



Nephrotic syndrome and vasculitis following SARS-CoV-2 vaccine: true association or circumstantial?

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The immunologic response following several varieties of vaccination (especially meningococcal C conjugate vaccines) has been described as a potential trigger for the development of nephrotic syndrome (NS) [1, 2]. Coronavirus disease 2019 (COVID-19) vaccine, administered worldwide, appears to be safe. However, rare reports of both *de novo* and recurrent NS and vasculitis are emerging.

Vaccines for the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) have been developed in an accelerated manner as a response to a pandemic. They use different mechanisms to generate immunity. Pfizer BNT162b2 and Moderna mRNA-1273 use a pioneer mechanism, a lipid nanoparticle nucleoside-modified mRNA that encodes SARS-CoV-2 spike (S) protein, which mediates host attachment and viral entry. AstraZeneca uses a replication-deficient chimpanzee adenovirus vector, containing the SARS-CoV-2 S protein. Studied subjects generated T cell response, CD8+ and CD4+ expansion, to a Th1-biased response with production of Interferon- γ , tumor necrosis factor- α (TNF- α), interleukin-2 and antibody (Ab) production predominantly of immunoglobulin G1 (IgG1) and IgG3 subclasses [3–5]. These immune responses might be associated with a recurrence of glomerular disease or as a possible trigger for podocytopathies.

To date, 11 NS [new onset (5 patients) and relapsed (6 patients)] linked to minimal change disease (MCD) (10 patients) or membranous nephropathy (1 patient) after SARS-CoV-2 vaccines—Pfizer BNT162b2 (4 patients, 3 patients), Moderna mRNA-1273 (1 patient, 0 patient), AstraZeneca (0 patient, 2 patients) or SINOVAC (0 patient, 1 patient) vaccine have been reported (Table 1) [6–15]. All cases appeared 3 days to 2 weeks after the first vaccine dose followed by remission under corticosteroid treatment, except in one patient with underlying diabetic change nephropathy [7].

As of this date, there are six cases of *de novo* crescentic glomerulonephritis after the SARS-CoV-2 vaccines—[Pfizer BNT162b2 (2 patients), Moderna mRNA-1273 (4 patients)] described in the literature (Table 2) [16–19]. Two patients had a past medical history significant for hypertension. Kidney

biopsies showed anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (Moderna mRNA-1273), IgA nephritis (Pfizer BNT162b2, Moderna mRNA-1273) and anti-glomerular basement membrane (anti-GBM) disease (Pfizer BNT162b2, Moderna mRNA-1273), respectively, each 2 patients. All patients were treated with corticosteroids and cyclophosphamide. Three and one patients required plasma exchange and rituximab, respectively. Two patients had improvement of symptoms and two remained in hemodialysis (Table 2) [16–19].

Vaccination (notably influenza) is a recognized trigger for the relapse of idiopathic NS [16] and ANCA-associated vasculitis [17]. Acute onset of MCD has been reported at 4 and 18 days following the influenza vaccine [1, 18] and 6 weeks following a tetanus–diphtheria–poliomyelitis vaccination [20, 21, 22]. The association between the timing of vaccination and the development of both new onset and relapsed MCD and/or membranous nephropathy raises questions as to the mechanisms involved. The strong temporal association with vaccination and MCD cases suggests a more generalized cytokine-mediated response [23] and/or a rapid T cell-mediated immune response to viral mRNA as a possible trigger for podocytopathy [13, 24]. The Pfizer–BioNTech vaccine is reported to induce robust T cell activation, as previously described, which might contribute to MCD. It is also possible that these phenomena are completely circumstantial and unrelated. Regardless, prompt initiation of steroid treatment should be considered. S protein data were not reported in most of the cases to raise the timing of the formation of the Ab and the glomerular disease finding. Is this more common than for the influenza vaccine? This cannot be answered at this moment as mass vaccination leads to clustering of rare side effects and true incidence is hard to define.

The mechanism of *de novo* ANCA-associated vasculitis post-SARS-CoV-2 vaccine remains to be elucidated but the temporal association suggests a neutrophilic immune response to the S protein or mRNA of SARS-CoV-2 in predisposed individuals. It is possible that the vaccines lead to proinflammatory

Table 1. NS following SARS-CoV-2 vaccine

Ref.	Country	Age/ sex	Past medical history	SARS-CoV-2 vaccine	Onset of symptoms	Kidney findings	Anti-Spike protein antibody	Treatment	Outcome
[6]	Israel	50/M	Healthy	Pfizer BNT162b2	10 days post first vaccine	New onset NS (Alb 1.93 g/dL, Pu 6.9 g/day) AKI (Scr from 0.78 to 6.6 mg/dL) KB: MCD, ATI	Positive 38.9 U/ mL	Prednisone 1 mg/kg	Remission 2 weeks later: Scr 0.97 mg/dL, Alb, 32 g/L UPCR 155 mg/g
[7]	USA	77/M	DM, obesity, CAD	Pfizer BNT162b2	7 days post first vaccine	New onset NS (Alb 3.0 g/dL, Pu 23.2 g/day) AKI (Scr from 1.3 to 2.33 mg/dL) KB: MCD, ATI, mild diabetic changes	NA	MP pulse 1 g daily, 3 days fol- lowed by oral prednisolone 60 mg daily	No change 3 weeks later: SCR 3.24 mg/dL, Pu 18.8 g/day
[8]	The Netherlands	80/M	VTE	Pfizer BNT162b2	7 days post first vaccine	New onset SN (Alb 2.1 g/dL, Pu 15.3 g/day) KB: MCD, ATI	NA	Oral prednisolone 80 mg daily	Remission after 10 days: UPCR 0.68 g/g
[9]	The Netherlands	61/F	AI hepatitis Hypo- thyroidism	Pfizer BNT162b2	8 days post first vaccine	New onset SN (Alb 1.03 g/dL, Pu 12 g/day) AKI (Scr normal to 3.6 mg/dL) KB: MCD	NA	Oral steroids (1 mg/kg/d)	Free of hemodialysis 3 weeks after Pu decreased to 2.3 g/day
[10]	France	34/F	Steroid-depen- dent MCD	Pfizer BNT162b2	10 days post first vaccine and few days post sec- ond vaccine	Relapse NS (UPCR 2.4 g/g) KB: not performed	NA	Oral prednisolone 0.5 mg/kg	Partial remission (UPCR 1.2 g/g). Received the second injection (27 days after the first one), with NS relapse a few days later (UPCR 3 g/g), leading to a new increase of steroid dose to 1 mg/ kg that finally allowed complete remission
[11]	Switzerland	22/M	Steroid-depen- dent MCD	Pfizer BNT162b2	3 days post first vaccine	Relapse NS (Alb 2.3 g/dL, Pu 3+) Scr 0.80 mg/dL KB: not performed	Positive 95.5 U/mL	Oral prednisolone 60 mg daily Tacrolimus 1 mg twice daily	No remission until 17 days Received second vaccine dose 6 weeks after the first one, while still on immunosup- pressive treatment without NS relapse Remission within 2 weeks
[12]	Japan	60/M	Steroid-sensi- tive MCD	Pfizer BNT162b2	8 days post first vaccine	Relapse NS (Alb 2.8 g/dL, UPCR 11.4 g/g) Scr 0.99 mg/dL KB: not performed	Positive, 196 U/ mL	Prednisolone 20 mg daily + CSA 1000 mg daily	Complete remission within 10 days. second vaccine dose administered under 15 mg daily of prednisolone without relapse
[13]	UK	30/M	Steroid/tacrol- imus-depen- dent MCD	AstraZeneca	Within 2 days post first vaccine	Relapse Pu (UPCR 142 mg/mmol) Scr stable at 0.93 mg/dL KB not performed	NA	Prednisolone 20 mg daily	Complete remission within 10 days. second vaccine dose administered under 15 mg daily of prednisolone without relapse
[13]	UK	40/F	Steroid/tacrol- imus-depen- dent MCD	AstraZeneca	Within 2 days post first vaccine	Relapse NS (3+) Scr stable at 1.19 mg/dL KB not performed	NA	Prednisolone 30 mg daily	Complete remission within 2 weeks Second vaccine dose administered under 15 mg daily of prednisolone without relapse
[14]	USA	63/F	HT, tobacco	Moderna mRNA- 1273	Less than 1 week post first vaccine	New onset NS (Alb 0.7 g/dL, Pu 13.4 g/day) Uncontrolled HT KB: MCD, ATI, focal AIN	NA	Candesartan 80 mg twice daily MP pulse 500 mg daily, 3 days followed by oral prednisolone 1 mg/kg	NA
[15]	Turkey	66/F	MN in remis- sion for 8 years HT, DM	SINOVAC	2 weeks post first vaccine	Relapse NS (Alb 2.6 g/dL, UPCR 9.24 mg/mg) KB: not performed	Positive	NA	NA

Alb, albumin; Scr, serum creatinine; AKI, acute kidney injury; CAD, coronary artery disease; CSA, ciclosporin A; KB, kidney biopsy; ATI, acute tubular injury; MN, membranous nephropathy; AIN, acute interstitial nephritis; MP, methylprednisolone; DM, diabetes mellitus; HT, hypertension; VTE, venous thromboembolism; M, male; F, female; UPCR, urine protein-creatinine ratio; Pu, proteinuria; AI hepatitis, auto-immune hepatitis; NA, not available.

Table 2. Crescentic glomerulonephritis following SARS-CoV-2 vaccine

Ref.	Country	Age/sex	Past medical history	SARS-CoV-2 vaccine	Onset of symptoms	Kidney findings	Treatment	Outcome
[16]	Switzerland	39/M	HTN	Moderna mRNA-1273	Immediately after second dose	AKI NS Macrohematuria KB: severe crescentic IgA GN	High-dose glucocorticoids + CYC	Serum creatinine normalized, proteinuria decreased but persistent microhematuria
[16]	Switzerland	81/M	Healthy	Moderna mRNA-1273	Shortly after second dose	AKI, non-nephrotic range Pu, elevated PR3-ANCA titer. KB: severe pauci-immune crescentic glomerulonephritis with capillary necrosis and vasculitis present in renal vessel walls	High-dose glucocorticoids + CYC and plasma exchange	Resolution of symptoms over 3 weeks with a decreased of PR3-ANCA
[17]	USA	52/M	HTN	Moderna mRNA-1273	2 weeks after second dose	AKI, Pu: 1+, hematuria, elevated PR3-ANCA titers KB: pauci immune crescentic GN and fibrinoid necrosis in 38/46 glomeruli	Rituximab initiated at 375 mg/m ² but developed adverse reaction One dose of CYC 7.5 mg/kg, prednisone	Worsening kidney function and hyperkalemia requiring hemodialysis
[18]	USA	Elderly/F	Healthy	Moderna mRNA-1273	2 weeks after second dose	AKI NS KB: diffuse, active and recent crescentic anti-GBM nephritis with mesangial IgA deposits	Methylprednisolone, CYC, plasma exchange and hemodialysis	Remains dialysis-dependent
[19]	Singapore	41/F	Gestational diabetes	Pfizer BNT162b2	1 day after the second dose	AKI NS KB: crescentic IgA GN with fibro-cellular and fibrous crescents	Pulse methylprednisolone, followed by oral prednisolone; I.V. CYC	NA
[19]	Singapore	60/F	Hypertlipidemia	Pfizer BNT162b2	1 day after the second dose	AKI NS KB: anti-GBM crescentic GN + ATI	Pulse methylprednisolone, followed by oral prednisolone; oral CYC; plasma exchange	NA

AKI, acute kidney injury; M, male; F, female; CYC, cyclophosphamide; GN, glomerulonephritis; HTN, hypertension; IF, immunofluorescence; I.V., intravenous; KB, kidney biopsy; PR3, proteinase 3; Pu, proteinuria; NA, not available; SCr, serum creatinine.

cytokines such as TNF and interleukin-1B, which can prime neutrophils leading to formation of neutrophil extracellular traps (NETs). Persistent NETs and prolonged exposure to their contents can lead to disruption of tolerance and formation of Abs to myeloperoxidase and proteinase 3. This could be the mechanism of triggering an ANCA-associated vasculitis [25]. However, crescents may take time to form, suggesting an unrecognized underlying pre-existing glomerulonephritis was present at the time of receiving SARS-CoV-2 vaccination, which more likely potentiated an immune response in the described patients. In addition, there is a seasonal variation of vasculitis that may be playing a role here as well [26], and not all related to the vaccine.

Reports of temporal and spatial clustering suggest that environmental factors such as infections may play a role in anti-GBM disease induction [27, 28]. Infectious associations, particularly with influenza A [29, 30], and high prevalence of prodromal upper and lower respiratory tract infection in a cohort of 140 Chinese patients [31] may account for the aforementioned seasonal or geographic ‘clustering’ of anti-GBM disease cases.

COVID-19 may be one such infection [32, 33], as suggested by a report of a cluster of cases in London during the current pandemic [34] with a 5-fold increased incidence. Although five of eight tested patients presenting with anti-GBM Ab were negative for SARS-CoV-2 infection by PCR, four had IgM and/or IgG Abs to SARS-CoV-2 S protein, raising the possibility that immune response to SARS-CoV-2 could be related to development of anti-GBM in some patients [34].

However, there is no anti-GBM case following vaccination reported in the literature. Therefore, one can ask the question about the seasonality of anti-GBM Ab and/or the possibility that these patients were already infected with COVID-19, since none of the patients reported had a serological test before vaccination. Whether current cases can be attributed to SARS-CoV-2 vaccine-related immune response warrants investigation.

Pharmacovigilance of SARS-CoV-2 vaccines will be important to determine the incidence of these potential adverse events since many millions of doses of the various available SARS-CoV-2 vaccines have been administered worldwide. However, we also should be mindful that this may be a coincidence and not causation, and vaccinations should be continued in order to end the pandemic.

CONFLICT OF INTEREST STATEMENT

K.D.J. is a consultant for Astex Pharmaceuticals, Natera, GlaxoSmithKline, ChemoCentryx and Chinook, a paid contributor to Uptodate.com and receives honorarium from the International Society for Nephrology and the American Society for Nephrology.

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