11-25-2021

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Kidney360

Glomerular Disease in Temporal Association with SARS-CoV-2 Vaccination: A Series of 29 Cases

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Key Points

- This study identified 29 patients with glomerular disease development in close temporal association with SARS-CoV-2 immunization.
- Kidney biopsies showed IgA nephropathy, minimal change disease, membranous nephropathy, crescentic GN, and collapsing GN.
- Patients with de novo collapsing GN in temporal association with SARS-CoV-2 vaccination had two APOL1 genomic risk alleles (high-risk genotype).

Abstract

Background Immune responses to vaccination are a known trigger for a new onset of glomerular disease or disease flare in susceptible individuals. Mass immunization against SARS-CoV-2 in the COVID-19 pandemic provides a unique opportunity to study vaccination-associated autoimmune kidney diseases. In the recent literature, there are several patient reports demonstrating a temporal association of SARS-CoV-2 immunization and kidney diseases.

Methods Here, we present a series of 29 cases of biopsy-proven glomerular disease in patients recently vaccinated against SARS-CoV-2 and identified patients who developed a new onset of IgA nephropathy, minimal change disease, membranous nephropathy, ANCA-associated GN, collapsing glomerulopathy, or diffuse lupus nephritis diagnosed on kidney biopsies postimmunization, as well as recurrent ANCA-associated GN. This included 28 cases of *de novo* GN within native kidney biopsies and one disease flare in an allograft.

Results The patients with collapsing glomerulopathy were of Black descent and had two *APOL1* genomic risk alleles. A brief literature review of patient reports and small series is also provided to include all reported cases to date (n=52). The incidence of induction of glomerular disease in response to SARS-CoV-2 immunization is unknown; however, there was no overall increase in incidence of glomerular disease when compared with the 2 years prior to the COVID-19 pandemic diagnosed on kidney biopsies in our practice.

Conclusions Glomerular disease to vaccination is rare, although it should be monitored as a potential adverse event.

KIDNEY360 2: 1770–1780, 2021. doi: https://doi.org/10.34067/KID.0005372021

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination is considered safe in patients with kidney disease and is prioritized in this population due to increased mortality from coronavirus disease 2019 (COVID-19) (1). However, given the ability to activate the immune system, immunizations carry a risk of exacerbating disease or inducing flares in patients with glomerulonephritides. Prior to the onset of SARS-CoV-2 vaccinations, there were rare reports of immunizations temporally associated with glomerular disease. The incidence of these adverse events is unknown, although is likely exceedingly rare and is primarily described in single patient reports. Minimal change disease (MCD) has been reported in temporal association with influenza, hepatitis B, and tetanus-diphteria-poliomyelitis vaccinations. Additionally, crescentic glomerulonephritis (GN) has been triggered by influenza and pneumococcal immunizations (2).

The mechanism for which vaccines could elicit an autoimmune response resulting in GN is unknown,

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but it potentially could result from molecular mimicry of an antigen with host proteins in individuals with underlying genetic susceptibility or particular HLA haplotypes. Molecular mimicry has been described to induce autoimmune reactions in conjunction with influenza, hepatitis B, and human papillomavirus immunizations (3).

Currently, more individuals are being vaccinated than in any other time period before, and vaccinations include different vectors (nanoparticles or adenoviral-based replication-deficient virions). This worldwide vaccination program for SARS-CoV-2 during the COVID-19 pandemic provides an opportunity to investigate vaccine-related glomerular diseases. Here, we describe 29 cases of glomerular disease temporally associated with SARS-CoV-2 vaccination reviewed at a single center.

Materials and Methods

Patient Selection

Kidney biopsies from patients who developed AKI, nephritic syndrome, or nephrotic syndrome within 1 month of either the first or second dose of SARS-CoV-2 vaccination were included in the study, following approval by the Solutions Institutional Review Board. The guidelines of the Declaration of Helsinki for the protection of human subjects were followed. Native and allograft biopsies, as well as new-onset and recurrent kidney disease, were investigated. All kidney biopsies of patients with SARS-CoV-2 vaccine with close temporal association (within 1 month) to development of kidney disease were included to avoid selection bias. No patients in this study had known prior COVID-19. Kidney biopsies were reviewed at a single center, and clinical information was provided from nephrologists for clinicopathologic correlation.

Clinical Assessment and Follow-Up

Biopsies were reviewed at a single center, and clinical information was obtained (demographics, vaccine type, temporality to symptom onset, laboratory parameters, medical comorbidities, treatments, and follow-up). Clinical parameters included demographics, vaccine type, temporality of vaccine to onset of symptoms, laboratory parameters, medical history, treatments, and clinical follow-up. Patient demographics included age, race/ethnicity (which was physician-ascribed race), and sex. SARS-CoV-2 immunization types were recorded (Pfizer-BioNTech BNT162b2 mRNA, Moderna mRNA-1273, AstraZeneca adenoviral ChAdOx1 nCoV-19, or Johnson & Johnson/Janssen adenoviral JNJ-78436735). Documented medical comorbidities included preexisting chronic kidney disease (CKD; GFR <60 ml/min prior to disease onset), autoimmune disease, hypertension, diabetes, smoking, chronic obstructive pulmonary disease, and obesity. The number of weeks elapsed between the first and second vaccine doses to the time of biopsy and the number of days from vaccination to onset of symptoms were noted. Laboratory values included serum creatinine, proteinuria, hematuria, serologies (antinuclear antibodies, ANCA, hepatitis B, hepatitis C, and HIV), and serum albumin (grams per deciliter). Clinical follow-up parameters included the time interval between biopsy and last follow-up, treatment(s) provided prior to and after biopsy, requirement of kidney replacement therapy (KRT)/dialysis, clinical response, serum creatinine, and proteinuria.

Biopsy Database Comparisons

The frequencies of glomerular diseases during the period of mass vaccination (January 1, 2021–July 1, 2021) were compared with 2 years of biopsies evaluated by our laboratory prior to the pandemic (January 1, 2018–December 31, 2019) through searching a PowerPath kidney biopsy database by natural language searches and/or ICD10 codes. Within our database, the racial distribution includes 48.3% Whites, 15.4% Blacks, 4.7% Hispanics, 2.8% Asians, 1.9% Native Americans, and 27.0% patients of unknown descent (4). This is representative of the kidney biopsy database, although the demographics of each individual clinical practice submitting these biopsies are unknown.

Pathologic Assessment

Histopathologic review included evaluation of light, immunofluorescence, and electron microscopy processed by standard techniques. Light microscopy parameters included mesangial expansion, mesangial hypercellularity, endocapillary hypercellularity, fibrinoid necrosis, crescent formation, segmental sclerosis (including type according to the Columbia classification), and presence/absence of microangiopathic changes within glomeruli. Tubulointerstitial changes evaluated included acute tubular injury, interstitial edema, interstitial inflammation, lymphocytic tubulitis, interstitial fibrosis, and tubular atrophy. Vascular assessment included degree of arteriosclerosis and arteriolar hyalinosis. Immunofluorescence included IgA, IgG, IgM, C3, C1q, albumin, fibrinogen, and κ- and λ-light chain staining for all cases and was graded on a 0–3+ scale. Ultrastructural features recorded included the presence/absence of subepithelial, subendothelial, and mesangial electron dense deposits, as well as the degree of podocyte foot process effacement.

For biopsies with membranous nephropathy (MN), immunostaining for antigenic targets was performed using antibodies against phospholipase A2 receptor (PLA2R; Sigma-Aldrich; catalog no. HPA012657), neural epidermal growth factor like-1 (NELL1; Novus Biologicals; catalog no. H00004745), thrombospondin type 1 domain containing 7A (THSD7A; Atlas Antibodies; catalog no. AMA91234), and exostosin 1 (EXT1; Invitrogen; catalog no. PA5–27958). For all antigens, presence of granular capillary loop staining (1+ or greater) was considered a positive result.

APOL1 Genotyping

Genotyping for APOL1 G1 and G2 risk alleles was performed in patients with collapsing glomerulopathy (CG). Briefly, APOL1 genotyping was performed by nested multiplex PCR to amplify the regions of the APOL1 gene carrying the G1 single nucleotide polymorphism (rs73885319) and the G2 six–base pair insertion/deletion (rs71785313). A ViiA 7 real-time PCR system was used to perform TaqMan PCR. Data were evaluated on ViiA7 sequence detection software. Allelic discrimination plots were used to determine the call results.

Statistical Analyses

Means±SDs were used to compare patients' ages. Other continuous variables were assessed by median±interquartile range (IQR). Frequency data were compared using chi-squared testing with GraphPad Prism software with a cutoff of $P=0.01$ for significance.

Literature Review

All patient reports and series describing glomerular disease in temporal association with SARS-CoV-2 vaccination were included in a review of the literature. PubMed and Google Scholar were used to identify articles, and only those written in the English language were included.

Results

Twenty-nine patients with kidney disease within 1 month of SARS-CoV-2 vaccination were identified; all had glomerular disease. Twenty-eight patients had native kidney biopsy (all of which were *de novo* GN), and there was one case of recurrent disease in a transplant recipient identified on allograft biopsy. Of the 29 patients, 27 received mRNA vaccines (11 Moderna, 12 Pfizer-BioNTech, and four unknown), and two received adenoviral vaccines (one Johnson & Johnson/Jensen and one AstraZeneca). Patients with an unknown vaccine type were vaccinated during a time period where only the Moderna and Pfizer-BioNTech vaccines were available under the Food and Drug Administration's emergency release authorization. Twenty-three patients who had mRNA vaccines received two vaccine doses. There were 12 men and 17 women, with a mean age of 55.2±19.3 years. Twenty patients were White, two were Black, three were Asian, one was Indian, and three were of Hispanic descent. Twenty-two patients had at least one comorbidity, including hypertension ($n=16$), diabetes mellitus ($n=7$), obesity ($n=9$), smoking ($n=2$), chronic obstructive pulmonary disease ($n=4$), autoimmune disease(s) ($n=8$), and CKD ($n=7$).

The most common presentation was AKI with concurrent nephritic or nephrotic syndrome ($n=15$), followed by nephritic syndrome ($n=11$) and nephrotic syndrome with preserved kidney function ($n=3$) (Table 1). A majority of patients had an elevated serum creatinine (median, 2.17±3.455 IQR, 1.195; 4.65), 28 had proteinuria (nephrotic range in 12 patients), 25 had hematuria, and 23 had hypoalbuminemia (of 27 with available data; median, 2.75±1.1 IQR, 2.3; 3.4). Five patients had hypocomplementemia (of 24 with available data). Twelve patients had antinuclear antibodies, and ten had a positive ANCA serology (Table 1). One patient had a positive hepatitis C serology (of 22 patients with data available), and one patient was HIV positive (of 18 patients with available data). There were no patients who were positive for hepatitis B sAg ($n=22$).

Prior to biopsy, six patients received immunosuppression, six had diuretic therapy, and five required dialysis. Three patients had oliguria. At follow-up (median, 20 days ±IQR 43, 13; 56; $n=27$ patients), 22 patients received immunosuppression (most commonly corticosteroids). Eight patients had full recovery of kidney function, with return to baseline creatinine, proteinuria, and albumin levels and absence of blood and protein on urinalysis. Five patients showed partial recovery, with a reduction in serum creatinine but with persistent hematuria and/or proteinuria. Fourteen patients had no improvement in kidney function, and five required dialysis (Table 1).

Biopsy diagnoses included IgA nephropathy (IgAN; $n=10$), MCD ($n=7$), CG ($n=2$), crescentic GN ($n=6$), MN ($n=3$), and diffuse lupus nephritis ($n=1$). One of the patients with CG had concurrent exostosin-positive MN. One patient with MN was positive for PLA2R. The remaining MN cases were negative for PLA2R, THSD7A, NELL1, and EXT. All patients with crescentic GN had a positive ANCA serology (Table 1). Additionally, two patients with IgAN had a positive ANCA, and one of which had crescentic disease. Both patients with CG were of Black descent and were homozygous for *APOL1* high-risk alleles (G1/G1 and G1/G2). Histopathologic features are shown in Table 2.

In three patients, confounding factors were present that could represent additional or alternative antigenic triggers. These included long-term nonsteroidal anti-inflammatory drug use in a patient with MCD, although there was no recent increase or change in nonsteroidal anti-inflammatory drug use prior to vaccination. There was one patient with crescentic GN who had prior hydralazine use, although use was discontinued prior to the time of biopsy. One patient with IgAN had concurrent HIV infection, although IgAN is an unlikely cause of HIV-associated immune complex disease of the kidney.

There was no significant increase in kidney biopsy diagnoses of glomerular diseases during this period of mass vaccination. Although not an epidemiologic study, the frequency of diagnoses during this period (1/1/2021–7/1/2021; $n=11{,}192$ cases) was compared with each diagnosis 2 years prior to the COVID-19 pandemic and SARS-CoV-2 vaccination (1/1/2018–12/31/2019) through searching a biopsy database ($n=36{,}389$ cases). The overall frequencies of these glomerular diseases were not increased during this period of mass vaccination compared with prior to the pandemic for MCD (1.8% versus 2.2%; $P=0.007$), IgAN (7.0% versus 7.2%; $P=0.70$), pauci-immune crescentic GN (4.4% versus 4.4%; $P>0.99$), CG (2.6% versus 2.3%; $P=0.06$), and MN (5.6% versus 5.4%; $P=0.41$). The slight, nonsignificant increase in CG during this time period may be related to COVID-19–associated nephropathy cases (5). The true incidence of glomerular disease is unknown, as this is from a single center, and not all patients with glomerular disease (particularly those with recurrence) would undergo kidney biopsy.

Discussion

In the recent literature, multiple cases of kidney disease temporally related to SARS-CoV-2 vaccination have been reported ($n=52$ patients), including IgAN ($n=20$) (6–16), MCD ($n=17$) (17–30), ANCA-associated pauci-immune crescentic GN ($n=5$) (31–34), antiglomerular basement membrane antibody disease ($n=2$) (6,35), MN ($n=3$; of which one was PLA2R positive and one was THSD7A positive) (36–38), membranous lupus nephritis ($n=1$) (39), IgG4-related kidney disease ($n=1$) (40), granulomatous interstitial nephritis ($n=1$) (41), thrombotic microangiopathy with

Table 1. Clinical and laboratory features of patients with severe acute respiratory syndrome coronavirus 2 vaccine–associated glomerular disease

Patient Number	Age, yr	Sex	Race	Vaccine Type	1st/2nd Dose[a]	Time	Indication	Diagnosis	Creatinine	Proteinuria	Albumin	Hematuria	Antinuclear Antibodies	ANCA	Treatment before Biopsy	Treatment after Biopsy	Follow-Up	Recovery	Follow-Up Creatinine	Follow-Up Proteinuria
1	67	F	B	Moderna	7 wk/3 wk	<1 wk	AKI, n.s.	CG	6.7	12	2.7	Pos	Neg	Neg	D	D; IS 1	12 wk	Partial	1.8	2.5
2	26	F	B	Moderna	5 wk/1 wk	<1 wk	AKI, n.s.	CG, MN	7.7	6	2.4	Pos	Pos	Neg	D; IS 1+IS 2	D; IS 3	1 wk	No	D*	D*
3	70	F	W	Pfizer	7 wk/3 wk	<1 wk	AKI, n.s.	MCD	2.2	19.2	1.5	Neg	Neg	ND	Diur	IS 1	4 wk	Yes	1	Neg
4	43	F	Indian	Pfizer	11 wk/7 wk	2 wk	n.s.	MCD	Unk	10	1.9	Neg	Neg	Neg	None	IS 1	4 wk	Yes	<1	Neg
5	79	M	Asian	mRNA[a]	2 wk	<2 wk	AKI, n.s.	MCD	2.1	4+	Low	Pos	Pos	Neg	IS 1; Diur	IS 1	4 wk	No	2.5	UA 3+
6	72	M	W	Moderna	9 wk/5 wk	1 wk	n.s.	MCD	0.7	16.1	2.7	Pos	Pos	Neg	Diur; ARB	IS 1, ACEI	2 wk	Yes	0.9	UA Pos
7	47	F	W	Pfizer	5 wk/1 wk	<2 wk	AKI, n.s.	MCD	6.1	>600 mg/dl	1.9	Neg	Neg	Neg	D	D; IS 1; ACEI	4 wk	No	4.3; D*	UA Pos; D*
8	23	M	W	AstraZeneca	2 wk	2 wk	AKI, n.s.	MCD	2.9	14	1.7	Pos	Pos	Neg	None	IS 1; Diur	3 wk	Yes	1.0	0.07
9	45	F	W	Moderna	<2 wk	<2 wk	n.s.	MCD	0.86	6	2.8	Pos	Neg	Neg	Diur	IS 1	NA	NA	NA	NA
10	33	F	W	Pfizer	4 wk/<1 wk	2 d	Nephritic	IgA N	1.1	0.6	4.0	Pos	Neg	Neg	None	None	None[a]	Unk	WNL	Unk
11	52	F	W	mRNA[a]	5 wk/2 wk	1 d, both	Hem	IgA N	1.7	0	ND	Pos	Neg	Neg	None	None	6 wk	Yes	<1	Neg
12	37	F	W	mRNA[a]	5 wk/<2 wk	12 d	Nephritic	IgA N	1.4	3.5	3.1	Pos	Neg	Neg	None	IS 1; ACEI	7 wk	No	Unk	UA Pos
13	35	M	W	Pfizer	6 wk/3 wk	1 d	Nephritic	IgA N	1.4	>300 mg/dl	4.2	Pos	Neg	Neg	ARB	IS 1; ARB	2 wk	No	Unk	Unk
14	72	F	Hisp	Pfizer	10 wk/7 wk	2 d	AKI, nephritic	IgA N	4.9	0.6	ND	Pos	Neg	Pos	IS 1	IS 1; IS 5	2 wk	No	4	UA Pos
15	57	M	W	Moderna	4 wk/ 3d	1 d	AKI, CKD, nephritic	IgA N	6.2	3+	2.5	Pos	Neg	Neg	Diur	IS 1; IS 5	4 wk	No	8; D*	Pos; D*
16	30	M	W	Pfizer	4 wk/<1 wk	1 d	Nephritic	IgA N	1.1	2	4.2	Pos	Neg	Neg	None	None	2 wk	Yes	1.1	UA Pos
17	40	F	W	Moderna	4 mo/3 mo	<1 wk	Nephritic	IgA N	1.3	30 mg/dl	3.4	Pos	Pos	Pos	None	ARB	2 wk	No	Unk	Unk
18	73	M	W	Pfizer	3 mo/2 mo	2 wk	AKI, nephritic	IgA N, AIN	3.4	0.5	1.9	Pos	Pos	Neg	None	IS 1	2.5 wk	Partial	1	2.4
19	66	M	Hisp	mRNA[a]	6 wk/3 wk	3 d	AKI, nephritic	IgA N, DN	9.77	3.3	2.4	Pos	Neg	Neg	D	D	4 mo	No	D*	D*
20	76	M	W	Pfizer	7 wk/<3 wk	11 d	AKI, nephritic	Cres GN	8.6	2+	2.3	Pos	Pos	Pos	D	D, IS 1, IS 4	3 wk	No	5.8	Unk
21	81	F	W	Pfizer	6 wk/3 wk	2 d	AKI, nephritic	Cres GN	3.1	1.8	3.4	Pos	Pos	Pos	None	IS 4, ARB	3 wk	No	2.2	2.3
22	76	F	W	Moderna	<1 wk	5 d	AKI, nephritic	Cres GN	3.0	2	3.1	Pos	Pos	Pos	IS 1	IS 1, IS 4	5 wk	Partial	1.1	2+
23	71	F	W	Moderna	4 mo/3 mo	2 wk	Nephritic	Cres GN	1.3	2.1	3.3	Pos	Pos	Pos	IS 1	IS 1, IS 4	1 wk	No	NA	NA
24	65	F	W	Pfizer	4 mo/3 mo	2 wk	AKI, nephritic	Cres GN	3.29	2.07	2.2	Pos	Neg	Pos	None	IS 1, IS 5	2 wk	No	4.83	2.9
25	79	F	W	Moderna	8 wk/5 wk	3 wk	Nephritic	Cres GN (recur)	1.12	20 mg/dl	4.0	Pos	Neg	Pos	IS 1, IS 3, IS 6	IS 4	4 mo	Yes	0.82	None
26	54	M	Asian	Moderna	12 wk/9 wk	1 d	Nephritic	MN	1.3	3+	3.4	Pos	Pos	Pos	None	IS 1, IS 4	8 wk	No	0.86	3.5
27	68	M	W	J+J	4 wk	< 4 wk	AKI, CKD, nephritic	MN	3.3	0.6	3.2	Neg	ND	Neg	Diur	Diur	3 wk	Partial	2.74	0.38
28	47	M	Asian	Moderna	8 wk/5 wk	6 d	Nephritic	MN	0.7	2.7	2.3	Pos	ND	Neg	None	None	2 wk	Partial	0.7	2.7
29	16	F	Hisp	Pfizer	4 wk	2 d	Nephritic	Diffuse LN	0.7	0.8	3	Pos	Pos	Pos	None	IS 1	2 wk	Yes	0.48	0.53

F, woman; B, Black; n.s., nephrotic syndrome; CG, collapsing glomerulopathy; Pos, positive; Neg, negative; D, dialysis; I.S. 1, immunosuppression 1: steroid therapy (methylprednisolone or high-dose prednisone); MN, membranous nephropathy; I.S. 2, immunosuppression 2: plasmapheresis; I.S. 3, immunosuppression 3: mycophenolate mofetil; D*, measurement unknown or inaccurate due to patient on dialysis (creatinine and/or proteinuria value unreliable); W, White; MCD, minimal change disease; ND, not done; Diur, diuretics; Unk, unknown; M, man; UA, urinalysis; ARB, angiotensin receptor blocker; ACEI, angiotensin-converting enzyme inhibitor; NA, not applicable; IgA N, IgA nephropathy; WNL, within normal limits; Hem, hematuria; Hisp, Hispanic; I.S. 5, immunosuppression 5 (cyclophosphamide); AIN, acute interstitial nephritis; DN, diabetic nephropathy; Cres GN, crescentic GN; I.S. 4, immunosuppression 4 (rituximab); I.S. 6, immunosuppression 6 (calcineurin inhibitor); J+J, Johnson & Johnson; LN, lupus nephritis.

[a]Patient 10 had no impairment of kidney function, where clinical follow-up would not be required for months.

Table 2. Histopathology of severe acute respiratory syndrome coronavirus 2 vaccine–related glomerular disease biopsies

Patient Number	Diagnosis	Global Glomerulosclerosis	Mesangial Matrix Expansion	Mesangial Hyper-cellularity	Endocapillary Hyper-cellularity	Necrosis	Crescents	Segmental Sclerosis	Acute Tubular Injury	Interstitial Fibrosis/ Tubular Atrophy	Arterio-sclerosis	Arteriolar Hyalinosis	Immunofluorescence	Mesangial Deposits	Subend-othelial Deposits	Subepi-thelial Deposits	Foot Process Effacement
1	CG	0/24	No	No	No	No	No	Yes	Yes	Mild	No	No	No staining	No	No	No	Severe
2	CG, MN	0/45	No	No	No	No	No	Yes	Yes	Mild	Mild	No	3+IgG and C3, gr cap loop	Yes	No	Yes	Severe
3	MCD	1/31	No	No	No	No	No	No	Yes	None	No	No	No staining	No	No	No	Severe
4	MCD	0/35	No	No	No	No	No	No	Yes	Mild	Mod	Mild	No staining	No	No	No	Severe
5	MCD	3/33	Yes	No	No	No	No	No	Yes	Mild	Mod	No	No staining	No	No	No	Severe
6	MCD	0/20	Yes	Yes	No	No	No	No	No	No	No	No	No staining	No	No	No	Severe
7	MCD	6/30	No	No	No	No	No	No	Yes	No	Mod	Mild	No staining	No	No	No	Severe
8	MCD	0/40	No	No	No	No	No	No	Yes	No	No	No	No staining	No	No	No	Severe
9	MCD	0/60	No	No	No	No	No	No	No	No	No	No	No staining	No	No	No	Severe
10	IgA N	1/29	Yes	Yes	Yes	No	No	Yes	No	No	No	No	3+IgA and C3 gr mes	Yes	Yes	No	None
11	IgA N	3/27	No	No	No	No	No	No	No	No	No	No	3+IgA gr mes	Yes	No	No	Mild.
12	IgA N	1/16	Yes	Yes	Yes	No	No	No	Yes	No	Mild	Mild	3+IgA+C3, 1+IgG gr mes	Yes	No	Yes	Mod
13	IgA N	0/86	Yes	Yes	No	No	Yes	No	Yes	No	No	No	3+IgA gr mes	Yes	No	No	Mod
14	IgA N	10/40	Yes	Yes	No	Yes	Yes	Yes	Yes	Mod	Mod	Mild	2+IgA+IgM, 3+C3, trace IgG gr mes	No	No	No	Mild
15	IgA N	23/52	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Severe	Mod	2+IgA, 1+C3 gr mes	Yes	No	No	Mod
16	IgA N	2/50	Yes	Yes	No	No	No	Yes	Yes	Mild	Mod	No	3+IgA, 2+IgG, 3+C3 gr mes	Yes	Yes	Yes	Mild
17	IgA N	6/19	Yes	No	No	No	No	No	Yes	Mild	Mod	No	3+IgA, trace IgG, 2+C3 gr mes	Yes	No	No	Mod
18	IgA N, AIN	1/13	Yes	No	No	No	No	No	Yes	No	N/A	Mild	3+IgA, 1+IgG, 2+IgM, trace C3 gr mes	Yes	No	No	Mod
19	IgA N, DN	35/46	Yes	Yes	No	No	No	Yes	No	Severe	Severe	Severe	1+IgA, 1+IgG, 1+IgM gr mes	No	No	No	Mod
20	Cres GN	1/24	No	No	No	Yes	Yes	No	No	Mild	Severe	No	2+IgA, 1+C3 gr mes	No	No	No	Severe
21	Cres GN	4/13	Yes	No	No	No	Yes	Yes	Yes	Mild	Severe	Mild	1+IgM, trace C3 gr mes	No	No	No	Mild
22	Cres GN	9/36	No	No	No	Yes	Yes	No	Yes	Mild	Severe	Mod	3+C3 gr mes	Yes	No	No	Severe
23	Cres GN	20/29	No	No	No	No	No	No	Yes	Mod	Severe	No	3+IgM, 1+C3 gr mes	Yes	No	No	Mod
24	Cres GN	5/30	No	No	No	Yes	Yes	No	Yes	Mod	N/A	No	1+IgG, 1+C3 gr cap loop	N/A	N/A	N/A	N/A
25	Cres GN	13/51	No	No	No	Yes	Yes	Yes	Yes	Mild	No	No	No staining	No	No	No	None
26	MN	3/15	No	No	No	No	Yes	Yes	Yes	No	No	Mod	3+IgG, 2+C3 gr cap loop	Yes	No	Yes	Severe
27	MN	20/29	No	No	No	No	No	Yes	Yes	Mild	Severe	No	2+IgG, 2+IgM gr cap loop	No	No	Yes	Severe
28	MN	1/39	No	No	No	No	No	No	No	Mild	No	No	3+IgG, 2+C3 gr cap loop	No	No	Yes	Severe
29	Diffuse LN	0/55	Yes	Yes	Yes	No	No	No	No	No	No	No	3+IgA, 3+IgG, 3+IgM, 3+C3, 3+C1q gr mes +gr cap loop	Yes	No	Yes	Mod

CG, collapsing glomerulopathy; MN, membranous nephropathy; gr cap loop, granular capillary loop; MCD, minimal change disease; Mod, moderate; IgA N, IgA nephropathy; gr mes, granular mesangial; AIN, acute interstitial nephritis; N/A, not applicable; DN, diabetic nephropathy; Cres GN, crescentic GN; LN, lupus nephritis.

sclerodermal renal crisis ($n=1$) (42), and T cell–mediated allograft rejection ($n=1$) (43) (Table 3). These reports included 27 cases of new-onset glomerular disease, with the remainder being relapses of patients with prior biopsy-proven GN (Table 3). Although we identified many of the same pathologic findings, unique to our series are cases of CG and proliferative lupus nephritis. Of note, there were no patients of African descent reported with vaccine-related glomerular disease in the literature, although race was not mentioned for all patients; only 12 of 52 patients had race mentioned, of which ten were White and two were of Asian descent. Although allograft rejection was reported in association with SARS-CoV-2 vaccination, we did not identify any cases of rejection at our institution.

Both mRNA and adenoviral vaccines have been associated with induction of glomerular disease in patients vaccinated against SARS-CoV-2. Although the vector varies (lipid nanoparticles versus replication-deficient adenovirus), the antigenic target is common between these—the SARS-CoV-2 spike protein. The mechanism for this phenomenon is unknown but potentially, could result from molecular mimicry of the spike protein with host peptides.

The most common disease manifestation in our series and in the literature is IgAN (44). An IgA immune response against SARS-CoV-2 spike protein (45) could trigger IgAN in patients who produce galactose-deficient IgA antibodies, as previously reported with influenza vaccine (46). In a study of 89 patients with IgAN who received at least one dose of SARS-CoV-2 vaccine, no patients had gross hematuria or impaired kidney function at follow-up (47). In 29 patients examined in a shorter time interval (mean=11 days), two patients had a mild increase in serum creatinine with mild hematuria and proteinuria. This suggests that although IgA flare is possible, the incidence is <10% of individuals who had self-resolved in this series (47).

CG, although a common cause of AKI in COVID-19, has not been previously described in the setting of vaccination. CG is well described in association with COVID-19 infection, in which the pathogenesis is thought to be related the inflammatory response against the virus acting as a "second hit" to *APOL1* risk alleles (48) rather than resulting from direct viral infection of the renal parenchyma. Likewise, the immune response to the SARS-CoV-2 spike protein from immunization may induce a similar "second hit" in susceptible individuals. Similarly, in patients with lupus, the immune response to COVID-19 disease or vaccination could be a trigger for disease flares (49).

Limitations

Given that there is only a temporal relationship between the onset of symptoms and vaccination, causality is unclear. It is possible that immunization did not trigger the onset of glomerular disease within all of these patients. The study was restricted to patients developing glomerular disease within 1 month of SARS-CoV-2 vaccination and did not compare with other time frames. This 1-month cutoff, although arbitrary, is similar to that of cases reported in the literature (Table 2).

Although there was no overall increase in glomerular disease diagnosed on biopsies during the time of mass SARS-CoV-2 vaccinations in our practice, there was no control group for comparison for a patient-control design, and we did not conduct an epidemiologic study. We are thus unable to determine the frequency of glomerular injury after vaccination. Further data are required to determine the true risk of induction or flare of glomerular disease in response to SARS-CoV-2 vaccination.

Conclusion

The current mass vaccination against the SARS-CoV-2 virus provides the ability to observe the association of glomerular disease with vaccination. Although there are cases of glomerular disease in temporal association with vaccination, we do not know the true incidence or prevalence of disease. Within clinical trials, patients who were immunosuppressed (including those with glomerular disease) were excluded. This results in a lack of safety and efficacy data for SARS-CoV-2 vaccines within this population (50). As patients with kidney disease have an increased risk of morbidity and mortality from COVID-19, it is a priority to immunize these individuals against SARS-CoV-2. Additionally, as poorer immune responses are generated in response to vaccination, more potent vaccines (*i.e.*, mRNA) and booster doses are recommended (1). Further data are required to determine the incidence of glomerular disease induction or recurrence in response to vaccination, response to therapy, and long-term clinical outcomes. To examine this, a registry has been created at the National Institutes of Health/National Institute of Diabetes and Digestive and Kidney Diseases to examine these outcomes (International Registry of COVID infection in Glomerulonephritis-2). We suggest that new-onset or recurrent glomerular disease should be monitored as a potential adverse event.

Disclosures

J.T. Henry reports ownership interest in Fort Smith Regional Dialysis. G. Schlessinger reports consultancy agreements with Medtronic and ownership interest in US Renal Care. Z. Karam reports honoraria from Spherix. R.M. Seipp reports honoraria from M3 Global Research and Spherix Global Insights. P.D. Walker reports consultancy agreements with Apellis and Travere and honoraria from Apellis and Travere. All remaining authors have nothing to disclose.

Funding

None.

Acknowledgments

A portion of this work was accepted as an abstract at the 2021 American Society of Nephrology annual meeting held virtually on November 4, 2021.

Author Contributions

T.N. Caza, C.P. Larsen, N. Messias, and P.D. Walker conceptualized the study; H. Amin, S.Y. Bae, E.J. Betchick, J. Brandt, C.A. Cassol, T.N. Caza, K.K. Chouhan, M.J. Diamond, J. Edwu-okwuwa, E.B. Elashi, S.L. Fabian, J.A. Flaxenburg, A. Frome, M. Haderlie, A. Hannoudi, R.S. Haun, J.T. Henry, E.T. Hoerschgen, B. Iqbal, Z. Karam, S. Khalillullah, E.H. Kim, C.P. Larsen, R.M. May, N. Messias, G. Schlessinger, M. Seek, R.M. Seipp, G. Shenoy, E. Ulozas, I. Vancea, P.D. Walker, J.L. Weatherspoon, and M.S. Ziadie were

Table 3. Severe acute respiratory syndrome coronavirus 2 vaccine–associated glomerular disease cases reported in the literature

Patient Number	*N*	Diagnosis	Age, yr	Sex	Type	1st/2nd	Time	Indication	Serum Creatinine	Proteinuria	Hematuria	Serum Albumin	Antinuclear Antibodies	ANCA	Treatment	Follow-Up	Recovery	Follow-Up Creatinine
6 (new)	2	IgAN; anti-GBM	41; 60	F; F	Pfi; Toz	2nd	1 d	Nephritic; AKI+n.s.	1.73; 6.12	2.03; 7.58	Yes; Yes	Unk	Pos; Neg	Unk	I.S. 1+I.S. 5; I.S. 1+I.S. 2	NA	NA	NA
7 (new)	2	IgAN; Cres GN	39; 81	M; M	Mod	1st	Unk	Nephritic; AKI	Inc; Inc	Pos; Pos	Yes	Unk	Unk	Unk; Pos	I.S. 1+I.S. 5; I.S. 1+I.S. 2+I.S. 5	NA	No; Yes	Unk
8 (recur)	3	IgAN	22; 41; 27	M; F; F	Mod; Pfi; Pfi	1st; 2nd; 2nd	2 d	Nephritic	Unk	0.34; 0.47; 1.9	Yes	Unk	Unk	Unk	I.S. 1+RAASi; I.S. 1+I.S. 3+I.S. 6; I.S. 1+I.S. 3+I.S. 6	Unk	Yes; Yes; Yes	Unk
9 (new)	2	IgAN	50; 19	F; M	Mod	2nd	2 d	Nephritic	1.7; 2.1	2.0; None	Yes	Unk	Neg; Unk	Neg; Unk	None	5 d; 2 d	Yes; Yes	Unk
10 (1 new, 1 recur)	2	IgAN	13; 17	M; M	Pfi	2nd	1 d	AKI+ nephritic	1.31; 1.78	1.1; 1.8	Yes; Yes	3.4; 3.8	Unk	Unk	ACEI; I.S. 1	1 wk; Unk	Yes; No	Unk
11 (recur)	2	IgAN	38	F; F	Mod	2nd	1 d	Nephritic	Unk	0.82; 0.59	Yes; Yes	Unk	Unk	Unk	None	21 d	Yes	Unk
12 (recur)	1	IgAN	52	F	Pfi	2nd	1 d	Nephritic	Unk	2.4	Yes	Unk	Unk	Unk	Unk	1 wk	Partial	Unk
13 (recur)	4	IgAN	22; 39; 50; 67	F; F; M; M	Mod; Mod; Mod; Mod	2nd	2 d; 2 d; 1 d; 4 wk	Nephritic	Unk; Unk; Unk; Unk	0.4; 0.9; 3.56; 2.10	Yes; Yes; Yes; Yes	Unk	Unk	Unk	None; None; RAASi; I.S. 1	4 wk; 4 wk; 4 wk; 4 wk	Yes; Yes; Yes; Yes	Unk; Unk; Unk; Unk
14 (new)	1	IgAN	30	M	Pfi	2nd	1 d	Nephritic	1.02	4+	Yes	Unk	Neg	Neg	RAASi	6 wk	Partial	1.03
15 (recur)	1	IgAN	78	F	Mod	1st	7 d	Nephritic	1.18	Unk	Yes	Unk	Neg	Neg	I.S. 1	Unk	Yes	Unk
16 (recur)	2	IgAN	Unk	Unk	Pfi	2nd	5 d	AKI+nephritic	3.53; 1.16	4.97;0.61	Yes	Unk	Unk	Unk	I.S. 1	2 mo	Yes	Unk
17 (new)	1	MCD	77	M	Pfi	1st	7 d	n.s.	2.33	4+	Unk	3.0	Unk	Unk	I.S. 1	21 d	No	3.74
18 (new)	1	MCD	50	M	Pfi	1st	4 d	AKI+n.s.	2.31	6.9	Unk	1.93	Neg	Neg	I.S. 1	17 d	Yes	0.97
19 (recur)	1	MCD	34	F	Pfi	1st	10 d	n.s.	Unk	2.4	Unk	Unk	Unk	Unk	I.S. 1	Unk	Partial	Unk
20 (recur)	2	MCD	30; 40	M; F	AZ	1st	2 d; 1 d	Nephritic; n.s.	0.931.19	0.21; 3+	Unk	4.7; Unk	Unk	Unk	I.S. 1; I.S. 1+I.S. 6	10 d; 14 d	Yes; Yes	Unk
21 (new)	1	MCD	63	F	Pfi	1st	7 d	n.s.	1.48	3+	Yes	0.7	Unk	Unk	ARB; I.S. 1	Unk	Unk	Unk
22 (new)	1	MCD	80s	M	Pfi	1st	7 d	n.s.	1.43	15.3	Unk	1.0	Unk	Unk	I.S. 1	10 d	Yes	Unk
23 (recur)	1	MCD	60s	M	Pfi	1st	8 d	n.s.	0.99	11.5	Unk	2.8	Unk	Unk	I.S. 1+I.S. 6	14 d	Yes	Unk
24 (recur)	1	MCD	22	M	Pfi	1st	3 d	n.s.	0.8	3+	Unk	2.3	Unk	Unk	I.S. 1+I.S. 6	17 d	Yes	Unk
25 (recur)	1	MCD	39	M	Pfi	1st	3 d	AKI+n.s.	1.8	8	Unk	2.7	Unk	Unk	I.S. 1	4 wk	Yes	Unk
26 (new)	1	MCD	61	F	Pfi	1st	8 d	n.s.	1.47	12	Unk	2.1	Neg	Neg	D; I.S. 1	21 d	Partial	Unk
27 (1 new, 2 recur)	3	MCD	33;41; 34	F; F; F	Mod; Pfi; Pfi	2nd	3 wk; 5 d; 4 wk	n.s.; n.s.; n.s.	Unk; Unk; Unk	6.4;14.4;12.9	Unk; Yes; Unk	2.3;2.6;2.8	Unk; Unk; Unk	Unk; Unk; Unk	Unk	Unk	Unk	Unk
28 (new)	1	MCD	51	M	J+J	1st	28 d	n.s.	1.54	8.6	Yes	1.6	Neg	Neg	I.S. 1	2 wk	Yes	0.95
29 (new)	1	MCD	71	M	AZ	1st	13 d	AKI+n.s.	10.6	20.5	Yes	2.6	Neg	Neg	I.S. 1; D	38 d	Yes	1.4
30 (new)	1	MCD	19	F	AZ	1st	8 d	n.s.	1.09	3.18	Unk	2.15	Unk	Unk	I.S. 1	Unk	Yes	Unk
31 (new)	1	Cres GN, ANCA	29	F	Pfi	2nd	7 wk	Nephritic; AKI	1.91	0.633	Yes	4.4	Unk	Pos	I.S. 1; I.S. 4; I.S. 5	10 wk	Yes	1.01
32 (new)	1	Cres GN, ANCA	52	M	Mod	2nd	14 d	Nephritic; AKI	8.41	1+	Yes	Unk	Unk	Pos	D; I.S. 5	Unk	No	Unk; D
33 (new)	1	Cres GN, ANCA	78	F	Pfi	2nd	8 d	Nephritic; AKI	3.54	2.05	3+	Unk	Unk	Pos, MPO	I.S. 1; I.S. 4	1 mo	Partial	1.71
34 (new)	1	Cres GN, ANCA	63	M	AZ	1st	2 d	Nephritic; AKI	2.91	2+	Yes	Unk	Unk	Pos	I.S. 1; I.S. 5	6 wk	Partial	2.09
35 (new)	1	Cres GN, anti-GBM	NA	F	Mod	2nd	14 d	AKI	7.8	1.9	Yes	Unk	Neg	Neg	D; I.S. 1+I.S. 2+I.S. 5	Unk	No	Unk

Table 3. (Continued)

Patient Number	N	Diagnosis	Age, yr	Sex	Type	1st/2nd	Time	Indication	Serum Creatinine	Proteinuria	Hematuria	Serum Albumin	Antinuclear Antibodies	ANCA	Treatment	Follow-Up	Recovery	Follow-Up Creatinine
36 (new)	1	MN	66	F	Sino	1st	14 d	n.s.	2.78	9.42	Unk	2.6	Unk	Unk	Unk	NA	NA	NA
37 (recur)	1	MN. THSD7A Pos	70	M	Pfi	2nd	1 d	n.s.	1.29	4.4	Yes	1.7	Unk	Unk	ARB; diuretics	2 mo	No	Unk
38 (new)	1	MN, PLA2R Pos (no biopsy)	76	M	Pfi; Mod (2nd)	1st	4 d	n.s.	0.86	6.5	Yes	1.6	Unk	Unk	I.S. 4	2 mo	Partial	1.15
39 (recur)	1	MLN	42	F	Pfi	1st	1 wk	n.s.	wnl	8.4	Neg	Low	Pos	Unk	I.S. 1; I.S. 3	3 wk	Partial	Unk
40 (recur)	1	IgG4 KD	66	M	Pfi	2nd	14 d	AKI	2.38	Unk	Unk	Unk	Neg	Unk	I.S. 1+I.S. 4	Unk	Yes	0.57
41 (new)	1	Gran TIN	77	M	AZ	1st	4 wk	AKI	2.78	Neg	Neg	Unk	Neg	Neg	I.S. 1	4 wk	Yes	Unk
42 (new)	1	TMA/SRC	34	F	Pfi	1st	<1 wk	AKI	2.07	0.8	Neg	Unk	Neg	Unk	ACEi	1 wk	Yes	Unk
43 (new)	1	TCMR	23	F	Pfi	2nd	8 d	AKI	4.07	Unk	Unk	Unk	Pos	Unk	I.S. 1+I.S. 3+I.S. 6	10 d	Partial	2.6

The designations of (new) or (recur) represent *de novo* glomerular disease or recurrent glomerular disease for each report. IgAN, IgA nephropathy; GBM, glomerular basement membrane antibody disease; F, woman; Pfi, Pfizer-BioNTec BNT162b vaccine; Toz, BioNTech Tozinameran mRNA vaccine; n.s., nephrotic syndrome; Unk, unknown; Pos, positive; Neg, negative; I.S. 1, immunosuppression 1: steroid therapy (methylprednisolone or high-dose prednisone); I.S. 5, immunosuppression 5 (cyclophosphamide); I.S. 2, immunosuppression 2: plasmapheresis; NA, not applicable (lack of follow-up data); Cres GN, crescentic GN; M, man; Mod, Moderna mRNA-1273 vaccine; Inc, XXX; RAASi; renin-angiotensin-aldosterone system inhibitor; I.S. 3, immunosuppression 3: mycophenolate mofetil; I.S. 6, immunosuppression 6 (calcineurin inhibitor); ACEI, angiotensin-converting enzyme inhibitor; MCD, minimal change disease; AZ, AstraZeneca AZD1222/ChAdOx1-nCoV-19 vaccine; D, dialysis; J+J, Johnson & Johnson; I.S. 4, immunosuppression 4 (rituximab); MPO, myeloperoxidase; MN, membranous nephropathy; Sino, Sinovac-Coronovac vaccine; THSD7A, thrombospondin type 1 domain containing 7A; ARB, angiotensin receptor blocker; PLA2R, phospholipase A2 receptor; MLN, membranous lupus nephritis; wnl, within normal limits; IgG4 KD, IgG4-related kidney disease; Gran TIN, granulomatous tubulointerstitial nephritis; TMA, thrombotic microangiopathy; SRC, scleroderma renal crisis; ACEi, angiotensin converting enzyme inhibitor; TCMR, acute T cell-mediated rejection.

responsible for data curation; T.N. Caza, A. Hannoudi, R.S. Haun, and C.P. Larsen were responsible for investigation; T.N. Caza, A. Hannoudi, R.S. Haun, C.P. Larsen, and R.M. May were responsible for formal analysis; T.N. Caza and R.S. Haun were responsible for methodology; C.P. Larsen was responsible for project administration; C.P. Larsen was responsible for resources; T.N. Caza, C.P. Larsen, and N. Messias were responsible for visualization; C.P. Larsen provided supervision; T.N. Caza and A. Hannoudi wrote the original draft; and C.A. Cassol, T.N. Caza, C.P. Larsen, and R.M. May reviewed and edited the manuscript.

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Received: August 17, 2021 **Accepted:** August 27, 2021

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