



Relapse of minimal change disease following the third mRNA COVID-19 vaccination: a case report and literature review

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Abstract

Mass vaccination is the most important strategy to terminate the coronavirus disease 2019 (COVID-19) pandemic. Reports suggest the potential risk of the development of new-onset or relapse of minimal change disease (MCD) following COVID-19 vaccination; however, details on vaccine-associated MCD remain unclear. A 43-year-old man with MCD, who had been in remission for 29 years, developed nephrotic syndrome 4 days after receiving the third dose of the Pfizer-BioNTech vaccine. His kidney biopsy revealed relapsing MCD. Intravenous methylprednisolone pulse therapy followed by oral prednisolone therapy was administered, and his proteinuria resolved within 3 weeks. This report highlights the importance of careful monitoring of proteinuria after COVID-19 vaccination in patients with MCD, even if the disease is stable and no adverse events occurred during previous vaccinations. Our case report and literature review of COVID-19 vaccine-associated MCD indicated that MCD relapse tends to occur later after vaccination and slightly more often following the second and subsequent vaccine doses than new-onset MCD.

Keywords mRNA vaccines · BNT162 vaccine · COVID-19 vaccine booster shot · Nephrotic syndrome · Recurrence

Introduction

Messenger RNA (mRNA) vaccines against the coronavirus disease 2019 (COVID-19) have rapidly emerged. These vaccines are a critical tool for controlling the COVID-19 pandemic [1, 2]. However, adverse events following vaccination remain unclear. Several reports have described cases of new-onset or relapse of minimal change disease (MCD) after COVID-19 vaccination [3–36]. Herein, we report a case of MCD relapse following the third dose of the Pfizer-BioNTech COVID-19 vaccine in a patient with MCD in long-term remission. Previously published cases of MCD following COVID-19 vaccination are summarized briefly.

Case report

A 43-year-old man with a history of nephrotic syndrome was referred to nephrology service due to frothy urine and lower limb edema, which occurred 4 days after receiving the third dose of the Pfizer-BioNTech COVID-19 vaccine. He developed nephrotic syndrome at the age of 3 years and underwent a kidney biopsy at the age of 6 years, which provided a diagnosis of MCD. He has been in drug-free remission since the age of 14 years. He had received the first and second doses of the Pfizer-BioNTech COVID-19 vaccine 9 and 8 months before his admission, respectively, with no adverse events. There were neither preceding infections nor drug use, which could trigger the nephrotic syndrome.

On admission, physical examination revealed marked generalized edema and weight gain of 13 kg. His blood pressure was 151/98 mmHg, pulse rate was 69 beats/min, and respiratory rate was 18/min with an oxygen saturation of 98% on room air. Urinalysis diagnosed 3+ proteins without red cells. The 24-h urinary protein excretion was 5.12 g/day; selectivity index for proteinuria was 0.11. Laboratory tests revealed a serum creatinine level of 1.0 mg/dL, estimated glomerular filtration rate of 66 mL/min/1.73m², albumin

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level of 1.7 g/dL, and low-density lipoprotein cholesterol level of 226 mg/dL. Complete blood count and coagulation test results were normal. Serological workup revealed no signs of an underlying systemic disease or malignancy. Chest X-ray film showed bilateral pleural effusions. As measured by the chemiluminescent immunoassay (Abbott Laboratories), the level of serum IgG antibodies to the SARS-CoV-2 spike protein was elevated to 6639 AU/mL on the 30th day after vaccination.

A kidney biopsy was performed to evaluate nephrotic syndrome. Light microscopy showed global sclerosis in one glomerulus and no abnormalities in the remaining 52 glomeruli (Fig. 1a, b). Tubular atrophy and interstitial fibrosis were absent, and mild hyalinosis of arterioles was observed (Fig. 1a, b). The immunofluorescence studies including IgG, IgA, IgM, and C3 were all negative. Electron microscopy revealed diffuse foot process effacement with no electron-dense deposits (Fig. 1c, d). Based on these findings, MCD relapse was diagnosed. Intravenous methylprednisolone was initiated at 1000 mg for 3 days followed by prednisolone

at 1 mg/kg daily. He responded well to steroid therapy and achieved complete remission of the nephrotic syndrome within 3 weeks. At 7 months after the initiation of treatment, he remained in complete remission with 7.5 mg of prednisolone.

Discussion

We report the case of MCD relapse following the third dose of the *Pfizer-BioNTech COVID-19 vaccine*. In the present case, MCD had been in remission for 29 years but relapsed a few days after the third vaccination. There were no triggers of an MCD relapse; therefore, the vaccination seemed to have caused the relapse. In July 2021, Lebedev et al. first reported a case of new-onset MCD after receiving the first dose of the *mRNA COVID-19 vaccine* [3]. Since then, reports of new-onset or MCD relapse following COVID-19 vaccination have been increasing [5–36]. The timing of MCD onset or relapse was reported at a median of 7 days

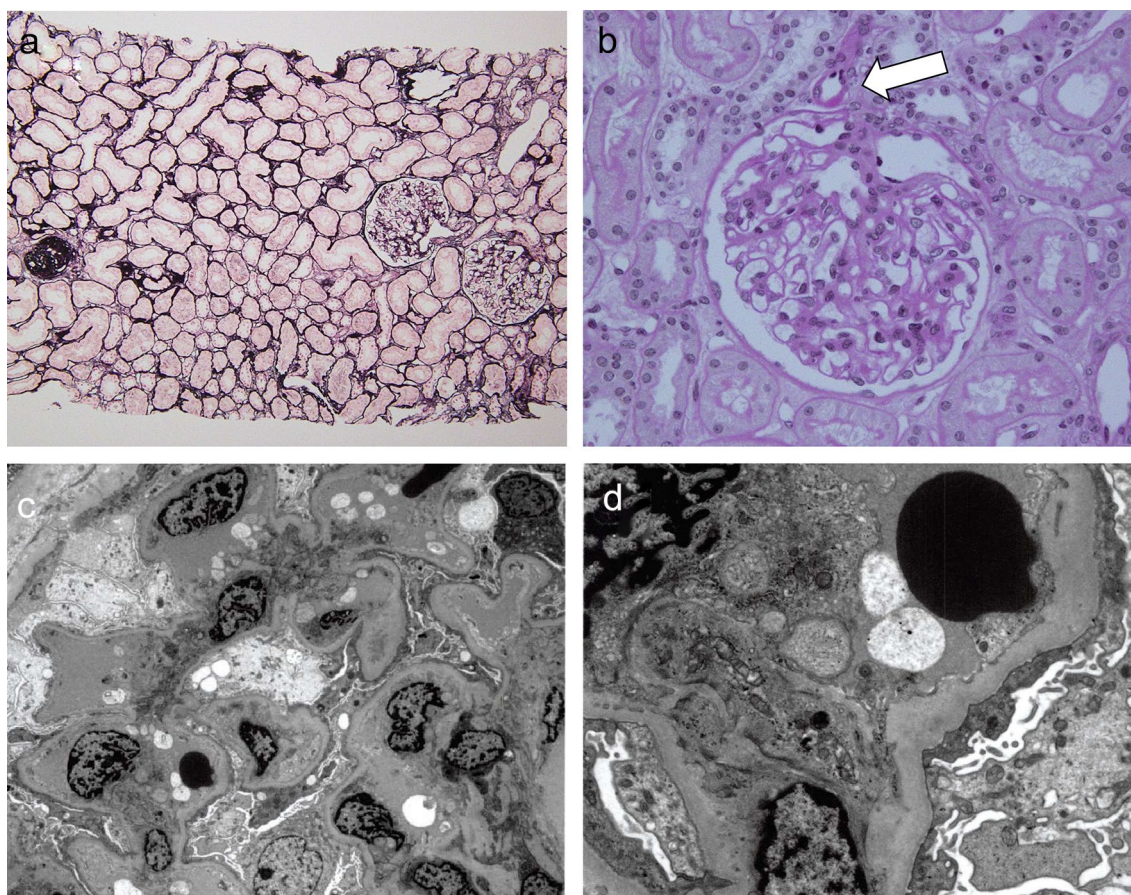


Fig. 1 Kidney biopsy findings. Light microscopy of representative glomerulus stained by **a** periodic acid–methenamine silver (original magnification, $\times 100$) and **b** periodic acid–Schiff (original magnification, $\times 400$), demonstrating minor glomerular abnormality. Hyalinosis

of an arteriole is observed (arrow). **c, d** Electron microscopy reveals diffuse podocyte effacement without electron–dense deposits (original magnification, $\times 1500$ and $\times 6000$, respectively)

after the first dose of the COVID-19 vaccine [4]; however, details of clinical characteristics of COVID-19 vaccine-associated MCD are unknown. We summarized the cases of new-onset and relapsed MCD following COVID-19 vaccination to determinate the clinical characteristics.

We identified 34 cases of relapses MCD and 30 cases of new-onset MCD following COVID-19 vaccination. The clinical characteristics of cases of MCD relapse and the present case are summarized in Table 1 [5–15]. 28 of

34 cases relapsed after receiving mRNA-based vaccines: 24 cases after receiving the Pfizer-BioNTech vaccine and four cases after receiving the Moderna vaccine. 23 cases (68%) of MCD relapse occurred after the first dose of the COVID-19 vaccine, nine cases (26%) occurred after the second dose, and two cases (6%) occurred after the third dose. In 14 cases (41%), relapse occurred within 10 days after the COVID-19 vaccination. Meanwhile, 30 cases of new-onset MCD following COVID-19 vaccination have been reported

Table 1 Case reports of minimal change disease (MCD) relapse following COVID-19 vaccination

Case	Age/sex	Type of vaccine/manu- facturer	Symptom onset time after vaccination (days)	Vaccine dose	MCD status prior to vaccination	Treatment	Response
Present case	43/M	mRNA/Pfizer	4	3rd	Remission for 29 years	mPSL pulse + PSL 1 mg/kg	CR
Klomjit [5]	67/F	mRNA/Moderna	21	2nd	Remission for 1 month	High-dose ster- oid + RTX	CR
Salem [6]	33/F	mRNA/Moderna	21	2nd	Remission for 16 years	NA	NA
	34/F	mRNA/Pfizer	28	2nd	Steroid sensitive	NA	NA
Komaba [7]	60s/M	mRNA/Pfizer	8	1st	Remission for 2 years	PSL 20 mg + CyA 100 mg	CR
Schwotzer [8]	22/M	mRNA/Pfizer	3	1st	Steroid depend- ent + TAC	PSL 60 mg	CR
Mancianti [9]	39/M	mRNA/Pfizer	3	1st	Remission for 37 years	PSL 1 mg/kg	CR
Kervella [10]	34/F	mRNA/Pfizer	10	1st	Steroid dependent	PSL 1 mg/kg	CR
Morlidge [11]	30/M	Vector/AstraZeneca	2	1st	Remission	PSL 20 mg	CR
	40/F	Vector/AstraZeneca	1	1st	Steroid depend- ent + TAC	PSL 30 mg	CR
Özkan [12]	33/F	Inactivated vaccine	14	2nd	Remission for 7 months	PSL 1 mg/kg	NA
Hummel [13]	38/M	Vector/AstraZeneca	14	1st	Remission for 5 years	PSL + MMF	CR
	74/M	mRNA/Pfizer	21	1st	Remission for 3 months	PSL + CNI	CR
	46/F	mRNA/Pfizer	11	1st	Remission for 6 months	PSL + CNI	CR
	23/M	mRNA/Pfizer	21	1st	Remission for 5 months	PSL + Obinutuzumab	CR
	30/F	mRNA/Pfizer	6	2nd	Remission for 1 year	PSL + RTX	CR
	36/F	mRNA/Pfizer	10/5	1st/2nd	Remission for 2 months	PSL + RTX	CR
	41/F	mRNA/Pfizer	30	1st	Remission for 2 years	PSL + CNI	CR
	16/M	mRNA/Pfizer	15	1st	Remission for 6 years	PSL	CR
	19/M	mRNA/Pfizer	21	1st	Remission for 2 years	PSL	CR
	40/M	mRNA/Pfizer	7	1st	Remission for 39 years	PSL	CR
	83/M	Vector/AstraZeneca	20	2nd	NA	PSL	PR
	53/F	mRNA/Pfizer	26	1st	Remission for 5 months	PSL	CR
	25/M	mRNA/Pfizer	21	1st	NA	PSL + MMF	CR
	19/M	mRNA/Pfizer	25	2nd	NA	PSL	CR
	15/M	mRNA/Pfizer	28	1st	Remission for 4 years	PSL	CR
	31/M	mRNA/Pfizer	21	1st	Remission for 7 years	PSL	CR
	21/M	mRNA/Pfizer	20	1st	Remission for 1 year	PSL	CR
	42/M	Vector/AstraZeneca	11	1st	Remission for 20 years	PSL	CR
	18/F	mRNA/Pfizer	14/9	1st/2nd	Remission for 4 years	PSL + MMF	CR
	16/F	mRNA/Moderna	1	2nd	Remission for 11 months	PSL	CR
	72/M	mRNA/Pfizer	2	3rd	Remission for 9 months	PSL	NA
Hartley [14]	40/M	mRNA/Pfizer	1	1st	Remission with PSL 10 mg	High-dose PSL + CyA	CR
Chandra [15]	71/M	mRNA/Moderna	7	2nd	Remission for 4 months	High-dose PSL + RTX	CR

TAC tacrolimus, mPSL methylprednisolone, PSL prednisolone, RTX rituximab, CyA cyclosporine, CR complete remission, PR partial remission, NA not available, MMF mycophenolate mofetil, CNI calcineurin inhibitor

(Table 2); 23 cases (77%) developed MCD after the first dose, and 22 cases (73%) were diagnosed within 10 days after vaccination [3, 5, 6, 14–36]. Given these findings, new-onset MCD tended to appear earlier after vaccination and to occur slightly more often after the first dose of vaccine than MCD relapse. Of the 34 MCD relapse cases, 26 were in drug-free remission, while 5, including the present case, occurred > 15 years after complete remission; almost all cases promptly achieved remission following steroid therapy.

Considering that more than 13 billion doses of vaccines against COVID-19 have been administered worldwide [37], the development of MCD might occur coincidentally following COVID-19 vaccination. However, there have been few reports of MCD after receiving other vaccines: only three cases following influenza vaccination and one case following hepatitis B vaccination [38–41], although these vaccines

have been extensively used. Moreover, MCD which had been in long-term remission (> 15 years) relapsed shortly after vaccination without other identifiable trigger not only in our case but also in other four cases [6, 9, 13]. These findings indicate that there appears to be some link between MCD development and COVID-19 vaccination. Further research is needed to investigate their association.

The precise pathogenesis of MCD is not fully understood; however, many studies suggest that MCD results from dysregulation of T cells, which leads to cytokine production and subsequent podocyte injury [42–44]. The mRNA vaccine against COVID-19 induces T cell activation and cytokine release, including interferon- γ , in healthy individuals [45]. Therefore, some reports have speculated that mRNA vaccine-induced T cell activation and cytokine release may play a role in the development of

Table 2 Case reports of new-onset minimal change disease following COVID-19 vaccination

Case	Age/Sex	Type of vaccine/manufacturer	Symptom onset time after vaccination (days)	Vaccine dose	Treatment	Response
Lebedev [3]	50/M	mRNA/Pfizer	4	1st	PSL 80 mg	CR
Klomjit [5]	83/M	mRNA/Moderna	28	2nd	High-dose PSL	CR
Salem [6]	41/F	mRNA/Pfizer	5	2nd	NA	NA
Hartley [14]	80s/F	mRNA/Pfizer	2	1st	PSL	CR
Chandra [15]	23/F	mRNA/Moderna	7	2nd	PSL 1 mg/kg	CR
	74/M	mRNA/Pfizer	2	2nd	no medication	CR
	72/F	Vector/AstraZeneca	14	1st	PSL 80 mg	CR
Dirim [16]	65/M	Inactivated/Sinovac	7	1st	PSL 1 mg/kg	CR
Unver [17]	67/F	Inactivated/Sinovac	7	1st	PSL + CyA	PR
D'Agati [18]	77/M	mRNA/Pfizer	7	1st	PSL 60 mg	PR
Maas [19]	80/M	mRNA/Pfizer	7	1st	PSL 80 mg	CR
Hanna [20]	60/M	mRNA/Pfizer	10	1st	PSL 1 mg/kg	CR
Weijers [21]	61/F	mRNA/Pfizer	1	1st	PSL 1 mg/kg	CR
Marinaki [22]	55/F	mRNA/Pfizer	4	1st	PSL 1 mg/kg	CR
Kobayashi [23]	75/M	mRNA/Pfizer	7	2nd	PSL 1 mg/kg	CR
Baskaran [24]	31/F	mRNA/Pfizer	21	2nd	high-dose PSL	CR
	55/M	Vector/AstraZeneca	7	2nd	PSL 60 mg	CR
Abdulgayoom [25]	45/F	mRNA/Pfizer	4	1st	PSL 60 mg	NA
Holzworth [26]	63/F	mRNA/Moderna	7	1st	PSL 1 mg/kg	NA
Thappy [27]	43/M	mRNA/Moderna	7	1st	high-dose PSL	PR
Lim [28]	51/M	Vector/Janssen	7	1st	PSL 0.8 mg/kg	CR
Leclerc [29]	71/M	Vector/AstraZeneca	13	1st	High-dose PSL	CR
Biradar [30]	22/M	Vector/AstraZeneca	15	1st	PSL 1 mg/kg	CR
Anupama [31]	19/F	Vector/AstraZeneca	8	1st	PSL 1 mg/kg	CR
Nagai [32]	22/M	mRNA/Pfizer	9	1st	PSL 1 mg/kg	CR
Dormann [33]	78/M	mRNA/Pfizer	4	1st	PSL 80 mg	PR
	31/F	Vector/Janssen	1	1st	PSL 70 mg + RTX	CR
Tanaka [34]	69/F	mRNA/Pfizer	9	1st	PSL 30 mg	CR
Mochizuki [35]	25/F	mRNA/Moderna	26	1st	PSL	CR
Pella [36]	18/M	mRNA/Pfizer	11	1st	mPSL 48 mg	CR

PSL prednisolone, RTX rituximab, CyA cyclosporine, mPSL methylprednisolone, CR complete remission, PR partial remission, NA not available

MCD [3, 4, 46]. In the present case, MCD relapsed after the third dose of the mRNA vaccine despite the absence of adverse events after the previous two vaccinations. A recent publication showed that the secondary or booster vaccinations notably enhanced cytokine secretion compared to the first vaccination [47–49]. This exaggerated immune response through additional vaccinations might finally trigger a relapse of MCD in susceptible patients. The optimal treatment strategy of COVID-19 vaccine-associated MCD has not been established. In our literature review, almost all cases were treated with steroid therapy and achieved disease remission; however, interestingly, one case of new-onset MCD achieved a spontaneous remission by 6 weeks without any medical treatment. Further cases and studies are required to investigate the pathogenesis and treatment of MCD following COVID-19 vaccination.

In summary, we present a case of MCD relapse following the third dose of mRNA COVID-19 vaccination in a patient with MCD who had been in long-term remission. Our case and literature review of COVID-19 vaccine-associated MCD indicate that MCD relapse tends to occur later after vaccination and slightly more often following the second and subsequent vaccinations compared to de novo MCD. Clinicians need to be aware of this association and closely monitor proteinuria in a patient with MCD who had received COVID-19 vaccines even if there have been no adverse events during previous vaccinations.

Declarations

Conflict of interest All the authors have declared no competing interest.

Human and animal rights statement This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent Informed consent was obtained from the patient for the publication of his clinical data.

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