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ANCA glomerulonephritis after the Moderna COVID-19 vaccination

To the editor: As coronavirus disease 2019 (COVID-19) vaccinations are administered globally on a massive scale, rare adverse events are being reported. We report a case of anti–neutrophil cytoplasmic antibody (ANCA) glomerulonephritis 2 weeks after receiving the COVID-19 (Moderna) vaccine.

A 52-year-old white man presented with headache and weakness 2 weeks after receiving his second dose of the Moderna (mRNA-1273) vaccine on April 15, 2021. Headache started the day after his second vaccination and was associated with weakness. Vitals were stable, and physical examination was unremarkable. His medical history included hypertension, and he was treated with amlodipine. He had no allergies and denied illicit drug use.

The initial laboratory results showed a creatinine of 8.41 mg/dl (baseline 1.11 mg/dl, 8 months prior), blood urea nitrogen of 82 mg/dl, sodium of 129 mEq/l, potassium of 5.0 mEq/l, bicarbonate of 21 mEq/l, and hemoglobin of 14.6 g/dl. Toxicology screen was negative. Urinalysis had 1+ proteinuria and microscopic hematuria with dysmorphic red blood cells. Renal ultrasound revealed no hydronephrosis. I.v. hydration was initiated. Additional serologic workup showed positive cytoplasmic ANCA titers and antibodies to proteinase-3 (PR3). Myeloperoxidase-O antibody was negative. Anti–glomerular basement membrane antibody was negative, and C3/C4 levels were normal. Despite hydration, creatinine worsened to 10.42 mg/dl, and after the return of the positive cytoplasmic ANCA, pulse dose steroids were begun.

A kidney biopsy (Figure 1) revealed cellular crescents and fibrinoid necrosis in 38 of 46 glomeruli, with some tubular injury. Immunofluorescence showed segmental fibrin staining the glomerular capillary loops, confirming fibrinoid necrosis. No immune complex–mediated deposits were seen on electron microscopy. Interstitial fibrosis and tubular atrophy were mild.

On the basis of serologic and biopsy findings, a diagnosis of pauci-immune necrotizing and crescentic glomerulonephritis was made. Rituximab was initiated at 375 mg/m^2, but the patient developed severe dyspnea and declined further doses. One dose of cyclophosphamide 7.5 mg/kg (per CYCLOPS trial dosing) was given; however, hemodialysis was initiated for hyperkalemia and worsening renal function. Currently, he continues to require dialysis, while on prednisone, and with a plan to repeat cyclophosphamide 2 weeks after the first dose.

With millions of doses of vaccines being administered worldwide for COVID-19, rare reports of adverse events are emerging, such as cases of minimal change disease.[1,2] To our knowledge, this is the first reported case of ANCA glomerulonephritis after receiving the COVID-19 vaccine. ANCA vasculitis has previously been reported after influenza vaccination.[3] In our case, the temporal association suggests a neutrophilic immune response to mRNA as a potential trigger. It is possible that the enhanced immune response after a second dose could be responsible for triggering PR3 antibodies. ANCA glomerulonephritis has been known to occur with certain medications such as hydralazine,[4] infections, and with malignant tumors.[5] With medication-induced ANCA vasculitis, usually myeloperoxidase-O titers are positive. However, in hematological malignancies, PR3 titers can be positive. PR3 is a bactericidal protein expressed by neutrophilic granules. Derangements in its expression and function have been linked to hematological malignancies and pauci-immune vasculitis. Greater analysis of the immune response induced by mRNA vaccines could provide better insight into the mechanism of various autoimmune reactions, including ANCA vasculitis.

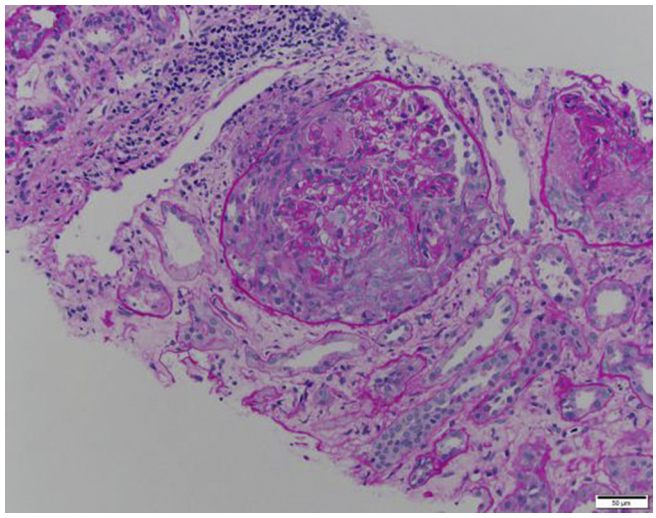

Figure 1 | Periodic acid–Schiff stain showing a glomerulus with a cellular crescent arising in the Bowman's space and destroying the mesangiocapillary architecture. Segmental capillary loop necrosis is also noted. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

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Kidney International (2021) **100,** 473–474; https://doi.org/10.1016/j.kint.2021.05.017

De novo vasculitis after mRNA-1273 (Moderna) vaccination

To the editor: The mRNA-1273 (Moderna) vaccine is a lipid nanoparticle–encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the cause of the current coronavirus disease 2019 (COVID-19) pandemic. In a randomized placebo-controlled phase 3 trial, the mRNA-1273 (Moderna) vaccine showed high efficacy at preventing COVID-19. Aside from transient local and systemic reactions, no safety concerns were identified.[1]

Here we report 2 patients who developed *de novo* vasculitis shortly after receiving the mRNA-1273 (Moderna) vaccine.

Patient 1 was a 39-year-old man with a history of treated arterial hypertension. After a well-tolerated first dose of mRNA-1273 (Moderna) vaccine, he had severe fever, flu-like symptoms, and macrohematuria immediately after the second dose. Diagnostic workup showed acute kidney injury (AKI) with nephritic syndrome. Repeat reverse transcription polymerase chain reaction (RT-PCR) testing for SARS-CoV-2 from nasopharyngeal swabs was negative. A kidney biopsy revealed severe crescentic IgA nephritis (Figure 1a–d). Treatment with high-dose glucocorticoids and cyclophosphamide was initiated. Over the following weeks, serum creatinine normalized and proteinuria significantly decreased, but microhematuria persisted.

Patient 2 was a healthy 81-year-old man. After the first dose of the mRNA-1273 (Moderna) vaccine, he had sustained flu-like symptoms, which significantly worsened after the second dose. Laboratory workup showed AKI, proteinuria in the nonnephrotic range, and an elevated proteinase 3 (PR3) anti–neutrophil cytoplasmic antibody (ANCA) titer. A pulmonary computed tomography scan demonstrated bilateral necrotic masses of the lung parenchyma and slight pleural effusion, without evidence of tumor or lymphadenopathy. Repeat RT-PCR testing for SARS-CoV-2 from nasopharyngeal swabs was negative; serologic testing for SARS-CoV-2 showed a positive anti-spike IgG and negative anti-nucleocapsid IgG. A kidney biopsy performed at day 22 after the second vaccine dose showed severe pauci-immune crescentic glomerulonephritis with capillary necrosis and vasculitis present in the renal vessel walls (Figure 1e–h). The patient was treated with high-dose glucocorticoids, cyclophosphamide, and plasmapheresis. Over the course of 3 weeks, the patient's symptoms disappeared, and renal function improved along with a significant decrease of PR3-ANCA and anti-spike IgG titer. Immunohistochemical staining for the SARS-CoV-2 spike protein was negative in both patients.

Appearance of AKI concurrently with serious systemic symptoms shortly after the second dose strongly suggests a causal mechanism. Isolated cases of SARS-CoV-2–induced IgA vasculitis and ANCA-associated vasculitis have been reported.[2,3] In contrast, 2 patients with preexisting IgA nephropathy have been reported to experience gross hematuria after receiving the mRNA-1273 (Moderna) vaccine, with spontaneous resolution after 3 days.[4] Two cases of minimal change nephropathy associated with the BNT162b2 mRNA (Pfizer-BioNTech) vaccine have also been described.[5,6]

To our knowledge, these are the first 2 cases of *de novo* vasculitis after vaccination with an mRNA-based vaccine.

The mechanism remains to be elucidated but is likely due to aberrant immune response to the spike protein or mRNA of SARS-CoV-2 in predisposed individuals.

We hope that this correspondence will prompt clinicians to consider vasculitis workup in the case of protracted systemic reactions, new-onset macrohematuria, or worsening kidney function after vaccination with mRNA-based SARS-CoV-2 vaccines. Given the massive scale-up of vaccination efforts worldwide, it is very likely that additional cases of vaccination-induced vasculitis will emerge. We strongly encourage additional reporting and communication for this rare, albeit severe, side effect of the mRNA-1273 (Moderna) vaccine.

DISCLOSURE

DGF reports unrestricted research grants from Otsuka and Boehringer Ingelheim and consulting fees from Otsuka and Alnylam. All the other authors declared no competing interests.

AUTHOR CONTRIBUTIONS

All authors contributed to the study design. MAA, ML, CS, and MM performed the data analysis. UH-D and DGF verified the data. All authors contributed to the data interpretation. MAA and ML wrote the first draft of the manuscript, which was subsequently revised by the remaining authors. All authors approved the final version of the manuscript before submission.