Pediatric Minimal Change Disease and AKI following the Pfizer-BioNTech COVID-19 Vaccine: causal or incidental correlation?

Nefrologo in corsia

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ABSTRACT
The global coronavirus 2019 (COVID-19) pandemic required vaccination even in children to reduce infection.
We report on the development of acute kidney injury (AKI) and minimal change disease (MCD) nephrotic syndrome (NS), shortly after the first injection BNT162b2 COVID-19 vaccine (Pfizer-BioNTech).
A 12-year-old previously healthy boy was referred to our hospital with complaints of peripheral edema and nephrotic range proteinuria.
Nine days earlier he had received his first injection BNT162b2 COVID-19 vaccine (Pfizer-BioNTech).
Seven days after injection, he developed leg edema, which rapidly progressed to anasarca with significant weight gain. On admission, serum creatinine was 1.3 mg/dL and 24-hour urinary protein excretion was 4 grams with fluid overload.
As kidney function continued to decline over the next days, empirical steroid treatment and renal replacement therapy with ultrafiltration were started and kidney biopsy was performed.
Seven days after steroid therapy, kidney function began to improve, gradually returning to normal.
The association of MCD, nephrotic syndrome and AKI hasn't been previously described following the Pfizer-BioNTech COVID-19 vaccine in pediatric population, but this triad has been reported in adults.
We need further similar case reports to establish the real incidence of this possible vaccine side effect.

KEYWORDS: nephrotic syndrome, Acute Kidney Injury (AKI), SARS-CoV-2 vaccines, pediatric population

Introduction

The global coronavirus 2019 (COVID-19) pandemic has shown an evolution in morbidity and mortality in the last years.
The advent of the vaccine has made it possible to modify the natural history of the disease as well as its transmission globally.
SARS-CoV-2 vaccines has good effectiveness with limited side effects and low rate of adverse event, among adults and pediatric population.
We describe a case on the development of acute kidney injury (AKI) with MCD nephrotic syndrome, shortly after first injection of the BNT162b2 COVID-19 vaccine (Pfizer-BioNTech).

Case report

A 12-year-old previously healthy boy was referred to our hospital with complaints of peripheral edema and nephrotic range proteinuria.
He received his first injection BNT162b2 COVID-19 vaccine (Pfizer-BioNTech) nine days before.
The first side effect was pain in the injection area.
He developed headache resistant to paracetamol seven days after injection, legs edema, which progressed to anasarca with significant weight gain from 65 kg to 76 kg.
On admission, blood pressure was 140/70 mmHg, and heart rate 80 beats/min.
Physical examination showed facial, upper and lower limbs and extremities edema, and evidence of ascites on POC ultrasound.
Previous laboratory test (13 months earlier) showed creatinine 0.78 mg/dL and negative protein urine test.
The patient and his family denied the use of non-steroidal anti-inflammatories and any other drugs-induced nephrotoxicity, before or after the vaccination.
Laboratory tests performed showed AKI with serum creatinine 1.3 mg/dL, serum urea nitrogen 85 mg/dL, albumin 2.2 g/dl, normal c3 and c4, negative ANA and ANCA testing. Molecular PCR test swab for SARS -CoV-2 was negative. Serology testing for HBV, HIV, HCV and SARS-CoV-2 was negative, but serology qualitative testing for SARS-CoV-2 for spike protein subunits S1 and S2 was positive for IgG. Urinalysis revealed proteins 185 mg/dL, β2 microglobulin 45 µg/L, and urinary sediment showed 10-15 red blood cells dysmorphic. Chest X-Ray was negative. The patient was admitted and intravenous infusion of human albumin (0,5 g/kg) was immediately administered; 24-hour urinary collection revealed proteinuria of 86 mg/m^2/h.
In four days after the admission kidney function continued to decline: serum creatinine increased to 4 mg/dL and the patient developed fluid overload with dyspnea and oliguria resisted to furosemide, spironolakton and thiazide-diuretic. On day six renal replacement therapy (RRT) with ultrafiltration was started and kidney biopsy was performed. Light microscopy examination showed 11 glomeruli characterized exclusively by mild mesangial hypercellularity, tubular obstruction with cytoplasmic degeneration, and the presence of flaking elements in the lumen. Immunofluorescence was negative. Electron microscopy showed GBM with aspects of rehash, stretches of capillary wall with tortuous course, and aspects of collapse, swelling and extensive fusion of the pedicels and no electron-dense deposits. High-dose pulse intravenous steroids with 1 g of methylprednisolone (MEP) was given daily for three days, followed by oral PDN 60 mg daily. Seven days after the beginning of steroid therapy, kidney function began to improve with creatinine 1.82 mg/dL, albumin 3.2 g/dL, 24-hour urine collection for protein of 58 mg/m^2/h, urine output increased, and renal replacement therapy was stopped after 5 sessions.
The patient was discharged in 15 days with a 10 kg weight loss, serum creatine 0.8 mg/dL, plasma

albumin 3.1 g/dL, urinalysis showed no further proteinuria and protein-creatine ratio was 0.5. His blood pressure was well controlled. The patient continued oral PDN 60 mg daily for 4 weeks, and then taped down to 40 mg for 4 weeks. After 4 and 8 weeks of outpatient steroid therapy and on discontinuation at 12 weeks complete remission of nephrotic syndrome was maintained. Parents did not consent to the second vaccine dose.

Discussion

Nephrotic syndrome is the most frequent glomerular disease in childhood. It is characterized by leakage of a large amount of proteins through the glomerular filter, leading to hypoalbuminemia, hyperlipidemia, decreased oncotic pressure, and edema. In overt forms, proteinuria exceeds 50 mg/kg/day or 40 mg/m^2/h, and the urine protein/creatinine ratio is > 2 mg/mg [1].

Histological examination renal biopsy shows minimal change on light microscopy with negative immunofluorescence and unspecific electronic response. Whether MCD and focal segmental glomerulosclerosis are different entities or two extremes of the same disease is currently debated [2]. Anyway, data collected in past decades on the pathogenesis of NS show an immunologic dysfunction of both T and B cells, and also suggest podocyte's direct role in activating cell pathways that cause proteinuria. Trigger events, such as viral infection, vaccination or allergens stimulate antigen-presenting cells (APCs) and activate T cells to induce cytokine release and B-cells to produce immunoglobulins. Several T-cell alterations have been described in NS: first of all, an imbalance between Th2 and Th1 Cell with an increase in production of Th2-specific interleukin 13 (IL-13), the reduction in frequency and function of T cells (T-regs) and the increase of Th17 cell activities. B cell pathway alterations have also been described, such as an increase in soluble form of CD23 (immunoglobulin-E receptor), a correlation between memory B cell repopulation and relapse after anti-CD20 therapy and circulating anti-CD40 autoantibodies. Moreover, the existence of other circulating permeability mediators (i.e. hemopexin, the soluble form of the urokinase-type plasminogen activator receptor, the cardiotrophin-like cytokine factor 1, and a hyposialylated form of the angiopoietin-like-4 glycoprotein) produced by abnormal T cell can directly affect podocytes and glomerular permeability barrier. In addition, podocytes can recognize microbial antigens by toll-like receptor (TLRs) and produce proteins leading to T-cells activation [3].

Throughout the literature, there are a lot of case reports that suggest a link between glomerular and autoimmune disease to immunization. MCD has been described after vaccinations against diseases such as meningitis C conjugate, influenza, hepatitis B, pneumococcus, diphtheria, tetanus, whooping cough, and measles. Moreover, some studies refer an increasing risk of relapsing subsequently vaccinations [4–10].

Additionally, evidence of temporal association between SARS-CoV-2 vaccinations and glomerular disease, including MCD with AKI and IgA nephropathy, is emerging in adults and in pediatric population [11–13].

Nakawaza E. et al report the first case of nephrotic syndrome subsequent to BNT162b2 COVID-19 vaccine (Pfizer-BioNTech). A previously healthy 15-year-old Japanese boy presented proteinuria, hypertension, eyelid, and lower extremities edema 4 days after the first injection of vaccine. Evaluation for secondary glomerular disease was negative. Twenty-one days after vaccination, 60 mg of oral daily prednisolone was started. He achieved complete remission in 12 days without complications such as hypertension or acute kidney injury. Biopsy was not performed [14].

Pondtip J. et al describe in a healthy 14-year-old boy a nephrotic syndrome 5 days after the first injection of the SARS-CoV-2 BNT162b2 evolving in AKI (anuria and creatinine of 9 mg/dL) at day ten from vaccination. Secondary causes of glomerular disease were excluded. The patient received three daily doses of pulse methylprednisolone followed by oral prednisolone, 60 mg daily. He also received

hemodialysis for 3 weeks. Light microscopy showed eighteen unremarkable glomeruli and diffuse tubular injury and interstitial inflammatory cell infiltration were noted. Immunofluorescence staining was negative. Electron microscopy showed diffuse foot process effacement, consistent with MCD [15].

Pella E. et al reported a case of an 18-year-old male adolescent who developed nephrotic syndrome eleven days after the first Pfizer-BioNTech injection. Diagnostic kidney biopsy showed no significant glomerular or tubular abnormalities in light microscopy with negative immunofluorescence and electronic picture referred to MCD. Treatment with methylprednisolone 48 mg daily was initiated and then tapered and leading to a complete remission six weeks later [16].

Our patient represents the second pediatric case reported of MCD subsequent to Pfizer-BioNTech vaccination. Differently we performed renal biopsy, despite not being recommended, because of the rapid decline of renal function and the need of hemodiafiltration. In addition to electronic picture of foot process effacement, on light microscopy we also found tubular obstruction and the presence of flaking element in lumen. We speculate that tubular involvement could be the cause of AKI.

All those cases showed typical clinical presentation characterized by vaccination, nephrotic syndrome, and AKI. In this report we described the first pediatric patient who experienced the same triad presented in adults; tubular edema with luminal obstruction and absence of significant glomerular change explained AKI evolution.

After vaccination, the vaccine's antigen is presented to T-cells by dendritic cells resulting in activation of antigen-specific effector T cells, that peak between 7 and 14 days after vaccination.

It is not currently possible to establish whether the occurrence of AKI and MCD with nephrotic-syndrome is triggered by vaccination or completely random.

Vaccine-disease correlation is an exclusive diagnosis. Diagnosis is based on timing (7-14 days after vaccination) and exclusion of other triggers in the absence of conclusive means demonstrating a causal link.

We suggest that all patients who develop AKI and nephrotic syndrome following COVID-19 vaccine administration undergo renal biopsy in the immediately next days.

We suggest the use of steroids intravenously and subsequently *per os* with subsequent tapering down.

This therapeutic approach has proved to be useful as well as decisive in the case of our patient.

We await any other reports of similar cases to establish the true incidence of this possible important side effect of the vaccine.

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