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, crescentic GN, and collapsing 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.

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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-diptheria-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,
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 (antibacterial 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 k- 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. HP-A012657), neural epidermal growth factor like-1 (NELL1; Novus Biologicals; catalog no. H00004745), thrombospodin 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 call.

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 use 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 PL2R. The remaining MN cases were negative for PL2R, 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) (35), MN (n=3; of which one was PL2R 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 | Time Indication | Diagnosis | Creatinine | Proteinuria | Albumin | Hematuria | Antinuclear Antibodies | Treatment before Biopsy | Treatment after Biopsy | Follow-Up | Follow-Up | Follow-Up | Treatment before Biopsy | Treatment after Biopsy | Follow-Up | Follow-Up | Follow-Up |
|----------------|---------|-----|------|-------------|--------------|----------------|-----------|------------|------------|-----------|----------|-----------------|------------------------|------------------------|------------|------------|------------|------------------------|------------------------|------------|------------|------------|
| 1              | 67 F    | B   | Moderna | 7 wk/3 wk <1 wk | AKI, n.s. | CG | 6.7 | 12 | 2.7 | Pos | Neg | Neg | 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 | 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 | 1.1 | Pos | Pos | Neg | D, IS 1 | IS 1 | 4 wk | Yes | 0.9 | UA Pos |
| 7              | 47 F    | W   | Pfizer | 5 wk/1 wk <2 wk | AKI, n.s. | MCD | 2.4 | >600 mg/dl | 1.9 | Neg | Neg | ND | D | IS 1, IS 2 | IS 1 | 4 wk | No | 4.3 | UA Pos |
| 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 | IS 2 | D; IS 3 | 1 wk | No | D* | D* |
| 10             | 33 F    | W   | Pfizer | 4 wk/1 wk 2 d | Nephritic | IgA N | 1.1 | 0.6 | 4.0 | Pos | Neg | None | None | None | None | None | Partial | 12 wk | Yes | 1.2 | 2.5 |
| 11             | 52 F    | W   | mRNA A | 5 wk/2 wk 1 d, both | Hem | IgA N | 1.7 | 0 | ND | Pos | Neg | Neg | None | IS 1 | IS 1 | IS 5 | 1 wk | No | 4 | UA Pos |
| 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 | IS 2 | IS 1 | 4 wk | No | IS 5 | IS 1 |
| 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 2 | IS 1 | 2 wk | No | IS 3 | IS 1 |
| 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/3 d 1 d | AKI, CKD, nephritic | IgA N | 6.2 | 3+ | 2.5 | Pos | Neg | Diur | IS 1 | IS 1 | IS 5 | 4 wk | No | 8 | D* | 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 | 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 | IS 2 | IS 1 | 2 wk | No | IS 1 | IS 1 |
| 18             | 73 M    | W   | Pfizer | 3 mo/2 mo 2 wk | Nephritic | IgA N, AIN | 3.4 | 0.5 | 1.9 | Pos | Neg | Neg | None | IS 1 | 2.5 wk | Partial | 1 | 2.4 |
| 19             | 66 M    | Hisp | mRNA A | 6 wk/3 wk 1 d | AKI, nephritic | IgA N, DN | 9.77 | 3.3 | 2.4 | Pos | Neg | Neg | D | IS 1 | IS 1 | IS 4 | 3 wk | No | 5.8 | UA |
| 20             | 76 M    | W   | Pfizer | 7 wk/3 wk <3 wk | AKI, nephritic | Cres GN | 8.6 | 2+ | 2.3 | Pos | Pos | Pos | D | IS 1, IS 4 | 3 wk | No | 5.8 | UA |
| 21             | 81 F    | W   | Pfizer | 6 wk/3 wk 2 d | AKI, nephritic | Cres GN | 3.1 | 18 | 3.4 | Pos | Pos | Pos | None | IS 1 | IS 4 | 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 | None | IS 1 | IS 1 | IS 1 | 4 wk | No | NA | NA |
| 24             | 65 F    | W   | Pfizer | 4 mo/3 mo 2 wk | AKI, nephritic | Cres GN | 3.29 | 207 | 2.2 | Pos | Pos | Pos | None | IS 1 | IS 2 | IS 1 | 2 wk | No | 4.83 | 2.9 |
| 25             | 79 F    | W   | Pfizer | 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 1 | IS 1 | 4 wk | No | 0.86 | 3.5 |
| 27             | 68 M    | W   | Pfizer | 4 wk/3 wk 1 d | Nephritic | IgA N | 1.3 | 0.6 | 3.2 | Neg | ND | Neg | Diur | IS 1 | Diur | 3 wk | Partial | 2.74 | 0.38 |
| 28             | 47 M    | W   | Moderna | 8 wk/5 wk 6 d | Nephritic | Diffuse LN | 0.7 | 0.8 | 3 | Pos | Neg | Pos | None | IS 1 | IS 2 | 2 wk | Yes | 0.48 | 0.53 |

F, woman; B, Black; n.s., nephrotic syndrome; CG, collapsing glomerulopathy; Pos, positive; Neg, negative; D, dialysis; IS, 1, immunosuppression 1: steroid therapy (methylprednisolone or high-dose prednisone); MN, membranous nephropathy; IS, 2, immunosuppression 2: plasmapheresis; IS, 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; IS, 5, immunosuppression 5 (cyclophosphamide); AIN, acute interstitial nephritis; DN, diabetic nephropathy; Cres GN, crescentic GN; IS, 4, immunosuppression 4 (rituximab); IS, 6, immunosuppression 6 (calcineurin inhibitor); J, Johnson & Johnson; LN, lupus nephritis.

*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 Hypercellularity | Endocapillary Hypercellularity | Necrosis | Segmental Sclerosis | Acute Tubular Injury | Tubular Atrophy | Arterio-sclerosis | Arteriolar Hyalinosis | Immunofluorescence | Subendothelial Deposits | Subepithelial Deposits | Foot Process Effacement |
|----------------|-----------|---------------------------|---------------------------|-------------------------------|----------|---------------------|---------------------|-------------------|-------------------|---------------------|------------------|------------------|------------------|--------------------------|
| 1              | CG        | 0/24                      | No                        | No                            | No       | No                  | Yes                 | Yes               | No                | No                  | No staining        | No               | No               | No                        |
| 2              | CG, MN    | 0/45                      | No                        | No                            | No       | No                  | Yes                 | Yes               | No                | No                  | No staining        | No               | Yes              | No                        |
| 3              | MCD       | 1/31                      | No                        | No                            | No       | No                  | Yes                 | No                | None              | No                  | No staining        | No               | No               | No                        |
| 4              | MCD       | 0/35                      | No                        | No                            | No       | No                  | Yes                 | No                | No                | No                  | No staining        | No               | No               | Severe                    |
| 5              | MCD       | 3/33                      | Yes                       | No                            | No       | No                  | Yes                 | No                | No                | No                  | No staining        | No               | No               | Severe                    |
| 6              | MCD       | 0/20                      | Yes                       | Yes                            | No       | No                  | No                 | No                | No                | No                  | No staining        | No               | No               | Severe                    |
| 7              | MCD       | 6/30                      | No                        | No                            | No       | No                  | Yes                 | No                | No                | No                  | No staining        | No               | No               | Severe                    |
| 8              | MCD       | 0/40                      | No                        | No                            | No       | No                  | Yes                 | No                | No                | No                  | No staining        | No               | No               | Severe                    |
| 9              | MCD       | 0/60                      | No                        | No                            | No       | No                  | No                 | No                | No                | No                  | No staining        | No               | No               | Severe                    |
| 10             | IgA N     | 1/29                      | Yes                       | Yes                            | No       | No                  | Yes                 | No                | No                | No                  | 3+ IgA and C3 gr mes | Yes              | No               | No                        |
| 11             | IgA N     | 3/27                      | No                        | No                            | No       | No                  | No                 | No                | None              | No                  | 3+ IgA gr mes       | Yes              | No               | No                        |
| 12             | IgA N     | 1/16                      | Yes                       | Yes                            | No       | No                  | Yes                 | No                | No                | No                  | 3+ IgA+C3, 1+ IgG gr mes | Yes              | No               | No                        |
| 13             | IgA N     | 0/86                      | Yes                       | Yes                            | No       | No                  | Yes                 | No                | No                | No                  | 3+ IgA gr mes       | Yes              | No               | Mod                       |
| 14             | IgA N     | 10/40                     | Yes                       | Yes                            | No       | Yes                 | Yes                 | Yes               | Yes               | Severe              | 2+ IgA+IgM, 3+ C3, trace IgG gr mes | No              | No               | No                        |
| 15             | IgA N     | 25/52                     | Yes                       | Yes                            | Yes      | Yes                 | Yes                 | Yes               | Severe             | Mod                 | 2+ IgA, 1+ C3 gr mes | Yes              | No               | No                        |
| 16             | IgA N     | 2/30                      | Yes                       | Yes                            | No       | No                  | Yes                 | No                | No                | Severe              | 3+ IgA, 2+ IgG, 3+ C3 gr mes | Yes              | Yes              | Mild                       |
| 17             | IgA N     | 6/19                      | Yes                       | No                             | No       | No                  | Yes                 | No                | Yes               | Mod                 | 3+ IgA, trace IgG, 2+ C3 gr mes | Yes              | No               | Mod                       |
| 18             | IgA N, AIN| 1/13                      | Yes                       | No                             | No       | No                  | No                 | No                | N/A               | Mild                | 3+ IgA, 1+ IgG, 2+ IgM, trace C3 gr mes | Yes              | No               | No                        |
| 19             | IgA N, DN | 35/46                     | Yes                       | Yes                            | No       | No                  | Yes                 | Yes               | Yes               | Severe              | 1+ IgA, 1+ IgG, 1+ IgM gr mes | No              | No               | Mod                       |
| 20             | Cres GN   | 1/24                      | No                        | No                             | No       | No                  | Yes                 | No                | No                | Severe              | 2+ IgA, 1+ C3 gr mes | No              | No               | Severe                    |
| 21             | Cres GN   | 4/13                      | Yes                       | No                             | No       | Yes                 | Yes                 | Yes               | Severe             | Severe              | 1+ IgM, trace C3 gr mes | No              | No               | No                        |
| 22             | Cres GN   | 9/36                      | No                        | No                             | No       | Yes                 | No                 | No                | No                | Severe              | 3+ C3 gr mes | Yes              | No                        |
| 23             | Cres GN   | 20/29                     | No                        | No                             | No       | No                  | Yes                 | No                | Severe             | Severe              | 3+ IgM, 1+ C3 gr mes | Yes              | No               | Mod                       |
| 24             | Cres GN   | 5/30                      | No                        | No                             | No       | Yes                 | No                 | Yes               | Mod               | N/A                 | 1+ IgG, 1+ C3 gr cap loop | N/A             | N/A              | N/A                        |
| 25             | Cres GN   | 13/51                     | No                        | No                             | No       | Yes                 | Yes                 | Yes               | Mild              | No                  | 3+ IgA, 2+ C3 gr cap loop | No              | No               | None                       |
| 26             | MN         | 3/15                      | No                        | No                             | No       | Yes                 | Yes                 | Yes               | No                | No                  | 3+ IgA, 2+ C3 gr cap loop | No              | No               | Severe                    |
| 27             | MN         | 20/29                     | No                        | No                             | No       | Yes                 | Yes                 | No                | Mild              | No                  | 2+ IgM, 2+ IgG gr cap loop | No              | No               | Severe                    |
| 28             | MN         | 1/39                      | No                        | No                             | No       | No                  | No                 | No                | Mild              | No                  | 3+ IgA, 2+ C3 gr cap loop | No              | No               | Severe                    |
| 29             | Diffuse LN| 0/55                      | Yes                       | Yes                            | No       | No                  | No                 | No                | No                | No                  | 3+ IgA, 3+ IgG, 3+ IgM, 3+ C3, 3+ C1q gr mes | No              | No               | Yes                        |

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 Glerulonephritis-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 Sphex. 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.

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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. Cas sol, T.N. Caza, K.K. Chouchan, 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. Hoenschgen, B. Iqbal, Z. Karam, S. Khalilullah, 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...
| Patient | Diagnosis | Age, yr | Sex | Type | 1st/2nd Time | Time | Indication | Serum Creatinine | Proteinuria | Hematuria | Serum Albumin | Antinuclear Antibodies | ANCA | Treatment | Follow-Up | Recovery | Follow-Up Creatinine |
|---------|-----------|---------|-----|------|-------------|------|------------|-----------------|-------------|-----------|--------------|------------------------|-------|-----------|-----------|---------|----------------------|
| 6 (new) | IgAN; anti-GM | 41, 60  | F, F | Ph | T | 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 | NA | NA | NA |
| 7 (new) | IgAN; Croz | 39, 81  | M, M | Mod | 1st | 1 | Nephritic; AKI | Inc; Inc | Pos; Pos | Yes | Unk | Unk | Unk | Pos; I.S. 5 | NA | No | Yes |
| 8 (recur) | IgAN | 22, 41; 27 | M, F; F | Mod; Ph | 2nd | 1; 2nd | 2 d | Nephritic | 0.34; 0.47; 1.9 | Yes | Unk | Unk | I.S. 1; I.S. 5 | Unk | Yes | Yes | Unk |
| 9 (new) | IgAN | 50, 19  | F, M | Mod | 2nd | 1 d | Nephritic | 1.7; 2.1 | 2.0; None | Yes | Unk | Neg; Unk | Unk | I.S. 1; I.S. 5 | 5; 2 d | Yes | Yes | Unk |
| 10 (new) | IgAN | 13, 17  | M, M | Ph | 2nd | 1 d | AKI = nephritic | 1.31; 1.78 | 1.3; 1.8 | Yes; Yes | 3.4; 3.8 | Unk | I.S. 1; I.S. 5 | Unk | 5 d; 2 d | Yes | Yes | Unk |
| 11 (recur) | IgAN | 38 | F; F | Ph | 2nd | 1 d | Nephritic | 0.82; 0.59 | Yes | Unk | Unk | None | I.S. 1 | Unk | 21 d | Yes | Unk |
| 12 (recur) | IgAN | 52 | F | Ph | 2nd | 1 d | Nephritic | 2.4 | Yes | Unk | Unk | None | I.S. 1; I.S. 5 | 1 wk | 4 wk; 4 wk; 4 wk; 4 wk | Yes | Yes | Unk |
| 13 (recur) | IgAN | 22, 39; 50; 67 | F; M; M | Mod; Mod | 1 d | 4 wk | Nephritic; n.s. | 0.931; 0.21; 3+ | Yes | Unk | I.S. 1; I.S. 5 | 10; 14 d | Yes | Yes | Unk |
| 14 (new) | IgAN | 30 | M | Mod | 2nd | 1 d | Nephritic | 1.02 | 4+ | Yes | Unk | Neg; Neg | RAASi | 6 wk | Partial | 1.03 |
| 15 (recur) | IgAN | 76 | F | Mod | 1st | 1 d | Nephritic | 1.18 | 4+ | Unk | Unk | I.S. 1; I.S. 5 | Unk | Yes | Unk |
| 16 (recur) | IgAN | 13 | M | Ph | 2nd | 1 d | Nephritic | 3.53; 1.16 | 4.97; 0.61 | Yes | Unk | Unk | Unk | I.S. 1; I.S. 5 | 2; 1 mo | Yes | Unk |
| 17 (new) | MCD | 77 | M | Ph | 1st | 1 d | Nephritic; AKI | 2.35 | 4+ | Unk | 3.0 | I.S. 1 | I.S. 1 | 21 d; 17 d | Yes | Unk |
| 18 (new) | MCD | 50 | M | Ph | 1st | 1 d | AKI = n.s. | 2.31 | 6+ | I.S. 1 | I.S. 1 | I.S. 1 | I.S. 1 | 21 d; 17 d | Yes | Unk |
| 19 (recur) | MCD | 34 | F | Ph | 1st | 1 d | Nephritic; n.s. | 0.931; 0.21; 3+ | Unk | I.S. 1; I.S. 5 | 10; 14 d | Yes | Yes | Unk |
| 20 (recur) | MCD | 30; 40 | M; F | AZ | 1st | 2 d; 1 d | Nephritic; n.s. | 0.931; 0.21; 3+ | Unk | I.S. 1; I.S. 5 | 10; 14 d | Yes | Yes | Unk |
| 21 (new) | MCD | 63 | F | Ph | 1st | 1 d | Nephritic | 1.48 | 3+ | Yes | 0.7 | Unk | Unk | Unk | Unk |
| 22 (new) | MCD | 81a | M | Ph | 1st | 1 d | Nephritic | 1.43 | 15.3 | Unk | 1.0 | I.S. 1; I.S. 5 | 10; 10 d | Yes | Unk |
| 23 (recur) | MCD | 60a | M | Ph | 1st | 1 d | Nephritic | 0.99 | 11.5 | Unk | 2.8 | I.S. 1; I.S. 5 | 14; 14 d | Yes | Unk |
| 24 (recur) | MCD | 42 | M | Ph | 1st | 1 d | Nephritic | 0.99 | 3+ | Unk | 2.3 | I.S. 1; I.S. 5 | 17; 14 d | Yes | Unk |
| 25 (recur) | MCD | 39 | M | Ph | 1st | 1 d | Nephritic | 1.8 | 8 | Unk | 2.7 | I.S. 1; I.S. 5 | 4 wk | Yes | Unk |
| 26 (new) | MCD | 61 | F | Ph | 1st | 1 d | Nephritic | 1.47 | 12 | Unk | 2.1 | D; I.S. 1; I.S. 5 | 21 d | Partial | Unk |
| 27 (new) | MCD | 33; 41; 34 | F; F; F | Ph | 2nd | 1 d | Nephritic; AKI | 3.12 | 6.28 | Unk | I.S. 1; I.S. 5 | 2; 4 wk | Yes | Unk |
| 28 (new) | MCD | 51 | M | Ph | 1st | 1 d | Nephritic | 1.54 | 8.6 | Yes | 1.6 | I.S. 1; I.S. 5 | 2 wk | Yes | Unk |
| 29 (new) | MCD | 71 | M | AZ | 1st | 1 d | Nephritic | 10.6 | 20.5 | Yes | 2.6 | I.S. 1; I.S. 5 | 38 | Yes | 14 |
| 30 (new) | MCD | 19 | F | AZ | 1st | 1 d | Nephritic | 1.09 | 3.18 | Unk | 2.15 | I.S. 1; I.S. 5 | Unk | Yes | Unk |
| 31 (new) | MCD | 29 | F | Ph | 2nd | 1 d | Nephritic; AKI | 1.91 | 6.63 | Unk | I.S. 1; I.S. 5 | 10 wk | Yes | 1.01 |
| 32 (new) | MCD | 52 | M | Ph | 2nd | 1 d | Nephritic; AKI | 8.41 | 3+ | Yes | Unk | Pos | D; I.S. 5; Unk | No | Unk |
| 33 (new) | MCD | 78 | F | Ph | 2nd | 1 d | Nephritic; AKI | 3.54 | 2.05 | Unk | I.S. 1; I.S. 4 | 1 mo | Partial | 1.71 |
| 34 (new) | MCD | 63 | M | AZ | 2nd | 1 d | Nephritic; AKI | 2.91 | 2+ | Unk | I.S. 1; I.S. 5 | 6 wk | Partial | 2.09 |
| 35 (new) | MCD | 78 | F | Ph | 2nd | 1 d | Nephritic; AKI | 7.8 | 1.9 | Yes | Unk | Neg | D; I.S. 1; I.S. 5 | Unk | No | Unk |
### Table 3. (Continued)

| No. | 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  | Sino      | 66      | F   | 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  | Unk       | ARB, diuretics | 2 mo    | No                   |
| 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              |
| 39  | (recur) 1      | MLN | F         | 42      | F   | Pfi    | 1st | 1 wk         | n.s.       | wnl      | 8.4         | Neg         | Low                     | Pos  | Unk       | I.S. 1; I.S. 3 | 3 wk    | Partial              |
| 40  | (recur) 1      | IgG4 KD | 66   | M     | Pfi   | 2nd    | 14 d | AKI          | 2.38       | Unk      | Unk         | Neg         | Unk                    | I.S. 1+I.S. 4 | Yes | I.S. 1     | 4 wk     | Yes     | Unk                   |
| 41  | (new) 1        | Gran TIN | 77   | M     | AZ    | 1st    | 4 wk | AKI          | 2.78       | Neg      | Neg         | Unk         | Neg                    | I.S. 1     | Yes | Unk        | 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         | Pos         | Unk                    | I.S. 1+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; Tox, 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, 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.
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