Case Reports in Nephrology and Dialysis

Case Rep Nephrol Dial 2022;12:44–49
DOI: 10.1159/000521981
Received: October 23, 2021
Accepted: December 9, 2021
Published online: March 21, 2022

Single Case

De novo Minimal Change Disease in an Adolescent after Pfizer-BioNTech COVID-19 Vaccination: A Case Report

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Keywords
Coronavirus disease 2019 · Minimal change disease · mRNA-based coronavirus disease 2019 vaccine · Nephrotic syndrome

Abstract
This is the first report in an adolescent of minimal change disease (MCD) after the first injection of the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech) with complete remission following steroid treatment. An 18-year-old white male with no prior medical history complained of gastrointestinal symptoms 11 days after his vaccination. Ascites and lower extremity edema were observed a few days later. He was admitted to a hospital as laboratory testing revealed proteinuria of 10.5 g/24 h, normal creatinine levels, and serum albumin of 1.8 g/dL, confirming the presence of nephrotic syndrome. Immunology and serology tests were unremarkable. A diagnostic kidney biopsy showed no significant glomerular or tubular abnormalities in light microscopy with negative immunofluorescence. Treatment with methylprednisolone 48 mg daily was initiated. A week after discharge, proteinuria declined to 1.2 g/24 h, and edema had disappeared, and 6 weeks later, complete remission was evident. As COVID-19 vaccination has been associated with the development of de novo and relapsing MCD, and this case provides additional support for this possible correlation.

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DOI: 10.1159/000521981

Introduction

Vaccines against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are considered to be one of the most effective public health interventions to terminate the global COVID-19 pandemic [1]. As mass vaccination programs are rising worldwide, variable side effects of these vaccines have been identified. We report the case of a full-blown nephrotic syndrome caused by minimal change disease (MCD) in an adolescent after the first injection of the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech).

Case Presentation

An 18-year-old white adolescent with no prior medical history was referred to our department due to occurrence of nephrotic syndrome. He had received the first injection of the Pfizer-BioNTech COVID-19 vaccine thirty days ago. Laboratory tests nineteen days before vaccination were normal, with serum creatinine of 0.98 mg/dL and normal urinalysis. Eleven days after his vaccination, the patient complained of gastrointestinal symptoms (i.e., nausea, epigastric pain, and bloating). He had a gastroenterology consultation and underwent an abdominal computed tomography, which reported the presence of ascites. Thirteen days after vaccination, the patient observed lower extremity edema and weight gain (~8 kg). Laboratory testing three days later revealed serum creatinine of 0.79 mg/dL but hypoalbuminemia (1.8 g/dL) and proteinuria (2 g/24 h). Since gastroscopy findings were normal, the patient was referred to the regional hospital for nephrology consultation. Repeated testing a week later revealed hypoalbuminemia (1.8 g/dL), nephrotic-range proteinuria (10.5 g/24 h), and high total cholesterol (432 mg/dL), following which the patient was admitted to our hospital. The chronology of the illness and trends of main laboratory tests are depicted in Figure 1.

On admission, blood pressure was 125/80 mm Hg, and the heart rate was 75 beats/min. Physical examination was unremarkable except for edema in the lower extremities. Laboratory tests revealed serum creatinine of 0.99 mg/dL, serum urea of 30 mg/dL, serum albumin of 1.7 g/dL, cholesterol of 457 mg/dL, and white blood cell count of 2,500 m/mm^3. Urinalysis revealed protein (100 mg/dL), and urinary sediment showed 2–3 red blood cells per high-power field. Twenty-four-hour urinary collection revealed proteinuria of 23.4 g. Chest radiograph showed unilateral pleural effusion, and kidney ultrasound was normal. Due to leucopenia, a hematologic consultation was performed; peripheral blood smear analysis showed activated monocytes and stimulated lymphocytes, indicating the possible effect of an infectious agent. Testing for human immunodeficiency virus, hepatitis B surface antigen, antibodies to hepatitis C virus, and polymerase chain reaction testing for SARS-CoV-2 were negative; antibodies to parvovirus, cytomegalovirus, herpes simplex virus, and *Toxoplasma gondii* were also negative. IgG antibodies to Epstein-Barr virus were identified, but polymerase chain reaction was negative. Antibodies to adenovirus (IgG and IgM) were also positive. WBC count progressively increased and returned to normal on hospitalization day 5. Levels of complement C3 and C4 were within reference ranges as well as antinuclear antibody, antineutrophil cytoplasmic antibody, and anti-glomerular basement membrane. Serum-free light chains levels, protein electrophoresis, and immunofixation were also normal.

From the first day of admission, the patient received prophylactic anticoagulation with low-molecular weight heparin, intravenous human albumin, and diuretics. Until day 5, weight loss of 10 kg was achieved. A percutaneous kidney biopsy consisted of two cylinders of renal tissue; one with 12 glomeruli was evaluated by light microscopy and one with 9 glomeruli with immunofluorescence in frozen sections. Light microscopy showed no significant glomerular or tubular abnormalities (Fig. 2); the interstitium and arterioles were also normal.

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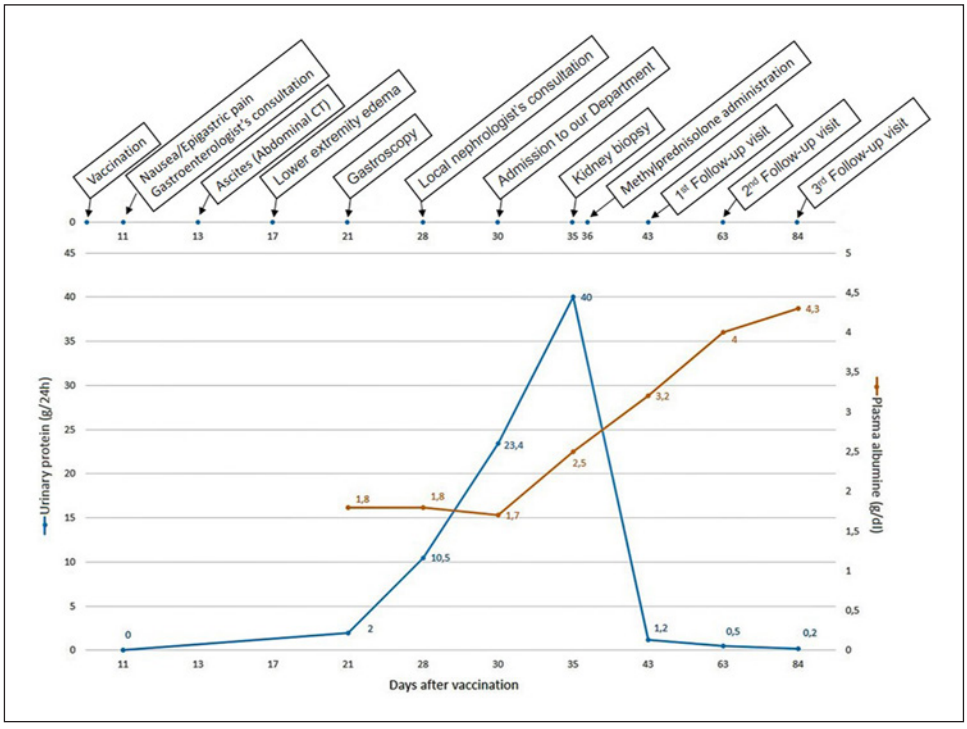

Fig. 1. Timeline of clinical events and trends in serum albumin (g/dL) and urinary protein (g/24 h) after vaccination.

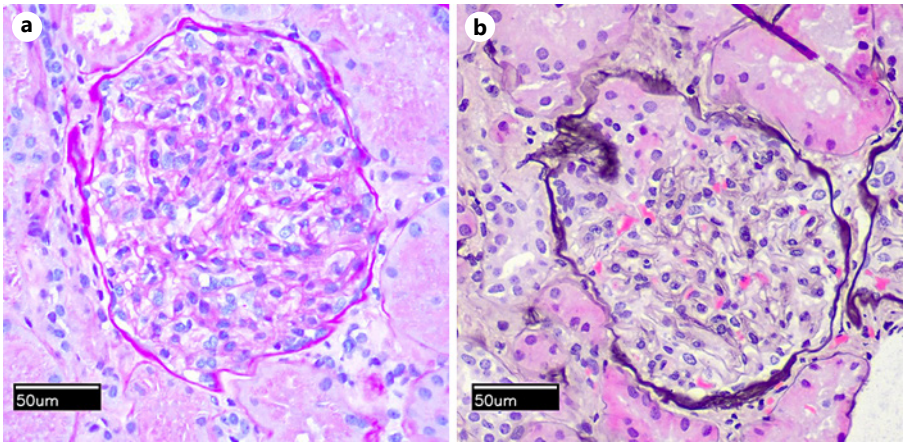

Fig. 2. Kidney biopsy findings. Light microscopy of representative glomerulus stained by (**a**) periodic acid-Schiff (original magnification, ×200) and (**b**) periodic acid-silver methenamine (original magnification, ×200).

Immunofluorescence revealed no staining of IgA, IgG, IgM, κ and λ light chain, C3, C4, and C1q. These findings were consistent with MCD.

On hospitalization day 6, the patient was started on 150 mg of irbesartan and 48 mg of methylprednisolone. The patient was discharged after 12 days in the hospital. At regular follow-up, 1 week later, serum albumin was 3.2 g/dL, proteinuria had decreased to 1.2 g/24 h, and an additional 10 kg of weight loss was achieved. Irbesartan treatment was stopped due to low blood pressure. Three weeks later, partial remission was evident with proteinuria of

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0.5 g/24 h and serum albumin of 4 g/dL, while complete remission of nephrotic syndrome was reported after another 3 weeks with serum albumin of 4.3 g/dL and 24 h-urinary protein of 0.2 g/24 h.

Discussion

The international deployment of mass vaccinations for COVID-19 is one of the most effective public health interventions for the COVID-19 pandemic [1]. However, a small but growing amount of case reports suggests that the immunologic response following several types of vaccines against COVID-19 is a potential trigger for the development of both de novo and recurrent glomerular diseases [2–4]. These reports include the development of MCD, IgA nephropathy, antineutrophil cytoplasmic antibody-associated vasculitis, anti-glomerular basement membrane disease, membranous glomerulopathy, and IgG4-related disease, associated with mRNA vaccines (Pfizer-BioNTech and Moderna), the adenoviral vector vaccine (AstraZeneca), and the vaccine based on inactivated virus (Sinovac) [2, 5–15]. Of note, MCD cases mostly occurred after the first injection of an mRNA vaccine, while most IgA nephropathy flares after the second injection.

Among the cases with de novo MCD, Lebedev et al. [5] reported a case presenting with nephrotic syndrome and acute kidney injury (AKI), in a 50-year-old previously healthy man 10 days after receiving the Pfizer-BioNTech COVID-19 vaccine, who achieved remission with steroid therapy. A similar case of MCD with nephrotic syndrome and AKI 7 days after the first dose of Pfizer-BioNTech COVID-19 vaccine was described by Maas et al. [6]. D'Agati et al. [7] reported a case with a new onset of MCD in a 77-year-old man with type 2 diabetes, with nephrotic syndrome and AKI 7 days after the Pfizer-BioNTech COVID-19 vaccine, who did not respond to steroids. Three cases of MCD relapse after a Pfizer-BioNTech COVID-19 vaccine and two cases of MCD relapse after receiving the Oxford-AstraZeneca COVID-19 vaccine have been reported, all of which responded to steroid or steroid plus cyclosporine treatment [8–11].

MCD is traditionally linked with different types of vaccines, including those for influenza, tetanus-diphtheria-poliomyelitis, and hepatitis B virus. The association between the timing of vaccination and the development of either a new onset or relapsing MCD raises questions about the mechanisms involved. The strong temporal association with vaccination and MCD cases suggests a more generalized cytokine-mediated response and/or a rapid T-cell-mediated immune response to viral mRNA as a possible trigger for podocytopathy [2–4]. The Pfizer-BioNTech vaccine is reported to induce robust T-cell activation, which might contribute to MCD [2]. The inevitable question is whether the appearance of MCD is coincidental or related to the vaccination.

In the present case, the podocyte injury was not confirmed by electron microscopy, following our routine clinical practice in patients of this age with this clinical presentation. It must be noted that in the absence of electron microscopy, the presence of other glomerulopathies with masked immune deposits in the samples examined cannot be entirely excluded; however, all the available clinical findings and patient's course strongly supports the diagnosis of MCD. Moreover, the association between COVID-19 vaccination and the appearance of MCD can only be based on timing and by exclusion as there are currently no conclusive means to prove causality. Although, in this patient, antibodies for adenovirus (IgM and IgG) were also detected, and he never presented any of the classic symptoms of an adenovirus infection (i.e., fever, upper and lower respiratory symptoms, pharyngitis, and conjunctivitis), and this finding cannot be causally evaluated.

Further reports are awaited to clarify the exact incidence of this adverse event, with the various available COVID-19 vaccines. So far, it is uncertain if and when the second or the

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"booster" dose should be administered in these patients and if the administration of another vaccine type would minimize the potential risk of relapse and should be recommended. Although the number of vaccine-linked cases is growing, it represents a small fraction of those individuals who have been safely vaccinated as millions of vaccines have been administered worldwide. The risk of glomerular disease, de novo or relapsing, from vaccination remains significantly lower than the risk of hospitalization and death due to COVID-19 infection, while on the other hand, both new-onset and relapsing MCD cases reported after vaccination were treated rather easily with first-line treatment [2]. Therefore, the international guidelines correctly recommend proceeding with COVID-19 vaccinations in glomerular disease patients [1].

Statement of Ethics

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. This is a case report and a medical/educational activity that does not meet the definition of "research," which is "a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge." Therefore, institutional Ethics Committee approval is not applicable in accordance with local/ national guidelines.

Conflict of Interest Statement

All the authors disclose that they do not have any financial or other relationships, which might lead to a conflict of interest regarding this paper.

Funding Sources

This paper was not supported by any source and represents an original effort of the authors.

Author Contributions

EP, MA: manuscript drafting; EP, MA, DK: literature search; EP, PS, MS, CN: responsible for the clinical care of patient; PS, AP: critical revision of the manuscript for intellectual content.

Data Availability Statement

All data regarding this case report are included in this article. Further inquiries can be directed to the corresponding author.

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