Original Article

Outcomes of Covid-19 Vaccine-Associated Glomerular Diseases (CVAGD) – A Case Series from India

Abstract

Background: Several cases of glomerular diseases following Covid-19 vaccination, especially mRNA vaccines, have been reported. However, there is little data on glomerular diseases associated with the two vaccines widely available in India (Covaxin and Covishield) and their long-term outcomes. **Materials and Methods**: This was a prospective observational study conducted between May 2021 and May 2023. Patients with new-onset or relapse of proteinuria, hematuria, or renal failure within 30 days of Covid-19 vaccination were included. Data on pre-existing renal disease, vaccine type, symptomatology, laboratory reports, kidney biopsy findings, and treatment details were collected. The clinical course and long-term renal outcomes were studied. **Results**: Sixteen patients with Covid-19 vaccine associated glomerular disease (CVAGD) were studied. The median age was 28 years (IQR 20.5–40) and median time of symptom onset was 14 days (IQR 10–16.5) after vaccination. Renal syndromes at presentation were nephrotic syndrome in seven patients (43.75%), nephritic syndrome in seven patients (43.75%), and rapidly progressive renal failure in two patients (12.5%). Kidney biopsy revealed minimal change disease in five patients (31.2%); IgA nephropathy in four patients (25%); C3 glomerulopathy, lupus nephritis, and focal segmental glomerulosclerosis in two patients each (12.5%); and pauci-immune glomerulonephritis (ANCA-associated vasculitis) in one patient (6.25%). Eleven patients were treated with immunosuppressive drugs. Median duration of follow-up was 20 months (IQR 18–21). At last follow-up, 11 patients had complete recovery of renal failure and proteinuria and 4 patients had partial recovery. **Conclusion**: The most common lesions in this series were minimal change disease and IgA nephropathy. The overall long-term outcome of CVAGD appears good.

Keywords: *Covid-19 vaccine-associated glomerular diseases, Glomerulonephritis, CVAGD, ChAdOX1-nCOV vaccine, BBV152*

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Introduction

The concerted effort to develop and expeditiously roll-out the Covid-19 vaccine has been hailed as one of the triumphs of 21st century medicine. While the mRNA vaccines, Pfizer-BioNTech and Moderna were predominantly used in the West, the two vaccines widely available in India were Covaxin (BBV152), an inactivated virus vaccine, and Covishield (SII – ChAdOx1 nCoV-19), an adenoviral vector vaccine. Several case reports of glomerular diseases following Covid-19 vaccination have been reported in literature. However, follow-up data of these patients are scarce.

Materials and Methods

This was a prospective descriptive study conducted between May 2021 and May 2023. The study was approved by the Institutional Review Board and patient consent was obtained. All patients with new-onset proteinuria or proteinuric relapse, new-onset hematuria or decreased GFR within 30 days of Covid-19 vaccination were included. Clinical data, including preexisting kidney disease, vaccine type, time to onset of symptoms, and details of initial treatment were collected. Laboratory investigations, including serum creatinine, serum albumin, urine microscopy, and urine spot protein-creatinine ratio were done. Kidney biopsy was performed for all patients and tissue specimens were subjected to light microscopy and immunofluorescence. Details of management protocols and long-term renal outcomes were collected.

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Categorical data were reported as numbers and percentage. Continuous data were reported as median with interquartile range (nonnormally distributed data) or mean with standard deviation (normally distributed data). As the sample size was small, descriptive statistics were used.

Results

Baseline characteristics

We treated 16 patients with Covid vaccine–associated glomerular disease (CVAGD) during the study period. Of them, eight patients were male (50%) and the median age was 28 years (IQR 20.5–40). Ten patients (62.5%) had a *de novo* glomerular disease and six had a relapse of a preexisting disease. All but one patient had presented after the first dose of the vaccine (93.75%). Eleven patients had received Covishield (68.75%) and five had received Covaxin (31.25%). The median time to symptom onset after vaccination was 14 days (IQR 10–16.5) after the first dose and 2 days after the second dose (one patient). Only one patient had a prior clinical Covid-19 infection. The common symptoms noticed were edema, macroscopic hematuria, and decreased urine output. The renal syndromes at presentation were nephrotic syndrome in seven patients (43.75%), rapidly progressive renal failure in two patients (12.5%), and nephritic syndrome in seven patients (43.75%). Kidney biopsy revealed IgA nephropathy in four patients (25%), endocapillary proliferative glomerulonephritis in two patients (12.5%), minimal change disease in five patients (31.2%), pauci-immune necrotizing glomerulonephritis (ANCA associated vasculitis) in one patient (6.25%), lupus nephritis in two patients (12.5%), and focal segmental glomerulosclerosis in two patients (12.5%). Five patients developed renal failure but none required kidney replacement therapy. Clinical characteristics of all patients are summarized in Table 1.

Clinical characteristics and initial treatment of patients by disease

Minimal change disease (n = 5)

The most common glomerulopathy in this series was minimal change disease (31.25%). Of the two relapses, one patient had suffered nephrotic syndrome in childhood and had been in remission for 10 years without any immunosuppression, while the other patient had steroid-dependent nephrotic syndrome for 3 years and had been in remission for 1 year with prednisolone monotherapy of 5 mg/day. Both patients had not undergone a kidney biopsy previously. One patient who had presented with AKI-KDIGO stage 3 had additional biopsy findings of acute tubular injury but he did not require RRT. All patients were treated with oral prednisolone 1 mg/kg/day. They achieved complete remission within 4 weeks, following which steroids were tapered and stopped.

IgA nephropathy (n = 4)

The second most common pathology was IgAN (25%). One patient had been diagnosed with IgAN 3 years ago but was asymptomatic. One patient presented with gross hematuria 2 days after the second dose of vaccine. He had also developed transient hematuria 7 days after the first dose which he had ignored. One patient was treated with oral steroids, while the rest were managed with anti-proteinuric measures. Three patients achieved complete recovery from proteinuria and one patient had partial recovery of proteinuria at 6 months.

FSGS (n = 2)

One patient was diagnosed only at the current presentation (FSGS tip variant), while another presented with a relapse after having been in complete remission for 18 months. Both patients were treated with oral steroids. The patient who presented with the relapse achieved complete remission within 3 weeks, following which steroids were tapered. The other patient developed excessive weight gain, cushingoid facies and acne; hence, he was switched to tacrolimus, following which he attained partial remission of nephrotic syndrome.

C3 glomerulonephritis (n = 2)

The first patient had a history of childhood nephritic syndrome, for which he had undergone kidney biopsy (the reports of which were untraceable) and had been treated with immunosuppressive medications for 2 months after which he had been lost to follow-up. He also had a twin brother who had suffered renal failure at the age of 12 and succumbed. The patient now presented with edema and dark brown urine after the first dose of vaccine. The second patient presented with hypertension and leg swelling 2 weeks after the vaccine. Both patients had microscopic hematuria, proteinuria, and low C3 levels at presentation and were treated with anti-proteinuric measures. Biopsy findings were endocapillary proliferation on LM and C3 dominance on IF. At follow-up, 12 weeks later, there was persistently low C3 and hence, a diagnosis of probable C3G was made. Electron microscopy could not be done for logistic reasons. Partial recovery of proteinuria was noted at 2 months in one patient and immunosuppression was deferred, while the other was lost to follow-up after 3 months.

Lupus nephritis (n = 2)

The first patient had symptoms of hair loss and arthralgia one year ago but she had not sought treatment. She developed symptoms eighteen days after the vaccine. Renal biopsy revealed lupus nephritis class 3. The second patient was a known case of SLE with mucocutaneous and musculoskeletal symptoms, on prednisolone and hydroxychloroquine, who presented with nephritic syndrome 10 days after the vaccine. She had lupus nephritis - Class 4 on renal biopsy. Both were treated with steroid and cyclophosphamide induction regimens,

Table 1: Clinical characteristics of patients with CVAGD

No	Age (years)	Gender	Vaccine	Dose	Onset time (days)	Presenting symptom	Diagnosis	S. Cr (mg/dl)	Urine PCR (g/g)	S. Cr (mg/dl)	S. Alb (g/dl)	Urine Protein (g/g)	Urine RBC (per HPF)
1	25	M	Covishield	1	15	Edema	MCD/ATI	N/K	N/K	4.5	2.1	3.7	<5
2	13	M	Covaxin	1	7	Edema	MCD	N/K	N/K	0.9	2.9	5.2	<5
3	28	F	Covishield	1	10	Edema	MCD	N/K	N/K	1	2.5	4.4	<5
4	21	M	Covishield	2	2	Hematuria	IgAN	0.9	N/K	1.2	3.8	0.8	15-20
5	31	M	Covaxin	1	20	Edema, rash	IgAN/ ATIN	N/K	N/K	1.8	3.6	0.9	<5
6	47	F	Covishield	1	15	Edema	IgAN M1	N/K	N/K	0.7	2.8	3.8	<5
7	20	M	Covishield	1	10	Edema	FSGS tip	N/K	N/K	0.8	2.7	3.9	<5
8	38	F	Covishield	1	14	Edema, HTN	Endocapillary proliferative GN/ C3GN	N/K	N/K	1.2	3.9	1	10-15
9	18	F	Covishield	1	18	Edema, decreased output	LN 3	N/K	N/K	3.4	3.2	2.8	05-10
10	52	F	Covaxin	1	14	Edema. Decreased urine	AAV	N/K	N/K	3.4	3.6	2.1	15-20
11*	21	M	Covishield	1	14	Edema	MCD	N/K	0.09	0.9	3.2	6.4	<5
12*	42	M	Covishield	1	7	Edema	MCD/uFSGS	1	0.1	1	2.4	13.2	<5
13*	32	F	Covaxin	1	14	Edema, HTN	IgAN	1	0.2	1.2	3.3	2.8	<5
14*	17	F	Covishield	1	20	Edema	FSGS	1.1	0.1	0.9	3	4.2	<5
15*	45	M	Covishield	1	20	Oedema, dark urine	Endocapillary proliferative GN/ C3GN	1	0.05	1.1	2.8	0.75	05-10
16*	28	F	Covaxin	1	10	Oedema	LN 4	0.8	0.4	2.1	2.9	2.8	<5

AAV: ANCA-associated vasculitis; ATI: acute tubular injury; ATIN: acute tubulointerstitial nephritis; C3GN: C3 glomerulonephritis; M: male; F: female; FSGS: focal segmental glomerulosclerosis; GN: glomerulonephritis; HTN: hypertension; IgAN: IgA nephropathy; LN: lupus nephritis; MCD: minimal change disease; N/K: not known; PCR: protein creatinine ratio. Asterisks*: relapses, HPF: high power field, CVAGD: covid vaccine associated glomerular disease, S. Cr: serum creatinine, Alb: albumin, uFSGS: unsampled focal segmental glomerulosclerosis

Table 2: Treatment and follow-up of patients with CVAGD

Case no.	Age	Diagnosis	Treatment	Response 3 months after initial treatment	Number of relapses	Follow-up duration (months)	Labs at last follow-up			
							S.Cr	U PCR g/g	S. Alb g/dL	Current status
1	25	MCD/ATI	Steroids, Tacrolimus	CR	2	22	1.2	0.5	3.1	PR
2	13	MCD	Steroids	CR	0	14	0.8	0.05	3.9	CR
3	28	MCD	Steroids	CR	0	20	0.9	0.06	3.6	CR
4	21	IgAN M1	Conservative	PR	0	24	1.1	0.12	4.1	CR
5	31	IgAN/ ATI	Conservative	CR	0	20	0.8	0.1	3.9	CR
6	47	IgAN M1	Steroids	CR	0	21	1.2	0.16	3.9	CR
7	20	FSGS- tip variant	Steroids, Tacrolimus	PR	1	20	1	0.8	3.2	PR
8	38	C3 G	Conservative	PR	0	18	1.1	0.13	3.8	CR
9	18	LN 3	Steroids, Cyclophosphamide	PR	0	17	1.2	0.2	3.8	CR
10	52	AAV	Steroids, Cyclophosphamide	PR	0	16	1.8	0.9	12	PR
11	21	MCD	Steroids	CR	0	19	0.9	0.04	4.1	CR
12	42	MCD/ uFSGS	Steroids	CR	0	19	1.0	0.02	4.2	CR
13	32	IgAN	Conservative	PR	0	20	1.1	0.10	3.8	CR
14	17	FSGS	Steroids	PR	1	18	0.9	0.14	3.8	CR
16	28	LN 4	Steroids, Cyclophosphamide	PR	0	21	1.3	1.2	3.7	PR

AAV: ANCA-associated vasculitis; ATI: acute tubular injury; ATIN: acute tubulointerstitial nephritis; C3G: C3 glomerulonephritis; CR: complete recovery; M: male; F: female; FSGS: focal segmental glomerulosclerosis; uFSGS: unsampled focal segmental glomerulosclerosis; GN: glomerulonephritis; HTN: hypertension; IgAN: IgA nephropathy; LN: lupus nephritis; MCD: minimal change disease; N/K: not known; PR: partial recovery, CVAGD: covid vaccine associated glomerular disease, S. Cr: serum creatinine, U PCR: urine protein creatinine ratio, S. Alb: serum albumin

followed by maintenance with mycophenolate mofetil. At 6 months' follow-up, both patients were in partial remission.

ANCA-associated vasculitis (n = 1)

One patient developed rapidly progressive renal failure with a peak serum creatinine of 4.5 mg/dL, 14 days after the first dose of Covaxin. Renal biopsy revealed pauci-immune necrotizing crescentic glomerulonephritis, and serology was positive for c-ANCA by indirect immunofluorescence. She was treated with steroids and cyclophosphamide (CYCLOPS regimen), and after 10 doses of cyclophosphamide, was switched to maintenance azathioprine. Serum creatinine reduced to 2.1 at the end of the induction regimen and there was partial recovery of proteinuria.

Treatment and long-term follow-up of patients with CVAGD

All patients with CVAGD (except those with MCD) received anti-proteinuric measures consisting of maximum-tolerated doses of RAS inhibition and blood pressure control. Of the 16 patients, 11 were treated with immunosuppressive drugs. The second dose of the vaccine was deferred in all 15 patients who had presented with symptoms after the first dose. Currently, 15 patients continue to be on follow-up. The median duration of follow-up was 20 months (IQR18–21). At the last follow-up in May 2023, all patients were symptom-free, 11 patients had complete recovery of renal failure and proteinuria, and 4 patients were in partial remission.

One patient with MCD who had initially attained remission with steroids developed multiple relapses and required the addition of tacrolimus. Similarly, one of the patients with FSGS who had initially achieved complete remission developed a relapse after 6 months. She was treated with a short course of steroids and has remained in complete remission.

The treatment and follow-up details are summarized in Table 2.

Discussion

Autoimmunity associated with vaccination is a known phenomenon. Some of the autoimmune phenomena reported after Covid-19 vaccination are immune thrombocytopenic purpura, Guillain–Barré syndrome, rheumatoid arthritis, Graves' disease, systemic lupus erythematosus, and several glomerular diseases. Molecular mimicry and cross-reactivity of antibodies can trigger autoimmunity. Secondarily, the vaccine adjuvant can activate inflammasomes and cause release of pro-

inflammatory DAMPs such as IL-1α and HMGB 1 (high mobility group, box 1). This upregulation of immunological pathways in genetically predisposed individuals is the basis of immune-mediated diseases after Covid-19 vaccination.

While there have been several case reports of glomerular diseases occurring *de novo* or relapsing after Covid-19 vaccination, most of them are associated with mRNA vaccines. Furthermore, follow-up data on these patients remain scarce. This case series focuses on glomerular diseases triggered by Covaxin and Covishield vaccines and their long-term outcomes.

The majority of patients in our series developed symptoms after the first dose of vaccine, with a median time of 14 days after vaccination. Similar to results seen from other registries like IRocGN2, the most common glomerular lesions were MCD and IgAN while other lesions like C3 glomerulonephritis, FSGS, lupus nephritis, and ANCA-associated glomerulonephritis were less common.[1] The median age was 28 years (IQR 19.5) with a wide range from a 13-year-old boy with MCD to a 52-year-old lady with AAV. Another large series of CVAGD had an age range of 19–83 years, with most patients presenting after the second dose.[2]

The mRNA vaccines were used predominantly in the West, with the Pfizer and Moderna vaccines implicated in 54.1% and 19.4% patients, respectively, in the IRocGN2 registry.[1] In India, Covaxin and Covishield were extensively used. Covaxin (BBV152) is a whole-virion β-propiolactone-inactivated SARS-CoV-2 vaccine manufactured by Bharat Biotech. The adjuvant used was Algel-IMDG, an imidazoquinolinone molecule absorbed on alum. IMDG is a TLR7/8 agonist used to augment cell-mediated immune response, particularly Th1 response. In addition to a robust humoral response, BBV152 was shown to increase the CD4+ CD45RO+CD27+ T cell population, which implies activation of CD27 (co stimulatory molecule) and the antigen recall memory T-cell response. There is also generation of early IFN I, which helps in viral clearance and generation of pro-inflammatory cytokines.[3,4] Covishield (SII-ChAdOx1 nCoV-19) was manufactured in Serum Institute of India Pvt. Ltd. (SIIPL) after technology transfer from Oxford University/AstraZeneca. It is a recombinant, replication-deficient chimpanzee adenovirus vector that encodes SARS-CoV-2 spike glycoprotein. The E1 and E3 genes of the adenovirus were removed, which renders the virus incapable of replication. Inside the host cell, the virus breaks free from the endocytic vesicle and enters the nucleus where the host machinery is used to translate to S protein. This S protein is displayed on the cell surface by MHC I. Immunization with Covishield induces a robust T cell and antibody response. A predominant Th1 response has been demonstrated involving cytokines like IFN γ, IL 2, and TNFα/β.[5]

While there is insufficient data to claim causality, there is temporal association, biological plausibility, and good strength of association as relapses have been demonstrated after vaccine re-challenge.[6–12] In this series, only one patient presented after the second dose. He had minor symptoms after the first vaccine, which reappeared rapidly after the second dose.

Optimal management and long-term outcomes of CVAGD are not known; however, standard immunosuppressive regimens have been used. The overall response to treatment was good with 11 patients in complete remission and 4 in partial remission at the end of follow-up. It is unclear whether the immunologic mechanisms of injury in CVAGD are different from *de novo* glomerular diseases and a better understanding of the immune pathomechanisms in CVAGD would throw light on the potential for spontaneous recovery without immunosuppression.

Though this is one of the largest series from India with long-term outcome data on CVAGD, there are several limitations. The number of patients is small, likely due to the low incidence of the disease and possibility of missed cases. Furthermore, the strength of the association between vaccination and CVAGD could not be studied because of the absence of a control group. We also lack information on the safety of additional doses of vaccine as rechallenge was not attempted. Intriguing questions such as how to proceed with the vaccination schedule in patients who develop CVAGD remain unanswered, and it is not known whether changing the vaccine type would reduce risk.

This series highlights the wide array of glomerular lesions observed after Covid-19 vaccination, with MCD and IgAN being the most common. The overall long-term outcome of patients with CVAGD appears good. While causality cannot be proven, the temporal association between the presentation/relapse of glomerular diseases and Covid-19 vaccination, in the absence of other inciting factors, is persuasive. Long-term follow-up and collaborative studies are required for further understanding of the pathogenesis, immune mechanisms, and management of these diseases.

Conflicts of interest

There are no conflicts of interest.

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