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CASE BASED REVIEW

ANCA-associated vasculitis following ChAdOx1 nCoV19 vaccination: case-based review

Arun Prabhahar[1] · G. S. R. S. N. K. Naidu[2] · Prabhat Chauhan[1] · Aravind Sekar[3] · Aman Sharma[2] · Alok Sharma[4] · Asheesh Kumar[5] · Ritambhra Nada[3] · Manish Rathi[1] · Harbir Singh Kohli[1] · Raja Ramachandran[1]

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Abstract

For the foreseeable future, vaccines are the cornerstone in the global campaign against the Coronavirus Disease-19 (COVID-19) pandemic. As the number and fatalities due to COVID-19 decline and the lockdown anywise rescinded, we recognize an increase in the incidence of autoimmune disease post-COVID-19 vaccination. However, the causality of the most vaccine-induced side effects is debatable and, at best, limited to a temporal correlation. We herein report a case of a 51-year-old gentleman who developed Anti-Neutrophil Cytoplasmic Antibody (ANCA)-associated vasculitis (AAV) 2 week post-COVID-19 vaccination. The patient responded favorably to oral steroids and rituximab. Additionally, we conducted a case-based review of vaccine-associated AAV describing their clinical manifestations and treatment response of this emerging entity.

Keywords COVID-19 vaccine · SARS-CoV-2 vaccine · ANCA-associated vasculitis · Auto-immunity · Glomerulonephritis

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection induces an exaggerated immune response in susceptible individuals [1, 2]. The development of autoantibodies in a tiny minority is consequential to the release of Proteinase-3 (PR-3), Myeloperoxidase (MPO) and other antigens by the neutrophils in response to SARS-CoV-2 infection. Epitope spreading and antigen mimicry are initial triggers for antibody production [3]. In addition, host characteristics may contribute to this viral susceptibility [4]. An ideal vaccine should effectively generate a controlled and long-lasting immune response with an impeccable safety profile. In a utopian world, before the rollout, the vaccine efficacy and safety need testing in all clinical conditions, including patients with autoimmune disease those on immunosuppressive therapy, as the aforementioned cohort(s) exhibit variable immune responses to both infection [5, 6] and vaccination [7, 8]. Unfortunately, the burgeoning of COVID-19 cases worldwide and its global ramifications mandated an expeditious vaccine rollout. Henceforth, vaccine trials did not include patients with autoimmune diseases, *or* the development of autoimmune diseases in healthy individuals underwent inadequate scrutiny. Drawing a parallel to COVID-19 infection, researchers worldwide cast doubt over the immunogenicity of the vaccines, with an exaggerated immune response similar to an SARS-CoV-2 infection [9]. Antigen presentation, cytokine profiling, bystander activation, epitope spreading, anti-idiotypic networks, polyclonal activation of B cells are all the mechanisms that may theoretically contribute to this exaggerated immune response [9].

A growing number of reports describe the onset and recurrence of glomerular diseases like anti-Glomerular Basement Membrane (anti-GBM) disease and AAV with the widespread use of the vaccines [10]. Mainly, these occurred

Arun Prabhahar, G. S. R. S. N. K. Naidu, Prabhat Chauhan, and Aravind Sekar are joint first authors.

✉ Raja Ramachandran
drraja1980@gmail.com

[1] Department of Nephology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[2] Department of Internal Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[3] Department of Histopathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India

[4] Dr Lal Pathlabs, New Delhi, India

[5] Department of Nephrology, IGMC, Shimla, India

in individuals who were susceptible to autoimmune diseases and those in remission with these disorders. Therefore, an accepted hypothesis is that AAV develops in patients with a susceptible genetic background and a simultaneous exposure to environmental or other risk factors [11]. Previously, numerous reports have described a temporal association of AAV to influenza vaccination [12]. The aforementioned observations strengthen our credence that the SARS-CoV-2 vaccine could induce an autoimmune response analogous to the infection/influenza vaccine as causality for AAV. Furthermore, with the recent evidence suggesting booster doses of COVID-19 vaccines besides the usual dosing (in the susceptible population) [13], it is pertinent to study the association of autoimmune diseases with COVID-19 vaccination comprehensively. Therefore, we present a 51-year-old gentleman developing a new-onset AAV following the ChAdOx1 nCoV19 SARS-CoV-2 vaccine with a case-based review of the literature of similar cases.

Case report

A 51-year-old gentleman with no prior comorbidity (serum creatinine 1.2 mg/dl, before his illness) presented with a 3-day history of low-grade fever with debilitating inflammatory polyarthritis. He was a non-smoker and did not have any similar complaints in the past. He (or his contacts) had no history of COVID-19 infection. He received the first dose of ChAdOx1 nCoV-19 Vaccine (COVISHIELD- manufactured by Serum Institute of India Pvt Ltd.) 15 days before the onset of present symptoms. However, for synovitis involving multiple joints, his physical examination was unremarkable. On investigating, he had deranged kidney functions (serum creatinine- 4.8 mg/dl), proteinuria (3.4 g/day) and microscopic haematuria (erythrocyte casts and 8–10 erythrocytes/high-power field), elevated inflammatory markers (erythrocyte sedimentation rate (ESR)—46 mm/hour and C-reactive protein—7 mg/L) and PR-3 ANCA positivity. Anti-Nuclear Antibody (ANA), double-stranded DNA antibody (dsDNA), anti-GBM antibody titres were negative, and serum complement levels were within normal limits. The blood and the urine cultures were negative. Kidney biopsy suggested pauci-immune crescentic glomerulonephritis (Supplemental Figure 1). Nineteen out of the 20 glomeruli biopsied showed crescents with predominant cellular crescents. With a diagnosis of PR3-AAV, he was referred to our hospital, and we started him on oral prednisolone (60 mg/day) and rituximab (375 mg/m^2 weekly for 4 weeks). We tapered oral prednisolone as per the low-dose steroid tapering schedule of the PEXIVAS trial [14]. At 20 weeks of follow-up, he had complete resolution of his constitutional symptoms and arthralgias, serum creatinine (2.3 mg/dl) and proteinuria (1.0 g/day) showing a steady decline, and microhaematuria subsided.

Search strategy and case selection

We conducted a case-based search in PubMed, with the following search (COVID-19 vaccine OR COVID-19 OR COVID-19 vaccination OR SARS-CoV-2 vaccine OR SARS-CoV-2 OR Oxford AstraZeneca OR Moderna OR Pfizer-BioNTech OR Sputnik OR Sinopharm OR BBV152/Covaxin OR Janssen OR CoronaVac OR Novavax) AND (ANCA OR ANCA related Glomerulonephritis OR ANCA-associated glomerulonephritis OR ANCA Associated Vasculitis OR Glomerulonephritis OR MPO ANCA OR PR-3 ANCA OR Pauci-immune glomerulonephritis OR De novo vasculitis OR Anti-Neutrophil cytoplasmic antibody OR Antineutrophil cytoplasmic antibody OR Myeloperoxidase OR Anti-proteinase-3) from 1st January 2020 to 15th November 2021. We included all the case reports published in the English literature of AAV in patients aged ≥ 18 years. Cases were excluded if the AAV developed after SARS-CoV-2 infection or disease manifestations without ANCA positivity or if the ANCA report was unavailable or untested. Additionally, we included articles detected on web-based search. The title, abstracts and the full texts of the case reports were individually checked by two authors (AP and PC) and considered for evaluation if both agreed.

Statistical analysis

Descriptive statistics are used to detail the baseline characteristics of the patients. We expressed the normally distributed continuous variables as mean ± standard deviation (range), non-normally distributed variables as medians with interquartile ranges (IQR) and categorical data as proportions. All analyses were performed using Graph Pad Prism 9, *San Diego*, CA 92108.

Results

The search criteria exhibited 350 articles from PubMed. Of the 350 reports, we identified 15 cases, and an additional web-based search revealed 13 cases (Supplemental Figure 1). Also, we included our case report for review. Finally, we analyzed 29 cases for review. The median age of the patients was 71 years (IQR 54 to 78). 15 cases were males and 14 were female, respectively. The individual case details are shown in Table 1.

Vaccine

Among the eight vaccines approved to prevent SARS-CoV-2 infection by the World Health Organization, we report an association of AAV with five (2 mRNA vaccines–mRNA-1273 (Moderna) and mRNA-BNT162b2 (Pfizer-BioNTech), viral vector vaccine–ChAdOx1 nCoV-19 (Oxford AstraZeneca), Ad26.COV2.S (Johnson and Johnson) and inactivated vaccine BBV152 (Covaxin) vaccines. Most reports were secondary to mRNA vaccines (22/29), 4 with ChAdOx1 nCoV-19, 2 with BBV152 and 1 with Ad26.COV2.S vaccine. Fourteen patients had symptoms after the first dose; the remaining 15 had after the 2nd. Three patients had worsening symptoms after administering the second dose (Table 1, patient numbers 1, 3 and 22) (Fig. 1).

Comorbidities and ANCA status

In addition, 17 patients had prior comorbidities (05 hypertension, 02 diabetes mellitus, 03 patients interstitial lung diseases, 02 malignancies, 01 cerebrovascular accident, 01 atrial fibrillation, 01 Graves' disease, 01 had both latent TB and Giant cell arteritis), in addition to AAV before vaccination. Twenty-four patients had a new-onset AAV. Among the ANCA subtypes, the most common association was with MPO (15 cases) ANCA alone, and four had PR-3 (4 cases) ANCA alone, 03 had dual (MPO and PR-3) positivity. One of the dual positive cases (Table 1, patient no. 6) was also on Propylthiouracil for Grave's disease and had auricular chondritis. In six cases, the ANCA subtype was not mentioned**.** ANA was positive besides ANCA in six cases. *Prema* et al. reported (Table 1, patient number 14) dual positivity for both PR-3 and GBM antibodies. *Gupta* et al. described a case of Fragile-X syndrome developing anti-MPO, anti-GBM antibody and ANA positivity (Table 1, patient no 10).

Symptoms

The reporting for constitutional symptoms was variable. At least 16 (55.1%) patients had constitutional symptoms at presentation. Twenty-two patients had renal involvement (93.1%) either as new-onset or recurrence of the glomerulonephritis. At least 24 (82.7%) patients had haematuria (2 among the 24 had macro-haematuria) at presentation. The median (maximum) serum creatinine was 3.82 (IQR 2.15 to 8.31) mg/dl. If we take AAV due to non- mRNA vaccines alone, the median maximum serum creatinine is 6.55 mg/dl (IQR 4.8 to 8.4). Ten patients (29.1%) had pulmonary involvement, of which 05 (17.2%) had alveolar haemorrhage (Table 1, patient numbers 7, 8, 14, 15 and 26). In addition, one patient had optic neuritis (Table 1, patient number 5), and one had auricular chondritis (Table 1, patient number 6) as the manifestation following vaccination among other organ involvement.

Relapsing disease

Five patients had relapses of AAV post-vaccination. Among them, four had prior renal involvement. All five cases had renal involvement (four had biopsy-proven crescentic glomerulonephritis). Four patients (80%) were MPO positive, and in one patient, the nature of ANCA was unavailable.

Kidney biopsies

Twenty-five patients (86.2%) underwent renal biopsies. The age (cellular, fibro cellular and fibrous), as well as the extent of crescents were variable. Twenty-one cases (84%) had crescentic glomerulonephritis (> 50% of glomeruli). In four cases (16%), the crescents were focal. Rupture of a glomerular capillary wall with periglomerular inflammation was seen in four cases (16%). Underlying tuft showed fibrinoid necrosis in 16 cases (64%). Mesangial expansion and proliferation were observed in three cases (12%). None of the biopsies reported endocapillary proliferation. Five biopsies (20%) had findings consistent with vasculitis. The information on Interstitial Fibrosis and Tubular Atrophy (IFTA) were available only in ten cases (40%). Seven (70%) and three (30%) cases had a mild and moderate degree of IFTA, respectively. Immunofluorescence findings were available for 24 cases. There were no significant deposits for immunoglobulins or complements in 18 cases (75%), fulfilling the definition criteria for pauci-immune crescentic glomerulonephritis. Linear deposits of IgG and light chains along the glomerular capillary wall were observed in three cases (Supplemental Table 1, patient numbers 10, 14 and 15). In two cases (Table 1 Patient numbers 10, 14), anti-GBM antibody titres were positive in serum, confirming coexistent Anti-GBM disease. A single patient (Supplemental Table 1, patient number 16) had 2 + intense deposits for Immunoglobulin A (IgA) in the mesangium, suggesting the diagnosis of concurrent IgA nephropathy. Similarly, another patient (Supplemental Table 1, patient number 18) had 3 + intense deposits for C3 (Complement Factor 3) in the mesangium. Furthermore, the electron microscopy showed immune complex type mesangial deposits, confirming concurrent C3 glomerulopathy. The electron microscopy findings were available in five cases. All cases had an effacement of foot processes of podocytes. The summary of renal biopsies is shown in Supplementary Table 1.

Table 1 Details of AAV patients post SARS-CoV2 vaccinations

S no	Study author	Age	Sex	Comorbidity	Relapse or new onset	Vaccine	Dose	Worsened with rechallenge	Time to onset (days)	Seromarkers	Kidney involvement	Kidney biopsy	Maximum serum creatinine (mg/dl)	Constitutional symptoms	Lung	Other clinical features	Treatment given	Follow-up duration (weeks)	Renal Outcome	General outcome
1	Anderegg et al. [31]	81	Male	Nil	New onset	mRNA-1273	1st and 2nd	Yes	NA	PR3	AKI, microscopic haematuria, non-nephrotic range proteinuria	Crescentic GN	NA	Yes	Necrotic masses, pleural effusion		Cyc + PLEX + steroids	3	Improved	Improved
2	Arjun Sekar et al. [32]	52	Male	HTN	New onset	mRNA-1273	2nd	NA	14	PR3	AKI, macroscopic haematuria, non-nephrotic range proteinuria	Crescentic GN	10.42	Yes	NA		Rtx (1dose) f/b Cyc + steroids	2	Dialysis dependent	NA
3	Shakoor et al. [33]	78	Female	HTN, DM, AF	New onset	mRNA-BNT162b2	1st and 2nd	Yes	16—1st, 6—2nd	MPO	AKI, microscopic haematuria, non-nephrotic range proteinuria, leukocyturia	Crescentic GN	3.54	Yes	NA		Rtx + Steroids	4	Improved	Improved
4	Dube et al. [34]	29	Female	congenital cystic lung disease, lung failure	New onset	mRNA-BNT162b2	2nd	NA	16	MPO	AKI, microscopic haematuria, non-nephrotic range proteinuria	Crescentic GN	1.91	NA	NA		Rtx + Cyc + steroids	10	Improved	Improved
5	Takenaka et al. [35]	75	Female	DM, dyslipidaemia	New onset	mRNA-BNT162b2	1st	NA	4	MPO	NA	NA	NA	NA	NA	Right eye optic neuritis	Steroids	4	NA	Improved
6	Okuda et al. [36]	37	Female	Graves' disease	New onset	mRNA-BNT162b2	1st	NA	12	MPO, PR-3	Nil	NA	0.6	Yes	NA	Auricular chondritis, skin rash	Oral steroids	4	NA	Improved
7	Villa et al. [37]	63	Male	Nil	New onset	ChAdOx1 nCoV-19	1st	NA	2	MPO	AKI, microscopic haematuria, non-nephrotic range proteinuria	Focal pauci-immune GN	2.91	Yes	Alveolar haemorrhage		Cyc + steroids	6	Partial response	Improved
8	Rachel David et al. [38]	75	Male	Renal limited MPA vasculitis	Relapse	ChAdOx1 nCoV-19	1st	NA	37	MPO	Microscopic haematuria	Crescentic GN	6.97	NA	Alveolar haemorrhage		Rtx + steroids	NA	Dialysis dependent	Improved

Table 1 (continued)

S no	Study author	Age	Sex	Comorbidity	Relapse or new onset	Vaccine	Dose	Worsened with rechallenge	Time to onset (days)	Seromarkers	Kidney involvement	Kidney biopsy	Maximum serum creatinine (mg/dl)	Constitutional symptoms	Lung	Other clinical features	Treatment given	Follow-up duration (weeks)	Renal Outcome	General outcome
9	Rachel David et al. [38]	74	Male	MPA without renal involvement	Relapse	ChAdOx1 nCoV-19	1st	NA	14	MPO	AKI	Crescentic GN	9.97	NA	Nil		Cyc + steroids	NA	Improved	Improved
10	Rajib K Gupta et al. [39]	23	Male	Fragile-X syndrome and Interstitial Lung Disease	New onset	mRNA-1273	2nd	NA	14	MPO, Anti-GBM, ANA	AKI, microscopic haematuria, non-nephrotic range proteinuria	Crescentic GN	14	Yes	NA		NA	NA	NA	NA
11	Samy Hakroush et al. [40]	79	Male	Hypertension, Degenerative disc disease	New onset	mRNA-BNT162b2	2nd	NA	14	MPO, ANA	Leukocyturia, microscopic Haematuria, nephrotic range proteinuria, AKI	Pauci-immune GN with myoglobin cast nephropathy	6.57	Yes	NA	Arthralgia	Cyc + steroids	NA	Improved	Improved
12	NattawatKlomjit et al. [41]	82	Female	NA	New onset	mRNA-1273	2nd	NA	28	MPO	AKI, Haematuria, Proteinuria	Crescentic GN	3.1	Yes	NA		Rtx + steroids	4	Partial response	Improved
13	Edoardo Conticini et al. [42]	77	Male	MPA with renal involvement	Relapse	mRNA-BNT162b2	1st	NA	NA	MPO	AKI, Haematuria	NA	1.55	NA	GGOs with sept thickening		Steroids	NA	Improved	Improved
14	J Prema et al. [43]	58	Male	Nil	New onset	BBV152	2nd	NA	14	PR3, Anti-GBM	Haemoptysis, AKI	Crescentic GN	8.4	NA	Alveolar haemorrhage		Cyc + PLEX + steroids	8	Partial response	Improved
15	Prema et al. [43]	45	Male	Nil	New onset	BBV152	1st	NA	12	MPO, ANA	Haemoptysis, AKI	Crescentic GN	9	NA	Alveolar haemorrhage		Cyc + PLEX + steroids	5	Partial response	Improved
16	Tiffany Caza et al. [44]	76	Male	Nil	New onset	mRNA-BNT162b2	2nd	NA	11	ANCA, ANA	AKI, Haematuria, Proteinuria	Crescentic GN	8.6	Nil	Nil		Rtx + steroids	3	Dialysis dependent	Nil
17	Tiffany Caza et al. [44]	81	Female	Nil	New onset	mRNA-BNT162b2	2nd	NA	2	ANCA, ANA	AKI, haematuria, proteinuria	Crescentic GN	3.1	Nil	Nil		Rtx	3	Partial response	Nil
18	Tiffany Caza et al. [44]	76	Female	Nil	New onset	mRNA-1273	1st	NA	5	ANCA, ANA	AKI, haematuria, proteinuria	Crescentic GN	3.0	Nil	Nil		Rtx + steroids	5	Partial response	Nil

Table 1 (continued)

S no	Study author	Age	Sex	Comorbidity	Relapse or new onset	Vaccine	Dose	Worsened with rechallenge	Time to onset (days)	Seromarkers	Kidney involvement	Kidney biopsy	Maximum serum creatinine (mg/dl)	Constitutional symptoms	Lung	Other clinical features	Treatment given	Follow-up duration (weeks)	Renal Outcome	General outcome
19	Tiffany Caza et al. [44]	71	Female	Nil	New onset	mRNA-1273	2nd	NA	14	ANCA, ANA	Haematuria, Proteinuria	Crescentic GN	1.3	Nil	Nil		Rtx + steroids	1	Nil	Nil
20	Tiffany Caza et al. [44]	65	Female	Nil	New onset	mRNA-BNT162b2	2nd	NA	14	ANCA	AKI, Haematuria, proteinuria	Crescentic GN	3.2	Nil	Nil		Cyc + steroids	2	Dialysis dependent	Nil
21	Tiffany Caza et al. [44]	79	Female	AAV	Relapse	mRNA-1273	2nd	NA	21	ANCA	Haematuria, Proteinuria	Crescentic GN	1.12	Nil	Nil		Rtx	16	Improved	Nil
22	Davidovic et al. [45]	54	Female	Seronegative arthralgia, MPA?	New onset	mRNA-BNT162b2	1st and 2nd	Yes	35 – 1st, 14—2nd	MPO	AKI, haematuria, proteinuria	Pauci-immune GN	2.11	Yes	Discrete opacities in radiology	Painful red eyes	Rtx + steroids	NA	Improved	Improved
23	Davidovic et al. [45]	78	Female	MPA	Relapse	mRNA-BNT162b2	2nd	NA	2	MPO	AKI, haematuria, proteinuria, dark urine	NA	8.23	Yes	Nil		Rtx + steroids	NA	Dialysis dependent	Improved
24	Shota Obata et al. [46]	84	Male	CVA, colon cancer, interstitial pneumonia	New onset	mRNA-BNT162b2	2nd	No	14	MPO	Microscopic haematuria, non-nephrotic proteinuria	Pauci-immune GN	1.22	Yes	Worsening of interstitial pneumonia		Steroids	8	Improved	Improved
25	Seif et al. [47]	66	Male	Hypertension, COPD, Latent TB, GCA	New Onset	mRNA-1273	2nd	No	21	MPO	Microscopic haematuria, non-nephrotic proteinuria	Crescentic GN	2.2	Yes	NA		Rtx + steroids	1	Partial response	Improved
26	Feghali et al. [48]	58	male	Nil	New onset	mRNA-1273	2nd	No	4	MPO, PR-3	AKI, Microscopic haematuria, non-nephrotic proteinuria	Crescentic GN	4.1	Yes	Consolidation, pleural effusion, alveolar haemorrhage		Rtx + Cyc + PLEX + steroids	10	Improved	Improved
27	Chen et al. [49]	70	Female	UTI	New onset	mRNA-1273	1st	NA	7	MPO	AKI, Macroscopic haematuria, Nephrotic range proteinuria	Crescentic GN	6.3	Yes	Consolidation, GGOs		Rtx + PLEX + steroids	3	Partial response	Improved

Table 1 (continued)

S no	Study author	Age	Sex	Comorbidity	Relapse or new onset	Vaccine	Dose	Worsened with rechallenge	Time to onset (days)	Sero-markers	Kidney involvement	Kidney biopsy	Maximum serum creatinine (mg/dl)	Constitutional symptoms	Lung	Other clinical features	Treatment given	Follow-up duration (weeks)	Renal Outcome	General outcome
28	Rukesh Yadav et al. [50]	54	Female	HTN, Uterine cancer	New onset	Ad26.COV2.S	1st	No	12	MPO, PR-3	AKI, Microscopic haematuria, non-nephrotic proteinuria	Crescentic GN	6.13	Yes	Nil		steroids	1	NA	NA
29	Index patient	51	Male	Nil	New onset	ChAdOx1 nCoV-19	1st	No	15	PR-3	AKI, microscopic haematuria, nephrotic range proteinuria	Crescentic GN	4.8	Yes	Nil	Arthralgia	Rtx + steroids	20	Partial response	Improved

AKI Acute Kidney Injury, *AF* Atrial Fibrillation, *ANA* Anti-Nuclear Antibody, *ANCA* Ant- Nuclear Cytoplasmic Antibody, *COPD* Chronic Obstructive Pulmonary Disease, *CVA* Cerebro-Vascular Accident, *Cyc* Cyclophosphamide, *DM* Diabetes Mellitus, *GBM* Glomerular Basement Membrane, *GCA* Giant Cell Arteritis, *GGO* Ground Glass Opacities, *GN* Glomerulonephritis, *HTN* Hypertension, *MPA* Microscopic Polyangiitis, *MPO* Myeloperoxidase, *NA* Not Available, *PLEX* Plasma-Exchange, *PR-3* Proteinase-3, *Rtx* Rituximab, *TB* Tuberculosis, *UTI* Urinary Tract Infection

Treatment

Most patients (96.5%) received immunosuppressive therapy, including steroids, cyclophosphamide and rituximab. In addition, five patients received plasma exchange (PLEX), of whom three had a diffuse alveolar haemorrhage. At the last follow-up, at least five continued to remain dialysis-dependent.

Discussion

In the present case-based review, we highlight the clinical features and outcome of COVID-19 vaccination-induced AAV. Renal involvement is reported in over three-fourths of the cases and most patients responded favorably to immunosuppressive therapy.

Vaccine-associated autoimmunity is a well-known entity caused by cross-reactivity to antigens or adjuvants. In the current report, most vaccine-associated AAV were with mRNA vaccines. These vaccines (mRNA vaccines) may cause differential stimulation of myeloid and dendritic cells, activating the downstream pathway to produce autoinflammation [15]. mRNA vaccines have a lesser risk of infection and insertion-related mutagenesis but generate antiviral neutralising immunoglobulins and stimulate strong immune responses by activating CD8 + and CD4 + T cells [16]. Also, mRNA vaccines may cause enhanced stimulation of innate and acquired immunity compared to inactivated vaccines or natural infection [16, 17]. This new-onset autoinflammation transpires in genetically predisposed individuals; these cases with compromised immune systems have a decreased clearance of nucleic acids predisposing to Neutrophil Extracellular Traps (NETs) [18]. NETs are highly proinflammatory and provide a sustained antigenic stimulus. This NETosis is a critical step in the pathogenesis of both cytokine storms in COVID-19 infection [19] and COVID-19-triggered AAV [20]. Finally, the vaccine-induced autoimmunity associated with COVID-19-inactivated vaccines can also be related to the immune response to the SARS-CoV-2 proteins or an exaggerated response to the m RNA vaccine. Still, the exact mechanism is not fully understood. None of the patients described of COVID-19 vaccine-associated AAV had tested positive for the infection, ruling out the infective virions as the responsible triggers for the disease pathogenesis.

Glomerular diseases mentioned in association with COVID-19 vaccines include IgA nephropathy [10], podocytopathies [10], lupus nephritis [21], crescentic glomerulonephritis, anti-GBM disease [10], IgG4 disease [22], and membranous nephropathy [23]. In an observational study from Japan [24], where IgA nephropathy is more prevalent and diagnosed earlier in life than the rest of the world, gross haematuria and proteinuria on screening urine examination

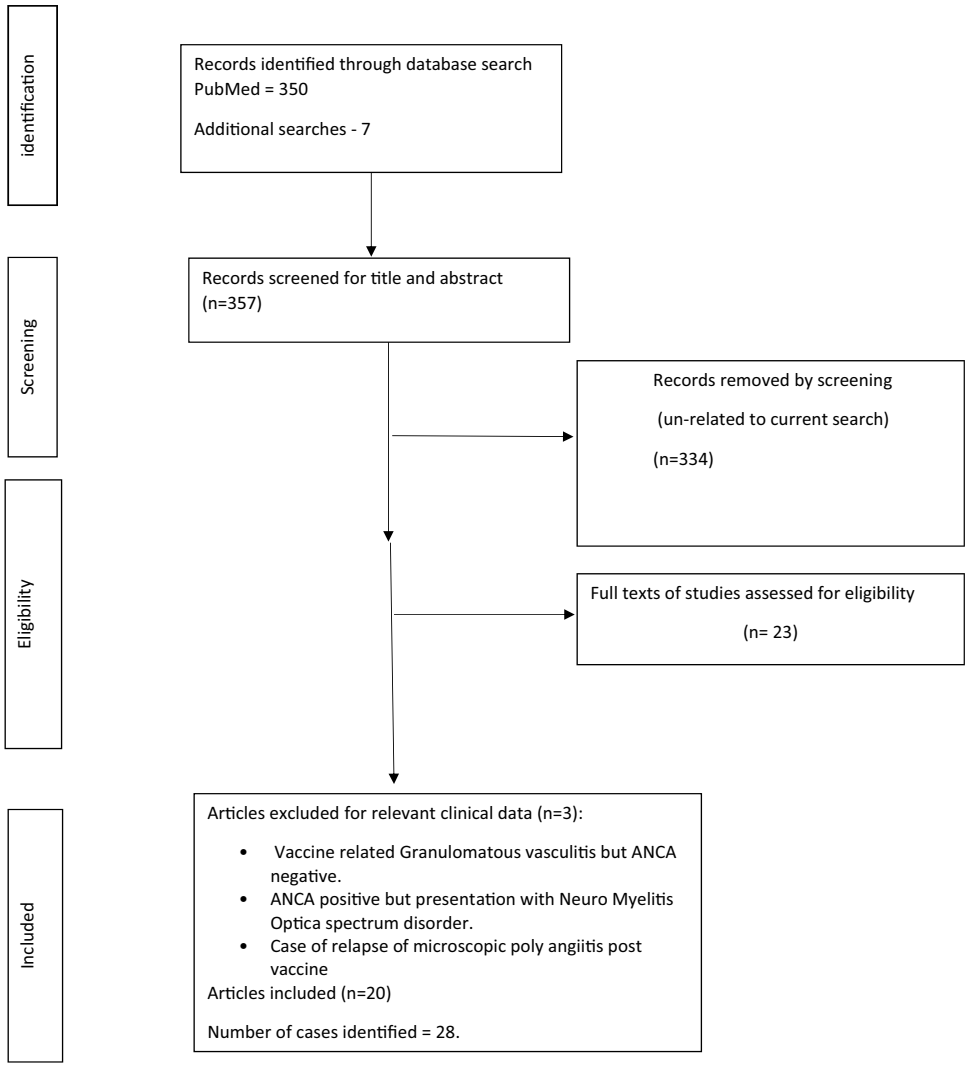

Fig. 1 Search strategy algorithm

post-vaccination have led to the identification of recurrence and new-onset IgA nephropathy associated with COVID-19 vaccination. Thus, routine urine examination and monitoring of renal function tests after vaccination can help detect glomerular diseases in susceptible individuals. Also, most of the patients described in the current review had urine abnormalities at presentation.

The global incidence and prevalence of AAV varies from 0.4 to 24 cases per million-person-years and 300 to 421 cases per million population, respectively [25]. The involvement of the kidney in AAV varies from 54 to 97% in various studies [26, 27]. The kidney involvement in the current series is comparable to the prior reports. Kidneys followed by lungs are the commonly affected organs in COVID-19 vaccine-associated AAV. Patients who developed AAV post-vaccination responded favorably to immunosuppressive therapy. Thus, based on the current review, we recommend immunosuppressive treatment to all patients with vaccine-mediated glomerulonephritis. However, researchers need to be mindful of rituximab treated patients responding poorly to further booster doses of COVID-19 vaccination, as a susceptible population [28].

Historically, most vaccine trials fail to address the vaccine-associated autoimmunity because of the variable manifestations and long latency between the inoculation and symptomatology [29]. Also, during the earlier phase of vaccination, which was during the pandemic, worldwide lockdowns with restricted access to healthcare may account for reduced reporting of adverse events post-vaccination. Fortunately, increased patient awareness of post-vaccine symptoms, along with a decline in the infection rates, may have resulted in a surge in reporting of vaccine-related side effects.

Undoubtedly, both mass vaccination for protection against COVID-19 and heightened awareness for detecting autoimmune diseases provide the ideal platform to prevent COVID-19 infection and study the association of autoimmune diseases with vaccines. In addition, it may pave the way for studying undiagnosed pathogenic mechanisms and newer

treatment options in autoimmune diseases. Kadkhoda et al. [30] reported that 57% of patients developed ANCA positivity post-COVID-19 infection. The aforementioned study is also a proof of concept for expeditious seroconversion as they tested most of the samples during hospital admission.

A temporal correlation of symptoms to vaccination forms the basis of the report; whether it equals causation considering the limited number of cases reported is debatable, short duration of follow-up, inadequate clinical and pathological data and lack of uniformity in immunosuppressive treatment are limitations to the study. To conclude, post-COVID-19 vaccination-associated AAV is rare. Grand scale vaccination against SARS-CoV-2 infection provides a suitable platform to observe and learn the association of AAV with vaccination. The number of autoimmune glomerular diseases associated with COVID-19 infection conspicuously outweighs the number of cases post-COVID-19 vaccination. Henceforth, the otherwise healthy population and individuals with autoimmune diseases in remission and on immunosuppressive therapy should be encouraged to continue with the vaccination with close monitoring of symptoms.

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Declarations

Ethical approval No ethical clearance required as it is a case report and case-based review.

Consent for publication Consent for publication taken from the patient for the case report.

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