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De Novo and Relapsing Glomerular Diseases After COVID-19 Vaccination: What Do We Know So Far?

Andrew S. Bomback, Satoru Kudose, and Vivette D. D'Agati

The international deployment of mass vaccinations for coronavirus disease 2019 (COVID-19) has raised new concerns for caregivers who specialize in kidney disease. A number of reports question the ability of transplanted patients on maintenance immunosuppression and patients with kidney failure on dialysis to mount sufficient antibody responses to confer immunity against the virus. At the same time, nephrologists are faced with a small but growing literature of case reports linking COVID-19 vaccines with heightened off-target immune responses leading to the sudden development of de novo or relapsing glomerular diseases.

Our group recently published a case of minimal change disease (MCD) presenting with abrupt onset of nephrotic syndrome 1 week after the first dose of the Pfizer-BioNTech vaccine,[1] as well as 2 cases of IgA nephropathy presenting as gross hematuria within 2 days of the second dose of the Moderna vaccine.[2] At the time of this writing, these cases join at least 16 other reports of kidney diseases arising within 3 weeks of COVID-19 vaccination, with most cases arising within the first week (Table 1). These reports include 26 patients with a variety of lesions—MCD (n = 10),[3-9] immunoglobulin A nephropathy (IgAN; n = 10),[2,10-14] antineutrophil cytoplasmic autoantibody (ANCA)–associated vasculitis (n = 2),[10,15] anti–glomerular basement membrane (anti-GBM) disease (n = 2),[14,16] membranous glomerulopathy (n = 1),[17] and IgG4-related disease (n = 1).[18] Most reported cases have been associated with mRNA vaccines (either Pfizer-BioNTech or Moderna), with the onset of glomerular disease occurring after the first or second dose. Fewer reported cases have occurred after the single-dose adenoviral vector vaccine (AstraZeneca) and the vaccine based on inactivated virus (Sinovac). Interestingly, most cases of MCD occurred after the first dose of either mRNA vaccine, whereas most IgAN flares occurred after the second dose. In some patients, the sudden onset of macrohematuria postvaccination unmasked a previously undiagnosed IgAN.

Since our publications on this subject, we have fielded a number of questions from nephrologists about their own newly diagnosed patients with similar presentations of glomerular disease following vaccination. Social media feeds (eg, Twitter, Facebook) have also included both patients and providers reporting such events. Therefore, at this moment in time, the number of unpublished cases of glomerular diseases linked to COVID-19 vaccination is likely to exceed the number of reported cases.

The link between glomerular disease onset and COVID-19 vaccination adds a new chapter to older medical literature concerning the risk of nephrotic syndrome after influenza vaccination. Acute onset of MCD has been described in adults following the influenza vaccine.[19,20] Retrospective[21] and, more recently, prospective[22] cohorts of children with nephrotic syndrome have shown a small rate of relapsing disease postvaccination that is no different from the relapse rate in unvaccinated children. These kinds of comparative analyses have not been reported in adults with nephrotic syndrome. The link between vaccines and glomerular lesions, however, is not just limited to influenza vaccines and podocytopathies. For example, the case of recurrent IgAN after COVID-19 vaccination reported by Rahim et al[11] had a similar disease flare 2 years earlier after receipt of a recombinant zoster vaccine (Shingrix). Flares of MCD have been reported after pneumococcal, smallpox, hepatitis B, and Tdap (tetanus, diphtheria, pertussis) vaccines.[23] And a previous review found a total of 65 patients across 45 published reports who developed vasculitis after influenza vaccination.[24] While a coincidental occurrence cannot be excluded, the close temporal association within days between vaccination and the de novo onset or flare of glomerular disease strongly suggests a potential pathogenetic association.

This pathogenesis of vaccine-associated glomerular lesions has not been fully elucidated for either the influenza or COVID-19 vaccines. The COVID-19 vaccines employ different technologies, with Pfizer-BioNTech and Moderna using mRNA delivery via lipid nanoparticles and AstraZeneca using an adenoviral vector. These vaccines share a similar end strategy of inducing the recipient's cells to synthesize the COVID-19 spike protein. While effective immune response to the spike protein involves both B and T cells, the rapidity of glomerular disease onset in relation to receipt of the COVID-19 vaccine implicates T cells as the more important mediators. T-cell responses to foreign mRNA provoke swift production of such cytokines as interferon γ, tumor necrosis factor α, and interleukin 2 that could trigger podocytopathies and augment B-cell production of disease-specific antibodies in the susceptible patient. Such cytokines or other soluble T-cell factors could amplify subclinical or quiescent glomerular diseases. Importantly, a similar pathogenesis has been proposed for how viral infections—a well-known trigger for all glomerular lesions—spur the onset of de novo and relapsing disease. These responses are analogous to the ability of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection itself to cause activation of diverse autoimmune and alloimmune diseases affecting the kidney.[25]

The mechanisms of immune activation postvaccination are critical to formulating answers to the next logical set of

Table 1. Kidney Diseases Linked to Receipt of COVID-19 Vaccination

Report	Age; Sex	Vaccine	Dose	Days From Vaccine to Onset	Presentation	Pathology Findings Postvaccine	Treatment	Response	Relapse After 2nd Dose, if Given
MCD, de novo									
D'Agati[1]	77 y; M	P-B	1st	7	NS, AKI	MCD w/ ATI	Cs	PR	Y
Holzworth[3]	63 y; F	Mod	1st	<7	NS, AKI	MCD w/ ATI & AIN	Cs	–[a]	
Lebedev[4]	50 y; M	P-B	1st	4	NS, AKI	MCD w/ ATI	Cs	CR	
Maas[5]	80s; M	P-B	1st	7	NS	MCD	Cs	CR	
Weijers[9]	61 y; F	P-B	1st	8	NS, AKI	MCD	Cs	PR	
MCD, relapse									
Kervella[6]	34 y; F	P-B	1st	10	SRP, E	NA	Cs	CR	Y
Komaba[7]	60s; M	P-B	1st	8	NS	NA	Cs	CR	
Morlidge[28]	30 y; M	AZ	1st	2	SRP, E	NA	Cs	CR	N
	40 y; F	AZ	1st	1	P, E	NA	Cs	CR	N
Schwotzer[8]	22 y; M	P-B	1st	3	NS	NA	Cs + CNI	CR	N
IgAN									
Anderegg[10]	39 y; M	Mod	2nd	<1	GH, AKI	Active IgAN	Cs + CYP	Remission of GH, Scr normalized	
Rahim[11]	52 y; F	P-B	2nd	<1	GH, NRP	NA	None	Remission of GH	
Kudose[2]	50 y; F	Mod	2nd	2	GH, AKI, SRP	Active IgAN	None	Remission of GH	
	19 y; M	Mod	2nd	2	GH	Active IgAN	None	Remission of GH	
Negrea[12]	38 y; F	Mod	2nd	<1	GH, SRP	NA	None	Remission of GH	
	38 y; F	Mod	2nd	<1	GH	NA	None	Remission of GH	
Perrin[13]	22 y; M	Mod	1st	2	GH	NA	None	Remission of GH	Y
	41 y; F	P-B	1st	2	GH	NA	None	Remission of GH	
	27 y; F	P-B	2nd	2	GH	NA	None	Remission of GH	
Tan[14]	41 y; F	P-B	2nd	1	GH, AKI, NRP	Active IgAN	–[a]	Remission of GH	
ANCA vasculitis									
Anderegg[10]	81 y; M	Mod	2nd	<22	AKI, SRP	PR3-ANCA GN	Cs + CYP + PLEX	"Improved"	
Sekar[15]	52 y; M	Mod	2nd	14	AKI, MH	PR3-ANCA GN	RTX + CYP	Dialysis	
Anti-GBM GN									
Sacker[16]	"older"; F	Mod	2nd	14	AKI, GH, SRP	Anti-GBM GN, IgAN	Cs + CYP + PLEX	Dialysis	
Tan[14]	60 y; F	P-B	2nd	1	AKI, GH, NRP	Anti-GBM GN	–[a]		
MGN, relapse									
Aydin[17]	66 y; F	S	1st	14	AKI, NRP	PLA_2R-associated MGN	–[a]	–[a]	
IgG4RD, relapse									
Masset[18]	66 y; M	P-B	2nd	14	AKI	NA	Cs + CNI	CR	

Abbreviations: AIN, acute interstitial nephritis; AKI, acute kidney injury; ANCA, antineutrophil cytoplasmic antibody; ATI, acute tubular injury; AZ, AstraZeneca; CNI, calcineurin inhibitor; CR, complete remission; Cs, corticosteroids; CYP, cyclophosphamide; E, edema; F, female; GBM, glomerular basement membrane; GH, gross hematuria; GN, glomerulonephritis; IgAN, immunoglobulin A nephropathy; IgG4RD, IgG4-related disease; M, male; MCD, minimal change disease; MGN, membranous glomerulopathy; MH, microscopic hematuria; Mod, Moderna; N, no; NA, not available (no biopsy performed); NRP, nephrotic-range proteinuria; NS, nephrotic syndrome; P, proteinuria; P-B, Pfizer-BioNTech; PLA_2R, phospholipase A_2 receptor; PLEX, plasmapheresis; PR, partial response; RTX, rituximab; S, Sinovac; Scr, serum creatinine; SRP, subnephrotic range proteinuria; w, with; Y, yes.
[a]Not reported.

clinical questions. How concerned should patients with glomerular diseases be about receiving the vaccine, and should their level of concern be influenced by whether their glomerular disease is active or in remission? Should these patients not be vaccinated at all? Should they be advised against mRNA vaccination in favor of another vaccine type? Is close laboratory monitoring following the vaccine helpful to survey for relapse?

The number of vaccine-linked cases—reported and unreported—is growing, but still represents an infinitesimally small fraction of those individuals who have safely received the vaccine. The risk of glomerular disease relapse from vaccination remains significantly lower than the risk of dialysis-requiring acute kidney injury (AKI) and/or death in a COVID-19–infected individual.[2,6] Glomerular disease risk from vaccination is also likely lower than glomerular disease risk from COVID-19 infection. For example, thus far only 2 cases of anti-GBM disease have been attributed to a COVID-19 vaccine[1,4] compared to 4 reported cases in the setting of COVID-19 infection.[2,7]

Therefore, we strongly recommend proceeding with COVID-19 vaccinations (as with all other available vaccinations) in glomerular disease patients. We also propose 2 important discussion points for patients: First, akin to the experience in transplanted patients, those glomerular disease patients on immunosuppression may not mount the same level of immune response and therefore may not achieve the same degree of sustained immunity to the virus as those off immunosuppression. Second, a small risk of relapsing disease is present up to 1 month after the second vaccine, during which time patients can self-monitor for signs and symptoms.

Kidney biopsy postvaccination in those IgAN patients developing gross hematuria has revealed active endocapillary hypercellularity, leukocyte infiltration, fibrinoid necrosis, and crescents, although these lesions can involve a minority of glomeruli.[2] Gross hematuria typically resolves rapidly within days. These findings raise questions about how aggressively the biopsy findings should be treated and whether a flare is more likely to be short-lived and transient once the vaccine-induced stimulus subsides. Yet other cases of MCD with AKI have proven slow to respond to corticosteroids and required intensive care unit admission for management of life-threatening fluid overload.[1] More experience with the postvaccination setting is needed to define the "natural history" of this newly identified occurrence and guide optimal therapeutic management.

A more specific and practical question is how to proceed with the vaccination schedule in this population. If new onset or activation of glomerular disease occurred after the first of 2 scheduled vaccines, should the second dose be postponed or canceled altogether? If yearly "booster" vaccines against COVID-19 are recommended, should such patients avoid repeat exposure to the vaccine? One possible strategy is to take another vaccine type to minimize the potential risk of relapse (eg, switching from mRNA- to adenoviral vector–based formulations for future vaccinations), as some patients have relapsed again on rechallenge with vaccinations of the same type (Table 1). Informed decision-making will require knowledge about infection risk, particularly against newer variants of COVID-19, in those who did not receive the full vaccination schedule. It will also require understanding the nature and severity of the glomerular disease in the individual patient. For example, postvaccination flare of gross hematuria without reduced kidney function in a young IgAN patient may not be comparable to severe nephrotic syndrome with AKI due to new-onset MCD in an older patient with diabetes.[1] As new reports and detailed data on individual responses emerge, these kinds of discussions will, one hopes, remain rare but become more informed in the coming months.

Article Information

Authors' Full Names and Academic Degrees: Andrew S. Bomback, MD, MPH, Satoru Kudose, MD, and Vivette D. D'Agati, MD.

Authors' Affiliations: Department of Medicine, Division of Nephrology (ASB), and Department of Pathology and Cell Biology (SK, VDD), Columbia University Irving Medical Center, New York, New York.

Address for Correspondence: Andrew S. Bomback, MD, MPH, Department of Medicine, Division of Nephrology, Columbia University Irving Medical Center, New York, NY 10032. Email: asb68@cumc.columbia.edu

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