EXCEPTIONAL CASE

Adult-onset nephrotic syndrome following coronavirus disease vaccination

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ABSTRACT

A 22-year-old healthy man was admitted for oedema 15 days after the first injection of the COVISHIELD coronavirus disease 2019 (COVID-19) vaccine (Oxford AstraZeneca) vaccine. Nephrotic syndrome was diagnosed and a kidney biopsy showed minimal change disease. Oral prednisolone was started at 1 mg/kg/day resulting in complete remission within 1 week.

Keywords: COVISHIELD, COVID-19 vaccine, minimal change disease, nephrotic syndrome, steroids

INTRODUCTION

The pandemic of coronavirus disease 2019 (COVID-19) represents a multi-faceted challenge for healthcare systems across the globe. The advent of novel vaccines is claimed to be a game-changer in the battle with this pandemic. Though a benefit of vaccines in preventing COVID-19 is proven and most of the side effects occur on the day of vaccination (6–8 h later) and resolve within 2–3 days, whether the COVID-19 vaccine can trigger the onset of nephrotic syndrome or other renal disease, and other major side effects, is still unknown.

We report a case of development of minimal change disease (MCD) with nephrotic syndrome and deranged liver enzymes, starting a few days after administration of the first injection of the COVISHIELD COVID-19 vaccine (Oxford AstraZeneca) at an authorized centre under medical supervision. On the same day, he had generalized weakness and body ache for which he took paracetamol 650 mg two tablets. A week later he noticed yellowish discoloration of urine and 4 days later developed sudden onset of periorbital and bilateral lower limb swelling. A pre-employment laboratory tests 5 months earlier had been normal, with serum creatinine 0.70 mg/dL and normal urinalysis. The patient took two tablets of paracetamol but denied use of non-steroidal anti-inflammatory drugs or alternative medications before or after the vaccination.

On admission, blood pressure was 130/70 mm Hg and heart rate 76 beats/min. Physical examination revealed pitting oedema in the lower extremities. Systemic examination was unremarkable. Laboratory tests revealed serum creatinine 0.72 mg/dL, serum albumin 2.33 g/dL, cholesterol 401 mg/dL and triglycerides 193 mg/dL. Urine microscopy showed 4+ proteinuria, no active sediments, urine protein–creatinine ratio (UPCR) 8.70:1 mg/mg, complete blood count-hemoglobin 15 g/dL, total counts 5800 cells/μL and platelets 308 000 cells/μL. Testing for hepatitis B virus (HBV) surface antigen and antibodies to hepatitis C virus gave negative results; liver function showed total

CASE REPORT

A 22-year-old previously healthy man was admitted to our centre following the appearance of periorbital and bilateral lower limb swelling. Fifteen days earlier, he had received the first injection of the COVISHIELD COVID-19 vaccine (Oxford AstraZeneca) at an authorized centre under medical supervision. On the same day, he had generalized weakness and body ache for which he took paracetamol 650 mg two tablets. A week later he noticed yellowish discoloration of urine and 4 days later developed sudden onset of periorbital and bilateral lower limb swelling. A pre-employment laboratory tests 5 months earlier had been normal, with serum creatinine 0.70 mg/dL and normal urinalysis. The patient took two tablets of paracetamol but denied use of non-steroidal anti-inflammatory drugs or alternative medications before or after the vaccination.

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bilirubin 0.43 mg/dL, total protein 5.07 g/dL, serum albumin 2.33 g/dL and serum globulin 2.74 g/dL. Aspartate aminotransferase was 57.5 IU/L and alanine aminotransferase 96.1 IU/L. Reverse transcriptase polymerase chain reaction testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) gave negative results. However, the titer of immunoglobulin G (IgG) antibodies to Spike (S) protein, which was determined in this case to detect antibodies that develop once a person has received the COVID-19 vaccination, was 1.43 µ/mL. Chest radiograph showed no evidence of any abnormality. Ultrasonography of kidneys showed right kidney 10.1 cm x 4.5 cm and left kidney 10.6 cm x 5.1 cm, both kidneys show normal shape and position. There was normal echogenicity, normal corticomedullary differentiation and no evidence of urinary tract obstruction.

A percutaneous kidney biopsy was performed the next day of admission. The results are shown in Figure 1. Fifteen glomeruli included in single core of renal tissue. Out of 15 glomeruli, 1 glomerulus is globally sclerosed, while all other glomeruli appear largely unremarkable. Tubules, interstitium and blood vessels appear largely unremarkable. Immunofluorescence for IgA, IgG, IgM, C3, C1q and Kappa, Lambda are negative. These findings were consistent with MCD.

The patient was started on tablet prednisolone 1 mg/kg/day dose and on follow-up after 1 week achieved remission, with UPCR 0.15:1 mg/mg; urine microscopy showed absent protein and increase in serum albumin to 2.8 g/dL from 2.33 g/dL on first visit. Transaminits also showed improvement.

DISCUSSION
In MCD the existence of an abnormal T-cells-producing circulating mediator was postulated as far back as 1974 by Shalhoub [1], and clinical and experimental studies [2, 3] have found evidence of imbalance in T-cell subpopulations during active phase of disease, with a prevalence of circulating CD8+ T suppressor cells, aggravating renal damage in mouse models of nephrotic syndrome [4] and a prevalence of a T helper 2 (Th2) cells [Th2; interleukin (IL)-4, IL-5, IL-9, IL-10 and IL-13] cytokine profile in patients [5], which is similar to the spontaneous model of idiopathic nephrotic syndrome in the Buffalo/Mna rat [6]. These observations are similar to clinical observation of an association between MCD and atopy, as allergies are driven by Th2 responses. Proteinuria including new-onset MCD and relapse of MCD after COVID-19 infection has been reported [7]. The exact cause of podocyte injury is unknown. The cytokine storm generating an immunological milieu with excessive production of Th2-generated cytokines acts as a trigger for the podocytopathy. Some immune mechanisms can result in immune complex deposition in the glomeruli, leading to glomerulonephritis. It is speculated that the systemic T-cell dysfunction results in the production of a glomerular permeability factor. This circulating factor directly induces foot process fusion, resulting in severe alteration of the glomerular filtration and resulting marked proteinuria [8].

Findings from a single-dose COVISHIELD COVID-19 vaccine study [9] showed vaccination-induced S-protein-reactive CD4+ T and CD8+ T cells with a T helper 1 (Th1)-type cytokine bias as well as CD8+ T cells with a cytotoxic phenotype. Th1-type immunity is thought to mediate protective antiviral immunity, whereas Th2-type responses have been linked with potentially adverse vaccine effects. Robust B-cell activation and proliferation were also observed after a single dose and anti-S-protein IgG (predominantly the Th1-associated IgG1 and IgG3 isotypes) were detected by Day 14 and maintained at Day 56.

There are three case reports of MCD post-vaccination with HBV [10–12] and one each after pneumococcus [13], influenza.
Systemic vasculitis has been reported in association with COVID-19 infection [14], tetanus–diphtheria–poliomyelitis [8] meningococcal C vaccines [15] and Pfizer COVID-19 vaccination [16], with mean duration ranging between 4 days and 4 months. Relapse of MCD has been documented after AstraZeneca vaccine [17].

Our case report raises the question of either possible causation or association of MCD with COVID vaccination that cannot be attributed yet without more reports of similar cases.

We suggest, therefore, that patients who develop nephrotic syndrome following COVID-19 vaccination should undergo a kidney biopsy. If MCD is confirmed, prompt initiation of treatment with oral corticosteroids, such as prednisone at a dosage of 1 mg/kg/day should be considered, as it seemed to be helpful in our patient.

**PATIENT CONSENT**

Informed consent was obtained from the patient to publish this case.

**CONFLICT OF INTEREST STATEMENT**

None declared.

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