample was retrieved for further evaluation. Glomeruli were unremarkable on light microscopy. Immunofluorescence on pronase-digested, paraffin tissue was performed and revealed segmental mesangial staining of IgA, kappa, and lambda. Electron microscopy revealed presence of mesangial deposits. Therefore, the partial nephrectomy sample revealed evidence of subclinical IgAN. In addition, we had 1 case of atypical anti-GBM nephritis, characterized by bright diffuse linear GBM staining for IgG, kappa, and lambda on immunofluorescence and mesangial proliferation and basement membrane duplication on light microscopy, without the necrotizing and crescentic phenotype typically found in classic anti-GBM nephritis.¹⁶

Table 1. Characteristics of initial presentation of patients with newly diagnosed and relapsed glomerulonephritis post-COVID-19 vaccination

						Onset after				Lat	ooratories dur	ing presentatio	on
Case	Age	Sex	Race	Diagnosis	Vaccine	which dose	Onset time (wk)	Presenting symptoms	Baseline SCr (mg/dl)	SCr (g/dl)	Urine RBC (/HPF)	Urine protein (g/d)	SAIb (g/di)
New	cases												
1	38	М	W	IgAN	Pfizer	2nd	2	Gross hematuria	1.3	1.6	51-100	0.32	NA
2	44	М	W	IgAN + acute interstitial nephritis	Moderna	1 st	2	AKI	1.1	2.5	21–30	14	3.7
3	66	М	W	IgAN	Moderna	1st	2	Gross hematuria	1.1	1.5ª	51-100	1.2	4.1
4	62	М	W	IgAN	Pfizer	2nd	6	AKI	1	2.2	31–40	0.9	4.2
5	77	М	W	Atypical anti-GBM nephritis	Pfizer	1st	1	Hypertension	1	1.8	51-100	1.6	NA
6	83	М	W	MCD + ATN	Moderna	2nd	4	AKI	1.19	2.19	<3	18	2.0
7	50	F	W	NELL-1 MN	Pfizer	2nd	4	Joint pain and proteinuria	0.84	0.7	3–10	6.5	3.5
8	82	F	W	MPO-ANCA	Moderna	2nd	4	AKI, hematuria, proteinuria	0.8	2.5 ^b	3–10	1.2	NA
Rela	osed c	ases											
9	67	F	W	MCD	Moderna	2nd	3	Edema	1	1.6	<3	19	2.5
10	29	F	А	FSGS (tip-variant)	Pfizer	2nd	3	Edema	0.6	0.6	<3	10	2.2
11	39	М	W	PLA2R MN	Pfizer	2nd	1	Edema	0.91	1.13	3–10	8.7	2
12	70	М	W	PLA2R MN	Moderna	2nd	4	Edema	1.7	2.1	<3	16.6	2.7
13	19	М	W	IgAN	Moderna	2nd	1	Gross hematuria	0.96	0.76	11–20	0.61	4.5

A, Asian; AKI, acute kidney injury; ATN, acute tubular necrosis; F, female; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HPF, high high-powered field; IgAN, IgA nephropathy; M, male; MCD, minimal change disease; MN, membranous nephropathy; MPO-ANCA, myeloperoxidase-antineutrophilic cytoplasmic antibody; NA, nonavailable; PLA2R: phospholipase A2 receptor; RBC, red blood cell; SAlb, serum albumin; SCr, serum creatinine; W, White. ^aSerum creatinine peaked at 2.2 mg/dl.

^bSerum creatinine peaked at 3.1 mg/dl.

Clinical Characteristics of Patients With Relapse of GN

Of the 5 patients who had a relapse, 2 patients had underlying phospholipase A2 receptor (PLA2R)-associated MN, 1 patient had relapse of MCD, and 1 patient originally had diagnosis of MCD but underwent a repeat kidney biopsy on relapse which revealed tipvariant lesion of primary FSGS, and 1 patient had underlying IgAN. All cases of relapse occurred after the second dose with onset ranging from 1 to 4 weeks. Detailed clinical characteristics of each patient are found in Table 1.

There was 1 patient with PLA2R-associated MN who was in complete remission with negative PLA2R Ab titer result and on no immunosuppression for 18 months before relapse. On relapse, the patient developed sudden-onset nephrotic syndrome and PLA2R Ab was elevated at 28 IU/ml. Another patient with PLA2Rassociated MN who was in remission for 8 months presented with nephrotic syndrome, and PLA2R Ab titer result was positive at 3 IU/ml on enzyme-linked immunosorbent assay and positive by indirect immunofluorescence (they were both previously negative). The patient with primary FSGS was in complete remission and off immunosuppression for 24 months before relapse and presented with nephrotic syndrome. The patient with MCD was originally diagnosed with having MCD 3 months before vaccination. She went into complete remission within 4 weeks of starting therapy with high-dose steroids with proteinuria down

to 200 mg per 24 hours. As a result, prednisone was tapered to 5 mg daily at which point she received her first dose of the vaccine. Nevertheless, 3 weeks after her second dose, she presented with worsening edema and was noted to have 19 g of protein in 24 hours. The patient with IgAN on last evaluation (2 months before vaccination) had serum creatinine level of 0.96 mg/dl, and urinalysis results revealed 50 to 100 red blood cells per high-powered field with 431 mg of protein per 24 hours. The patient also developed gross hematuria 24 hours after the second dose of COVID-19 vaccination. He had a similar reaction after influenza vaccination a year before.

Treatment and Clinical Follow-Up

Of 13 patients, 9 (69%) received immunosuppression (5 of 8 [63%] had new diagnosis and 4 of 5 [80%] were recurrence). The other 4 patients were treated conservatively. There were 10 patients who have available follow-up data ranging from 1 to 5 months. Of these, 8 patients responded to the treatments (6 treated with immunosuppression and 2 treated conservatively with angiotensin-converting enzyme inhibitor). Patient number 3 who responded to therapy had developed symptoms after the first dose and had further elevation in creatinine after the second dose (peak creatinine 2.2 mg/dl) which then subsequently improved to 1.4 mg/dl. One patient with IgAN and acute interstitial nephritis and the patient with atypical anti-GBM nephritis were both treated with immunosuppressive

Table 2. Treatment and follow-up of patients with newly diagnosed and relapsed glomerulonephritis post-COVID-19 vaccination

								Lap	oratories du	ring last follow	/-up	
Case	Age	Sex	Diagnosis	Vaccine	Treatment	Response	F/U time (mo)	SCr (g/dl)	Urine RBC (/HPF)	Urine protein (g/d)	SAlb (g/dl)	Duration of remission before relapse (m)
New c	ases											
1	38	М	IgAN	Pfizer	Conservative	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	NA
2	44	М	IgAN+ interstitial nephritis	Moderna	High-dose steroid	NR	3	3.6	3–10	5.6	3.8	NA
3	66	М	IgAN	Moderna	Prednisonea	R	5	1.4	3–10	0.3	NA	NA
4	62	М	IgAN	Pfizer	Conservative	R	1.5	2.0	<3	0.2	NA	NA
5	77	М	Atypical anti-GBM	Pfizer	Prednisone + mycophenolate	NR	1.5	2.9	51-100	0.3	4	NA
6	83	М	MCD + ATN	Moderna	High-dose steroid	R	1	1.2	<3	2	2.7	NA
7	50	F	NELL-1 MN	Pfizer	Conservative	R	2	0.7	<3	0.4	4.3	NA
8	82	F	MPO-ANCA	Moderna	${\sf High-dose\ steroid\ +\ rituximab}$	R	1	2.3	NA	NA	NA	NA
Relaps	sed ca	ISes										
9	67	F	MCD	Moderna	${\sf High-dose\ steroid\ +\ rituximab}$	R	2	1.5	0–2	0.07	4.4	1
10	29	F	Primary FSGS	Pfizer	${\it High-dose\ steroid\ +\ tacrolimus}$	R	3.5	0.7	<3	3.7	3.2	24
11	39	М	PLA2R MN	Pfizer	Tacrolimus	R	1	1.1	3–10	5.7	2.9	18
12	70	М	PLA2R MN	Moderna	Obinutuzumab	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	8
13	19	М	IgAN	Moderna	Conservative	Unknown	Unknown	Unknown	Unknown	Unknown	Unknown	6

ATN, acute tubular necrosis; F, female; F/U, follow-up; FSGS, focal segmental glomerulosclerosis; GBM, glomerular basement membrane; HPF, high high-powered field; IgAN, IgA nephropathy; M, male; MCD, minimal change disease; MN, membranous nephropathy; NA, nonapplicable; NR, no response; PLA2R, phospholipase A2 receptor; R, response; RBC, red blood cell; SAlb, serum albumin; SCr, serum creatinine.

^aPrednisone was initiated for treatment of pericarditis.

therapy but have not yet responded and have had progression of their kidney disease. Both of these patients developed symptoms after the first dose of the vaccine but proceeded to receive the second dose. Additional treatment details and outcomes are outlined in Table 2.

Clinical Characteristics of Patients From Published Literatures

We found a total of 20 articles related to COVID-19 vaccines and GN published since inception until July 25, 2021. There were 27 cases including 13 cases of newly diagnosed GNs (48%) and 14 cases of relapse (52%) (Table 3). IgAN was the most common pathology (11 cases [41%]: 4 new and 7 relapse) followed by MCD (10 cases [37%]: 4 new and 6 relapse). Other pathologies include 2 cases of anti-GBM (7%) (both new cases), 2 cases of ANCA vasculitis (7%) (both new cases, 1 case of myeloperoxidase-ANCA and 1 case of proteinase 3-ANCA), 1 case of ANCA-negative granulomatous vasculitis (4%) (relapse), and 1 case of PLA2R-associated MN (4%) (relapse). Median age was 41 years, and 48% were male. Nevertheless, patients tended to be younger in the relapse group (median age 38 years) compared with the newly diagnosed group (median age 56 years) (Table 4).

BNT162b2 (Pfizer) vaccine was the most common vaccine administered (15 of 27 patients, 55%) followed by mRNA-1273 (Moderna) (8 of 27 patients, 30%). There were 3 patients who received AstraZeneca vaccine (11%), and only a single patient who received inactivated vaccine (4%) (CoronaVac by Sinovac) (Table 4).

Of 27 patients, 15 patients (56%) developed symptoms after the first dose whereas the remaining (12 patients, 44%) developed symptoms after the second dose. Nevertheless, patients newly diagnosed with having GN tended to develop symptoms after the second dose (7 of 13 patients, 54%) and those with relapses tended to develop symptoms after the first dose (9 of 14 patients, 64%) (Table 4).

Clinical Characteristics and Follow-Up of Patients by Disease IgA Nephropathy

In our case series, there were 5 cases of IgAN (4 new and 1 relapse). In the literatures, there were 11 cases of IgAN reported (4 new and 7 relapse). Gross hematuria was the most common presentation followed by AKI. Nevertheless, in most patients, gross hematuria was often self-limited and seldom required immunosuppression. Of the total of 16 patients, only 3 patients received immunosuppression and 1 patient had superimposed acute interstitial nephritis as well. All cases of relapsed IgA improved spontaneously within 1 to 2 weeks.

Primary Podocytopathy

In our case series, there were 2 cases of MCD (1 new and 1 relapse) and 1 case that was previously MCD but on repeat biopsy revealed a tip-variant FSGS lesion. In the literatures, there were 10 cases (4 new and 6 relapse). All cases in our series developed symptoms after the second dose, whereas all MCD cases in the literature developed symptoms after the first dose. All patients received immunosuppression. One patient with new MCD responded rapidly to therapy. One

able 3. Summary of published cases of newly diagnosed and relapsed glomerulonephritis	able 3.	Summary	of l	published	cases	of	newly	diagnosed	and	relapsed	glomerulone	ohritis
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Authors	Case	e Age	Sex	Underlying disease	Vaccine	Symptoms	Onset after which dose	Onset	Diagnosis	Treatments	Outcomes
New cases											
Lebedev <i>et al.</i> ¹⁰	1	50	М	No	mRNA (Pfizer)	Nephrotic syndrome, AKI, HTN	1st	D 10	MCD	High-dose steroid	Proteinuria and AKI significantly improved at 2 wks
D'Agati <i>et al.</i> 6	2	77	М	DM type 2	mRNA (Pfizer)	Nephrotic syndrome, AKI, HTN	1st	1 wk	MCD	High-dose steroid	Proteinuria and SCr not improved at 3 wks
Holzworth <i>et al.</i> 7	3	63	F	HTN, tobacco dependence	mRNA (Moderna)	Nephrotic syndrome, uncontrolled HTN	1st	<1 wk	MCD	High-dose steroid	NA
Maas <i>et al.</i> ³⁵	4	80	F	NA	mRNA (Pfizer)	Nephrotic syndrome, HTN	1st	1 wk	MCD	High-dose steroid	Proteinuria reduced from 15 g/d to >0.7 g/d at d 10
Sekar <i>et al.</i> ¹²	5	52	М	HTN	mRNA (Moderna)	Headache, AKI, hematuria	2nd	2 wks	PR3-ANCA vasculitis	RTX (side effects) and then i.v. CyC $+$ steroid was started	Dialysis was started. 2nd dose of i.v. CyC was planned
Shakoor <i>et al.</i> ³⁶	6	78	F	HTN, DM type 2	mRNA (Pfizer)	AKI, hematuria, proteinuria	1 st	2 wks	MPO-ANCA vasculitis	High-dose steroid and RTX	SCr improved from 3.5 to 2.3 mg/dl
Gillion <i>et al.</i> ¹³	7	77	М	No	Adenovirus vector (AstraZeneca)	Fever, night sweat, and AKI	1st	4 wks	ANCA-negative granulomatous vasculitis	High-dose steroid	SCr was normalized at 4 wks
Kudose <i>et al.</i> ³⁷		50 19		HTN, APS Microscopic hematuria	mRNA (Moderna) mRNA (Moderna)	Gross hematuria Gross hematuria	2nd 2nd	D 2 D 2	lgAN IgAN	Conservative Conservative	Hematuria resolved in 5 d Hematuria resolved in 2 d
Tan <i>et al.</i> ³⁸	10 11			GDM Hyperlipidemia	mRNA (Pfizer) mRNA (Pfizer)	Gross hematuria Gross hematuria	2nd 2nd	D 1 D 1	lgAN Anti-GBM	$\begin{array}{l} \mbox{High-dose steroid} + \mbox{IV CyC} \\ \mbox{High-dose steroid} + \mbox{oral CyC} + \mbox{PLEX} \end{array}$	NA NA
Hanna <i>et al.</i> 17	12	17	М	No	mRNA (Pfizer)	Gross hematuria, AKI, proteinuria	2nd	<24 h	IgAN	High-dose steroid	SCr improved (duration not reported)
Sacker <i>et al.</i> ³⁹	13	_	F	No	mRNA (Moderna)	AKI, hematuria, proteinuria	2nd	2 wks	Anti-GBM	High-dose steroid, CyC, PLEX	Remained dialysis dependent
Relapsed cas	es										
Negrea <i>et al.</i> ¹⁸	1	38	F	IgAN in remission	mRNA (Moderna)	Macroscopic hematuria	2nd	8–24 h	IgAN	Conservative	Spontaneously resolved
	2	38	F	IgAN in remission	mRNA (Moderna)	Macroscopic hematuria	2nd	8–24 h	IgAN	Conservative	Spontaneously resolved
Perrin <i>et al.</i> 11	4	22 41 27	F	lgA vasculitis Kidney transplant On hemodialysis	mRNA (Moderna) mRNA (Pfizer) mRNA (Pfizer)	Macroscopic hematuria Macroscopic hematuria Macroscopic hematuria	1st 1st 2nd	D 2 D 2 D 2	IgAN IgAN IgAN	Conservative Conservative Conservative	Spontaneously resolved Spontaneously resolved Spontaneously resolved
Hanna <i>et al.</i> 17	6	13	М	DM type 1	mRNA (Pfizer)	Gross hematuria, AKI	2nd	<24 h	IgAN	Conservative	Hematuria and AKI resolved within 1 wk
Rahim <i>et al.</i> ¹⁹	7	52	F	IgAN treated with ACEi	mRNA (Pfizer)	Gross hematuria, worsening proteinuria	2nd	<24 h	IgAN	Conservative	Hematuria resolved within 1 wk
Schwotzer <i>et al.</i> ⁴⁰	8	22	М	Steroid-dependent MCD	mRNA (Pfizer)	Nephrotic syndrome	1st	D 3	MCD	High-dose steroid + TAC	Remission was achieved at d 17 after treatment
Kervella <i>et al.</i> ⁸	9	34	F	Steroid-dependent MCD	mRNA (Pfizer)	Nephrotic syndrome	1st	D 10	MCD	High-dose steroid	Remission was achieved shortly after treatment
Komaba <i>et al.</i> 9	10	65	М	MCD in remission	mRNA (Pfizer)	Nephrotic syndrome	1st	D 19	MCD	${\ \ High-dose \ steroid + cyclosporine}$	Remission was achieved at 2 wks

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Authors	Case Age Sex	le Sex	Underlying disease	Vaccine	Symptoms	Onset after which dose	Onset	Diagnosis	Treatments	Outcomes
Morlidge et al. ¹⁴	11 30	∑ 0	11 30 M MCD previously freated with RTX, TAC, and prodmissne	Adenovirus vector (AstraZeneca)	Foamy urine	lst	D 2	MCD	High-dose steroid	Remission was achieved at 10 d
	12 40	щ	12 40 F MCD on prednisone and TAC maintenance	Adenovirus vector (AstraZeneca)	Foamy urine	lst	D 2	MCD	High-dose steroid	Remission was achieved at 2 wks
Mancianti <i>et al.</i> ⁴¹	13 39	Ξ 6	13 39 M MCD in remission for 37 yr	mRNA (Pfizer)	Nephrotic syndrome	lst	1 wk	MCD	High-dose steroid	Remission was achieved at 4 wks
Aydin <i>et al.</i>	Aydin <i>et al.</i> ¹⁵ 14 66 F		HTN; DM type 2; MN previously on cyclosporine and steroid but off 7 yr ago	Inactivated virus (Sinovac)	Nephrotic syndrome, AKI	lst	2 wks	PLA2R-associated MN	NA	NA
ACEi, angiot membrane;	ensin angiot GDM, gesta	otensin- tational	ACEI, angiotensin angiotensin-converting enzyme inhibitor: AKI, acute kidney injury; ANCA, membrane: GDM, gestational diabetes; HTN, hypertension; IgAN, IgA nephropathy; M, m	or; AKI, acute kidney inji on; IgAN, IgA nephrop	ury; ANCA, antineutrophil cytol athy; M, male; MCD, minimal	olasmic antibodi: change disease;	es; APS, ai ; MN, mer	ntiphospholipid syndrome; CyC, o mbranous nephropathy; MPO, m	cyclophosphamide; DM, diabetes m nyeloperoxidase; NA, nonapplicable	ACE; angiotensin angiotensin-converting enzyme inhibitor; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibodies; APS, antiphospholipid syndrome; CyC, cyclophosphamide; DM, diabetes mellitus; F, female; GBM, glomerular basement membrane; GDM, gestational diabetes; HTN, hypertension; IgAN, IgA nephropathy; M, male; MCD, minimal change disease; MN, membranous nephropathy; MPO, myeloperoxidase; NA, nonapplicable; PLA2R, phospholipase A2 receptor; PLEX

proteinase 3; RTX, rituximab; SCr, serum creatinine; TAC, tacrolimus plasma exchange; PR3, N Klomjit et al.: COVID-19 Vaccination and Glomerulonephritis

patient with relapse of MCD did not respond to highdose steroids and received rituximab to which the patient responded. The patient with primary FSGS had partial response to prednisone in combination with tacrolimus.

Membranous Nephropathy

In our case series, there were 3 cases of MN in which 2 cases were associated with PLA2R (relapse) and 1 case with NELL-1 (new). The patient with NELL-1-associated MN had age-appropriate cancer screening completed with negative results. On the basis of literature review, there has been 1 case of PLA2R-associated MN after inactivated vaccine. All patients in our series developed nephrotic syndrome after the second dose. The patient with NELL-1-associated MN significantly improved after conservative management. Proteinuria improved from 6.5 g/d to 0.4 g/d within 3 months after angiotensin-converting enzyme inhibitor initiation. Of 2 patients with PLA2R-asociated MN, only 1 patient from our series has follow-up data. The patient was restarted on tacrolimus. At 1 month, proteinuria and serum albumin improved from 8.7 g/d to 5.7 g/d and 2.0 g/dl to 2.9 g/dl, respectively.

Anti-GBM and ANCA–Associated Vasculitis

In our case series, there was 1 case of atypical anti-GBM nephritis. In the literatures, there have been 2 cases of classic anti-GBM nephritis. The patient from our series presented 1 week after the first dose with symptom of uncontrolled hypertension (systolic blood pressure level >200 mm Hg), whereas the other 2 cases from literatures presented within 2 weeks after the second dose. Outcome data were available in 2 patients (one from our series and another from the literature). Our patient did not respond to mycophenolate and highdose steroid, and his serum creatinine level continued to rise. He has now been initiated on cyclophosphamide, but it is too early to know the response. Another patient received cyclophosphamide, plasmapheresis, and high-dose steroid, but the patient did not respond and has remained on dialysis.

We had 1 patient with myeloperoxidase-ANCAassociated vasculitis, and in the literature, there were 2 cases of ANCA-associated vasculitis, one associated with myeloperoxidase and another with proteinase 3. In addition, there was a single case report of ANCAnegative granulomatous vasculitis post adenoviral vector vaccine. Our patient presented with shortness of breath and fatigue 4 weeks after the second dose. The patient was found to have AKI, serum creatinine level of 2.5, with microscopic hematuria and subnephrotic range proteinuria. Subsequently, serum creatinine level increased to 3.1, and a kidney biopsy was done which revealed pauci-immune crescentic GN. The patient was

Table 4. Clinical characteristics of patients with GN post-COVID-19 vaccine from previously published literatures and current case series

Characteristics	Current case series $(n = 13)$	Literatures ($n = 27$)	Total $(n = 40)$
Age (yr)	62 (19–83)	41 (13–80)	50 (13–83)
Male sex, <i>n</i> (%)	9 (69)	13 (48)	22 (55)
Underlying disease, n (%)			
- Autoimmune disease	5 (38)	NA	NA
- Diabetes	2 (15)	NA	NA
- Cancer	3 (23)	NA	NA
New vs. recurrent disease, n (%)			
- New	8 (62)	13 (48)	21 (53)
- Recurrent	5 (38)	14 (52)	19 (47)
Diagnosis, n (%)			
- IgA nephropathy	5 (38)	11 (41)	16 (40)
- Minimal change disease	2 (15)	10 (37)	12 (30)
- Membranous nephropathy	3 (23)	1 (4)	4 (10)
- Anti-GBM disease	1 (8)	2 (7)	3 (7)
- ANCA vasculitis	1 (8)	2 (7)	3 (7)
- Focal segmental glomerulosclerosis	1 (8)	_	1 (3)
- ANCA-negative granulomatous vasculitis	_	1 (4)	1 (3)
Vaccine type, n (%)			
- BNT162b2 (Pfizer)	6 (46)	15 (55)	21 (53)
- mRNA-1273 (Moderna)	7 (54)	8 (30)	15 (37)
- Adenovirus vector (AstraZeneca)	_	3 (11)	3 (7)
- Inactivated vaccine (CoronaVac by Sinovac)	_	1 (4)	1 (3)
Symptoms occur after 1st or 2nd dose, n (%)			
- 1st dose	3 (23)	15 (56)	18 (45)
- 2nd dose	10 (77)	12 (44)	22 (55)
Onset			
- New case s/p 1st dose	1 (1, 2)	1 (1, 4)	1 (1, 4)
- New case s/p 2nd dose	4 (2, 6)	1 (1, 2)	2 (1, 6)
- Relapse case s/p 1st dose	_	1 (1, 2)	1 (1, 2)
- Relapse case s/p 2nd dose	3 (1, 4)	1 (1, 1)	1 (1, 4)
Laboratory on presentation			
- Serum creatinine (mg/dl)	1.6 (0.6, 2.5)	1.7 (0.7, 8.4)	1.7 (0.6, 8.4)
- Serum albumin (g/dl)	3.1 (2, 4.5)	2.7 (0.7, 4.7)	2.9 (0.7, 4.7)
- Hematuria, n (%)	9 (75)	15 (58)	24 (63)
- Urine protein (g/d)	6.5 (0.3, 19)	2.0 (0.3, 23.2)	2.2 (0.3, 23.2)
Treatment, n (%)			
- Conservative management	4 (31)	9 (33)	13 (32)
- Immunosuppression	9 (69)	18 (67)	27 (68)
Outcome, ^a n (%)			
- Response	8 (80)	21 (91)	29 (88)
- Not response	2 (20)	2 (9)	4 (12)

ANCA, antineutrophil cytoplasmic antibodies; GBM, glomerular basement membrane; GN, glomerulonephritis; NA, nonavailable; s/p, status post. ^aThere were only 10 patients in our case series and 23 patients from the literatures with follow-up outcome.

treated with rituximab and high-dose prednisone, and serum creatinine level 1 month post-treatment improved at 2.3 mg/dl. From the literature, patients with myeloperoxidase-ANCA and ANCA-negative granulomatous vasculitis responded to therapy with improvement in serum creatinine. In contrast, the patient with proteinase 3-ANCA-associated vasculitis required initiation of dialysis.

DISCUSSION

Our case series is the largest series to report on both newly diagnosed and relapsed cases of GN post-COVID-19 vaccination. All patients in our series received mRNA vaccines. The BNT162b (Pfizer) and mRNA-1273 (Moderna) are the 2 most widely used vaccines in the United States after their use was approved under emergency use authorization by the US Food and Drug Administration. Most patients in our series developed kidney-related symptoms after the second dose, but the onset of symptoms varied from 1 week after the first dose to 6 weeks after the second dose. Taking into account cases reported in the literature, the onset of symptoms has been reported as early as few hours after the first dose.^{17–19} It is possible that some patients in our series may have had signs of kidney injury (e.g., elevated creatinine, proteinuria, or microscopic hematuria) between the first and second

doses but had not been medically evaluated in that interim. In addition, the 3 patients who had developed symptoms after the first dose proceeded to receive the second dose as their presentations at the time were not attributed to the COVID-19 vaccine. Even though the median age was 62 years, the range varied from 19 to 83 years of age. This wide range of presentation has also been noted in the other recent reports in the literature ranging from 13 to 80 years of age (Table 4).

The mRNA vaccine has been developed and refined for nearly 2 decades, but it was not used clinically until only recently.²⁰ The vaccine contains purified modified mRNA and a vehicle that helps deliver mRNA into host cells.²⁰ After injection, mRNA will be translated into target protein which in turn results in immune system activation. Growing evidence from several large phase 3 randomized controlled trials and real-world data have revealed superiority of mRNA vaccine over inactivated vaccine.^{1,2,21,22} This may be partly due to their ability to induce robust cell-mediated and Ab-mediated immune responses.³ Indeed, they have been found to induce neutralizing Ab to the level far beyond convalescent serum.²³ Moreover, the neutralizing Ab after mRNA vaccine seems to be higher than that of adenoviral vector COVID-19 vaccine.²³ The cellmediated response results from up-regulation of CD4+ and CD8+ T cells accompanied by increasing interferon γ secretion.³ The CD4+ T cell response from mRNA vaccine has been found to confer partial protection to nonancestral strain of SARS-CoV-2 and endemic coronavirus suggesting immune crossover.²⁴ Similarly, another study was found to have crossreactivity of Ab to SARS-CoV-2 spike protein and nucleocapsid to other self-human antigens, such as transglutaminase 3, extractable nuclear antigen, myelin basic protein, mitochondria, α-myosin, thyroid peroxidase, collagen, and claudin.²⁵ Therefore, it is conceivable that this higher immunogenicity and crossreactivity could lead to unexpected and perhaps nonspecific immune activation that may aggravate, unmask, or incite autoimmune processes. Similar to the cases of GN, this immune activation after mRNA COVID-19 vaccination has been associated with cases of myocarditis, particularly in young males.⁵ A detailed investigation in a single patient with myocarditis revealed up-regulated specific natural killer cells but absence of Th17 and certain cytokines that are often associated with myocarditis suggesting underlying host-related factors can play a role in development of autoimmunity.⁴ Indeed, we observed a high prevalence of autoimmune diseases in our series, and it is likely that this underlying immune dysregulation is a risk factor for development of GN or relapse of the disease.

It is noteworthy that many of the reported GNs in association with COVID-19 vaccination have also been noted with the COVID-19 infection itself. Podocytopathy and collapsing glomerulopathy in addition to cases of anti-GBM disease and ANCA–associated vasculitis have all been reported.^{26–29} The pathophysiology of GNs in association with COVID-19 infection is complex and may include direct cytotoxicity to the podocytes in addition to immune dysregulation.^{27,28} It is possible that the immune response to COVID-19 vaccine mimics what happens in response to natural infection thus resulting in GN in susceptible patients.

Relapse of GN after vaccination when there is upregulation of both cell-mediated (e.g., in cases of relapse of MCD)³⁰ and Ab-mediated immunity (e.g., relapse of PLA2R-associated MN) is conceivable. But why do some patients develop new GN? One possibility is that they have underlying immune dysregulation which in turn makes them predisposed to development of GN. As noted previously, 38% of the individuals in our series had altered autoimmunity at baseline. Another possibility is that the disease perhaps was present before the vaccination, but patient was clinically asymptomatic. This may be the case in patients with new IgAN. We were able to reveal for the first time that in at least 1 patient with "new" diagnosis of IgAN, the IgA deposits were indeed present before the vaccination. This patient had a previous partial nephrectomy sample available from 7 years before, and review of this sample confirmed IgA deposits. This case provides proof that in some individuals, the vaccine only results in a "flare" of the already present disease rather than development of new IgA antibodies that are deposited in the kidney. Although we cannot confirm this finding in other cases of IgAN owing to lack of prevaccination kidney specimen, it is likely that cases with earlier onset of symptoms postvaccination have already had IgA deposits. IgAN was the most often noted GN post-COVID-19 vaccination both in our series and based on review of the literature. This finding might be explained by the fact that IgA comprises the major Ab response early after mRNA COVID-19 vaccination.³¹

The development of GN (e.g., IgAN and MCD) after vaccination is not new and has been reported in humans and animal models.^{32–34} It is likely that the mRNA vaccine results in a more potent immune response and therefore associated with a higher rate of GN compared with other types of vaccine (inactivated virus). It is important to also note that this unwanted immune activation occurs in only a very small percentage of vaccinated patients. The exact incidence is unknown as some cases may not have been reported in the literature or may not have been recognized. The

rarity of GNs post–COVID-19 vaccine may be similar to the cases of myocarditis in association with the mRNA vaccines, and thus far, the Centers for Disease Control and Prevention endorses continuation of COVID-19 vaccination owing to benefit over risk profile.⁵

At this point in time, outcome of newly diagnosed and relapsed GNs post-COVID-19 vaccine seems favorable in patients with nephrotic syndrome and IgAN. Most IgAN cases who presented with gross hematuria spontaneously remitted without specific intervention. Approximately 69% of the patients in our case series developed AKI, but most of them developed AKI stage 1. Of the 10 patients with available follow-up data, 8 have responded to therapy (conservative and immunosuppression). One case of IgAN has had a progressive course. This patient, however, also had features of acute interstitial nephritis on his kidney biopsy results which may have contributed to progression of the disease. In contrast, patients with anti-GBM and ANCA-associated vasculitis particularly seem to have fewer desirable outcomes. One patient with atypical anti-GBM nephritis has had progressive disease after treatment with highdose steroids and mycophenolate mofetil. His treatment has been changed to cyclophosphamide, and additional follow-up at this point is not available. None of the patient from our case series required dialysis. Nevertheless, there were 2 patients from the literature including anti-GBM and proteinase 3-ANCA vasculitis who did not respond to therapy and thus required dialysis initiation. Taken together, of 40 reported cases, only 2 patients (5%) have been reported to require dialysis. Longer term follow-up is needed to better understand the trajectory and kidney outcome of these patients.

Our case series has limitations. Even though it is the largest series reported thus far, the sample size is still limited. This is likely in part due to the fact that the incidence is low, but we cannot exclude the possibility that some cases may have been missed. Another limitation is lack of long-term data on these patients. Even though in short-term outcomes seem favorable we need longer term follow-up of these patients. Finally, we cannot prove with certainty that the vaccine resulted in development of new or relapse of the GN, but certainly the temporal association is compelling.

In summary, this case series in combination with cases published thus far in the literature provides data on 40 patients with new and relapsed GN post–mRNA COVID-19 vaccine. As mass vaccination efforts continue, and recognizing the overwhelming benefits of vaccination for individuals with chronic kidney disease who are at increased risk of devastating COVID-19 complications (including death, dialysis, long

COVID-19 infection), nephrologists and other physicians should be aware of this association and remain vigilant when evaluating patients postvaccination especially when there are symptoms of kidney-related injury present.

DISCLOSURE

All the authors declared no competing interests.

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