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Original Article

Long-Term Renal Prognosis Evaluation of Glomerulonephritis Developig After Severe Acute Respiratory Syndrome Coronavirus 2 Infection and Vaccination

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ABSTRACT

Objective: The aim of this study was to investigate the long-term prognosis of patients of glomerulonephritis (GN) developıng after Severe acute respiratory syndrome coronavirus 2 (Sars-Cov-2) infection and vaccinatıon patients.

Methods: In this case series, we reported a total of 24 newly diagnosed glomerulonephritis cases after SARS-CoV-2 mRNA vaccine SARS-CoV-2 infection. We recorded the urea creatinine, albumin, proteinuria, albuminuria values at 1st, 3rd, 6th, 12th, and 24th month follow-ups from our patients' file records. We evaluated their treatment responses and long-term renal prognoses.

Results: A total of 24 patients were evaluated. Glomerulonephritis developed after vaccination in 18 patients (75%) and after infection in 6 patients (25%). The most common glomerulonephritis in our case series was membranous glomerulonephritis (MN)(13 of 24, 54%). 5 patients had IgA nephropathy (IGAN) (20%), 3 had idiopathic immune complex glomerulonephritis (ICGN, 12.5%), 1 had anti-glomerular basement membrane disease (Anti-GBM), 1 had minimal change disease (MCD) and 1 had MPO-ANCA associated glomerulonephritis. Only 4 of the patients are followed up in remission in the 2nd year.

Conclusion: Long-term follow-up data on glomerulonephritis developing after vaccination and infection remains scarce in the literature. We present the long-term follow-up results of our glomerulonephritis patients who developed the condition after vaccination and infection, aiming to contribute to addressing this knowledge gap. Our clinical observations suggest that patients who developed glomerulonephritis post-infection exhibited poorer treatment responses. Therefore, despite ongoing vaccine discussions, we reiterate the importance of community vaccination as a crucial protective measure.

INTRODUCTION

The SARS-CoV-2 pandemic is a serious disease with high mortality and morbidity that has affected millions of people. The development of de novo glomerulonephritis after infection is remarkable. In addition to directly damaging cells, the virus also disrupts the immune system and causes damage to various organs. The kidneys are frequently affected because they are among the organs where the virus's receptors are dense. The SARS-CoV-2 virus binds to cells through a protein called angiotensin-converting enzyme 2 (ACE2). This protein is also densely found in the kidneys. The virus can cause damage indirectly by directly damaging the kidneys or by triggering the immune system. [1] Although kidney biopsy findings mostly show acute tubular damage, other pathologies such as glomerular diseases can also be seen. Glomerular diseases that are likely to have a causal relationship with SARS-CoV-2 infection are frequently reported in the literature, are more common in the SARS-CoV-2 era compared to the pre-SARS-CoV-2 era, or have plausible mechanistic explanations such as immune dysregulation, autoantibody production, cytokine up-regulation, complement activation, or direct viral toxicity.[2,3]

On the other hand, the development of GN associated with SARS-CoV-2 vaccination is also noteworthy. Rapid and mass SARS-CoV-2 vaccination has been one of the main strategies to control this pandemic. The use of recently developed mRNA vaccines such as BNT162b2 (Pfizer) and mRNA-1273 (Moderna) has provided effec-

tive protection against severe SARS-CoV-2 infection.[4,5] mRNA vaccines use lipid nanoparticles as a vehicle to deliver genetically modified mRNA. When injected, the mRNA is translated into the target protein and generates a strong immune response.[6] These vaccines have so far been found to have a high safety profile and side effects for both mRNA vaccines are mostly related to injection site reactions. Severe reactions are rare. However, since mass vaccination, autoimmune reactions such as myocarditis, newly diagnosed or recurrent GN, thyroiditis have been reported.[7,8] Most cases have been associated with mRNA vaccines (Pfizer and Moderna).[9-12] However, rare cases of GN associated with inactivated virus vaccine (CoronaVac from Sinovac) have also been reported.[13] The most common GN reported so far are Membranous GN and IgAN. However, it is unclear whether the SARS-CoV-2 vaccine triggers an immune response that triggers the production of IgA antibodies (Ab) in the kidneys and the formation of new deposits, or whether the immune response to the vaccine only reveals the presence of previously formed deposits. In conclusion, autoimmune glomerular diseases have been reported both after SARS-CoV-2 infection and vaccination. In our article, we examined our cases of GN that developed after SARS-CoV-2 vaccination and SARS-CoV-2 infection. When we review the current literature, there are case series reports. However, it is currently unknown what the late-term prognosis of these cases will be. In our study, we aimed to examine the long-term prognosis of these patients.

MATERIALS AND METHODS

In this case series, we reported a total of 24 newly diagnosed GN cases after SARS-CoV-2 mRNA vaccines or SARS-CoV-2 infection. We included GNs that developed within 3 months after vaccination(one or more times vaccination) and infection in our study. Our study included patients who only had COVID infection and were not vaccinated, or patients who only had COVID vaccination and did not have COVID infection. We excluded patients whose symptom onset was more than 3 months after vaccination and infection. Patients who had any additional infection during this three-month period were also excluded. We reviewed all GN cases reported in the literature. We recorded the urea creatinine, albumin, proteinuria, albuminuria values at 1st, 3rd, 6th, 12th, and 24th month follow-ups from our patients' file records. We evaluated their treatment responses and long-term renal prognoses. The renal pathology results of all patients were evaluated by an experienced renal pathologist in our hospital's pathology unit. Clinical data and initial characteristics, vaccine type, onset of symptoms, laboratory data, treatments, and results were obtained from medical records. In our study, glomerulonephritis diagnosis, follow-up and response criteria were defined according to the KDIGO guideline.

Patients with postvaccination glomerulonephritis and patients with postinfectious glomerulonephritis were described separately.

Statistical Analysis

Since the sample size was quite small and analytical statistics were not applied, we used descriptive statistics in this report.

Our study is original and is not being evaluated in any other journal. We would like to state that the authors have no conflict of interest and all ethical rules regarding the article have been followed

Written informed consent was obtained from the participants and an ethics committee decision was obtained by the ethics committee of our hospital with 29/11/2024 date and 2024/010.99/10/10 permission number.

RESULTS

In addition to the basic demographic and clinical characteristics of newly diagnosed GNs after SARS-CoV-2 vaccination and infection; 2-year long-term follow-up and prognosis of the patients were reported. A total of 24 patients were evaluated. GN developed after vaccination in 18 patients (75%) and after infection in 6 patients (25%). The mean age of our patients was 49 (min-max: 22-81). Eleven of them were female (49%). The most common GN in our case series was membranous glomerulonephritis (MN) (13 of 24, 54%). Five patients had IgA nephropathy (IGAN) (5 of 24, 20%), 3 had idiopathic immune complex glomerulonephritis (ICGN), 1 had anti-glomerular basement membrane disease (Anti-GBM), 1 had minimal change disease (MCD) and 1 had MPO-ANCA associated glomerulonephritis. The mean age of the 18 patients who developed GN after vaccination was 51.7 (min-max: 31-81). Eleven patients were male and 7 were female. The most common GN after vaccination was membranous nephritis (12, 67%). Two patients were diagnosed with IGA nephritis (11%), 2 patients with idiopathic ICGN (11%), 1 patient with MPO ANCA vasculitis (5.5%) and 1 patient with MCD (5.5%). Seventeen of the 18 patients (94%) who developed GN after COVID-19 vaccination had received BNT162b2 (Pfizer) vaccination. There was 1 patient who had not received mRNA vaccination (Sinovac). Fifteen of the 17 patients who received mRNA vaccination had received at least 2 doses of vaccine. Nine of the patients applied after the 3rd dose, 6 after the 2nd dose, and 3 after the 4th dose. The mean duration of symptom onset was 28.3 (min-max: 4-90) days. 16 patients applied with complaints of edema. The initial symptom in two patients was acute renal failure. The mean serum creatinine level at the time of diagnosis was 1.09 (min-max: 0.4-3.1) mg/dl. Eight of the 12 MN patients had microscopic hematuria. The mean proteinuria of the patients was 7.02 g/day. The mean serum

albumin level was 2.76 g/dl. The initial clinical and laboratory features of our 18 patients who

developed GN after Covid 19 vaccination are presented in Table 1.

The mean age of 6 patients who developed GN after

SARS-CoV-2 infection was 39.5 (min-max: 22-64). 4 were female and 2 were male. 3 patients were diagnosed with IGAN, 1 patient with MN, 1 idiopathic ICGN, and 1 ANTI-GBM. The mean duration of symptom onset after infection was 30.5 (min-max: 18-50) days. 4 patients presented with edema; 1 patient with dark urine color; and 1 patient with nausea and vomiting. The patient with rapidly progressive glomerulonephritis had a creatinine level of 23 mg/dl at presentation. The other patients' creatinine levels at presentation ranged from 0.4 mg/dl to 1.5 mg/dl. The mean proteinuria amount of the patients was 7.1 g/day. The mean serum ablbumin level was 3.86 g/dl. The initial clinical and laboratory features of our 18 patients who developed GN after SARS-CoV-2 infection are presented in Table 2.

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

Case	Age	Sex	Diagnosis	Vaccine			Onset after which dose	Onset time (day)	Presenting symptoms	SCr (mg/dl)	Urine RBC (/HPF)	Urine protein (g/day)	SAlb (g/dl)
				B	S	T							
1	31	M	MN	2			2nd	27	Edema	0.9	15	1.5	2.2
2	48	M	MN		2	1	3rd	25	Edema	0.8	1	11.7	1.7
3	62	M	MN	2	2		4th	90	Edema	0.9	17	16.6	2.1
4	67	M	MN	2	2		4th	20	Edema	1.2	22	11	2.5
4	53	F	MN	2	2		4th	7	Edema	0.5	14	7.2	2.5
6	31	M	MN	3			3rd	60	Edema	0.9	23	5.1	3.5
7	34	M	MN	2			2nd	23	Edema	1.6	2	10.6	2.7
8	71	M	MN	3			3rd	63	Edema	0.6	2	3.8	3.4
9	65	M	MN	2			2nd	37	Edama	1.5	9	8.4	2.0
10	41	F	ICGN	1	2	1	3rd	5	Edema	0.5	22	3	2.3
11	50	M	MN	2			2nd	5	Edema	0.6	8	8	2.5
12	51	M	MPO ANCA VASCULIT	3			3rd	4	AKI	3.1	93	4.7	3.4
13	51	F	MN	3			3rd	70	Edema	0.4	32	4.5	3.2
14	48	F	MCD	2			2nd	30	Edema	0.4	0	3.2	3.8
15	32	M	IGAN	3			3rd	32	AKI	2.2	19	5.6	3.5
16	81	F	MN	1	2		3rd	2	Edema	1.2	2	5.4	2.8
17	75	F	IGAN	2			2rd	6	Edema	1.38	44	14	2.7
18	40	F	ICGN	3			3rd	4	Edama	1.0	36	2.1	2.9

AKI: acute kidney injury; F: female; HPF: High-powered field; IgAN: IgA nephropathy; ICGN: Immune-complex glomerulonephiritis; M: male; MCD: Minimal change disease; MN: Membranous nephropathy; MPO-ANCA: Myeloperoxidase-antineutrophilic cytoplasmic antibody; RBC: Red blood cell; Salb: Serum albumin; SCr: Serum creatinine; B: Pfizer-BioNTech, S: Synovac, T:Turcovac

Table 2. Characteristics of initial presentation of patients with newly diagnosed glomerulonephritis post–COVID-infection.

Case	Age	Sex	Diagnosis	Onset time after Covid 19 (day)	Presenting symptoms	SCr (mg/dl)	Urine RBC (/HPF)	Urine protein (g/d)	SAlb (g/dl)
1	37	F	IgA	25	Edema	1.5	2	4.8	3.4
2	64	M	MN	18	Edema	1.1	0	9.6	3
3	25	F	IgA	26	Edema	1.5	47	5.0	3.9
4	22	F	ICGN	50	Edema	0.4	14	1.2	4.4
5	30	M	IgA	45	Darkening of urine color	1.0	19	2.3	4
6	59	F	RPGN (Anti GBM)	19	Nausea Vomiting (ARF)	23	49	19.7	2.5

F: Female; HPF: High-powered field; IgAN: IgA nephropathy; ICGN: Immune-complex glomerulonephiritis; M: Male; MCD: Minimal change disease; MN: Membranous nephropathy; MPO-ANCA: Myeloperoxidase-antineutrophilic cytoplasmic antibody; RBC: Red blood cell; Salb: Serum albumin; SCr: Serum creatinine.

Table 3. Treatment and follow-up of patients with newly diagnosed glomerulonephritis post–COVID-19 vaccination

Case	Diagnosis	Treatment	SCr (mg/dl)	Urine protein g/d)	SAlb (g/dl)	Response (3.mo)	Treatment	SCr (mg/dl	Urine protein g/d)	SAlb (g/dl)	Response (6.mo)	Treatment	SCr (mg/dl	Urine protein g/d)	SAlb (g/dl)	Response	
1	MN	CsA+Steroid	0.9	12.5	2.7	NR	Cyc+ high dose steroid	0.8	2.9	3.4	R		1	0.2	4.5	R	nüks
2	MN	Cyc+ high dose steroid	0.7	6.8	1.9	R	Cyc+ high dose steroid	0.7	0.3	4.2	R		0.8	3.5	4.3	nüks	PR
3	MN	Cyc+ high dose steroid	0.8	11.9	2.1	NR	Cyc+ high dose steroid	0.9	5	2.2	NR	RTX	NA				
4	MN	Cyc+ high dose steroid	0.9	9.6	2	NR	RTX	1.1	4.1	2	NR	EXİTUS					
5	MN	Cyc+ high dose steroid	0.6	5.8	2.6	NR	Cyc+ high dose steroid	0.6	11	2.7	R		0.7	0.3	4.4	R	R
6	MN	Conservative	0.9	5.1	3.4	NR	RTX	1.1	10.6	3.1	R		1	1.8	3.9	R	nüks
7	MN	Cyc+ high dose steroid	1.4	4.1	2.5	R	Cyc+ high dose steroid	1.1	0.2	3.6	R	NA					
8	MN	Cyc+ high dose steroid	0.8	4.5	3.8	NR	NA										
9	MN	Cyc+ high dose steroid	2.1	6.1	1.9	R	Cyc+ high dose steroid	1.0	3	2.8	NR	NA					
10	ICGN	Mmf +1mg/kg steroid	0.6	3.6	2.4	NR	Mmf +1mg/kg steroid	0.5	5.4	2.5	NR	Mmf +1mg/kg steroid	0.5	2.7	3.2	PR	PR
11	MN	RTX	0.7	3.9	2.8	NR	RTX Maintence	0.7	4.6	3.4	R	RTX Maintence	0.5	0.1	4.6	R	R
12	MPO ANCA VASCULIT	RTX	2.6	6.2	3.2	PR	RTX Maintence	1.8	2.4	3.5	PR	RTX Maintence	1.4	0.8	3.5	PR	PR
13	MN	RTX	0.5	1.7	3.8	PR	RTX	0.5	0.5	3.8	R	Conservative	0.5	0.1	4.2	R	R
14	MCD	1MG/KG STREOID	0.5	3.7	3.7	NR	CyA	0.6	4.5	3.9	NR	CyA	0.6	3.5	4	NR	NR
15	IGA	PULSE STEROID	2.7	5.5	3.4	NR	STEROID MAINTENCE	2.6	1.2	3.6	NR	HEMODIALYSIS+ RENAL TRANSPLANTATION					
16	MN	STREOID+CyA	1.4	3.2	2.9	NR	STREOID+CyA	1.5	1.2	3.3	PR	CyA	1.3	0.4	4.2	R	NUKS+RTX
17	IGA	1MG/KG STREOID	1.28	2.2	3.5	NR	LOW DOSE STREOID	1.4	0.6	4.3	PR	Conservative	1.3	0.1	4.3	PR	PR
18	ICGN	MMF+ STEROID	0.8	1.1	3	PR	MMF+ STEROID	0.7	0.6	3.3	R	Mmf+Steroid	0.5	0.1	4.7	R	R

CA: Cylosprine; Cyc: Cylophospamide; F: Female; IgAN: IgA nephropathy; ICGN: Immune-complex glomerulonephiritis; M: Male; MCD: Minimal change disease; MN: Membranous nephropathy; MPO-ANCA: Myeloperoxidase-antineutrophilic cytoplasmic antibody; MMF: Mycofenolat; RTX: Rituxımab; Salb: Serum albumin; SCr: Serum creatinine

Of the 12 patients diagnosed with MN after vaccination, 7 received high-dose steroids and cyclophosphamide as initial treatment; 2 received steroids + cyclosporine; and 2 received rituximab. 1 patient was followed up with only conservative treatment. The patients' 3rd and 6th month treatment responses were evaluated. 8 patients were unresponsive at the 3rd month follow-up. Their treatments were revised appropriately. 3 patients were unresponsive at the 6th month follow-up. Their treatments were revised appropriately. 1 patient died at the 1st year follow-up. 2 patients did not come for follow-up. 1 patient developed relapse. 3 out of 7 patients developed relapse at the 2nd year follow-up. 3 patients are being followed up in remission. 1 patient is being followed up in partial remission.

One of the two patients diagnosed with IGAN was given pulse steroid + maintenance, and the other was given 1mg/kg/day steroid treatment. In the 3rd month follow-up, both of them were unresponsive. In the 6th month follow-up, partial remission was achieved in 1 patient. The other unresponsive patient was started on hemodialysis in the 11th month. Renal transplantation was performed afterwards. The other patient is being followed up with conservative treatment in partial remission.

MMF + steroids were given to 2 patients diagnosed with idiopathic ICGN. Partial remission was achieved in 1 patient. The other patient was unresponsive. Treatments were extended to 6 months. One patient entered remission in the 6th month. The other patient was unresponsive. Partial remission was achieved in the unresponsive patient in the 1st year. The other patient is being followed up in remission. The patient who developed MPO-ANCA vasculitis was given RTX treatment. Partial remission was achieved in the 3rd month. He is still being followed up in partial remission with maintenance RTX treatment. The patient diagnosed with MCD was started on 1mg/kg/day steroids. Treatment was changed due to lack of response in the 3rd month. Currently being followed with cyclosporine + conservative treatment without response. The treatment responses and follow-ups of the patients are presented in Table 3.

Treatments given to patients who developed GN after SARS-CoV-2 infection are presented in Table 4. One patient diagnosed with idiopathic ICGN is being monitored in remission. While 2 patients continue hemodialysis, 3 patients are being monitored in our outpatient clinic due to chronic renal failure.

DISCUSSION

We will start our discussion flow by discussing GNs seen after vaccination in accordance with our tables, and then continue by discussing denovo GNs developing after sars cov2 infection.

A) GNs developing after vaccination: Our case series is one of the large case series reported after SARS-CoV-2 vaccination. In our series, unlike most other series, we only examined the development of denovo glomerulonephitis. We did not include recurrent GN cases in our series. When the literature on this subject is examined, in a recent article they wrote in 2021, Klomjit et al.[2] reported 13 cases of GN associated with SARS-CoV-2 vaccination (denovo+recurrent). In another case series published by Caza et al.[14] in 2021, 29 cases were presented. In this series, 28 of the GNs that developed de novo were in the

Table 4. Treatment and follow-up of patients with newly diagnosed post–COVID-19 enfections

			RESPONSE									
			1(mo)			6(mo)			1(y))			2(y)
Case	Diagnosis	Treatment	SCr (mg/dl)	Urine protein (g/d)	SAlb (g/dl)	SCr (mg/dl)	Urine protein (g/d)	SAlb (g/dl)	SCr (mg/dl)	Urine protein (g/d)	SAlb (g/dl)	
1	IgAN	High dose steroid	1.5	2.9	3.8	1.8	2.1	3.6	2.2	0.3	4.3	Stage 4 CKD
2	MN	Cyc+high dose streoid	1.6	10.7	1.8	1.6	7.6	1.7	1.8	15.4	2.4	HD
3	IgAN	Steroid	1.6	2.7	3.9	1.6	3.1	3.9	2.6	3.2	3.8	Stage 5 CKD
4	ICGN	MMF+ steroid	0.4	0.3	3.8	0.5	0.1	5	0.5	0.1	4.8	Remission
5	IgAN	Conservative	1.3	1.2	4.5	1.1	1.1	4.5	1.4	1.3	3.9	Stage 2 CKD
6	RPGN (Anti GBM)	Steroid	The patient has been undergoing hemodialysis since onset after diagnosis.									

Cyc: Cylophospamide; F: Female; IgAN: IgA nephropathy; ICGN: Immune-complex glomerulonephiritis; M: Male; MCD: Minimal change disease; MN: Membranous nephropathy; MMF: Mycofenolat; Salb: Serum albumin; SCr: Serum creatinine.

native kidney, while 1 was seen in a renal transplant patient. In the SARS-CoV-2 related incidence study compiled by Diebold et al.[15] from all country pathology records in Switzerland in 2021, 229 patients were presented. In 2022, Lim et al.[16] presented 5 cases. In the study conducted by Kim et al.[1] in South Korea, 19 cases of GN developed after vaccination and 7 cases after SARS-CoV-2 infection were presented. When the number of cases in the series published in the literature is examined, we think that our series will contribute to the literature. The average age of the 18 patients who developed GN after vaccination (F/M: 11/7) was 51.7. The age of the patients included in our study ranged from 31 to 81 (average 51 years). This wide age range is also consistent with the findings in other studies. Renal problems after vaccination have been reported in people between the ages of 13 and 80 (17). 94% of patients who developed GN after SARS-CoV-2 vaccination had received the BNT162b2 (Pfizer) vaccine. There was 1 patient who had not received the mRNA vaccine (Sinovac). 85% of those who received the mRNA vaccine had received at least 2 doses of the vaccine. Nine of the patients presented after the 3rd dose, six after the 2nd dose, and three after the 4th dose. In most of the patients in our study, symptoms indicating renal problems appeared after the second dose of the vaccine. However, these symptoms were also seen in a period starting 3 days after the first dose and extending up to ten weeks after the second dose. In the studies conducted by Thammathiwat et al,[17] the majority of cases developed GN after mRNA vaccinations and after the second dose, similar to our series. The literature shows that similar problems can occur even just a few hours after the first dose.[18-23] In fact, the development of glomerulonephritis after vaccination has been reported in animal models before and is especially seen in GN types such as IgAN and MCD.[21,22] Since mRNA vaccines trigger a stronger immune response, it can be expected that they increase the risk of GN compared to other types of vaccines. However, this situation is not seen in all vaccinated individuals, but in a very small portion. Considering that there may be cases not reported in the literature, the exact incidence is unknown. GN after SARS-CoV-2 vaccination is a rare condition. Currently, our Ministry of Health and vaccine committees recommend that SARS-CoV-2 vaccination continue, considering the general benefits of vaccines. In our series, the mean symptom onset time was 28.3 (min-max: 4-70) days. 16 patients applied with edema. The initial symptom in two patients was acute renal failure. In some patients in our study, there may have been findings indicating kidney damage (high creatinine, protein loss in urine, or microscopic blood) between the first and second doses, but these patients may not have seen a doctor at that time, so this may not have been noticed. In addition, 7 patients who had problems after the first dose also received a second dose, since this condition was not thought to be related to the vaccine at that time. In our series, the most common GN after vaccination was membranous nephritis (12, 67%). In the study conducted by Klomjit et al.,[23] they found membranous nephritis as the second most common GN, unlike our series. This may be due to different immune responses of different ethnicities or the inadequacy of the sample size due to the small number of cases. Two patients were diagnosed with IGA nephritis (11%), two patients with idiopathic immune complex (11%), one patient with MPO ANCA vasculitis (5.5%), and one patient with MCD (5.5%). In another study conducted by Maas et al.,[24] podocytopathies (minimal change disease + membranous GN) were presented as the most common nephropathies after vaccination.[24] Since 10 of our patients diagnosed with MN were high risk, they were given cyclophosphamide and steroid treatment. Rituximab was given to two patients with intermediate risk. During follow-up, 2 patients developed recurrence in the 2nd year. Appropriate second-line treatment was given to the patients who developed recurrence. These patients are continuing to be followed up in our outpatient clinic. Immunoglobulin A nephropathy (IgAN) has been identified as a possible outcome following the administration of COVID-19 vaccines, especially those using mRNA technology. Numerous studies suggest that the onset of IgAN may occur shortly after vaccination and may be associated with a variety of clinical presentations and prognoses. One case series determined that 25% of individuals with vaccine-associated glomerular diseases were diagnosed with IgAN, which usually occurred within two weeks of vaccination.[25] Another study documented a single case of IgAN among ten cases of biopsy-confirmed glomerular disease after vaccination, suggesting that preexisting conditions may be exacerbated by the vaccine.[26] Pathogenic Mechanisms Experimental evidence suggests that administration of a second dose of mRNA vaccine may trigger IgAN through activation of the immune system with specific changes in both vaccination and IgAN-associated gene expression.[27] Most patients diagnosed with IgAN after vaccination had favorable prognoses and significant improvement was observed in follow-up evaluations.[25] Immunosuppressive therapy methods were frequently used, reflecting the necessity of meticulous management of renal complications that occur after vaccination.[25] Although the association between COVID-19 vaccine and IgAN is clearly seen, it is important to recognize that these events are relatively rare compared to the total vaccinated population. Continued research is mandatory to comprehensively elucidate the mechanisms underlying these observations and their long-term consequences. One of the two patients who developed IGA nephritis after SARS-CoV-2 vaccination did not respond to treatment. Hemodialysis was initiated. He subsequently underwent renal transplantation. The other patient responded to steroid therapy. One of our patients with Mpo vasculitis is being followed under rtx maintenance therapy. When we reviewed the literature, 15 out of 16 patients required immunosuppression for vasculitis. Thirteen patients were given steroids and other agents, while 2 patients were given only steroids. Three patients received plasmapermesis; 2 of them received cyclophosphamide and 1 received rituximab. Five patients (31.3%) required dialysis and 2 were

able to stop dialysis after treatment. Only 2 out of 16 patients achieved complete recovery, 10 had permanent renal dysfunction, 3 remained dialysis dependent and 1 patient died.[28,29] When we interpret the literature, our patient's response to treatment is pleasing. Our minimal change patient did not respond to steroids and is still being followed up. We re-evaluated the steroid unresponsiveness in this patient. There were 11 glomeruli in the biopsy. The biopsy material contained 10% medulla. Considering the treatment response, this case may also be an undiagnosed FSGS case. 2 of our patients were diagnosed with denovo idiopathic immune complex glomerulonephritis and are being followed up in remission. As a result, in the long-term follow-up of patients who developed GN after SARS-CoV-2 vaccination; 3 out of 18 patients had complete remission in the 3rd month and 3 had partial remission. In the 6th month, 11 out of 18 patients had remission (partial+complete). In the 1-year follow-up, 1 patient had relapse. In the 2-year follow-up, 3 patients who were in remission had relapse. Our patients are still being followed up in our outpatient clinic.

B) Our GNs developing after Sars cov 2 infection: In our series, 3 of the 6 patients who developed GN after covid infection had IGA, 1 had MN, 1 had ICGN. 1 had anti-GBM. 2 of the 3 patients who developed IGA nephritis were followed up with immunosuppressive treatment and 1 with conservative treatment. Patients receiving steroid treatment are currently being followed up with stage 4-5 CKD diagnosis and still without entering HD. Our patient with membranous GN diagnosis is entering HD. Our patient with ICGN diagnosis is being followed up in remission. Our patient with anti-GBM diagnosis applied with RPGN clinic. Despite plasmapheresis and appropriate immunosuppressive treatment, hemodialysis continues. The ICGN patient is still being followed up in our outpatient clinic after entering remission with appropriate treatment. The renal biopsy findings of Klomjit et al.[23] after COVID 19 infection and the prognoses of the patients were evaluated. In their report published in 2023 by Wang et al.,[27] in their large case study examining GNs developing after COVID-19 infection and vaccination between 2021 and 2023, among patients with primary GN, COVID-19 infection was severe in 1 out of every 8 cases and was associated with subsequent deterioration, whereas GNs developing after vaccination were milder. These results support COVID-19 vaccination for the following. In our series, similar to this series, the GN treatment response seen after COVID infection seems to be worse than GN after vaccination. Due to the small number of cases, we could not perform group statistics in our series. We can only present our clinical observations. The relationship between glomerulonephritis and SARS-CoV-2 infection is multifaceted and includes both direct effects of the virus and potential vaccine-related triggers. Studies show that glomerular diseases, especially IgA nephropathy and podocytopathies, are frequently reported in patients after infection. After SARS-CoV-2 infection, common diagnoses include podocytopathies (25.1%) and IgA nephropathy (16.7%).[1] A significant increase in ANCA-associated vasculitis was observed, with 13.9% of patients experiencing this condition post-infection, compared to 5.6% in pre-COVID cohorts.[3] It is noteworthy that many of the cases of glomerulonephritis observed after COVID-19 vaccination were actually observed during COVID-19 infection itself. The GNs associated with this condition include the more common anti-GBM disease and ANCA-associated vasculitis, as well as other types such as podocytopathy and collapsing glomerulopathy. The pathophysiology of glomerulonephritis associated with COVID-19 infection is quite complex. Not only irregularities in the immune system, but also direct damage to kidney cells (podocytes) by the virus may be effective in the development of this condition. So why do some people develop new glomerulonephritis after vaccination? The answer to this question may lie in imbalances in the underlying immune system. In other words, an immune system disorder that already exists in some people may exaggerate the immune response to the vaccine, leading to glomerulonephritis. It is possible that the immune response to the vaccine mimics the response to natural infection, resulting in glomerulonephritis in susceptible individuals. Overactivity of both the cellular (e.g., relapses of minimal change disease) and antibody-mediated (e.g., relapses of PLA2R-associated membranous nephropathy) immune system may play a role in the recurrence of glomerulonephritis after vaccination.

The limitations of our study are the small number of patients. In addition, statistical analysis between the two groups could not be performed due to the small number of patients. We only presented our observational findings.

Conclusion

In summary, the development of glomerulonephritis after COVID-19 vaccination and infection is closely related to imbalances in the underlying immune system. The immune response to the vaccine and infection may trigger an already existing tendency for glomerulonephritis in some individuals or may cause the emergence of new glomerulonephritis. This situation can be explained by different mechanisms such as both the direct damage caused by the virus to the kidney cells and excessive reactions in the immune system. Long-term follow-up results of glomerulonephritis developing after vaccination and infection are particularly limited in the literature. What is the prognosis and treatment response in GN patients after the Covid pandemic? We shared the long-term follow-up results of our GN patients after vaccination and infection to contribute to the answer to this question. Based on our clinical observations, we can say that the treatment responses of our patients who developed GN after infection were poor. As a result, despite the current vaccine discussions, we would like to emphasize once again the importance of community vaccination in terms of protection.

Ethics Committee Approval

The study was approved by the Kartal Dr. Lütfi Kırdar City Hospital Ethics Committee (Date: 29.11.2024, Decision

No: 2024/010.99/10/10).

Informed Consent

Retrospective study.

Peer-review

Externally peer-reviewed.

Authorship Contributions

Concept: S.Y., P.O.; Design: S.Y., E.O.; Supervision: S.Y., P.O.; Fundings: S.Y., E.O.; Materials: S.Y., P.O.; Data collection &/or processing: S.Y., E.O.; Analysis and/or interpretation: S.Y., P.O.; Literature search: S.Y., E.O.; Writing: S.Y., P.O.; Critical review: S.Y., E.O.

Conflict of Interest

None declared.

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SARS-CoV-2 Enfeksiyonu ve Aşılamadan Sonra Gelişen Glomerülonefritlerin Uzun Dönem Prognozları

Amaç: Bu çalışmanın amacı, Şiddetli Akut Solunum Yolu Sendromu Koronavirüs 2 (Sars-Cov-2) enfeksiyonu ve aşılaması sonrası gelişen glomerülonefritli hastaların uzun dönem prognozunu araştırmaktır.

Gereç ve Yöntem: Bu vaka serisinde, SARS-CoV-2 mRNA aşısı veya SARS-CoV-2 enfeksiyonundan sonra yeni teşhis edilen toplam 24 GN vakasını bildirdik. Hastalarımızın dosya kayıtlarından 1., 3., 6., 12. ve 24. ay takiplerinde üre kreatinin, albümin, proteinüri, albüminüri değerlerini kaydettik. Tedavi yanıtlarını ve uzun vadeli renal prognozlarını değerlendirdik.

Bulgular: Toplam 24 hasta değerlendirildi. GN 18 hastada (%75) aşılamadan sonra, 6 hastada (%25) enfeksiyondan sonra gelişti. Olgu serimizdeki en sık GN membranöz glomerülonefrit (MN) idi (24 hastanın 12'si, %50). 5 hastada IgA nefropatisi (IGAN) (%20), 3 hastada idiyopatik immün kompleks glomerülonefriti (ICGN,%12.5), 1 hastada anti-glomerüler bazal membran hastalığı (Anti-GBM), 1 hastada minimal değişiklik hastalığı (MCD) ve 1 hastada MPO-ANCA ilişkili glomerülonefrit vardı. Hastalardan sadece 4'ü 2. yılda remisyonda takip edilmektedir.

Sonuç: Aşılama ve enfeksiyondan sonra gelişen glomerülonefrit (GN) ile ilgili uzun vadeli takip verileri literatürde hala nadirdir. Aşılama ve enfeksiyondan sonra durumu geliştiren GN hastalarımızın uzun vadeli takip sonuçlarını sunarak bu bilgi boşluğunu gidermeye katkıda bulunmayı amaçlıyoruz. Klinik gözlemlerimiz, enfeksiyondan sonra GN geliştiren hastaların daha zayıf tedavi yanıtları sergilediğini göstermektedir. Bu nedenle, devam eden aşı tartışmalarına rağmen, toplum aşılamasının kritik bir koruyucu önlem olarak önemini yineliyoruz.

Anahtar Sözcükler: Aşılama; glomerulonefrit; Sars-Cov-2 enfeskiyonu.