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Original Article

ORIGINAL ARTICLE

Clinical spectrum of gross haematuria following SARS-CoV-2 vaccination with mRNA vaccines

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ABSTRACT

Background. Novel messenger RNA (mRNA)-based vaccines play an important role in current vaccination campaigns against SARS-CoV-2. They are highly efficacious and generally well tolerated. Vaccination in patients with immune-mediated kidney diseases is recommended. A number of cases with *de novo* or relapsing glomerulonephritis shortly after vaccine application have been reported, some of which presented with gross haematuria.
Methods. We collected 10 cases of macrohaematuria following mRNA-based severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) vaccination at our tertiary care institution and referring centres. Additionally, we pooled all 25 published cases from the literature with ours to analyse their clinical characteristics.
Results. Most macrohaematuria episodes (72.2%) began within 2 days after vaccination, the majority after the second dose. In some individuals, repeated episodes occurred after subsequent doses of the same vaccine. A total of 65.7% of patients never had macrohaematuria before. A total of 45.7% were known to suffer from immunoglobulin A nephropathy (IgAN); the rest had no prior renal diagnosis. IgAN was the most frequent new diagnosis, but anti-neutrophil cytoplasmic antibody-associated vasculitis and anti-glomerular basement membrane disease were also identified. Acute kidney injury (AKI) occurred in 28.6% of patients, with an increase in serum creatinine not meeting Kidney Disease: Improving Global Outcomes AKI criteria in 28.6%. Treatment ranged from conservative management, renin–angiotensin–aldosterone system inhibitors, steroids and cyclophosphamide to plasmapheresis. While renal outcomes were mainly favourable in isolated IgAN, they were poor in patients with additional or isolated small vessel vasculitis.
Conclusion. Awareness of gross haematuria after SARS-CoV-2 vaccination is important. Close follow-up and additional work up, particularly in individuals without known underlying kidney disease or worsening renal function, is essential. For patients with vaccine-associated macrohaematuria, an alternative vaccine class might be considered for subsequent vaccinations.

Keywords: case series, COVID-19, glomerulonephritis, macrohaematuria, vasculitis

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INTRODUCTION

Great vaccination efforts have been undertaken worldwide to combat the coronavirus disease 2019 (COVID-19) pandemic. More than 50% of the world's population had received at least one dose of vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by mid-November 2021 [1]. A major pillar of many national vaccination campaigns are the novel messenger RNA (mRNA) vaccines BNT162b2 (Pfizer-BioNTech) and mRNA-1273 (Moderna). While trials leading to initial emergency use authorization of these vaccines in the USA and Europe did not indicate major safety concerns, post-marketing observations—in particular in view of their large-scale use—will shed light on potential rare side effects and side effects in special populations [2, 3]. SARS-CoV-2 vaccination in immune-mediated kidney diseases is generally highly recommended [4].

Recently a number of patients with relapsing or *de novo* glomerulonephritis (GN) associated with one of these two vaccines have been reported [5–7]. There were several patients with gross haematuria—mainly due to immunoglobulin A nephropathy (IgAN)—among the published cases. Globally, IgAN is the most common GN, with significant geographic differences regarding its prevalence [8].

Here we report 10 patients with gross haematuria following a first, second or third dose of mRNA-based SARS-CoV-2 vaccine, including histological findings in 4 patients, to our knowledge the largest case series so far.

In addition to our case series, we reviewed the existing literature—mainly published as letters—in order to summarize and further illustrate the clinical spectrum of affected patients. A better understanding of the clinical course and the underlying pathophysiology is required to discuss potential risks of the vaccination with patients and for optimal nephrologic care.

MATERIALS AND METHODS

Cases were identified in the outpatient department of the Division of Nephrology, the Institute of Pathology and Molecular Pathology of the University Hospital Zurich and by referring centres. Written informed consent was provided by all participants. Published cases were identified by a PubMed (National Library of Medicine) search using the following search terms by 26 October 2021: glomerulonephritis OR gross hematuria OR macrohematuria OR hematuria OR igan OR anca OR anti-gbm AND covid vaccination. The reported estimated glomerular filtration rate (eGFR) is based on the Chronic Kidney Disease Epidemiology Collaboration creatinine equation [9]. Data were analysed by descriptive statistics. Results are expressed as median and interquartile range (IQR) for numerical variables and absolute and relative frequencies for categorical variables. All analyses were performed using SPSS Statistics 26 (IBM, Armonk, NY, USA).

RESULTS

Cases and review of the literature

Here we report a series of 10 patients with gross haematuria following mRNA-based SARS-CoV-2 vaccination managed at our tertiary care institution or referring nephrology centres. Table 1 summarizes the clinical data. None of the patients had a suspicion for or diagnosis of SARS-CoV-2 infection prior to vaccination. Detailed case descriptions are provided in the Supplementary data. Table 1 also shows the 25 published cases of macrohaematuria following mRNA-based SARS-CoV-2 vaccination from our literature search and added to our cases in order to analyse the clinical pattern of 35 cases in total [6, 10–21]. Results are summarized in Table 2 and Figure 2.

FIGURE 1: Macrohaematuria seen in Patient 3 at different time points following the second dose of mRNA-1273.

Patient characteristics and clinical presentation of gross haematuria

The median age of the already reported and our patients was 40 years ([26–52], range 13–70). Slightly more male patients were reported. Most cases with reported race had a White ethnic background. Case numbers of gross haematuria after both mRNA-based vaccines were similar, with a few more reports following mRNA-1273 compared with BNT162b2. Only two affected patients had received kidney replacement therapy at the time of vaccination (one on haemodialysis and one with kidney transplant). Figure 2A illustrates the time of onset of gross haematuria after the first or second vaccination. A total of 72.2% of the episodes, including one relapse, began within 2 days after vaccination and as early as 3 h after injection. The vast majority of macrohaematuria episodes began after the second dose. Patient 9 was the first patient with a reported occurrence of macrohaematuria after the third dose. Three of the five patients who experienced gross haematuria after the first dose had signs of relapse or ongoing inflammation after the second dose—one patient with a second episode of macrohaematuria, one with isolated worsening of skin lesions [15] and one with a further increase in serum creatinine [6]. Patient 1 was the first reported patient to receive a vector-based vaccine as a second dose after an initial mRNA vaccination. He exhibited no signs of relapse. One patient from the literature refused a second vaccination [16]. In most cases, gross macrohaematuria lasted not longer than 7 days and rarely several weeks. Three patients (8.6%) experienced several episodes of gross haematuria in the weeks after vaccination. Most patients (65.7%) had never experienced gross haematuria before (Figure 2B). General symptoms were common.

Underlying glomerular diseases

A total of 16/35 patients (45.7%) were known to suffer from IgAN, all but one with a biopsy-proven diagnosis (Figure 2C). A total of 19/35 patients (54.3%) had no prior renal diagnosis. However, two of them (5.7%) had been diagnosed with microhaematuria

Table 1. Clinical characteristics of individual patients with gross haematuria after mRNA-based SARS-CoV-2 vaccination

Patient	Age (years)	Gender	Race	Vaccine[a]	Dose	Onset (days after vaccination)	Additional time points (days after vaccination)	*De novo* GN	GN	Biopsy after vaccination	Years of or years after biopsy-proven diagnosis	Gross haematuria before	Duration (days of first episode)	Kidney replacement therapy at time of vaccination
1	51	M	White	Pfizer	1	0	no relapse after vector-based vaccination	Yes	IgAN (new diagnosis, clinically suspected)	No	–	No	1.5	–
2	37	F	Asian	Moderna	2	1	–	Yes	IgAN (new diagnosis)	Yes	0	No	1	–
3	53	MTF	White	Moderna	2	1	–	No	IgAN	No	2016	No	7	–
4	20	M	White	Moderna	2	1	18 and 42 after second dose	Yes	IgAN (new diagnosis)	Yes	0	No	3	–
5	45	M	White	Pfizer	2	44	–	No	IgAN	No	2017	No	4	–
6	41	F	White	Moderna	2	2	–	No	IgAN (clinically suspected before)	No	2013 suspected (no biopsy)	Yes	2	–
7	25	F	White	Pfizer	2	24	42 after second dose	Yes	IgAN (new diagnosis)	Yes	0	No	3	–
8	43	F	White	Pfizer	2	1	–	No	IgAN	No	0	Yes	14	–
9	63	M	White	Pfizer	3	3	–	No	IgAN	No	2020	Yes	3	
10	69	M	White	Pfizer	2	33	–	Yes	IgAN/ANCA (new diagnosis)	Yes	0	No	21	–
Abramson *et al.* [10]	30	M	Western European/ South American	Moderna	2	1	–	Yes	IgAN (new diagnosis)	Yes	0	No	2	–
Anderegg *et al.* [11]	39	M	Not reported	Moderna	2	0	–	Yes	IgAN (new diagnosis)	Yes	0	Not reported	Not reported	–
Hanna *et al.* [12]	13	M	White	Pfizer	2	0	–	No	IgAN	No	0.5	No	2	–
	17	M	White	Pfizer	2	0	–	Yes	IgAN (new diagnosis)	Yes	0	No	4	–
Klomjit *et al.* [6]	38	M	White	Pfizer	2	14	–	Yes	IgAN (new diagnosis)	Yes	0	Not reported	Not reported	–
	66	M	White	Moderna	1	14	further elevation of serum creatinine after second dose	Yes	IgAN (new diagnosis)	Yes	0	Not reported	Not reported	–
	19	M	White	Moderna	2	1	–	No	IgAN	No	2014	Yes	Not reported	–
Kudose *et al.* [13]	50	F	White	Moderna	2	2	–	Yes	IgAN (new diagnosis)	Yes	0	No	5	–
	19	M	White	Moderna	2	2	–	Yes	IgAN (new diagnosis)	Yes	0	No	2	–

Table 1. Continued.

Case	Age	Gender	Race	Vaccine[a]	Dose	Onset (days after vaccination)	Additional time points (days after vaccination)	De novo GN	GN	Biopsy after vaccination	Years of or years after biopsy-proven diagnosis	Gross haematuria before	Duration (days of first episode)	Kidney replacement therapy at time of vaccination
Negrea *et al.* [14]	38	F	White	Moderna	2	0	–	No	IgAN	No	2005	Yes	3	–
	38	F	White	Moderna	2	0	–	No	IgAN	No	2019	No	3	–
Park *et al.* [15]	22	F	Not reported	Moderna	2	2	–	No	IgAN	No	IgA vasculitis at age of 10 years	Not reported	7	–
	39	F	Not reported	Moderna	2	2	–	Yes	IgAN (new diagnosis, clinically suspected)	No	–	No	7	–
	50	M	Not reported	Moderna	2	1	–	Yes	IgAN (new diagnosis)	Yes	0	No	Not reported	–
	67	M	Not reported	Moderna	1	30	Skin worsening after second dose (not kidney)	Yes	IgAN (new diagnosis)	Yes (skin)	0	No	Not reported	–
Perrin *et al.* [16]	22	M	Not reported	Moderna	1	2	25 after first dose, 2 after second dose	No	IgAN	No	2019	No	Not reported	–
	41	F	Not reported	Pfizer	1	2	Second dose not applied	No	IgAN	No	2005	Yes	Not reported	KTx
	27	F	Not reported	Pfizer	2	2	–	No	IgAN	No	2020	No	Not reported	HD
Plasse *et al.* [17]	Not reported	M	Not reported	Pfizer	2	5	–	No	IgAN	No	2018	Yes	At least 5 days	–
	Not reported	M	Not reported	Pfizer	2	0	–	No	IgAN	No	2020	No	3	–
Rahim *et al.* [18]	52	F	Asian	Pfizer	2	0	–	No	IgAN	No	2017	Yes	5	–
Tan *et al.* [19]	41	F	Asian	Pfizer	2	1	–	Yes	IgAN (new diagnosis)	Yes	0	No	Not reported	–
	60	F	Asian	Pfizer	2	1	–	Yes	Anti-GBM disease (new diagnosis)	Yes	0	No	At least 6 weeks	–
Nagai *et al.* [20]	70	F	Not reported	mRNA vaccine (not specified)	2	9	–	Yes	Anti-GBM disease (new diagnosis)	Yes	0	No	Not exactly reported	–
Sacker *et al.* [35]	“older”	F	Not reported	Moderna	2	14	–	Yes	IgAN/anti-GBM disease (new diagnosis)	Yes	0	No	14	–

Table 1. Continued.

Case	AKI	Treatment initiated	*Outcome*	Symptoms	Anti-spike IgG antibody titers	Covid infection prior	Medical history Medication
1	–	None	Spontaneous resolution, FU 3.5 weeks	None	Yes	No	Allergies, asthma
2	–	RAASi	PU decreased, FU 3.5 weeks	Fever, difficulties breathing, myalgia, arthralgia	N/A	No	Pneumonia in childhood
3	SCr↑	None	Spontaneous resolution to BL SCr, PU, MH, FU 3 weeks	Fever, malaise	Yes	No	Gluten, fructose and histamine intolerance, restless legs syndrome; Medication: estradiol, cholecalciferol
4	Yes	RAASi	SCr normalized, PU significantly decreased, MH persisted, FU 7 weeks	Fever, chills, body aches, dizziness	Yes	No	Allergic rhinoconjunctivits
5	–	None	Spontaneous resolution, FU 2 months	Fever, chills, myalgia, dizziness	N/A	No	None Medication: RAASi, rosuvastatin, cholecalciferole
6	–	None	Spontaneous resolution	None	N/A	No	None
7	SCr↑	RAASi	Spontaneous resolution, FU 1.5 months	Fever, chills	NA	No (but before biopsy)	None
8	SCr↑	Steroids, CYC, RAASi (already given)	SCr normalized, PU stable, FU 10d	Fever, headache	NA	No	APC resistance, chronic autoimmune thyroiditis; Medication: CYC, steroids, RAASi, TMP/SMX, PPI, darbepoietin alpha
9	SCr↑	None	SCr normalized, FU 2 weeks	Chills, fatigue, headaches, body aches	Yes	No	Ankylosing spondylitis; Medication: infliximab, dapagliflozin, influenza vaccination
10	Yes	Steroids, CYC, HD	HD, FU 1.5 months	Fatigue, loss of appetite, hypertension	NA	No	Hypertensive cardiomyopathy, benign prostatic hyperplasia, depression; Medication: escitalopram, dutasteride/tamsulosin

Table 1. Continued.

Case	AKI	Treatment initiated	*Outcome*	Symptoms	Anti-spike IgG antibody titers	Covid infection prior	Medical history Medication
Abramson *et al.* [10]	–	RAASi	PU decreased, FU 6 weeks	Fever, chills, headache	Not reported	No	None
Anderegg *et al.* [11]	Yes	Steroids, CYC	SCr normalized, PU significantly decreased, MH persisted, FU several weeks	Fever, flu-like symptoms	Not reported	Not reported	Treated hypertension
Hanna *et al.* [12]	Yes	None	Spontaneous resolution, FU 1 week	Vomiting	Not reported	No	Type 1 diabetes mellitus; Medication: RAASi
	Yes	Steroids	Improvement of SCr, FU unclear	Hypertension	Not reported	No	None
Klomjit *et al.* [6]	SCr↑	None	Unknown, FU unknown	Not reported	Not reported	Not reported	Not reported
	SCr↑	Steroids (for pericarditis)	Improvement of SCr, PU and MH, FU 5 months	Not reported	Not reported	Not reported	Not reported
	–	None	Unknown	Not reported	Not reported	Not reported	Not reported
Kudose *et al.* [13]	SCr↑	Not reported	Not reported	Fever, generalized body aches	Not reported	Not reported	Hypertension, obesity, APLS, PU and microhaematuria before; Medication: amlodipine, furosemide, olmesartan, warfarin, enoxaparin
	–	Not reported	Not reported	Not reported	Not reported	Not reported	6 months of microhaematuria
Negrea *et al.* [14]	–	None	PU increased, FU 3 weeks	Body aches, headache, fatigue, fever and chills	Not reported	No	Medication: RAASi
	–	None	Spontaneous resolution, FU 3 weeks	Body aches, headache, fatigue, fever and chills	Not reported	No	Medication: RAASi (earlier CyC, steroids)
Park *et al.* [15]	–	None	Spontaneous resolution, FU 1 month after second dose	Not reported	Not reported	Not reported	IgA vasculitis at age of 10 years treated with steroids
	–	None	Spontaneous resolution, FU 1 month after second dose	Not reported	Not reported	Not reported	None
	SCr↑	RAASi	SCr improved but above BL, PU and MH at BL after FU 1 month after second dose	Not reported	Not reported	Not reported	Arterial hypertension
	Yes	Steroids (1 week)	SCr improved but above BL, PU and MH at BL FU 1 month after second dose, improvement of skin	Rash (lower extremities)	Not reported	Not reported	Arterial hypertension; Medication: RAASi
Perrin *et al.* [16]	–	None	Spontaneous resolution, transient proteinuria, FU 1 month after second dose	Arthralgia	N/A	Not reported	RAASi (earlier steroids for 6 months)
	SCr↑	None	Spontaneous resolution, FU 1 month after second dose	Leukocytosis	No	Not reported	Medication: Tac, MPA, steroids for KTx
	–	None	Spontaneous resolution, FU 1 month after second dose	Abdominal pain, urticarial, moderate pancytopenia	Yes	Not reported	Medication: RAASi (earlier steroids for 1 month)

Table 1. Continued.

Case	AKI	Treatment initiated	*Outcome*	Symptoms	Anti-spike IgG antibody titers	Covid infection prior	Medical history Medication
Plasse *et al.* [17]	Yes	Steroids, RAASi	Return to BL SCr within 1 month and BL PU within 2 months	Fever, chills, body aches, dysuria	Not reported	No	Not reported
	SCr↑	None	Not reported	Body aches	Not reported	No	Medication: RAASi
Rahim *et al.* [18]	–	None	Improved proteinuria within 1 week	Fever, myalgias, body aches, lower back pain bilaterally	Not reported	No	Medication: RAASi
Tan *et al.* [19]	Not reported	Steroids, CYC	Not reported	Headache, myalgia, hypertension	N/A	No	Gestational diabetes
	Yes	Steroids, CYC, PLEX	Not reported	Hypertension	N/A	No	Hyperlipidaemia
Nagai *et al.* [20]	Yes	Steroids, CYC, PLEX	Dialysis-independent (eGFR 6 mL/min/1.73 m^2), PU and haematuria partially remained	Mild fever, generalized fatigue	Not reported	Not reported	Centipede bites
Sacker *et al.* [35]	Yes	Steroids, CYC, PLEX, HD	HD	Fever, anoraexia, nausea	N/A	No	None

[a]Moderna, mRNA-1273; Pfizer-BioNTech, BNT162b2 mRNA.

APC, activated protein C; APLS, anti-phospholipid syndrome; F, female; FU, follow-up; HD, haemodialysis; KTx, kidney transplantation; M, male; MH, microhaematuria; MTF, male to female; MPA, mycophenolic acid; N/A, not available; PPI, proton-pump inhibitor; PU, proteinuria; SCr, serum creatinine; Tac, tacrolimus; TMP/SMX, trimethoprim/sulfamethoxazole.

Table 2. Summary of clinical characteristics of patients ($n = 35$) with gross haematuria after mRNA-based SARS-CoV-2 vaccination

Clinical characteristics		Values
Age (years), median [IQR]		40 [26–52]
Gender, *n* (%)	M	18 (51.4)
	F	16 (45.7)
	MTF	1 (2.9)
Ethnicity, *n* (%)	White	18 (51.4)
	Asian	4 (11.4)
	Western European/South American	1 (2.9)
	Not reported	12 (34.3)
Vaccine, *n* (%)	mRNA-1273	18 (51.4)
	BNT162b2	16 (45.7)
	Not reported	1 (2.9)
Beginning of GH after first, second or third dose, *n* (%)	First dose	5 (14.3)
	Second dose	29 (82.9)
	Third dose	1 (2.9)
Signs of relapse, ongoing inflammation after second dose, *n* (%)	Gross haematuria	1 (2.9)
	Worsening of skin lesions	1 (2.9)
	Rise in serum creatinine	1 (2.9)
	None (change to vector-based vaccine)	1 (2.9)
	No second dose	1 (2.9)
History of GH, *n* (%)	No	23 (65.7)
	Yes	8 (22.9)
	Not reported	4 (11.4)
General symptoms, *n* (%)	No	2 (5.7)
	Yes	26 (74.3)
	Not reported	7 (20)
Renal diagnosis prior to vaccination, *n* (%)	Yes IgAN	16 (45.7)
	No	19 (54.3)
New renal diagnosis, *n* (%)	IgAN	15 (42.9)
	Biopsy-proven	13 (37.1)
	Suspected IgAN	2 (5.7)
	IgAN/ANCA	1 (2.9)
	IgAN/anti-GBM disease	1 (2.9)
	Anti-GBM disease	2 (5.7)
Change in SCr	Outcome according to kidney function	
SCr stable, *n* (%)		14 (40)
	Spontaneous resolution to baseline	9/14
	Proteinuria decreased	3/14
	Unknown	1/14
	Not reported	1/14
SCr increase, *n* (%)		10 (28.6)
	Spontaneous resolution/resolution to baseline	5/10
	Improvement but above baseline	2/10
	Unknown	1/10
	Not reported	2/10
AKI, *n* (%)		10 (28.6)
	Spontaneous resolution/resolution to baseline	4/10
	SCr improved but above baseline	2/10
	Preterminal renal failure	1/10
	HD	2/10
	Not reported	1/10
Not reported, *n* (%)		1 (2.9)
	Not reported	1/1
Treatment initiated, *n* (%)	RAASi	5 (14.3)
	Steroids	10 (28.6)
	CYC	6 (17.1)
	PLEX	3 (8.6)
	None	17 (48.6)
	Not reported	2 (5.7)

F, female; GH, gross haematuria; M, male; MTF, male to female; SCr, serum creatinine.

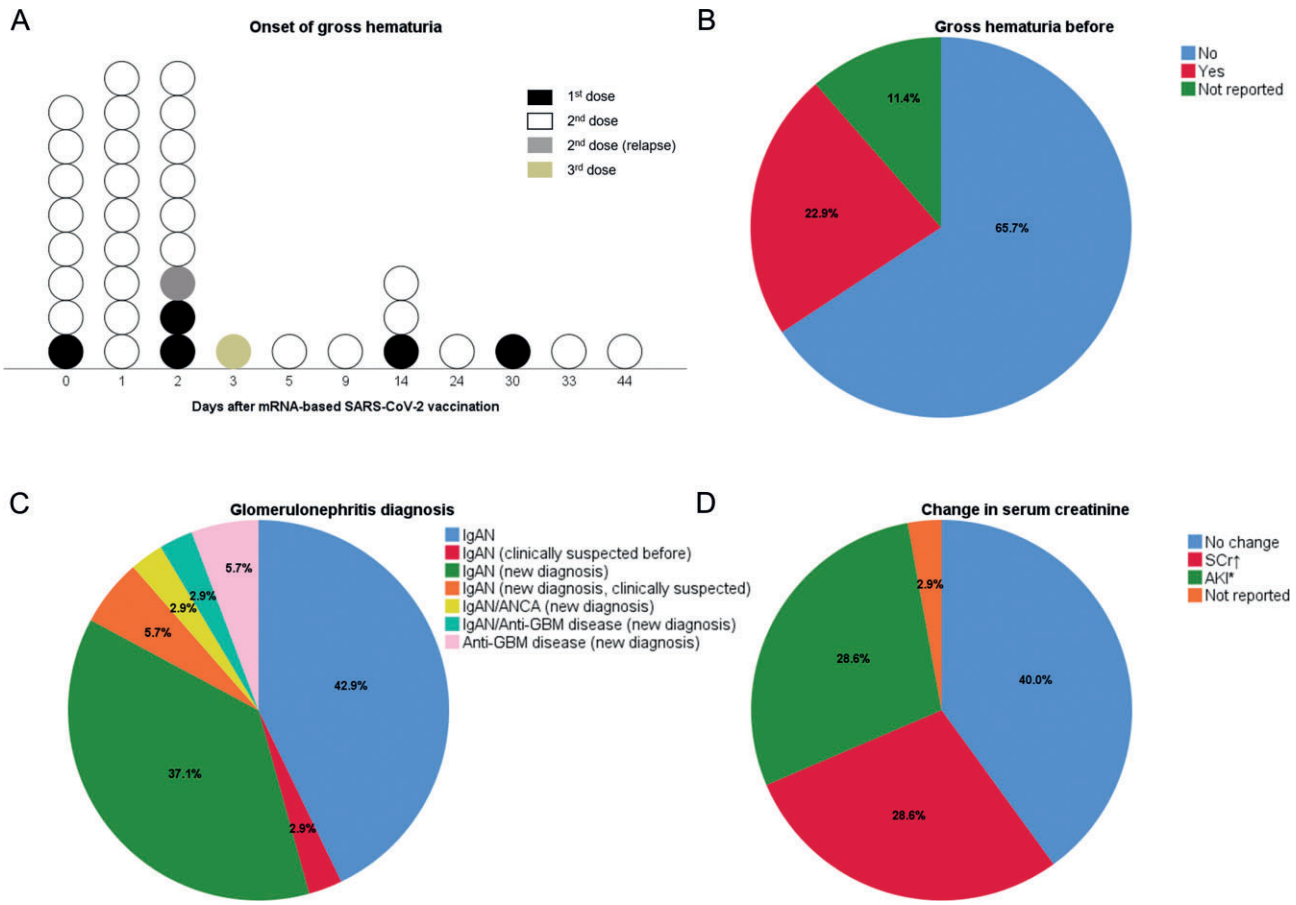

FIGURE 2: **(A)** Onset of gross haematuria after mRNA-based SARS-CoV-2 vaccination. Each circle represents the first episode of one patient after a vaccination dose, including one relapse ($n = 36$). **(B)** Occurrence of gross haematuria in relationship to SARS-CoV-2 vaccination ($n = 35$). **(C)** Diagnosis of GN in the affected patients ($n = 35$). **(D)** Change in serum creatinine after mRNA-based SARS-CoV-2 vaccination ($n = 35$). Please note that if AKI criteria according to KDIGO were not fulfilled despite an increase in serum creatinine, patients were categorized as SCr↑. *AKI comprises AKI according to the KDIGO or rapid decline in renal function if not specified any further in the report. SCr, serum creatinine.

before and in one patient (2.9%) IgAN could be demonstrated retrospectively in an earlier nephrectomy sample [6, 13]. A total of 16 of the patients received a kidney biopsy after vaccination, 1 a skin biopsy, while 2 were clinically suspected to suffer from IgAN without histologic proof (Patient 1, [15]). A total of 15 biopsies revealed IgAN, while 2 of these patients were diagnosed with additional small vessel vasculitis on top of IgAN [one anti-neutrophil cytoplasmic antibody-associated small vessel vasculitis (AAV), one anti-glomerular basement membrane (GBM) disease]. Two patients were diagnosed with isolated anti-GBM disease.

Kidney function, treatment and outcome

Figure 2D illustrates the change in serum creatinine in 34 affected patients (97.1%) with reported renal function.

A total of 14 patients (40%) had stable serum creatinine despite gross haematuria. The majority was treated supportively while renin–angiotensin–aldosterone system inhibitor (RAASi) was begun in two of them (Patient 2, [10]). Their outcome was favourable, with spontaneous resolution to baseline or at least a decline in proteinuria.

An increase in serum creatinine not meeting the Kidney Disease: Improving Global Outcomes (KDIGO) criteria for acute kidney injury (AKI) was reported in 10 patients (28.6%). Most patients were managed conservatively. RAASi was begun in two patients (Patient 7, [15]). One patient received steroids for pericarditis and one patient was already on steroids, cyclophosphamide (CYC) and RAASi (Patient 8, [6]). Information about the course was provided for seven patients—five patients with normalization of kidney function and two patients with a decrease in serum creatinine to a level above baseline.

AKI was seen in 10 patients (28.6%), with AKI stage 3 or rapid decline of renal function in 7 patients (20%)—3 isolated IgAN, 1 IgAN/ANCA, 2 IgAN/anti-GBM disease and 1 isolated anti-GBM disease. Treatment in AKI patients ranged from conservative treatment to RAASi, corticosteroids, CYC and plasma exchange (PLEX). All patients with AKI stage 3 or rapid functional decline received steroids. Three patients with IgAN had favourable outcomes—one of them was treated with CYC in addition to steroids. Two patients with IgAN and additional small vessel vasculitis remained dialysis dependent (one IgAN/ANCA, one IgAN/anti-GBM), one patient with anti-GBM disease remained with severely impaired kidney function and one with IgAN/anti-GBM without a reported outcome. All of them had received steroids and CYC. The cases with isolated or additional anti-GBM disease also received PLEX.

In most cases, proteinuria normalized or declined. The observation time reported differed.

DISCUSSION

Various reports in the literature have described the occurrence of glomerular diseases, such as minimal change disease (MCD), membranous nephropathy (MN), focal segmental glomerulosclerosis (FSGS), IgAN, AAV and anti-GBM disease, following SARS-CoV-2 vaccination [5–7]. By far the most common GN associated with COVID-19 vaccination is isolated IgAN, with a total of 31 biopsy-proven cases in the literature and 3 suspected cases (Table 1) [6]. The second most common glomerular disease to date is MCD, with 15 reported cases reviewed by Klomjit *et al.* [6]. Both new-onset and relapses of pre-existing glomerular diseases have been described.

With 10 cases, our series is the largest so far to describe gross haematuria after COVID-19 vaccination. A total of 35 cases of gross haematuria after COVID-19 vaccination have been reported in total, including ours (Table 1). In 28/35 cases isolated, IgAN was the definite cause and in 3/35 it was the suspected cause. In 3/33, anti-GBM without or in combination with IgAN ($n = 1$) was the cause and in 1/33 cases PR3-ANCA-associated GN with IgAN was the cause. No case of Alport syndrome has been reported. In most cases with macrohaematuria caused by isolated IgAN (biopsy-proven or clinically suspected), the course was largely benign and self-limiting. However, 4/31 were treated with steroids and 3/31 with a combination of CYC and steroids (one was already on this medication at the time of vaccination). All four cases with ANCA-associated GN or anti-GBM with or without IgAN received aggressive immunosuppression with high-dose steroids and CYC with or without PLEX with moderate success.

Macrohaematuria is a peculiar symptom, since it is immediately obvious and of major concern to the patient. For this reason, patients are likely to present to their healthcare provider, triggering a nephrologic workup. Thus the probability that this condition is missed is rather low compared with other less apparent manifestations of kidney disease such as AKI, proteinuria or microhaematuria. Detection bias could be the reason, why IgAN is the most frequent GN associated with COVID-19 vaccination in the literature. Another explanation could be that IgAN is the most common GN worldwide. If the COVID-19 vaccination unspecifically triggers autoimmune glomerular diseases, the probability of triggering or unmasking pre-existing IgAN is highest. Moreover, there is a greater chance for the accidental coincidence of COVID-19 vaccination and IgAN primary manifestation or flare.

With one exception, all reported cases of IgAN and glomerular gross haematuria after vaccination concern mRNA vaccines [6, 22, 23]. Most other GN cases reported in association with COVID-19 vaccination occurred with mRNA vaccines. Only rare incidents have been reported after vector or inactivated virus-based vaccines [23–27]. One explanation for the preponderance of reported IgAN cases associated with mRNA vaccines may be their overall more frequent use compared with vector (AstraZeneca, Janssen/Johnson & Johnson, Sputnik V) or inactivated virus vaccines (Sinovac Biotech), particularly in Western countries from which most reports originate. Underreporting from countries that mostly use non-mRNA vaccines cannot be excluded. Another explanation for the more frequent reports of glomerular macrohaematuria after mRNA vaccine is the potentially more pronounced immune activation due to stronger stimulation of the innate immune system compared with other vaccines [28, 29]. It is also possible that these vaccines cause IgAN via a specific mechanism. Wisnewski *et al.* [30] showed that mRNA vaccination caused an early and strong IgA response in humans. It is known that exogenous RNA binds to intracellular Toll-like receptors (TLRs) 3 and 7 [31]. Recently it was shown that endosomal TLR7 activation in B cells can stimulate the production of galactose-deficient IgA1 in IgAN-promoting renal inflammation [32]. mRNA vaccines could therefore, to a greater extent than other vaccine types, elicit a strong IgA response. Interestingly, while IgA dominates the initial antibody response to SARS-CoV-2 infection [33] and IgAN is the most common glomerular disease elicited by COVID vaccination, it is rarely seen associated with SARS-CoV-2 infection [34].

Cases from the USA (18 cases) and European countries Switzerland (11 cases, including ours) and France (3 cases) accounted for 32 of the 33 cases (97%) with isolated IgAN (31 cases) or IgAN and additional small vessel vasculitis (two cases) and macrohaematuria [6, 10–18, 35]. The observation that the relative frequency of published cases after the use of mRNA-1273 compared with BNT162b2 (18 versus 14 cases, ratio 1.29) was higher, although the vaccine was used less frequently overall in these countries through 26 October 2021 (173.6 versus 326.5 million doses, ratio 0.53), might be a consequence of the approximately 3-fold higher content of mRNA (100 versus 30 µg) in the Moderna vaccine [1–3]. However, a reporting bias cannot be excluded and further studies are certainly needed.

More than 70% of the patients in our series and most published cases developed symptoms within 3 h to 2 days after the vaccination (range 0–44 days). Most cases of macrohaematuria occurred after the second vaccine dose. This is in stark contrast to cases of MCD. A total of 10/15 MCD cases reported occurred after the first dose [5, 6, 36]. Also, the delay between injection and manifestation of symptoms was longer (which could possibly be due to detection bias). These dissimilarities suggest different pathophysiologic mechanisms leading to glomerular damage after COVID-19 vaccination. Bomback *et al.* [5] suggest a more important role of T cells in MCD. T cells are known to rapidly respond to foreign mRNA by producing soluble factors that might cause podocyte dysfunction, explaining the phenomenon of disease manifestation following the first dose. Alternatively in IgAN patients with macrohaematuria after the second dose, damage could have been present after the first dose, but was missed because of being asymptomatic. We report the first case of gross haematuria occurring after the third dose. More cases can be expected as booster vaccinations are increasingly recommended.

Since macrohaematuria is so obvious, one could conclude that gross haematuria probably represents only the 'tip of the iceberg' and less evident glomerular sequelae of vaccination might get missed. Lim *et al.* [37] scrutinized this question. They retrospectively investigated 29 patients with known IgAN who had kidney function and urine evaluated after SARS-CoV-2 vaccination and found that 2/29 had mildly increased serum creatinine with an increase in haematuria and proteinuria. None required intensification of therapy. Since there was no control group in their study, it is unclear whether deterioration was caused by the vaccination. They also reported that in their cohort of 145 patients with IgAN, none experienced an episode of gross haematuria. It is unclear, what the exact incidence of macrohaematuria after COVID-19 immunization is, because many cases might not get published [5]. Also, reporting of vaccine adverse effects via the World Health Organization pharmacovigilance system Vigibase (https://www.who-umc.org/vigibase/vigibase/) appears to be incomplete (Supplementary data, Table S1). As of 7 October 2021, only 19 cases of macrohaematuria following COVID-19 vaccination had been reported, which is fewer cases than published in the literature. However, the overall risk of experiencing gross

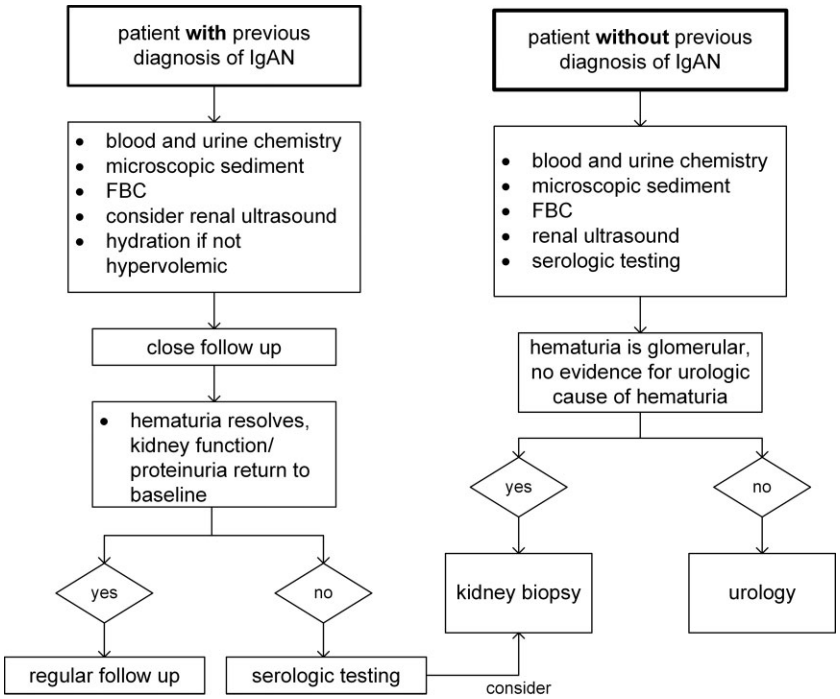

FIGURE 3: Suggested algorithm for work-up of patients with macrohaematuria following mRNA-based SARS-CoV-2 vaccination. FBC, full blood count.

haematuria, *de novo* or a flare of IgAN still appears to be extremely low in view of the ~3.82 billions individuals having received at least one dose of the vaccine worldwide (6.82 billion doses as of 24 October 2021) [1].

Of note, only a few cases of macrohaematuria or IgAN after influenza vaccination have been reported in the literature [6, 38], despite millions of patients getting immunized every year. This could be due to the different type of vaccine (mRNA versus inactivated whole virus in the case of influenza) or the different epitopes involved (spike protein versus haemagglutinin and neuraminidase). We therefore speculate that the finding of more frequent cases of gross haematuria/IgAN after COVID-19 compared with influenza vaccination is evidence that these cases are indeed caused by the vaccination and are not coincidental with it.

Suggested management of patients with gross haematuria after SARS-CoV-2 vaccination

How should physicians manage patients with gross haematuria after COVID vaccination? Patients with pre-existing kidney disease should be sensitized to symptoms such as gross haematuria, oedema or an increase in blood pressure before vaccinating. If gross haematuria occurs, there is a high likelihood that it is caused by IgAN. When a patient with known IgAN presents with gross haematuria, blood and urine chemistry should be done (Figure 3). We also suggest a full blood count to assess the severity of blood loss and to exclude other potential causes of haematuria, such as severe thrombopaenia. Immune thrombocytopaenia (ITP) has been described after COVID vaccination [39, 40]. In addition, renal ultrasound might be considered to exclude nephrolithiasis or malignancy. Patients should be instructed to hydrate sufficiently and be followed closely for resolution of symptoms and reversal of AKI if present. If symptoms do not improve or kidney function deteriorates, serologic testing and renal biopsy should be obtained to exclude crescentic IgAN or additional small vessel vasculitides.

In patients with no previous IgAN and gross haematuria, we suggest a complete workup for nephritic syndrome and other causes of gross haematuria. If symptoms and laboratory signs do not normalize rapidly or if there is serologic evidence of an underlying autoimmune kidney disease, renal biopsy should be urgently performed.

Re-exposition in patients with previous vaccination-associated glomerular disease

One dilemma is how to continue vaccination if gross haematuria occurs after the first or second dose. Up to now, few reports have described this situation. Perrin *et al.* [16] reported one patient with pre-existing IgAN who developed gross haematuria after the first dose of mRNA-1273 and who relapsed after the second. Klomjit *et al.* [6] report on one patient with IgAN who developed gross haematuria and an increase in serum creatinine after the first dose of mRNA-1273. After the second dose he suffered from further deterioration of renal function. Another patient with IgAN suggested by skin biopsy showed worsening of skin lesions, not renal function, after the second dose of mRNA-1273 [15]. Two additional patients, one with IgAN and interstitial nephritis after mRNA-1273 and another with atypical anti-GBM disease after BNT162b2, received a second dose of their initial vaccine [6]. Both patients received immunosuppression but did not respond well and had progression of their kidney disease. Whether this was a consequence of the initial manifestation of kidney disease or whether the second vaccination dose contributed to the deterioration is impossible to determine. In our patient (Patient 1), the second dose of the mRNA-1273 was withheld to avoid a flare. At the time of the first vaccination, the patient had no

detectable anti-spike antibodies. He received a second vaccination with the vector-based Ad26.COV2-S (Janssen/Johnson & Johnson) after the first mRNA-1273 dose without experiencing another episode of haematuria or albuminuria.

Five patients described in the literature with MCD (either *de novo* or pre-existing) after the first COVID-19 vaccination were rechallenged with the same vaccine as initially administered. Two relapsed (both with BNT162b2 mRNA) and three did not (two with AstraZeneca and one with BNT162b2 mRNA) [25, 41]. For one patient who relapsed after the second dose, no information is available regarding immunosuppression at rechallenge [42]. The second patient was on 0.4 mg/kg prednisone at relapse during his first vaccination and 0.5 mg/kg at the second relapse following rechallenge. All patients who did not relapse upon rechallenge were either on corticosteroids (15 mg/day) or on corticosteroids plus tacrolimus [25, 41]. The findings indicate that, at least in MCD, corticosteroids do not seem to suppress a relapse upon rechallenge.

In conclusion, we suggest that patients with new-onset or a relapse of a GN who require an additional dose should be immunized with an alternative vaccine, i.e. individuals who have received an mRNA-based formulation should receive a vector-based vaccine and vice versa. Protein-based vaccines might be an additional future alternative.

CONCLUSION

Macrohaematuria can be an adverse effect of mRNA-based COVID-19 vaccines occurring after the first vaccination. We therefore recommend that nephrologists alert their patients to this. Furthermore, we propose that patients who exhibit glomerular disease upon vaccination and require an additional dose should receive a different type of vaccine.

To date, there are no studies regarding the true incidence of glomerular disease after SARS-CoV-2 vaccination and how often it is a coincidence. According to the currently available data, it is a very rare event and the probability of severe renal damage caused by COVID-19 and its complications is assumed to be significantly higher [43].

SUPPLEMENTARY DATA

Supplementary data are available at *ckj* online.

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DATA AVAILABILITY STATEMENT

The data underlying this article are available in the article and in its online supplementary material.

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AUTHORS' CONTRIBUTIONS

A.R. and H.S. designed the study, performed the analysis and wrote the manuscript. B.H. and A.G. provided and illustrated the histological findings. All authors were involved in patient care, data collection and review of the manuscript.

CONFLICT OF INTEREST STATEMENT

H.S. has received speaker fees and honoraria for advisory boards from Mundipharma and AstraZeneca regarding SGLT2 inhibitors and a travel grant from Mundipharma. The other authors have nothing to declare. The results presented in this article have not been published previously in whole or part, except in abstract form.

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