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Case Report

New-onset Nephrotic Syndrome with Minimal Change Disease Following Pfizer-BioNTech COVID-19 Vaccine: A Case Report and Literature Review

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Abstract

Background: Vaccination is underway in tremendous numbers worldwide while COVID-19 infection remains serious. Relapse of nephrotic syndrome following vaccination during the remission phase has been reported, and a causal relationship has been considered. However, new-onset nephrotic syndrome in the background of large-scale vaccinations over a short period of time may be incidental and unrelated to the vaccine.

Case Presentatio: A 40-year-old Japanese woman with no history of kidney disease developed nephrotic syndrome following the first dose of Pfizer-BioNTech COVID-19 vaccine, which rapidly resolved with corticosteroid pulse therapy. She presented with a significant weight gain and anasarca 1 week after the vaccination. Laboratory examination revealed massive proteinuria (16.8 g/day) and severe hypoalbuminemia (1.2 g/dL). A renal biopsy revealed minimal change disease. She was treated with steroid pulse therapy and oral predonisolone (40 mg/day). She recovered completely 1 week after the steroid therapy. Throughout the course of her illness, no acute kidney injury or renal dysfunction were observed.

Conclusion: Nephrotic syndrome is an extremely rare side effect when compared to the number of vaccinations; and it does not warrant witholding the vaccination as long as it is recognized that it is steroid-responsive.

Keywords: Covid-19 vaccine; Minimal change disease; Nephrotic syndrome; Steroids

Abbreviations: MCD: Minimal Change Disease; COVID-19: Coronavirus 19

Background

The pandemic of coronavirus disease-2019 (COVID-19) poses a multi-faceted challenge for healthcare systems across the world. The emergence of new vaccines was seen as a game-changer in the battle against this pandemic. Vaccination is underway in tremendous numbers worldwide while COVID-19 infection remains serious. Relapse of nephrotic syndrome following vaccination during the remission phase has been reported, and a causal relationship has been considered [1-3]. However, new-onset nephrotic syndrome in the background of large-scale vaccinations over a short period of time may be incidental and unrelated to the vaccine. We report a case of new-onset nephrotic syndrome characterized by Minimal Change Disease (MCD) following the first dose of Pfizer-BioNTech COVID-19 vaccine.

Case Presentation

A 40-year-old Japanese woman, who had no history of allergies or urinary abnormalities on her previous health examination, noticed foamy urine 5 days after receiving the first dose of Pfizer-BioNTech COVID-19 vaccine. On examination at the hospital 8 days after the vaccination, her blood pressure was 120/74 mmHg and pulse rate was 86/min; she was found to have anasarca and a significant weight gain of 4.4 kg. Laboratory examination revealed severe hypoalbuminemia, hypercholesterolemia, and massive proteinuria without hematuria (Table 1). A diagnostic workup for connective tissue disease was negative. Computed tomography images of her chest and abdomen did not show any significant abnormalities. Renal biopsy was performed the day after admission (9 days after the vaccination). The renal biopsy findings are shown in Figure 1. Light microscopy showed no obvious abnormalities, indicating the absence of tubulo-interstitial damage.(Figure 1a) Immunofluorescence staining was negative for immunoglobulins and complement factors (Figure 1b). Electron microscopy revealed epithelial foot process effacement (Figure 1c). These findings led to a diagnosis of MCD with nephrotic syndrome. Steroid pulse therapy (methylprednisolone 1000 mg/ day administered intravenously for three days) was started with a diagnosis of nephrotic syndrome, following which prednisolone 40 mg/day was administered orally (Figure 2). Twelve days after steroid therapy, her urinary protein decreased to 0.4 g/day, and her edema resolved with a 5-kg reduction in body weight. She achieved complete remission of nephrotic syndrome 13 days after the treatment and was discharged after 4 weeks with continued oral steroid treatment. She has been maintaining complete remission of nephrotic syndrome with tapered doses of oral steroids for more than 6 months after discharge.

Table 1. Laboratory findings

<Peripheral blood>		
WBC	5510	/μl
RBC	509	x10⁴/μl
Hgb	16.3	g/dl
Hct	49.4	%
Plt	12.4	x10⁴/μl
<Urine>		
pH	6.5	
SG	1.006	
Protein	(3+)	
	16.1	g/gCr
	14	g/day
Occult blood	(±)	
Glucose	(−)	
Keton	(−)	
<Urine sediment>		
RBC	4	/HPF
WBC	1	/HPF

<Blood chemistry>		
AST	22	IU/l
ALT	15	IU/l
ALP	56	IU/l
γGTP	143	IU/l
LDH	176	IU/l
CK	312	U/l
TP	5.6	g/dl
Alb	1.2	g/dl
TC	478	mg/dl
LDL-C	290	mg/dl
HDL-C	58	mg/dl
Na	138	mEq/l
K	3.9	mEq/l
Cl	104	mEq/l
BUN	10	mg/dl
Cre	0.58	mg/dl
UA	5.2	mg/dl
eGFR	90.3	ml/1.73m²/m
HbA1c	5.4	%

<Immunological findings>		
CRP	0.13	mg/dl
HBsAg	(−)	
HCV Ab	(−)	
TPHA	(−)	
IgG	350	mg/dl
IgA	171	mg/dl
IgM	119	mg/dl
C3	160	mg/dl
C4	38	mg/dl
CH50	67.7	IU/ml
P-ANCA	<10	U/ml
C-ANCA	<10	U/ml
Centromere Ab	(-)	
ANA	(-)	
Anti-dsDNA	<1.0	
Anti-CCP	7.5	

Table 1: Laboratory finding.

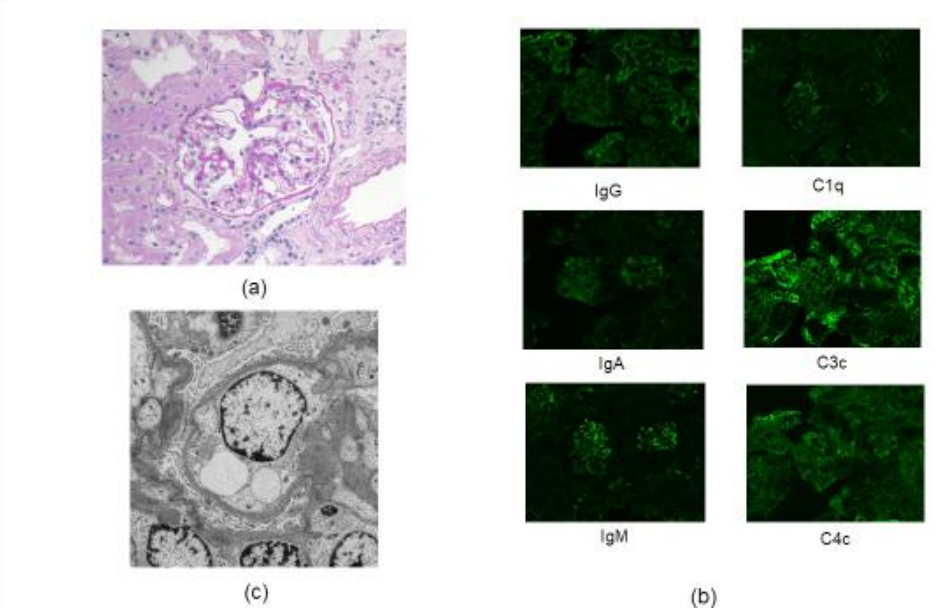

Figure 1: Renal biopsy findings: Light mocroscopy PAS stain (**a**) showed no obvious abnormalities, indicating the absence of tubulo-interstitial damage, immunofluorescence staining (b) was negative for immunoglobulins and complement factors and electron microscopy (**c**) demonstrating effacement of the epithelial foot process with no dense deposits.

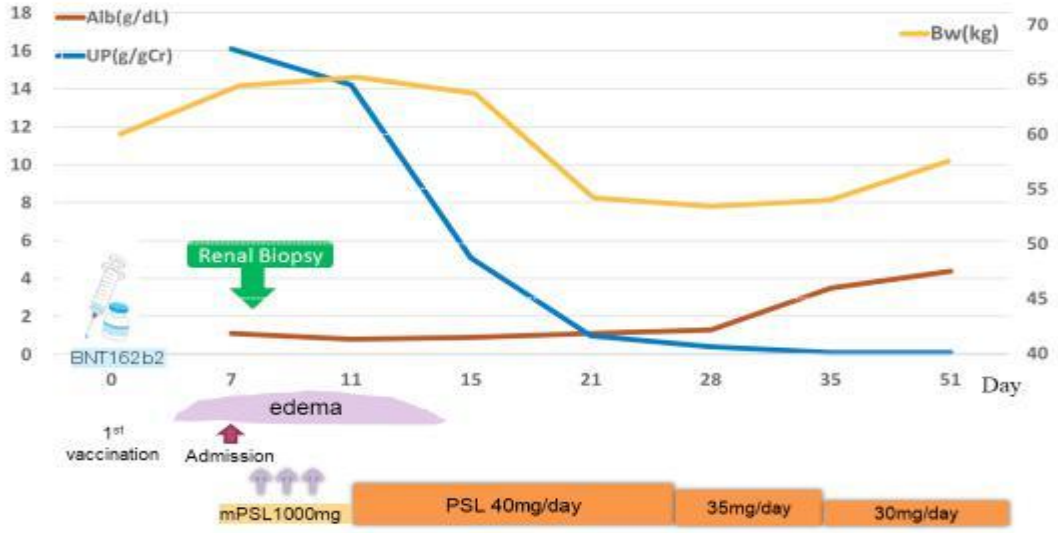

Figure 2: Clinical course: Clinical events and trends in serum albumin (g/dL), urinary protein (g/gCr) and serum creatinine (mg/dl)

Discussion

Vaccination is underway in tremendous numbers worldwide while COVID-19 infection continues to remain serious. By September 2022, the number of vaccinations has exceeded 323 million in Japan alone, which is a huge number when compared to previous vaccines. Relapse of nephrotic syndrome after vaccination during the remission phase has been reported [1-4], and a causal relationship has been considered. However, regarding new-onset nephrotic syndrome in the background of large-scale vaccinations over a short period of time, the vaccination may have been coicidental with the spontaneous onset of nephrotic syndrome. Two cases of nephrotic syndrome have

reportedly occured after administering the first dose of COVID-19 vaccine; a period of spontaneous remission was followed by a relapse after receiving the second dose of the vaccine [5,6]. These two cases were treated with steroids after the relapse of nephrotic syndrome and achieved complete remission [5,6]. Based on these cases, we believe that vaccination and new-onset of nephrotic syndrome may have a causal relationship, as in our case. The pathogenesis of COVID-19 vaccination-induced MCD and nephrotic syndrome remains unestablished. However, dysregulation of T-cell-mediated immunity is widely speculated to be the main cause. Increased production of permeability factors from enhanced type 2 T-helper cell activity causing cytokine release has been hypothesized as contributing to the development of MCD [7].

Recently, several cases of new-onset nephrotic syndrome after COVID-19 vaccination (Table 2) [8-24] have been reported from various countries. This indicates that the COVID-19 vaccine is used worldwide without regional differences; there is no gender or age difference with a wide age range (15-80 years). Apart from the messenger RNA vaccines (Pfizer-BioNTech, Moderna), adenovirus vector vaccines (Oxford AstraZeneca, Janssen, ChAdOx1) have also been used. The frequency by type of vaccine is proportional to the frequency of actual use. Mostly, the time to symptom-onset was about 1 week after the first vaccination as in our case, while IgA nephritis occurred one or a few days after the second dose [2]. It has been proposed that in "new onset of" IgA nephritis, IgA deposits were present before vaccination and that the vaccine only resulted in a "flare" [2]. Renal biopsy findings in all the cases were of MCD as in our case, except for one case of membranous nephropathy [10]. Although acute kidney injury was not present in our case, it was seen in 10 out of the 17 cases, and both nephrotic syndrome and acute kidney injury responded to steroid therapy.

Study	Country	Age/Sex	Types of vaccine	1st or 2nd	Symptom onset time after vaccination days	Renal pathology	AKI	Treatment	Response
8	Israel	50/M	Pfizer-BioNTech	1st	4 days	MCD	+	PSL	O
9	USA	63/F	Moderna	1st	7 days	MCD	+	mPSL + PSL	O
10	Singapore	70/M	Pfizer-BioNTech	1st	7 days	MN	+	ARB, Diuretics	×
11	India	19/F	ChAdOx1	1st	8 days	MCD	+	PSL	O
12	Canada	66/M	Pfizer-BioNTech	1st	10 days	MCD	+	Ramipril/PSL	O
13	Qatar	43/M	Moderna	1st	7 days	MCD	−	PSL	O
14	Qatar	45/F	Pfizer-BioNTech	1st	4 days	MCD	−	PSL/Furosemide	O
15	India	22/M	Oxford AstraZeneca	1st	14 days	MCD	−	PSL	O
16	Netherlands	61/F	Pfizer-BioNTech	1st	1 day	MCD	+	PSL	O
17	Japan	71/M	Pfizer-BioNTech	1st	7 days	MCD	−	PSL	O
18	Germany	31/F	Janssen	1st	3 days	MCD	−	mPSL + PSL	O
18	Germany	20/F	Pfizer-BioNTech	1st	5 days	MCD	−	PSL	O
19	Korea	51/M	Janssen	1st	7 days	MCD	+	PSL	O
20	USA	77/M	Pfizer-BioNTech	1st	7 days	MCD	+	PSL	×
21	Canada	71/M	Oxford AstraZeneca	1st	13 days	MCD	+	PSL	O
22	Netherlands	80/M	Pfizer-BioNTech	1st	7 days	MCD	+	PSL	O
23	Japan	22/M	Pfizer-BioNTech	1st	16 days	No data		PSL	O
24	Japan	15/M	Pfizer-BioNTech	1st	4 days	No data	−	PSL	O

	Our case	40/F	Pfizer-BioNTech	1st	5 days	MCD	–	PSL	O

Table 2: Reported cases of new onset nephrotic syndrome after COVID-19 vaccination.

Conclusion

Nevertheless, nephrotic syndrome is an extremely rare side-effect when compared to the number of vaccinations; and it does not warrant witholding the vaccination as long as it is recognized that it is steroid-responsive. Rather, the risk of COVID-19 infection in the unvaccinated is more serious. However, caution must be exercised for the second dose of COVID-19 vaccine in patinets with new-onset nephrotic syndrome. Our case is also being carefully followed up with tapering corticosteroids until the second dose. Therefore, considering the risk of COVID-19, we recommend vaccination keeping in mind the possibility of this side-effect. Further studies should be conducted and more case reports of new-onset nephrotic syndrome following COVID-19 vaccination are needed for us to understand this phenomenon better.

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