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De Novo Glomerular Diseases after COVID-19 Vaccination: Consequence or Coincidence?

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Abstract

Introduction: Vaccination against COVID-19 has proven highly effective in preventing severe forms of the disease. However, the literature reports several cases associating renal damage and the anti-COVID vaccine. The aim of our work was to report a case series of patients who developed glomerulopathy after anti-COVID-19 vaccine. We evaluated the type of vaccine, the clinico-biological profile, and the anatomopathological, therapeutic and evolutionary aspects. **Material and Methods:** Prospective descriptive study conducted at the Nephrology Department of CHU IbnSina in Rabat between December 2021 and June 2022 including 9 patients who presented with glomerulopathy after the 1st dose of anti-COVID-19 vaccine. We excluded patients followed for nephropathy. **Results:** The mean age of our patients was 33 ± 16 years with a sex ratio of 0.8. Six patients received an inactivated vaccine, 2 patients received a mRNA vaccine and 1 patient received a viral vector vaccine. The mean delay between the onset of signs and the date of the first vaccine dose was 3.1 +/− 0.65 months (1 - 6 months). All patients had a nephrotic syndrome, 2 pure and 7 impure: 3 patients had acute renal failure and microscopic hematuria, 2 patients had microscopic hematuria and 2 patients had acute renal failure. Histologically, focal segmental glomerulosclerosis (FSGS) was noted in 4 patients, lupus nephropathy in 3, and membranous nephropathy (MN) in 2. Specific treatment was administered to each patient, depending on the histological type of renal involvement and the context. After 6 months, complete remission was achieved in 5 patients, with no improvement in 2, and one patient was placed on hemodialysis. One patient died of another cause. **Conclusion:** The causal link between anti-COVID 19 vaccination and renal disease is highly probable, but remains to be confirmed.

Keywords

Glomerulopathy, Vaccination, COVID-19

1. Introduction

Vaccination against COVID-19 has proven highly effective in preventing severe forms of the disease. However, studies have reported several immune-mediated reactions, including cases of myocarditis and de novo glomerulonephritis or relapses occurring after COVID-19 vaccination. Nevertheless, the number of cases was limited, and histopathological abnormalities were heterogeneous [1] [2] [3].

Associations between vaccines and de novo glomerulopathies have frequently been reported in the past. Specifically, minimal change disease has been described following various types of vaccines such as influenza, pneumococcal, hepatitis B, and tetanus-diphtheria-polio [4], although the pathogenic mechanism remains unclear.

Thus, in our study, we report nine cases of de novo glomerulopathy following COVID-19 vaccination confirmed by renal biopsy. We evaluated the type of vaccine, clinical-biological profile, as well as anatomopathological, therapeutic, and evolutionary aspects of our patients.

2. Material and Methods

This study is a prospective descriptive investigation conducted at the Nephrology Department of IbnSina University Hospital in Rabat between December 2021 and June 2022, encompassing 9 patients.

All patients exhibiting new-onset proteinuria and/or impaired renal function in the context of glomerulopathy, as confirmed by renal biopsy within 6 months of receiving the first dose of an anti-COVID-19 vaccine, were included in our study. Patients with a history of renal disease were excluded.

Clinical and biological data were extracted from medical records and documented on a predefined form. This form was completed for each selected case.

We collected demographic data (age; gender) and personal and family medical history of the patients.

We recorded the type of COVID-19 vaccine administered and dosage, and interval between the first vaccine dose and symptom onset.

We specified circumstances of diagnosis: hypertension, renal failure, macroscopic hematuria, and edema.

The clinical-biological profile of the patients was recorded at admission and each month throughout the study period. The parameters studied are as follows:

- Clinical manifestations: hypertension, renal failure, macroscopic hematuria, urinary tract infection.
- Laboratory findings including serum creatinine levels and 24-hour proteinuria.

We reported the outcome of patients 6 months after the onset of follow-up.

Complete remission is defined as a reduction of proteinuria to <0.3 g/day and serum albumin >30 g/l and normal renal function.

Partial remission is defined as a reduction of proteinuria to 0.3 - 3 g/day and a decrease >50% from baseline, and stable serum creatinine.

Spontaneous remission is defined as a reduction of proteinuria to <0.3 g/day and serum albumin >30 g/l and normal renal function without an immunosuppressive treatment.

Data were analyzed utilizing IBM SPSS Statistics 25 software. Quantitative variables were expressed as either mean ± standard deviation or median with interquartile range.

3. Results

We reported 9 patients who all presented with de novo glomerulopathy occurring after COVID-19 vaccination. The mean age of our patients was 33 ± 16 years, with a sex ratio of 0.8.

The mean delay between the onset of signs and the date of the first vaccine dose was 3.1 +/− 0.65 months (1 - 6 months).

Most of our patients received inactivated vaccine (6/9 patients), 2 patients received mRNA vaccine and only one patient received vector vaccine. All patients presented a nephrotic syndrome, including 5 with renal failure.

In our series, Focal segmental glomerulosclerosis (FSGS) was the most frequent glomerulopathy noted in 4 patients. These patients received oral corticosteroid therapy, with the exception of one patient who had osteogenesis imperfect a contraindicating corticosteroid therapy. Progression was marked by complete remission in 2 patients, spontaneous remission in the patient who did not take immunosuppressive therapy, and recourse to 2nd-line treatment with Rituximab in one patient.

Class IV lupus nephropathy was noted in 3 patients, all of whom received immunosuppressive therapy (corticosteroids and cyclophosphamide). In only one of these patients was the course favorable, with complete remission. However, one patient was put on dialysis because he showed signs of chronicity at renal biopsy, which could be explained by the long delay between the 1st dose of vaccine and the diagnosis of glomerulopathy. The last patient died of septic shock following pneumopathy.

And finally, membranous nephropathy (MN) was noted in 2 patients who received the Jha protocol (corticosteroid therapy and cyclophosphamide) with complete remission in one patient and recourse to Rituximab in the 2nd patient. Of these 2 patients, only one was PLA2R positive.

Table 1 summarizes the details of the 9 cases.

4. Discussion

Post-vaccination glomerulopathy (GN) has been reported by several research teams. While most cases have been associated with mRNA and vector-type vaccines [5]-[11], rare instances of GN linked to inactivated vaccines have also been documented [12].

Lebedev *et al.* first reported a case of minimal change disease (MCD) occurring on day 3 after the initial vaccine dose [13]. In the literature, MCD and IgA

Table 1. Demographic, clinico-biological, histological, therapeutic and evolutionary characteristics of the 9 patients.

	Age/Sex	ATCD	Symptome	Vaccine/Dose	Delay (Days)	Renal Biobsy	Creat (umol/L)	Treatment	Evolution
1	19/M	Aucun	NS + RF Hématurie	mARN/1	60	FSGS	132.6	Oral CT	CR
2	22/F	Ostéogenèse imparfaite	NS Hématurie	Inactivated Vaccine/2	7	FSGS	56.5	Symptomatic	SR
4	39/F	Aucun	NS	Inactivated Vaccine/1	90	FSGS	63.6	Oral CT	CR
3	21/F	Aucun	NS	Inactivated Vaccine/2	30	FSGS	49.5	OraL CT -> Ritux	No Remission
5	22/M	Aucun	NS Hématurie	mARN/1	7	MN	64.5	Jha Protocol	CR
6	67/M	Aucun	NS + RF	Inactivated Vaccine/3	80	MN	221	Jha Protocoe -> Ritux	No Remission
7	43/F	Aucun	NS + RF	Inactivated Vaccine/2	120	LN IV	137	CT + CYC	CR
8	44/M	Aucun	NS + RF Hématurie	Inactivated Vaccine/1	90	LN IV	1547	CT + HD	Chronic HD
9	34/F	Aucun	NS + RF Hématurie	Vector/1	30	LN IV	884	CT + CYC + Ritux + HD	Death (septic shock)

M: male; F: female; ATCD: antecedent; NS: nephrotic syndrome; RF: renal failure; FSGS: focal segmental glomerulosclerosis; MN: membranous nephropathy; LN: lupus nephropathy; CR: complete remission; SR: spontaneous remission; HD: hemodialysis; CT: corticosteroid therapy; Ritux: rituximab; CYC: cyclophosphamide.

nephropathy are the most frequently observed glomerulopathies following COVID-19 vaccination [5] [6] [7] [8]. Subsequent studies have reported cases of membranous nephropathy (MN) [7] [9] [10], FSGS [7], and lupus nephropathy [11] [12]. All these glomerulopathies were observed in our study cohort.

In view of the cases reported in the literature, the onset of symptoms has been reported as early as a few hours or days after the first dose [14] [15]. In our case, most patients consulted us late, and it should also be noted that most had FSGS rather than IgA nephropathy, suggesting a rapid immune response.

This association between vaccine and glomerulopathy has long been reported in the medical literature. Acute onset of MCD has been described in adults after receiving influenza vaccine [4] [16]. However, this link is not limited to influenza vaccines and podocytopathies. Several cases of relapse of MCD have been reported after vaccinations against pneumococcus, smallpox, hepatitis B, tetanus, diphtheria, and pertussis [17]. For example, Rahim *et al.* reported the case of a 52-year-old patient who presented with a relapse of IgA nephropathy after a recombinant herpes zoster vaccine, and 2 years later recurred after vaccination

against COVID-19 [15]. Although coincidence cannot be ruled out, the temporal association between vaccination and glomerulopathies strongly suggests a potential pathway.

The pathogenesis remains unclear. Various hypotheses have been proposed, including immune system dysregulation in predisposed individuals or a mechanism of molecular mimicry. Vojdani *et al.* demonstrated immune reactivity between anti-COVID-19 antibodies and 28 tissue antigens [18]. These findings underscore the potential risk of autoimmunity with COVID-19 vaccines based on cross-reactivity between human tissues and the virus. Alternatively, it may be the activation of pre-existing asymptomatic glomerulopathy [19].

Upon comparison with various published studies, the overall prognosis appears favorable, with complete remission either spontaneously or after immunosuppressive treatment. In our series, two patients required second-line treatment, and one patient underwent chronic dialysis due to the lack of improvement and the presence of chronicity signs on renal biopsy. The last patient succumbed to septic shock following pneumonia. Longer-term follow-up is warranted to gain a better understanding of the trajectory and renal evolution of these patients.

5. Limitations

Although our sample size is limited, primarily due to the low incidence rate, it's imperative to recognize the possibility of overlooked cases.

Furthermore, our lack of long-term data on these patients poses another limitation. Although short-term outcomes appear promising, a comprehensive understanding necessitates prolonged follow-up.

Lastly, while we cannot definitively establish the vaccine's causative role in the development or relapse of glomerulonephritis, the temporal association certainly presents a compelling argument.

6. Conclusions

There are several case reports of different types of glomerulopathies following COVID-19 vaccination. Our paper reports a case series of patients with newly biopsy proven renal disease that developed within 6 months of vaccination. The causal link between COVID-19 vaccination and kidney disease is highly probable, but has yet to be confirmed.

Considering the billions of doses of anti-COVID vaccine administered, the relatively small number of cases observed suggests a low incidence of disease. However, the possibility of glomerulopathy should always be considered in patients presenting with nephrological symptoms after vaccination.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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