Nephrotic syndrome with minimal change disease after the Pfizer-BioNTech COVID-19 vaccine: two cases

James Leon Hartley,[1] Neil Bailey,[2] Asheesh Sharma,[3] Howida Shawki[4]

[1]Nephrology, Royal Liverpool University Hospital, Liverpool, UK
[2]Nephrology, Warrington and Halton Teaching Hospitals NHS Foundation Trust, Warrington, UK
[3]Nephrology, Royal Liverpool and Broadgreen Hospitals NHS Trust, Liverpool, UK
[4]Histopathology, Royal Liverpool and Broadgreen University Hospitals NHS Trust, Liverpool, UK

Correspondence to
Dr James Leon Hartley;
james.hartley@rlbuht.nhs.uk

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SUMMARY

We present two cases of nephrotic syndrome with minimal change disease after the Pfizer-BioNTech COVID-19 vaccine. We discuss the initial presentation, investigation and management of these patients along with a discussion around the current evidence base for vaccine-induced nephrotic syndrome.

BACKGROUND

This is a potential serious adverse event from vaccination that may become more common as the vaccination roll-out continues to gather pace in the UK and across the globe. We wanted to highlight the complication of nephrotic syndrome after vaccination so this syndrome can be studied further and managed effectively.

CASE PRESENTATION

Minimal change disease (MCD) is the most common cause of nephrotic syndrome in children. This contrasts with adults where MCD is a less frequent cause of nephrotic syndrome especially in older patients. Most cases of MCD are idiopathic; however, there are various secondary causes including drugs, malignancies, viral infections and it has been suggested, vaccinations.[1–3]

We present two cases of nephrotic syndrome caused by MCD after recent administration of the Pfizer-BioNTech COVID-19 vaccine.

Case 1

A woman in her 80s was transferred to our institution after attending a peripheral hospital on the advice of National Health Service (NHS) 111. The patient had no medical nor family history. She had developed leg, arm and hand swelling, 2 days after receiving the Pfizer-BioNTech COVID-19 vaccine. The vaccine was administered uneventfully. Two days after receiving the vaccine dose, the patient noticed her feet and ankles were swollen and painful, limiting her mobility. Over the next few days, she also developed painful swelling of the hands and arms. Along with the swelling, she also noticed a drop in her urine output, but no other urinary symptoms. She saw her general practitioner who initiated routine blood tests and urine tests. While awaiting these investigations, the patient became more concerned about the swelling as it had become more painful and she was now housebound. Subsequently, she was admitted to hospital for investigation. She did not take any regular medications, and there was no history of allergies. She did not smoke, did not drink alcohol and lived alone independently. She was a keen walker and golfer.

On arrival to hospital, she was noted to be markedly oedematous. There was oedema to the groins bilaterally with marked sacral oedema and oedema to the biceps in the arms. The hands were swollen with no evidence of joint swelling or erythema. Cardiorespiratory and abdominal examination was unremarkable. Her vital signs were stable, however she was hypertensive with a blood pressure of 163/58. Her urine dipstick revealed 3+ protein and 2+ blood. Her routine admission blood tests revealed acute kidney injury from baseline normal renal function (see table 1). Nephrotic syndrome was confirmed with a urine albumin–creatinine ratio (ACR) of 866 mg/mmol and 24-hour urine collection for protein of 18.2 g/24 hours. Chest X-ray, ECG and transthoracic echocardiography were normal as were her liver function tests. Her COVID-19 PCR was negative and COVID-19 antibody also negative.

The main differential diagnoses for nephrotic syndrome are MCD, focal segmental glomerular sclerosis and membranous glomerulonephritis. While these predominantly remain renal biopsy-derived diagnoses, there are some less frequent systemic pathologies that account for secondary causes of nephrotic syndrome. Prior to performing a renal biopsy, we obtained further diagnostic tests to look for evidence of the potential secondary causes of nephrotic syndrome including complement levels, a connective tissue disorder screen, a vasculitis screen, a myeloma screen, haemoglobin A1C and a usual viral panel. We also completed an anti-phospholipase A2 receptor antibody (PLA2R) serological screen which is the main known target antigen in membranous glomerulonephritis. Membranous glomerulonephritis is the most common cause of nephrotic syndrome in this patient's age group; her serum PLA2R was negative.

She was treated with intravenous loop diuretics and anticoagulated with low molecular weight heparin in view of decompensated nephrotic syndrome, and transferred to the regional nephrology unit for further diagnostic assessment, including a renal biopsy.

A routine COVID-19 PCR admission swab at our hospital returned as negative and repeat COVID-19 antibodies were also sent that were negative. Her blood pressure was controlled with amlodipine and

Table 1 Admission blood tests and investigations

Urea and electrolytes		Normal values
Sodium	148 mmol/L	135–145 mmol/L
Potassium	4.5 mmol/L	3.5–5.3 mmol/L
Bicarbonate	20 mmol/L	22–29 mmol/L
Urea	17.4 mmol/L	2.5–7.5 mmol/L
Creatinine	310 (baseline 86) mmol/L	53–100 mmol/L
Estimated glomerular filtration rate	12 mL/min/1.73 m^2	>60 mL/min/1.73 m^2
Full blood count		
Haemoglobin	107 g/L	115–165 g/L
Mean cell volume	78.2 fL	85–105 fL
Platelets	621×10^9/L	150–400×10^9/L
White cell count	9.4×10^9/L	3.8– 11.0 x 10^9/L
Neutrophil count	10.3×10^9/L	2.0–7.5×10^9/L
C reactive protein	9 mg/L	<5 mg/L
Liver function tests	Normal	
Albumin	22 g/L	35–50 g/L
Haemoglobin A1C	45 mmol/L	<41 mmol/L
Hepatitis B, C, HIV	Negative	
Clotting		
Prothrombin time	10.3 s	
Activated partial thromboplastin time	31.0 s	
Further biochemistry		
Adjusted calcium	2.31 mmol/L	2.20–2.60 mmol/L
Phosphate	1.52 mmol/L	0.80–1.50 mmol/L
Renal screen		
Anti-neutrophil cytoplasmic antibody	Negative	
Complement	Normal	
Anti-glomerular basement membrane antibody	Negative	
Anti-phospholipase A2 receptor antibody	Negative	
Myeloma screen	Negative	
Serum free kappa	84.6 mg/L	3.3–19.4 mg/L
Serum free lambda	65.4 mg/L	5.71–26.3 mg/L
Kappa:lambda ratio	1.29	0.26–1.65
Antinuclear antibody	Negative	
Anti-double-stranded DNA antibody	Negative	
Connective tissue disease screen	Negative	
IgG	6.77 g/L	6.13–13.0 g/L
IgA	3.80 g/L	0.4–3.5 g/L
IgM	0.29 g/L	0.53–3.34 g/L
Haematinics		
Ferritin	228 ng/L	
Transferrin saturation	61%	
Iron	17.2	
Transferrin	1.21	
Total iron binding capacity	28	
Thyroid function tests		
Thyroid-stimulating hormone	92	
T4	6.3	
Urine studies		
Total protein 24-hour urine	18.2 g/24 hours	<0.15 g/24 hours
Albumin–creatinine ratio	866.3 mg/mmol	<3.5 mg/mmol
Viral panel		
Influenza A/B	Negative	
Respiratory syncytial virus	Negative	
COVID-19 PCR	Negative	
Venous blood gas		
pH	7.39	7.35–7.45
Bicarbonate	21 mmol/L	25–30 mmol/L
Base excess	−3 mmol/L	
Lactate	1.1 mmol/L	0.5–2.0 mmol/L

bisoprolol, along with her current high-dose intravenous furosemide. She was started on levothyroxine for incidental hypothyroidism. A kidney biopsy was performed on day 2 of admission without complication. The kidney biopsy was consistent with MCD along with acute interstitial nephritis (see figures 1 and 2). Following histological confirmation, she was started on high-dose oral steroids with bone and gastroprotection along with continuing diuresis.

Case 2

A man in his 40s returned for urgent outpatient review. His medical history was notable for Wolf-Parkinson-White syndrome for which he had a cardiac ablation in 2009, along with MCD-related nephrotic syndrome, initially presenting in August 2019. He was treated with high-dose oral prednisolone, promptly achieving a complete remission. He relapsed in January 2020, and again responded promptly to high-dose steroid therapy. He relapsed again in July 2020 during the weaning of his steroid therapy. He was felt to have steroid-sensitive, steroid-dependent disease and was also suffering significant side effects from his cumulative exposure to steroid therapy. A decision was made to treat him with a 12-week course of oral cyclophosphamide

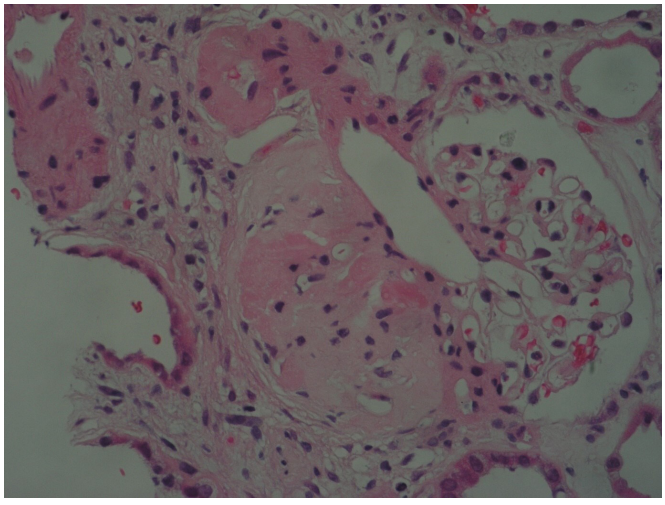

Figure 1 Light microscopy H&E staining. Case 1: there were 42 glomeruli in the biopsy sample from two cores. The glomerulus shown is one of two showing segmental sclerosis. There was no evidence of epithelial proliferation, crescents, necrosis or thrombosis. The glomerular basement membrane had evidence of some focal thickening but no spikes or splitting. There was acute tubular damage with the arteries showing mild to moderate intimal fibrosis consistent with hypertension.

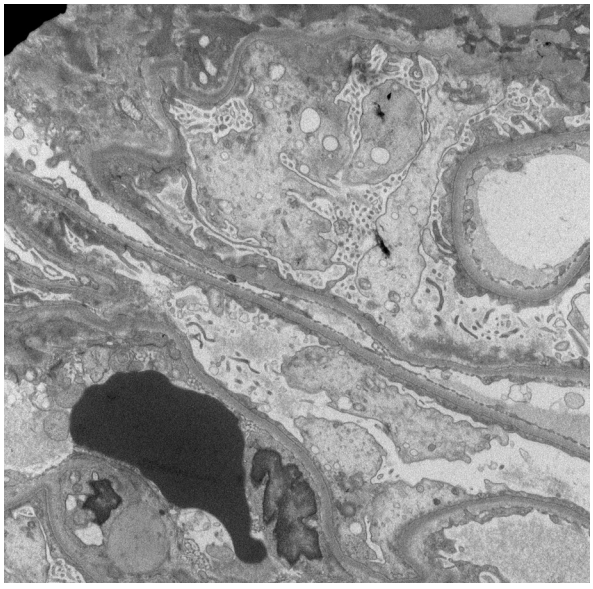

Figure 2 Electron microscopy. Case 1: demonstrates effacement of the epithelial foot processes with no electron dense deposits seen. We have not included immunohistochemical staining as this was negative for IgG, IgM, IgA, C3 and C1q.

alongside his steroids, in the hope of achieving a more durable remission. He tolerated treatment well and achieved a further complete remission.

He was recalled for urgent outpatient review as he had had a telephone consultation where he reported rapid full body swelling. Interestingly, this had occurred 1 day after he had received the first dose of the Pfizer-BioNTech COVID-19 vaccine. He also had diarrhoea and vomiting. On review in clinic, his observations were stable, however he had marked global oedema concerning for relapse of nephrotic syndrome. His blood tests revealed normal renal function with albumin 26 mmol/L (see table 2). His urine ACR was 801 mg/mmol signifying relapse of nephrotic syndrome, most likely MCD, thought due to the COVID-19 vaccination. His medications, when recalled for outpatient review, were: prednisolone 10 mg once daily (maintenance), ramipril 5 mg once daily, evacal one tablet two times per day, omeprazole 20 mg two times per day, colecalciferol 20 000 units once a month, bisoprolol 7.5 mg once daily, amlodipine 5 mg once daily, risedronate 35 mg once weekly. He was started on oral furosemide, high-dose prednisolone and ciclosporin (as a steroid-sparing agent) with the aim of managing him as an outpatient.

OUTCOME AND FOLLOW-UP

Follow-up case 1 and 2

After 4 weeks of outpatient steroid therapy, case 1 had complete remission of nephrotic syndrome with albumin 36 g/L and urine ACR 8.1 mg/mmol. Her oedema had also resolved, and her furosemide stopped. She continued on a weaning course of prednisolone. Her renal function had also markedly improved with creatinine 106 mmol/L and estimated glomerular filtration rate 43 mL/min/1.73 m^2 (see table 3). Her blood pressure was well controlled. Her weight was 57.4 kg from 67.0 kg on admission. She had regained her mobility and felt well with no other symptoms nor steroid side effects. She did not consent to the second vaccine dose.

Case 2 also achieved prompt remission with prednisolone and ciclosporin with albumin 46 g/L and urine ACR 0.2 mg/mmol 4 weeks post-initiation of treatment (see table 4). His weight had reduced, and oedema had settled. Urinalysis showed no further proteinuria. He was continued on a weaning course of prednisolone alongside ciclosporin. Again, he did not consent to the second vaccine dose.

Table 2 Initial blood tests and investigations

Urea and electrolytes		Normal values
Sodium	142 mmol/L	135–145 mmol/L
Potassium	4.2 mmol/L	3.5–5.3 mmol/L
Urea	7.5 mmol/L	2.5–7.5 mmol/L
Creatinine	108 mmol/L	53–100 mmol/L
Estimated glomerular filtration rate	73 mL/min/1.73 m^2	>90 mL/min/1.73 m^2
Full blood count		
Haemoglobin	180 g/L	115–165 g/L
Mean cell volume	87.6 fL	85–105 fL
Platelets	194×10^9/L	150–400×10^9/L
White cell count	10.2×10^9/L	3.8–11.0 x 10^9/LL
Neutrophil count	5.99×10^9/L	2.0–7.5×10^9/L
Liver function tests		
Alkaline phosphatase	87 IU/L	30–130 IU/L
Bilirubin	8 µmol/L	0–17 µmol/L
Alanine aminotransferase	72 IU/L	0–40 IU/L
Gamma-glutamyl transferase	60 IU/L	0–55 IU/L
Albumin	26 g/L	35–50 g/L
Further biochemistry		
Adjusted calcium	2.46 mmol/L	2.20–2.60 mmol/L
Phosphate	1.45 mmol/L	0.80–1.50 mmol/L
Urine studies		
Albumin–creatinine ratio	800.7 mg/mmol	<3.5 mg/mmol

DISCUSSION

New presentations and relapses of nephrotic syndrome have long been linked with viral infections, especially those affecting the upper respiratory tract.[4] There is evidence emerging that this may also be true with COVID-19. We know that during acute COVID-19 infections, the virus can invade renal tissue, predominantly the proximal tubular cells and podocytes and can lead to a significant degree of proteinuria.[5] There are anecdotal accounts linking COVID-19 infections and the de novo presentation of nephrotic syndrome including MCD[6 7] in addition to relapses of known nephrotic syndrome.[8] While the pathophysiology of such a response remains unclear, it seems more plausible that the immune response to COVID-19 rather than direct effects of the virus, as in other viral infections, may trigger MCD in susceptible patients.

The roll-out of vaccines against COVID-19 has revolutionised the fight against the disease, with mass vaccination in the UK showing impressive results. Vaccination not only reduces severe disease and hospitalisation but is also effective at reducing mild disease.[9] Clearly, vaccination will be a major part of the ongoing global management of COVID-19, with the long-term effects and rarer complications of the vaccine roll-out yet to be discovered.

Given such an effective immune response against the spike protein of the virus, it is plausible that this, like in acute COVID-19 infection, could be a sensitising event leading to the development of nephrotic syndrome or MCD. In our cases, both patients received their COVID-19 vaccine just prior to developing de novo disease as in case 1 or relapsing as in case

Table 3 Case 1 post-4 weeks' steroid treatment, blood tests and investigations

Urea and electrolytes		Normal values
Sodium	137 mmol/L	135–145 mmol/L
Potassium	5.3 mmol/L	3.5–5.3 mmol/L
Bicarbonate	27 mmol/L	22–29 mmol/L
Urea	13.4 mmol/L	2.5–7.5 mmol/L
Creatinine	106 (baseline 86) mmol/L	53–100 mmol/L
Estimated glomerular filtration rate	43 mL/min/1.73 m^2	>60 mL/min/1.73 m^2
Full blood count		
Haemoglobin	113 g/L	115–165 g/L
Mean cell volume	81.1 fL	85–105 fL
Platelets	410×10^9/L	150–400×10^9/L
White cell count	16.3×10^9/L	3.8–11.0 x 10^9/L
Neutrophil count	14.8×10^9/L	2.0–7.5×10^9/L
C reactive protein	<5 mg/L	<5 mg/L
Liver function tests	Normal	
Albumin	36 g/L	35–50 g/L
Haemoglobin A1C	50 mmol/L	<41 mmol/L
Further biochemistry		
Adjusted calcium	2.53 mmol/L	2.20–2.60 mmol/L
Phosphate	1.04 mmol/L	0.80–1.50 mmol/L
Urine studies		
Albumin–creatinine ratio	8.1 mg/mmol	<3.5 mg/mmol

2. Autoimmune complications have long been thought to be rare complications of vaccination. Indeed, throughout the literature, there is a collection of case reports that suggest a link with glomerular and autoimmune pathology to immunisation. MCD specifically has been linked with the administration of the influenza vaccine,[1 2] hepatitis B vaccination,[10 11] pneumococcal vaccine,[12] diphtheria, tetanus and whooping cough vaccine,[13] measles vaccines,[14] and now also Pfizer-BioNtech COVID-19 vaccine.[3]

Table 4 Case 2 post-4 weeks' treatment, blood tests and investigations

Urea and electrolytes		Normal values
Sodium	143 mmol/L	135–145 mmol/L
Potassium	4.1 mmol/L	3.5–5.3 mmol/L
Urea	10.2 mmol/L	2.5–7.5 mmol/L
Creatinine	105 mmol/L	53–100 mmol/L
Estimated glomerular filtration rate	75 mL/min/1.73 m^2	>90 mL/min/1.73 m^2
Full blood count		
Haemoglobin	173.0 g/L	115–165 g/L
Mean cell volume	89.8 fL	85–105 fL
Platelets	142×10^9/L	150–400×10^9/L
White cell count	13.7×10^9/L	3.8–11.0 x 10^9/L
Neutrophil count	8.59×10^9/L	2.0–7.5×10^9/L
Liver function tests		
Alkaline phosphatase	59 IU/L	30–130 IU/L
Bilirubin	25 µmol/L	0–17 µmol/L
Alanine aminotransferase	79 IU/L	0–40 IU/L
Gamma-glutamyl transferase	44 IU/L	0–55 IU/L
Albumin	46 g/L	35–50 g/L
Further biochemistry		
Adjusted calcium	2.36 mmol/L	2.20–2.60 mmol/L
Urine studies		
Albumin–creatinine ratio	0.2 mg/mmol	<3.5 mg/mmol

Studies looking at relapse rates of MCD and nephrotic syndrome related to vaccination are small and the data are mixed. A trial in France suggests no increase in relapse rate with the influenza vaccine in children with idiopathic nephrotic syndrome.[15] However, data from Japan demonstrated that with the influenza vaccine, there was an increased relapse rate in children with idiopathic nephrotic syndrome, but this was not statistically significant. However, the relative risk of a relapse post-vaccine was significantly greater if patients were not in remission at the time of the vaccine.[16] An earlier study from the UK reported significant increases in the relapse rate of idiopathic nephrotic syndrome 12 months after the meningitis C conjugate vaccine.[17] All of these studies are retrospective and have small sample sizes, clearly more research is needed in this area.

The pathophysiology of MCD remains uncertain and likewise the sensitising events that trigger the development of the disease, or relapses, are not fully understood. It has long been hypothesised that the pathological mechanism of MCD is a circulating permeability factor. This is proposed to be produced by abnormally functioning T cells resulting in podocyte damage, evidenced by abnormal numbers of T cell subpopulations during active disease with a predominance of helper T cell-associated cytokines in patients and animal models.[18] COVID-19 vaccine trial data suggest induction of both humoral and T cell responses[19] as in acute COVID-19 infection. One possibility is that triggering a T cell immune response in susceptible individuals through vaccination could act as a sensitising event, leading to an abnormal T cell response and disease activation.

The above literature, and the temporal association between vaccination and disease onset and relapse in our cases, support a causal link; however, this cannot be proven. Moreover, this does not undermine current population-wide vaccination efforts. We know that patients with nephrotic syndrome are also at a greater risk of infection and severe manifestations of these infections, both due to the disease pathology and the immunosuppressive treatment strategies employed to treat these patients. This makes the protection that vaccination offers a vital part of their treatment.

Learning points

- We present two cases of nephrotic syndrome after the Pfizer-BioNTech COVID-19 vaccine.
- Nephrotic syndrome may occur after any immune-sensitising event and has previously been described with other vaccines.
- We cannot be sure that these cases are linked to the vaccine; however, we would like to highlight the clear temporal relationship of these two cases after the vaccine was administered.
- Further work is needed in this area along with reporting of new nephrotic syndrome cases after the Pfizer-BioNTech vaccine in order for us to understand this phenomenon better.
- As the vaccine roll-out continues, we may start to see more cases of nephrotic syndrome; it would be useful to have a collective approach to these patients in order to treat their nephrotic syndrome effectively and return their renal function and fluid balance to normal.

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follow-up. NB, as the second author, compiled literature review and references. AS, as the third author, oversaw preparation of the manuscript for publication and aided with literature review. HS provided histopathology slides and comments.

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